NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Contents:

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

Premeeting briefing
Cabozantinib for previously treated advanced renal cell carcinoma

This slide set is the premeeting 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.

COMMON ABBREVIATIONS	
AE	Adverse event
BSC	Best supportive care
CI	Confidence interval
CR	Complete response
DIC	Deviance information criteria
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
FE	Fixed effects
FKSI	Functional Assessment of Cancer Therapy Kidney Symptom Index
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility value
ICER	Incremental cost effectiveness ratio
IRC	Independent radiology committee
ITT	Intent-to-treat
IV	Intravenous
LY	Life year
MSKCC	Memorial Sloan-Kettering Cancer Centre
mTOR	Mammalian target of rapamycin
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PD-1	Programmed death 1

COMMON ABBREVIATIONS	
PFS	Progression-free survival
PH	Proportional hazards
PITT	Primary endpoint intent-to-treat
PIM	Promising innovative medicine
PPS	Post-progression survival
PR	Partial response
QALY	Quality adjusted life year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank preserving structural failure time
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SRE	Skeletal related events
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TRAE	Treatment related adverse event
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Key clinical issues for consideration

- Would cabozantinib be used as second- or third-line treatment, or both? Do the trial results permit the effectiveness of cabozantinib to be considered separately for each line of therapy?
  - Are there any other subgroups that should be considered separately?
- Are the results from METEOR generalizable to the NHS?
  - Does the proportion of patients with ECOG performance status of 0 reflect patients seen in clinical practice?
  - Can the results be extrapolated to the specific place in therapy in which cabozantinib would be used (if any)?
  - Is treatment duration likely to differ?
- Which analysis is the more appropriate for assessing PFS, the primary endpoint intent-to-treat, or the intent-to-treat?
- Is the effectiveness of cabozantinib likely to wane beyond the end of the trial?

Key clinical issues for consideration (cont.)

- Cabozantinib appeared more effective compared with everolimus than nivolumab was compared with everolimus. Which trial reflect the survival benefit of everolimus more accurately?
- Should the NMA assume proportional hazards for PFS? For OS?
- The company's network meta-analysis included trial populations that differed in baseline prognosis scores, 'maturity', number of previous treatments and adjustments for cross-over and subsequent treatments. Is this analysis robust enough to inform decision-making?
- Is the ERG's NMA assuming that axitinib and everolimus have equal efficacy more appropriate than the company's NMA?

Background

- Renal cell carcinoma (RCC) originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons)
- In 2013, 9,900 new kidney cancer cases were diagnosed in England
  - ~46% of people diagnosed had advanced disease (stage III or IV)

Stage III	Tumour is either locally advanced and/or has spread to regional lymph nodes
Stage IV	Tumour has spread beyond the regional lymph nodes to other parts of the body

- Most commons symptoms of advanced RCC: blood in the urine (haematuria), a palpable mass in the flank or abdomen and abdominal pain

Current NICE guidance for advanced and/or metastatic RCC

	Treatment	NICE recommendation
1st line	Sunitinib (TA169)	**Recommended only if**: • Person suitable for immunotherapy • 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 subsequent line	Axitinib (TA333)	Recommended after first-line tyrosine kinase inhibitor (TKI) or cytokine
	Nivolumab (TA417)	**Recommended**
	Everolimus (TA219)	**Not recommended** but ongoing CDF reconsideration appraisal issued draft guidance with positive recommendation*
	Sorafenib, sunitinib (TA178)	**Not recommended**

* The draft guidance recommends everolimus 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.

Treatment pathway

1st line	Pazopanib* ★ TA215	Sunitinib* ★ TA169			
2nd line	Axitinib ★ TA333	Everolimus ✪ • Currently available via CDF • Ongoing CDF reconsideration appraisal	Nivolumab Recommended TA417	Cabozantinib ?	
3rd line	Axitinib ★ TA333	Nivolumab Recommended TA417	Best supportive care?	Cabozantinib ?	

★: oral tyrosine kinase inhibitors

✪: oral mammalian target of rapamycin (mTOR) inhibitor

CDF: Cancer Drug Fund; *has 2nd line marketing authorisation

Source: figure 5 p. 34 company submission

Decision problem

Company submission matched scope

	NICE scope
Population	People who have received previous VEGF-targeted therapy for advanced renal cell carcinoma
Comparators	• Axitinib • Everolimus • Nivolumab • Best supportive care
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects • Health-related quality of life

VEGF, vascular endothelial growth factor

Source: table 1 p. 12 company submission

Cabozantinib

MARKETING AUTHORISATION
advanced renal cell carcinoma in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

KEY RESULTS

Clinical data
- 1 open-label RCT cabozantinib vs. everolimus (METEOR)
- METEOR: cabozantinib reduces risk of death vs. everolimus; HR 0.66 (95% CI 0.53-0.83)
- Network meta-analysis: median PFS longer with cabozantinib (7.8 mts) than with axitinib (4.9 mts)

Cost effectiveness data
Results include **PAS for cabozantinib and comparators** and are confidential. They are presented in PART 2 of the PMB

KEY ISSUES

2nd/3rd line positioning
Appropriate comparators depends on the on the place of cabozantinib in treatment pathway

NMA
Unreliable results because populations are heterogeneous, cross-over present, OS data immature, and no adjustment for subsequent treatment

Survival estimates
Limitation in OS and PFS survival estimates and extrapolations; waning effect not considered by the company

End of life
Company: life expectancy < 24 months with axitinib, everolimus, nivolumab (median OS);
Mean estimates are confidential and presented in PART 2 of the PMB

Cabozantinib (Cabometyx) Ipsen

- Protein kinase
- Inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling, and metastatic progression of cancer
- Indicated for '**advanced renal cell carcinoma in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy**'
- Administered orally, 60 mg once daily
- List price £5,143 for a 30-tablet pack of 60 mg cabozantinib (£171.43 per tablet)
  - Average cost of a course of treatment = [redacted] (based on median duration of treatment of 8.3 months in main trial)

Impact on patients and carers

- Patients with terminal illness and ‘uncommon cancer’ such as kidney cancer are disadvantaged
- There is a lack of 2nd line NICE-approved treatments for patients with kidney cancer – cabozantinib a useful alternative option
- The clinical trial results appear promising
- The toxicity is in line with what would be expected with other VEGF-targeted therapy
- Impact on quality of life appears acceptable
- Clinicians are already used to giving oral VEGF-targeted therapy
- May have additional benefits because of its multi-targeted approach
- Diagnosis of kidney cancer may be delayed, so life-prolonging treatment becomes even more necessary

Company's clinical evidence

1 main trial vs. everolimus (ongoing CDF reconsideration)

Trial	METEOR
Design	**Open-label** RCT (n=658, randomised 1:1 to cabozantinib or everolimus; **no cross-over allowed**)
Population	Adults with advanced RCC that progressed after at least 1 VEGFR-TKI therapy (no limit on the number of previous therapies)
Intervention	Cabozantinib 60 mg orally once daily
Comparator	Everolimus 10 mg orally once daily
Outcomes	• **1°**: progression-free survival (time to IRC-assessed disease progression per RECIST criteria, or death from any cause) • **2°**: overall survival, overall response rate • '**Additional**': health-related quality of life, safety and tolerability
Treatment period	For as long as treatment conferred a clinical benefit as per the investigator (including after progression), until unacceptable toxicity occurred, or the patient needed subsequent anti-cancer treatment
Subsequent treatments	55% (cabozantinib) vs. 50% (everolimus) of patients received subsequent treatment after stopping study drug

IRC, Independent radiology committee, FKSI-19, Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index; mTOR, mammalian target of rapamycin; VEGF-TKI, vascular endothelial growth factor tyrosine kinase inhibitor

Source: table 11 p. 47 company submission

Analyses populations

Population	Definition	Data cut-off
Primary end point intent-to-treat population (PITT)	• First 375 patients randomised • Only used to determine the primary end point (PFS)	• 22 May 2015 (duration of follow-up 21.4 months)
Intent-to-treat population (ITT)	• All randomised patients • Used for all efficacy analyses except PFS	• Overall survival: 31 December 2015 (duration of follow-up 28.7 months) • Objective response: 22 May 2015 (duration of follow-up 21.4 months)
Safety population	• All patients who received any dose of study treatment	• 31 December 2015 (duration of follow-up 28.7 months)

Baseline characteristics

Over 70% of patients in METEOR received only 1 prior VEGF-TKI

Characteristic	PITT		ITT	
	Cabozantinib N= 187	Everolimus N= 188	Cabozantinib N= 330	Everolimus N= 328
Age — year				
Median (range)	62	61	63	62
Range	36–83	31-84	32-86	31–84
ECOG performance-status score — no. (%)				
0	129 (69)	116 (62)	226 (68)	217 (66)
1	58 (31)	72 (38)	104 (32)	111 (34)
Prior VEGFR tyrosine kinase inhibitors — no. (%)				
1	137 (73)	136 (72)	235 (71)	229 (70)
≥2	50 (27)	52 (28)	95 (29)	99 (30)

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PITT, Primary endpoint intent-to-treat population, VEGF-TKI, vascular endothelial growth factor tyrosine kinase inhibitor

Source: table 12 p. 56 company submission

Baseline demographic and clinical characteristics (cont.)

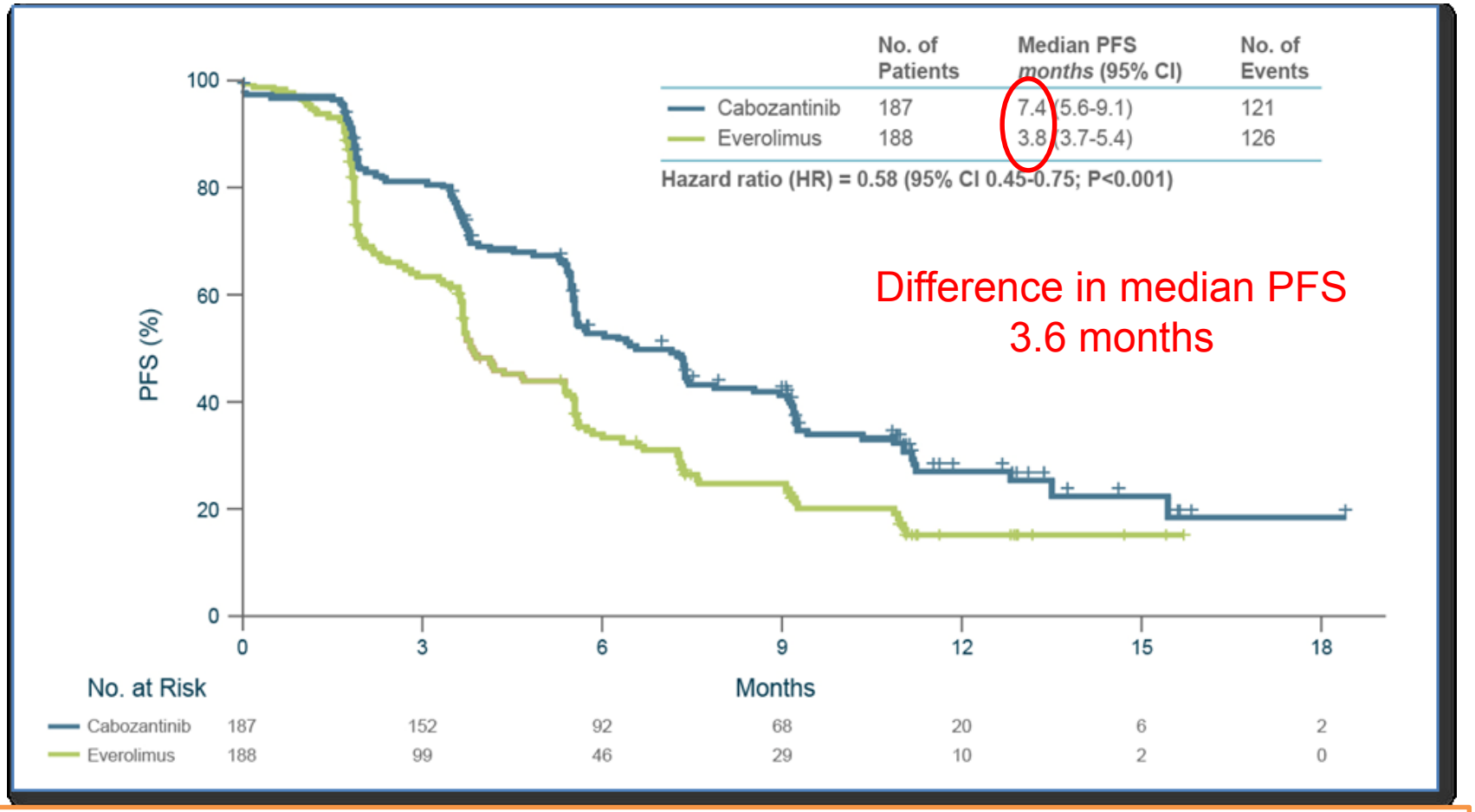
Characteristic	PITT		ITT	
	Cabozantinib N= 187	Everolimus N= 188	Cabozantinib N= 330	Everolimus N= 328
Previous systemic therapy — no. (%)				
Sunitinib	114 (61)	113 (60)	210 (64)	205 (62)
Pazopanib	87 (47)	78 (41)	144 (44)	136 (41)
Axitinib	28 (15)	28 (15)	52 (16)	55 (17)
Sorafenib	11 (6)	19 (10)	21 (6)	31 (9)
Bevacizumab	1 (<1)	7 (4)	5 (2)	11 (3)
Interleukin-2	11 (6)	13 (7)	20 (6)	29 (9)
Interferon alfa	6 (3)	13 (7)	19 (6)	24 (7)
Nivolumab	9 (5)	11 (6)	17 (5)	14 (4)
Radiotherapy — no. (%)	56 (30)	61 (32)	110 (33)	108 (33)

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PITT, Primary endpoint intent-to-treat population

Source: table 12 p. 56 company submission

METEOR Kaplan-Meier curve for PFS

Cabozantinib significantly increases PFS (PITT population)

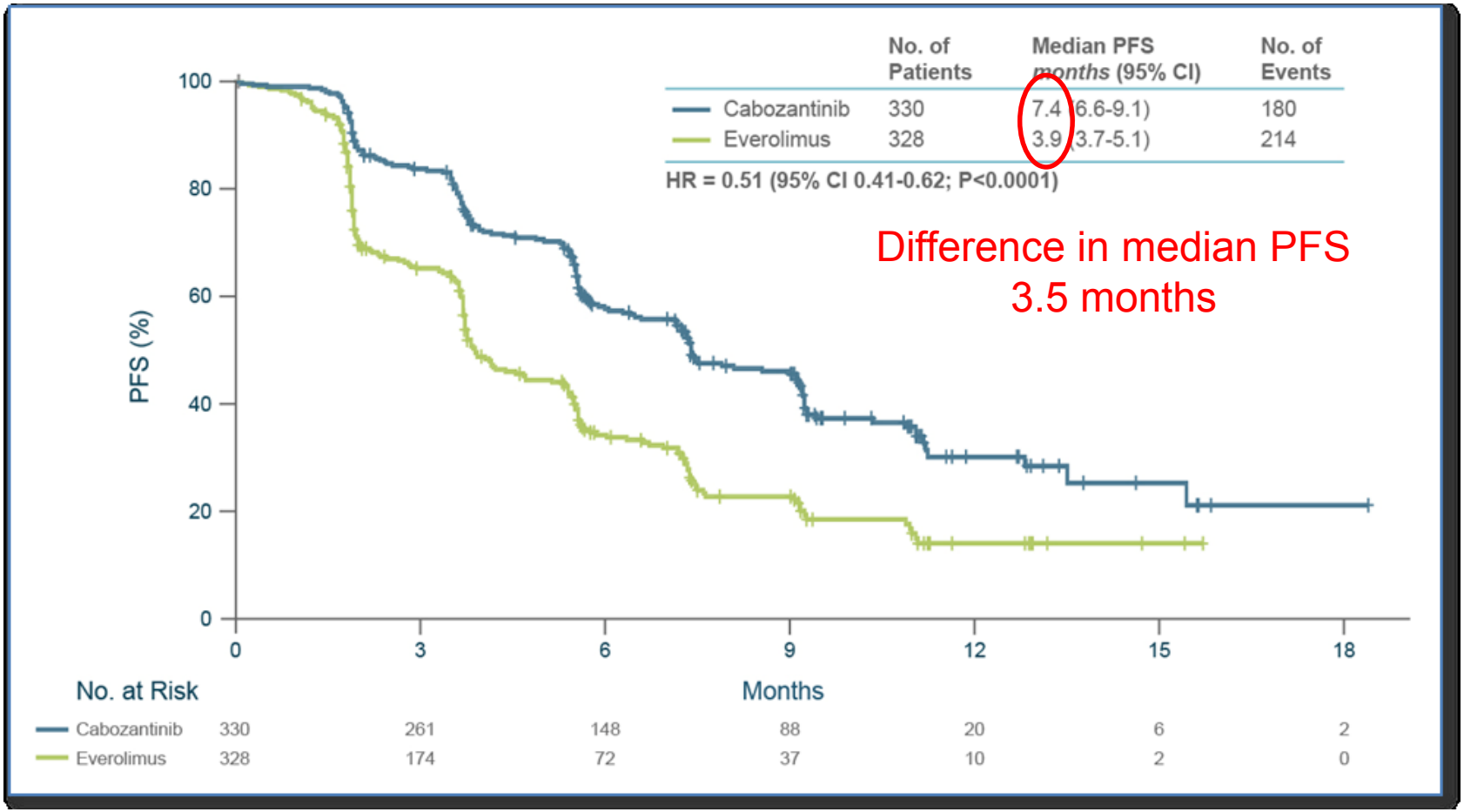


ERG comment: The use of the primary end point intention to treat analysis (PITT) has limited use in decision-making compared with the full ITT population

Source: figure 11 p. 61 company submission

METEOR Kaplan Meier estimates of PFS

Cabozantinib significantly increases PFS (ITT)



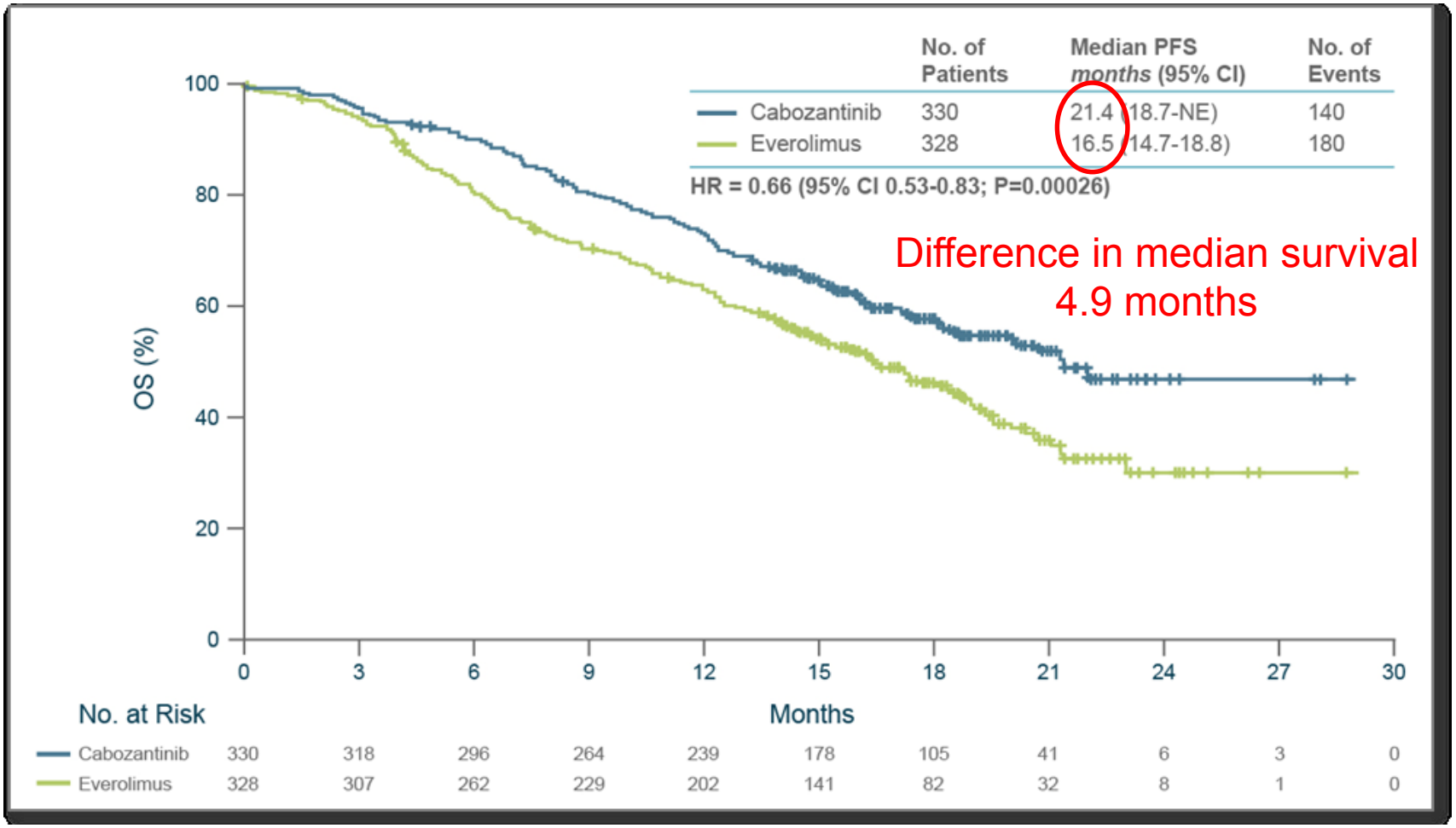
Source: figure 12 p. 57 company submission

pre-meeting briefing document

METEOR Kaplan Meier estimates of OS

Cabozantinib significantly lowers risk of death (ITT)

Median follow-up = 18.7 months



Source: figure 13 p. 63 company submission

pre-meeting briefing document

METEOR Health related quality of life

No clinically significant differences between treatment groups

- METEOR measured health-related quality of life using the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19) and EQ-5D-5L
- **FKSI-19**
  - Over time: total score was similarly sustained in each arm, according to the company
  - Mean change from baseline: cabozantinib -3.48, everolimus -2.21 (effect size [ES] difference -0.13)
  - Treatment side effects subscale
    - ◊ Cabozantinib: diarrhoea and nausea worse (ES -0.77 and -0.34 respectively)
    - ◊ Everolimus: shortness of breath worse (ES +0.30)
- **EQ-5D-5L**
  - There were no clinically significant treatment differences in EQ-VAS or EQ-Index scores between the 2 treatment groups (ES= [redacted])

Source: section 4.7 p. 64 company submission

Post-hoc subgroup analyses[1]

OS favours cabozantinib in ≥2 prior VEGFR-TKI subgroup (ITT), but result not statistically significant

[1]Patients either had sunitinib or pazopanib or both as previous therapy

Source: figure 15 p.69 company submission

pre-meeting briefing document

Adverse events

- Adverse events (AEs) with cabozantinib are consistent with those reported by other VEGFR-TKI treatment options for advanced RCC.
- The proportion of patients experiencing an AE was the same for both the cabozantinib and everolimus treatment groups (92%) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%).
- The most common treatment-emergent adverse events (TEAEs) of any grade in the cabozantinib group compared with the everolimus group were diarrhoea (75% vs 28%), fatigue (59% vs 47%) and nausea (52% vs 30%).
- The company stated that most TEAEs were managed through study drug dose reductions.
- The TEAEs that were most likely to lead to stopping cabozantinib were decreased appetite and fatigue.
- The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus) and fatigue (11% vs 7%, cabozantinib vs everolimus).

Source: section 4.12 p. 100 company submission

Adverse events (cont.)

	Cabozantinib (n=331)	Everolimus (n=322)
Grade ≥3 serious adverse events, n (%)	130 (39)	129 (40)
Median duration of exposure (months)	8.3 (IQR 4.2-14.6)	4.4 (IQR 1.9-86)
Most common Grade ≥3 serious adverse events, n (%)		
Abdominal pain	9 (3)	3 (1)
Pleural effusion	8 (2)	7 (2)
Pneumonia	7 (2)	13 (4)
Pulmonary embolism	7 (2)	1 (<1)
Anaemia	5 (2)	10 (3)
Dyspnoea	4 (1)	10 (3)
Deaths during AE reporting period*	26 (8)	25 (8)
Deaths assessed as treatment-related	1	2

* Grade 5 AEs were classified as deaths

Serious AEs of grade $\underline{\geq}$ 3 had similar frequency as those observed with everolimus (39% vs. 40%), despite an almost two-fold longer exposure to cabozantinib.

Source: section 4.12 p. 100 company submission

ERG comments on METEOR

- Open-label design is a potential source of bias particularly for subjective outcomes such as HRQoL.
- METEOR data for the subgroup of people with 2 or more previous VEGF-TKIs did not address the NICE decision problem for the potential third-line treatment positioning of cabozantinib. This is because the comparator in METEOR is everolimus, which the ERG's clinical experts advised is mainly used as a second-line treatment and infrequently, if at all, as a third-line treatment. The ERG therefore considers the key comparators for cabozantinib in the third-line setting to be BSC and nivolumab.

Source: section 3.1 p. 45 ERG report

Company's network meta-analysis

- To compare cabozantinib with axitinib, nivolumab, and BSC, the company performed a Bayesian network meta-analysis (NMA)
- The company presented 2 evidence networks
  1. **OS and PFS** using HRs and KM curves
  2. **Time to treatment discontinuation (TTD)** using median treatment duration data and KM curves
- In total, the company identified 19 studies including some on technologies outside the scope of the appraisal
- The final evidence base for the NMA included 4 randomised controlled trials (RCTs) in addition to METEOR (see next slide)
  - The RCTs differed in that some allowed cross-over and others did not. The number and type of previous therapies received, and the baseline prognostic scores also varied across RCTs.

Source: section 4.10.1 p. 71 company submission

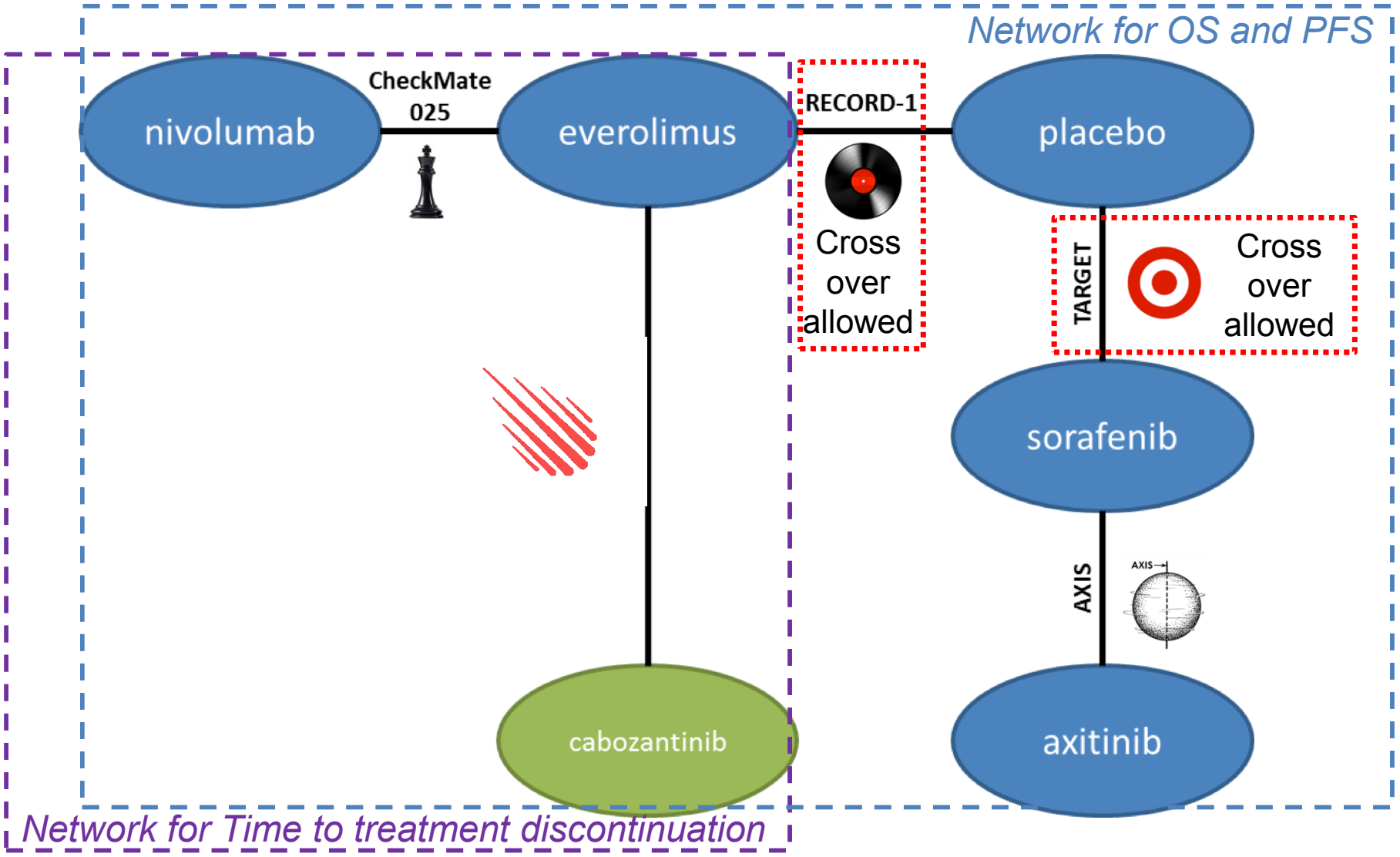
Studies included in the final evidence base for indirect treatment comparison

Study name	Design	Population	Treatment groups	Primary end point
RECORD-1	Double-blind RCT, cross-over	Adults with clear cell mRCC that progressed during or within 6 months of stopping sunitinib and/or sorafenib	Everolimus Placebo	PFS
CheckMate	Open-label RCT	Adults with clear cell mRCC that progressed after 1–2 previous regimens of antiangiogenic therapy	Nivolumab Everolimus	OS
TARGET	Double-blind RCT, cross-over	Adults with clear cell mRCC that progressed after 1 systemic treatment within the previous 8 months not including VEGFR pathway inhibitors	Sorafenib Placebo	OS
AXIS	Double-blind RCT	Adults with clear cell mRCC that progressed despite first-line systemic therapy (sunitinib, bevacizumab plus interferon-alfa, temsirolimus or cytokines)	Axitinib Sorafenib	PFS

RCT, randomised controlled trial; mRCC, metastatic renal cell carcinoma; PFS, progression-free survival; OS, overall survival

Source: table 23 p.77 company submission

Network meta-analysis



Source: figure 18 p. 82 company submission

Company's network meta-analysis

Considerable differences between included trial populations

Difference	Degree of heterogeneity and availability of subgroup results
Cross-over study design	• RECORD-1 (everolimus) and TARGET (sorafenib) allowed treatment switching (cross-over) • The company used: – From RECORD-1: HR for OS adjusted for cross-over using the RPSFT model – From TARGET: analysis censoring patients at time of cross-over
Type and number of prior therapies	• The company noted variation in the number of previous therapies allowed, the distribution of these therapies in patient cohorts, and the availability of results for subgroups by prior therapy • The company could not estimate results for subgroups by prior therapy
Baseline prognosis scores	• TARGET did not include any patients with 'poor' MSKCC prognosis • Some trials did not present subgroup analyses by MSKCC prognosis • The company could not estimate results for subgroups by MSKCC prognosis (poor/intermediate/favourable) based on the available HRs or Kaplan-Meier curves

Key: BSC: best supportive care; HR, hazard ratio; ITT, intention-to-treat; KM, Kaplan-Meier; MSKCC, Memorial Sloan-Kettering Cancer Centre; OS, overall survival; PFS, progression free survival; RPSFT , rank-preserving structural failure time

Source: section 4.10.2 p. 83 company submission

Company's network meta-analysis

Methodology

- Company considered that the proportional hazards assumption did not hold for TARGET and CheckMate025
- Therefore, the company chose to base its NMA on parametric survival curves, rather than HRs
- The company used a fixed-effect model because the estimates were 'almost identical' to the random-effect model, but more stable and faster to run
- The company tested 5 parametric distributions
  - It chose the log-normal distribution for all 3 outcome measures (progression-free survival, overall survival, and time to treatment discontinuation)

Company's network meta-analysis (OS and PFS)

Cabozantinib progress later and live longer compared with each comparator

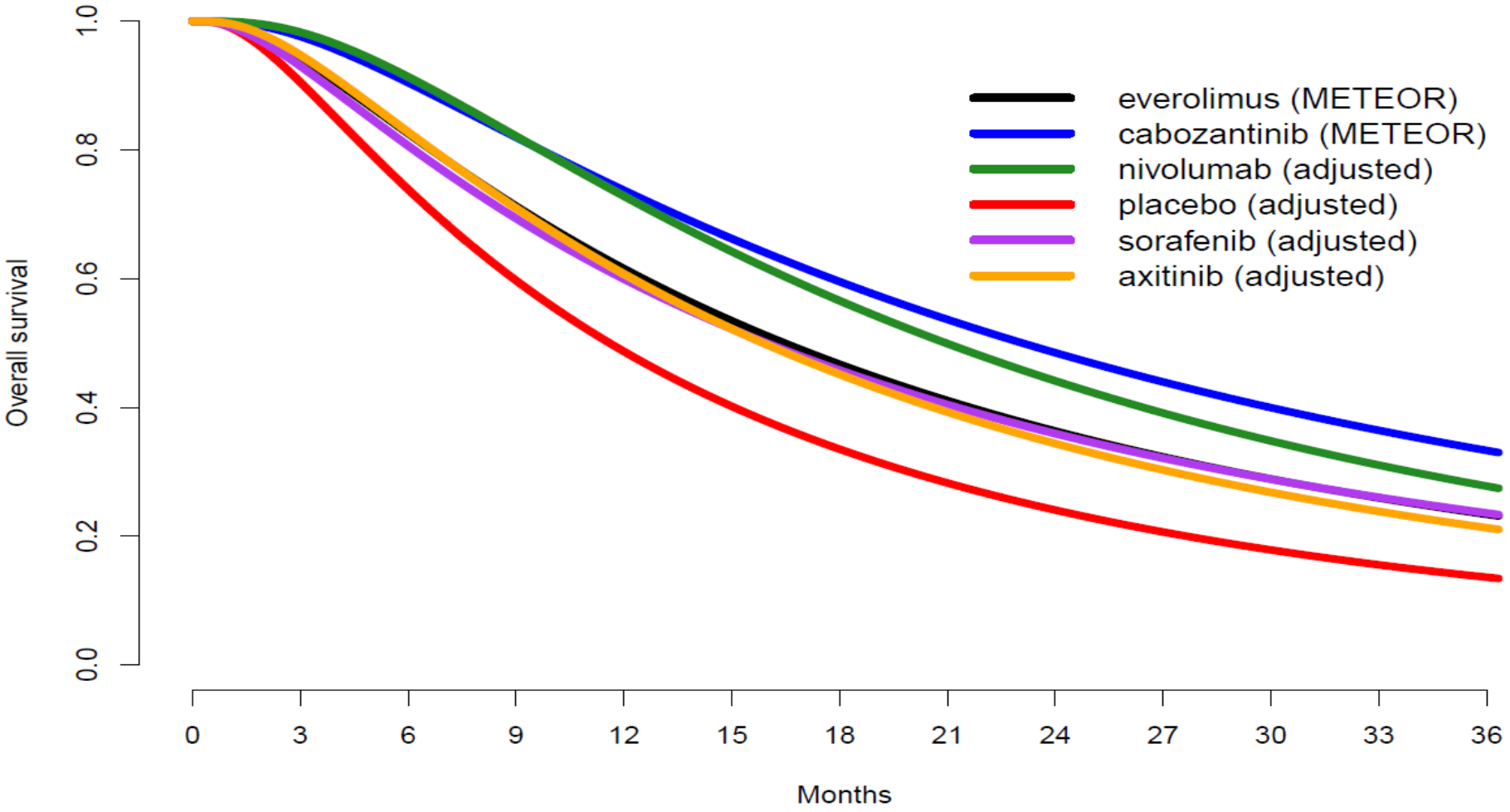
	NMA result (fixed-effect, log-normal distribution)	
	Median OS (months)	**Median PFS (months)**
Cabozantinib	22.9	7.8
Axitinib	15.7	4.9
Everolimus	16.3	4.4
BSC	11.5	2.4
Nivolumab	20.8	5.1

Key: OS, overall survival; PFS, progression free survival; BSC, best supportive care

Source: table 39 p. 99 company submission

Company's network meta-analysis

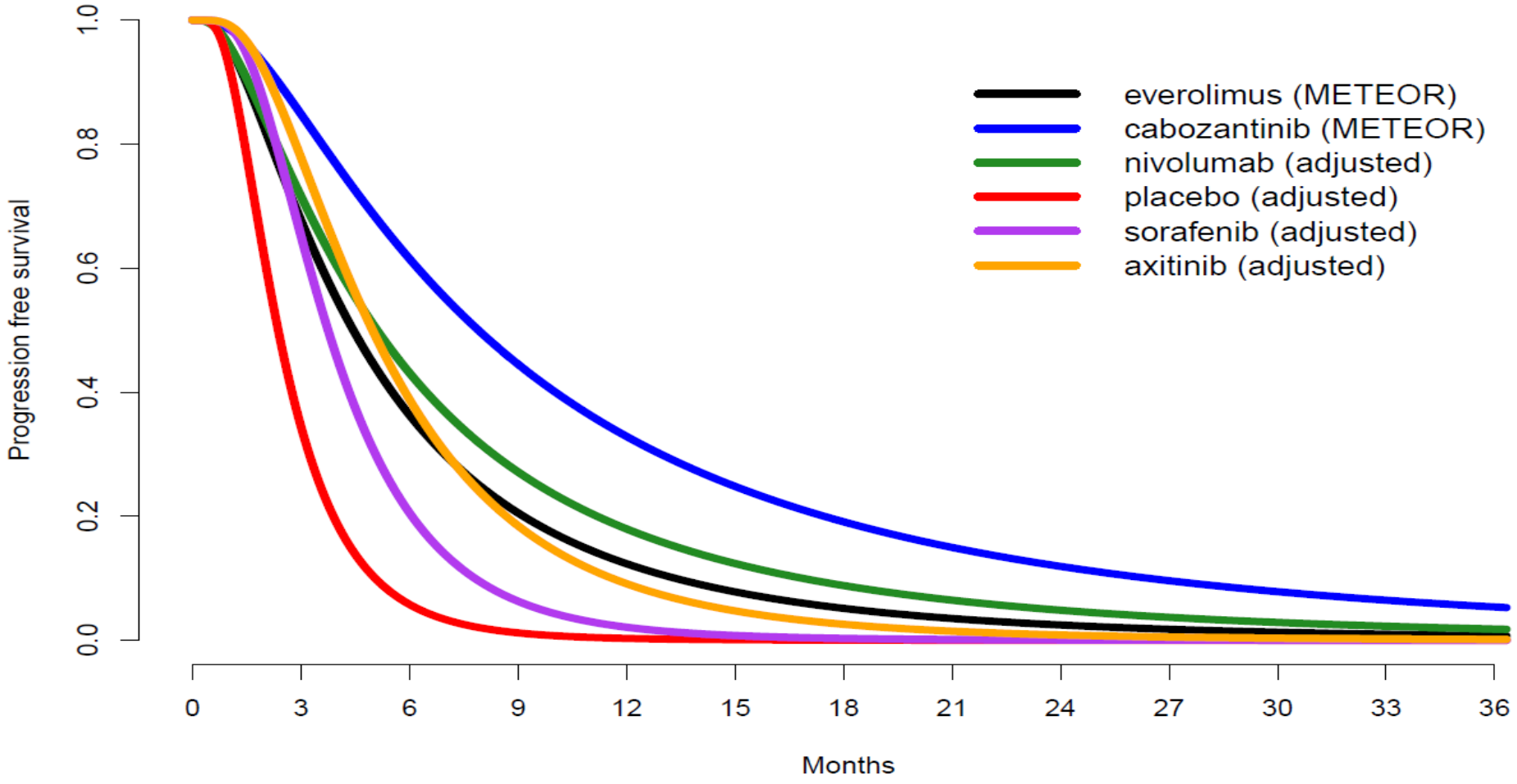
Cabozantinib compared with each of the comparators improves OS



Source: figure 21 p.98 company submission

Company's network meta-analysis

Cabozantinib compared with each of the comparators improves PFS



Source: figure 21 p.98 company submission

Company's network meta-analysis (TTD)

TTD longer with cabozantinib compared with everolimus and nivolumab

	Median TTD (months)
Cabozantinib	9.0
Everolimus	5.0
Nivolumab	7.4

Key: TTD, time to treatment discontinuation

Source: table 40 p.100 company submission

ERG comments on network meta-analysis

Issue	ERG's comments
Heterogeneity of NMA trials, cross-over study design, immature OS data	•The results of network meta-analysis may be unreliable because of the heterogeneity of the trials included in the network in terms of the presence/absence of cross-over design, number and type of prior therapies, and baseline prognostic scores. Additionally there was cross-over in TARGET that could not be adjusted for and the use of immature OS data for TARGET led to biases in the results (i.e., only 41% deaths observed at cross-over censoring point). •ERG concerned about the OS estimate for axitinib (AXIS) generated by the NMA. This is because axitinib is only linked to the network via TARGET (see slide 27), which is a placebo-controlled trial and if it is assumed that sorafenib is likely to be more effective than placebo using immature survival data is likely to underestimate the benefit of sorafenib over placebo. •Not adjusting for subsequent active treatments in AXIS (axitnib vs. sorafenib) may have biased the treatment effect on OS which could have minimised the difference in OS.

ERG comments on network meta-analysis (cont.)

Issue	ERG's comments
No suitable data for second- and third-line positioning for advanced RCC	• In response to a clarification request from the ERG, the company provided an NMA for the subgroup of patients who had second-line treatment – The ERG stated that the results of this analysis were unreliable as the data for the comparators were based on the ITT populations, rather than the subgroup of patients who had second-line treatment in those trials. • The company provided no analysis for the 3rd line position because there were no suitable data from the trials for the comparators to inform this analysis.

ERG exploratory analysis

Similar treatment ranking to company's NMA

- Analysis aimed to explore the impact of assuming axitinib and everolimus have equal efficacy
- The ERG analysis excludes TARGET from the NMA because the ERG assumes the axitinib and everolimus are equally effective.

Treatment	Median OS (months)		Median PFS (months)	
	Company's NMA	ERG's NMA	Company's NMA	ERG's NMA
Cabozantinib	22.9	22.0	7.8	7.8
Axitinib	15.7	16.3	4.9	4.7
Everolimus	16.3	16.3	4.4	4.7
Placebo	11.5	10.1	2.4	1.9
Nivolumab	20.8	20.4	5.1	5.2

Source: section 4.5 p.100 ERG report

Key clinical issues for consideration

- Would cabozantinib be used as second- or third-line treatment, or both? Do the trial results permit the effectiveness of cabozantinib to be considered separately for each line of therapy?
  - Are there any other subgroups that should be considered separately?
- Are the results from METEOR generalizable to the NHS?
  - Does the proportion of patients with ECOG performance status of 0 reflect patients seen in clinical practice?
  - Can the results be extrapolated to the specific place in therapy in which cabozantinib would be used (if any)?
  - Is treatment duration likely to differ?
- Which analysis is the more appropriate for assessing PFS, the primary endpoint intent-to-treat, or the intent-to-treat?
- Is the effectiveness of cabozantinib likely to wane beyond the end of the trial?

Key clinical issues for consideration (cont.)

- Cabozantinib appeared more effective compared with everolimus than nivolumab was compared with everolimus. Which trial reflect the survival benefit of everolimus more accurately?
- Should the NMA assume proportional hazards for PFS? For OS?
- The company's network meta-analysis included trial populations that differed in baseline prognosis scores, 'maturity', number of previous treatments and adjustments for cross-over and subsequent treatments. Is this analysis robust enough to inform decision-making?
- Is the ERG's NMA assuming that axitinib and everolimus have equal efficacy more appropriate than the company's NMA?

Cost effectiveness

Key cost issues for consideration

- Is it appropriate to take the utility values directly from METEOR for all comparisons? Should the values be age-adjusted?
- Should the model include wastage for nivolumab?
- Should the model include treatment waning for cabozantinib?
- Does the committee prefer probabilistic analyses?
- The model is most sensitive to the modelling of PFS and OS. Which parametric distributions and assumptions are most appropriate for the modelling of PFS and OS?
- Should the model use estimates of relative effectiveness from the network meta-analysis (as in the company's base case) or assume that axitinib is as effective as everolimus (as in the ERG's analyses)?
- Does cabozantinib meet the criteria for a 'life-extending treatment at the end of life'?

Model structure

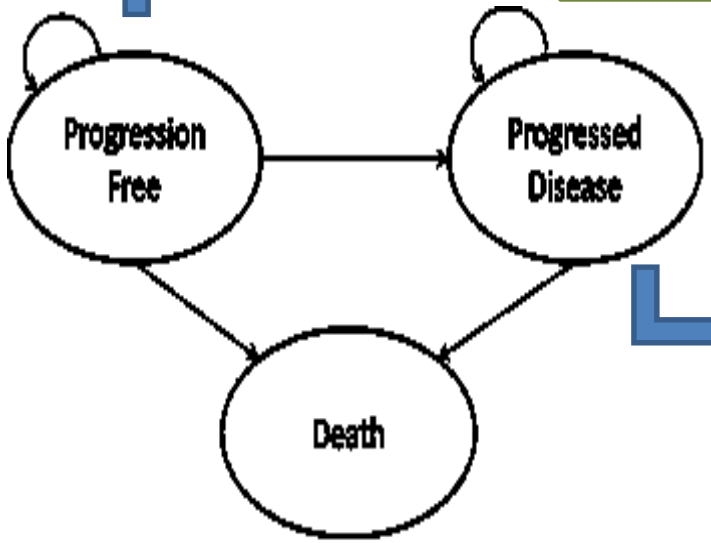
Partitioned-survival (area-under-curve) model

ITT population in METEOR (mean age 61 years)

- Cabozantinib

- Everolimus
- Axitinib
- Nivolumab
- Best supportive care

PFS modelled based on ITT rather PITT



Time in each state estimated from survival curves

Time on treatment captured independently from disease progression, so may be longer than PFS

4-week cycle length (reflecting frequency of follow-up visits in METEOR); 30-year time horizon

Source: figure 25 p.114 company submission

Population in the model and METEOR

Company's base case	ERG comment	ERG amended base case
Population included in METEOR is in line with NICE final scope: adults with advanced RCC who had been previously treated with at least one VEGF-inhibitor	METEOR trial contained a high proportion of patients with an ECOG performance status of 0 (67%) and that this would be reflective of the fitter patients found in current practice	As per company's base case
Cabozantinib positioned in 2nd **and 3rd line** setting	No evidence of subgroup analysis for patients who have received 1, 2 or ≥3 prior therapies because equivalence effectiveness was assumed • No availability of 3rd line subgroup data from the NMA • Results for 2nd line confirmed that changing the population is likely to impact on the ICER	As per company's base case

ECOG, Eastern Cooperative Oncology Group; ICER, incremental cost-effectiveness ratio, NMA, network meta-analysis; RCC, renal cell carcinoma; VEGF-TKI, vascular endothelial growth factor tyrosine kinase inhibitor

Source: section 5.5.3 p146 ERG report

Intervention and comparator technologies

Intervention	Scheduled dosage	Time to treatment discontinuation (TTD)
Cabozantinib[1]	60 mg/day orally	• As observed in METEOR
Everolimus[1]	10 mg/day orally	• As observed in METEOR
Axitinib	10 mg/day orally	• No TTD curves were identified from the literature • The PFS distribution generated from the NMA was used as a proxy for TTD
Nivolumab	3 mg/kg intravenously every 2 weeks	• Based on the NICE STA for nivolumab
Best supportive care	-	-

[1]Modelled dosages took into account the treatment interruptions and dose reductions observed in METEOR.

Company's analyses

2 analyses presented

	'NMA-based' analysis	'Trial-based' analysis
Comparators	• Everolimus • Axitinib • Nivolumab • Best supportive care	• Everolimus
Data source	Network meta-analysis (NMA)	METEOR only
Survival modelling	• Re-generated Kaplan-Meier data from CheckMate 025, AXIS, RECORD-1 and TARGET, as well as METEOR • Efficacy curves of axitinib, nivolumab and BSC estimated from the NMA adjusted to the everolimus group of METEOR	• Parametric survival curves fitted to Kaplan-Meier data from METEOR, and extrapolated beyond trial follow-up

Clinical parameters and variables

NMA-based analysis

	PFS nivolumab, axitinib and BSC	**OS** nivolumab, axitinib and BSC	**TTD** nivolumab, BSC
Assume PH	No	No	No
Type of model	Independent models for each treatment group		
Distribution	Log-normal	Log-normal	Log-normal
ERG comments: curve choice	Log-normal reasonable, but poor fit to data	Log-normal appropriate, but effect of axitinib uncertain	Log-normal appropriate

- Key limitation is that same distribution had to be used for all comparators to estimate PFS and OS
  - Some of the curves had a poor fit
  - 'A serious limitation', potentially unreliable estimates of treatment effect, and uncertain ICERs

Source: section 5.3.1 p119 company submission

Clinical parameters and variables

Trial-based analysis

	PFS	OS	TTD
Assume PH	No	No	No
Type of model	Independent models for each tx group		
Distribution	Log-logistic	Log-logistic	Log-normal
ERG comments: curve choice	Log-normal best fit for cabozantinib but not everolimus	Weibull more appropriate: avoids long tail and log-cumulative hazard plots indicative of hazard functions of a Weibull	Appropriate but lack of justification on the choice of distribution
	Other alternatives not fully considered/tested as scenario analyses		

Source: section 5.3.1 p119 company submission

Health-related quality of life

- METEOR collected health-related quality of life data measured using the EQ-5D-5L questionnaire.
- The company included utility in the model based on the analysis of patient-level data from METEOR.
- It used utility specific to health states independent of treatment before or after disease progression.
- The company applied a utility decrement to reflect the decrease in health-related quality of life associated with adverse events.

Source: section 5.4.4 p.134 company submission

Health-related quality of life

Utility values sourced from METEOR for all treatments

	PFS	PPS	Trial	Measure
All treatments	0.817	0.777	METEOR	EQ-5D-5L

Key: AE, adverse event; CS, company submission; PFS, progression-free survival; PPS, post-progression survival

- Utility values from alternative sources are shown in the table below

Source	PFS	PPS	Trial	Measure
Axitinib TA	0.692	0.610	AXIS	EQ-5D US tariff
Nivolumab TA	0.800	0.730	CheckMate025	EQ-5D
Swinburn et al. 2010	0.795	0.355	-	EQ-5D

Key: AE, adverse event; CS, company submission; PFS, progression-free survival; PPS, post-progression survival

Source: table 62, 65 p.135 company submission

Health-related quality of life

Utility decrements for adverse events

- Utility decrement of -0.055 estimated from METEOR, then weighted by the proportion of patients who had grade 3-4 adverse events for each treatment

Treatment	Weighted AE disutility
Cabozantinib	-0.03
Everolimus	-0.02
Axitinib	-0.03
Nivolumab	0.00

Source: section 5.5.7 p166 ERG report

pre-meeting briefing document

Health-related quality of life

ERG comments

Company's base case	ERG comment	ERG amended base case
Utility values used for PFS (0.817) and PPS (0.777) states	The ERG's clinical experts suggested that the utility values for PFS and PPS were higher than expected in clinical practice. The utility values for these states are expected to be closer to those used for axitinib in TA333.	ERG ran a scenario analysis using utility values from TA333
Estimate of utility decrement associated with adverse events	The initial utility decrement for adverse events used by the company (-0.055) may be an underestimate given equivalent values from the literature. The impact of adverse events on the ICER was small, although the clinical experts expected it to be significant.	As per the company's base case

Source: section 5.5.7 p166 ERG report

Resource use and costs

- The company included the following cost categories:
  - Treatment cost
    - ◊ The total costs of treatments per patient were adjusted for dose intensity, taken from the respective trial data
    - ◊ Nivolumab (only intravenous treatment) associated with additional costs of equipment and staff costs for monitoring; no wastage assumed.
  - Cost of adverse events
  - Progression-free survival health-state costs
  - Progressed health-state costs
  - Terminal care cost
- Based on UK reference costs, literature and expert opinion

Source: section 5.5 p.136 company submission

pre-meeting briefing document

Resource use and costs

ERG comments

Company's base case	ERG comment	ERG amended base case
Include cost of GP visits before disease progression	Patients are more likely to be seen by consultants during this period every 4 weeks on average instead	Exclude of general practitioner costs
Include sorafenib as subsequent treatment option	Sorafenib should not be included as subsequent therapy as it is not reimbursed in the UK	As per company's base case

Source: section 5.5.8 p.168 ERG report

Cost-effectiveness results

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

Company	ERG
• Base case[1] – Deterministic – Probabilistic	• Base case – Deterministic – Probabilistic • Scenario analysis on the ERG's base case (deterministic), which include the 'waning effect' scenario (requested by NICE)

[1]The company corrected its original base case in response to a request for clarification from the ERG. The results presented here are those of the corrected base case.

Equality issues

- There are no equality issues related to the use of cabozantinib.

Innovation as per the company's submission

- Cabozantinib is the first therapy for advanced RCC that has evidence of significant improvement in OS, PFS and ORR compared with an active comparator (everolimus)
- Cabozantinib met the "promising innovative medicine" criteria of
  - Treatment of a life-threatening or seriously debilitating condition with high unmet need
  - Likelihood of major advantage over current treatments
  - Reasonable expectation of a positive benefit-risk profile

Source: section 2.5 p.24 company submission

Key cost issues for consideration

- Is it appropriate to take the utility values directly from METEOR for all comparisons? Should the values be age-adjusted?
- Should the model include wastage for nivolumab?
- Should the model include treatment waning for cabozantinib?
- Does the committee prefer probabilistic analyses?
- The model is most sensitive to the modelling of PFS and OS. Which parametric distributions and assumptions are most appropriate for the modelling of PFS and OS?
- Should the model use estimates of relative effectiveness from the network meta-analysis (as in the company's base case) or assume that axitinib is as effective as everolimus (as in the ERG's analyses)?
- Does cabozantinib meet the criteria for a 'life-extending treatment at the end of life'?

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cabozantinib for previously treated advanced renal cell carcinoma

Final scope

Remit/appraisal objective

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

Background

Renal cell carcinoma (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 90% of the cases).[1] There are several different types of RCC, with the main ones divided into 5 categories: clear cell, papillary (types 1 and 2), chromophobe, oncocytic and collecting duct carcinoma. Clear cell is the most common form of RCC accounting for approximately 80–90% of cases.[2]

The tumour node metastases system is used to grade RCC into stages I to IV. Advanced RCC, in which the tumour is either locally advanced and/or has spread to regional lymph nodes, is generally defined as stage III. Metastatic RCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is generally defined as stage IV.

Early, small RCC tumours are usually asymptomatic; the diagnosis of early RCC is usually incidental after abdominal scans for other indications. The most common presenting symptoms of metastatic and/or advanced 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 and/or metastatic disease later on.

In 2013, 9,900 new kidney cancer cases were diagnosed in England.[3] In 2013, approximately 46% of people diagnosed with kidney cancer had stage III or IV disease and 27% had stage IV disease.[3] The 5-year survival rate for metastatic RCC is approximately 10%.[4]

The aim of treatment is to stop the growth of new blood vessels within the tumour. After failure of prior systemic treatment with a tyrosine kinase inhibitor or cytokine, 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 is not subject to statutory funding. Sorafenib, sunitinib and everolimus are not recommended after initial therapies have failed in NICE guidance (NICE technology appraisal guidance 178 and 219). Everolimus is available in England for metastatic RCC through the Cancer Drugs Fund (at the time the final scope was written) for people who have had prior treatment with only one previous tyrosine kinase inhibitor. Everolimus is also available for second or third line treatment of metastatic RCC where disease has progressed on or after treatment with VEGF-targeted therapy through the Cancer Drugs Fund. Everolimus is subject to ongoing NICE CDF transition review [ID1014]. An ongoing NICE technology appraisal is in development for nivolumab for previously treated advanced or metastatic RCC [ID853].

The technology

Cabozantinib (brand name unknown, Ipsen) inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. It is orally administered.

Cabozantinib does not currently have a marketing authorisation in the UK for previously treated RCC. It has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for 'the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy'.

Intervention(s)	Cabozantinib
Population(s)	People who have received previous VEGF-targeted therapy for advanced renal cell carcinoma
Comparators	• axitinib • everolimus • nivolumab (subject to ongoing NICE appraisal [ID 853]) • best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rates • 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	If the evidence allows the following subgroups will be considered. These include: • previous lines of treatment • prognostic score 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: '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 [ID1014], 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. Appraisals in development: 'Nivolumab for previously treated advanced or metastatic renal cell carcinoma'. NICE technology appraisal guidance [ID853]. Publication expected October 2016.

	'Pazopanib for the second line treatment of metastatic renal cell carcinoma (discontinued)' NICE technology appraisals guidance [ID70]. Related Guidelines: 'Referral guidelines for suspected cancer' (2005). NICE guideline 27 Review date June 2015. '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, National Cancer Drugs Fund List, Feb 2016. NHS England (May 2016) Manual for prescribed specialised services. Section 105. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf NHS England: B14. Specialised Urology. NHS Care and Clinical Reference Groups. Link accessed: 26th February 2015 http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b14/ Department of Health (2014) The national cancer strategy: 4th annual report https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report

References

1. American Cancer Society (2014) Kidney Cancer (Adult) - Renal Cell Carcinoma. Accessed October 2015.

2. Patient.co.uk: Renal Cancer. Accessed October 2015.

3. Cancer Research UK (2013) Kidney cancer incidence statistics. Accessed March 2016.
4. GP Notebook - Clear Cell Cancer. Accessed February 2016.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabozantinib for previously treated metastatic renal cell carcinoma [ID931]

Matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • Ipsen (cabozantinib) Patient/carer groups • Black Health Agency • British Kidney Patient Association • Cancer Black Care • Cancer Equality • Cancer 52 • Helen Rollason Cancer Charity • HAWC • Independent Cancer Patients Voice • James Whale Fund for Kidney Cancer • Kidney Cancer Support Network • Kidney Cancer UK • Kidney Research UK • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • 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 Psychosocial Oncology Society • British Renal Society • British Uro-Oncology Group • Cancer Research UK • Renal Association	General • Allied Health Professionals Federation • Association of Renal Industries • 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 • Welsh Urological Society Comparator companies • Bristol-Myers Squibb (nivolumab) • Novartis (everolimus) • Pfizer (axitinib) Relevant research groups • Cochrane Prostatic Diseases and Urologic Cancers Group • 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 • Public Health Wales

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

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

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Company evidence submission

11 October 2016

File name	Version	Contains confidential information	Date
ID931_cabozantinib_company evidence submission_ACIC-10 Oct16 Final	V1.0	Yes	11 October 2016

Contents

Tables and figures

Abbreviations

AE	Adverse event
AIC	Akaike's Information Criteria
BIC	Bayesian Information Criteria
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse events
DIC	Deviance information criteria
DRS	Disease related symptoms
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	US Food and Drug Administration
FE	Fixed effects
FKSI	Functional Assessment of Cancer Therapy Kidney Symptom Index
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ICUR	Incremental cost utility ratio
IFN	Interferon
IL2	Interleukin 2
IMDC	International Metastatic RCC Database Consortium
IRC	Independent radiology committee
ITT	Intent-to-treat
IV	Intravenous
LLN	Lower limit of normal
LY	Life year

MCMC	Markov Chain Monte Carlo
MCBS	Magnitude of Clinical Benefit Scale
MET	Hepatocyte growth factor receptor protein
MSKCC	Memorial Sloan-Kettering Cancer Centre
MTA	Multiple technology appraisal
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NCPE	National Centre for Pharmacoeconomics
NE	Not estimable
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PD-1	Programmed death 1
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
PH	Proportional hazards
PITT	Primary endpoint intent-to-treat
PIM	Promising innovative medicine
PPES	Palmar-plantar erythrodysaesthesia syndrome
PPS	Post-progression survival
PR	Partial response
QALY	Quality adjusted life year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank preserving structural failure time
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SRE	Skeletal related events
STA	Single technology appraisal

TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TRAE	Treatment related adverse event
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WTP	Willingness to pay

1 Executive summary

Renal cell carcinoma (RCC) is the collective name for a group of cancers that originate in the kidney within the epithelium of the proximal renal tubules. It accounts for approximately 80% of kidney cancer cases.[1]

RCC is divided into stages that describe how widespread the disease has become. In the early stages of the disease RCC is relatively asymptomatic and often detected incidentally during medical investigation for other conditions.[1] Advanced RCC includes both locally advanced RCC that cannot be removed by surgery and metastatic RCC.

Due to the often indolent course of RCC, patients typically present with advanced disease. Approximately 35% of patients present with metastatic disease at initial diagnosis[2] and up to 40% of patients develop metastasis after surgery for initially localised disease.[3]

Metastatic symptoms frequently include airway obstruction, venous thromboembolism, bone pain, skeletal-related events (SREs) and hypercalcaemia[3] imposing significant morbidity and poor prognosis.

The symptoms of advanced disease and the generally poor prognosis for patients with advanced RCC can also significantly impact on all domains of patient health related quality of life (HRQoL) including physical and psychosocial function.[4]

Survival is dependent on the stage of the disease and the relative 5-year survival rate for advanced RCC is approximately one in ten. [5]

There is no cure for advanced RCC and the goals of treatment are to extend life and delay disease progression while relieving physical symptoms and maintaining function.[6] Advanced RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. The elucidation of the pathogenesis of RCC has played a key role in the development of targeted therapies focused on two pathways that are commonly de-regulated in RCC: the vascular endothelial growth factor receptor (VEGFR) pathway which is targeted by tyrosine kinase inhibitors (TKIs) such as axitinib, sunitinib and pazopanib, and

the mammalian target of rapamycin (mTOR) pathway which is targeted by mTOR inhibitors such as everolimus. More recently, nivolumab a programmed death 1 (PD-1) immune checkpoint inhibitor has become available for the treatment of RCC after prior therapy. Standard of care for patients with advanced RCC in England typically consists of the sequencing of VEGFR TKIs for first and subsequent lines of therapy. For patients who fail first-line therapy, active treatment options include axitinib (standard of care and recommended by NICE [TA333][7]) or everolimus (available through the Cancer Drugs Fund). Neither axitinib nor everolimus are associated with a proven overall survival (OS) advantage. Nivolumab is currently being appraised by NICE, via a single technology appraisal, for use in the second line setting and while associated with an OS benefit compared with everolimus, an improvement in PFS has not been seen.[8]

Unmet need

Despite the advances in targeted therapies for RCC, few treatments have shown an OS benefit, and none have shown a significant improvement in all three efficacy endpoints of OS, progression-free survival (PFS) and objective response rate (ORR) when compared with standard-of-care treatment in a randomised Phase 3 trial in previously treated patients with renal cell carcinoma.[9,10]

There is a need for more effective therapy options for advanced RCC following failure of first-line VEGFR treatment that have proven OS benefits as well as PFS and ORR benefits and which provide a further treatment option for clinicians and patients.

Cabozantinib

Cabozantinib, an oral once-a-day tablet, is the first therapy for advanced RCC that has demonstrated, versus an active comparator (everolimus), significant improvement in all three key efficacy parameters: overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). In the pivotal Phase 3 randomised controlled trial (METEOR), cabozantinib significantly improved OS by 4.9 months compared with everolimus (HR 0.66)

and PFS by 3.5 months (ITT population) (HR 0.51).[10] Modelled OS and PFS estimates from a network meta-analysis (NMA) suggest superior OS and PFS benefits of cabozantinib over both axitinib and best supportive care (BSC).

The adverse events observed with cabozantinib were consistent with those reported by other VEGFR-TKI treatment options for advanced RCC. In the case of cabozantinib, they were managed with supportive care, dose interruptions and dose modifications, which were effective in limiting or preventing treatment-associated discontinuations.

In recognition of its innovative nature, cabozantinib was assigned Promising Innovative Medicine (PIM) designation in July 2016 after meeting the PIM criteria of treatment of a life-threatening or seriously debilitating condition with high unmet need; likelihood of major advantage over current treatments; and reasonable expectation of a positive benefit risk profile.

Administration of oral cabozantinib will utilise existing NHS infrastructure and resources with no additional requirements. Any required dose reductions and treatment interruptions can be managed remotely via the telephone.

End of life criteria

Cabozantinib for the treatment of patients with advanced RCC who have received prior VEGF-targeted therapy meets NICE's end of life criteria:

- Patients with advanced RCC who have received prior therapy have a median life expectancy of less than 24 months[11]
- Cabozantinib (compared to everolimus) improves OS by 4.9 months[10]
- A small patient population will be potentially eligible for cabozantinib in England (n=1,037 in year 1).

1.1 Statement of decision problem

The decision problem addressed in this submission is in line with the final scope see Table 1

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People who have received previous VEGF-targeted therapy for advanced renal cell carcinoma	As per scope	
Intervention	Cabozantinib	As per scope	
Comparator (s)	• Axitinib • Everolimus (not recommended by NICE but currently funded via the Cancer Drugs Fund) • Nivolumab (subject to ongoing NICE appraisal [ID 853]) • Best supportive care	As per scope	Axitinib is the only medicine currently recommended by NICE (TA333)[7] for use after failure of treatment with a first–line tyrosine kinase inhibitor or cytokine and is the most relevant comparator. At the decision problem meeting Ipsen were advised that, as the single technology appraisal of nivolumab is currently ongoing and nivolumab is not established standard of care, it is not a relevant comparator. Nivolumab has been retained in the decision problem with the view that, if recommended, nivolumab will be available and being used in clinical practice at the time cabozantinib is considered by the Appraisal Committee.

Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope	
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.	As per scope	
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • previous lines of treatment • prognostic score 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.	As per scope	
Special considerations including issues related to equity or equality	N/A	N/A	

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Approved name: Cabozantinib Brand name: CABOMETYX®▼
Marketing authorisation/CE mark status	CHMP positive opinion received 21 July 2016 Marketing authorisation received 9 September 2016
Indications and any restriction(s) as described in the summary of product characteristics	CABOMETYX®▼ is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. Therapy should be initiated by a physician experienced in the administration of anticancer medicinal products.
Method of administration and dosage	CABOMETYX®▼ is for oral use. The recommended dose of CABOMETYX®▼ is 60 mg once daily. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reductions of CABOMETYX®▼ therapy.
Key: CHMP, Committee for Medicinal Products for Human Use; RCC, renal cell carcinoma	

1.3 Summary of the clinical effectiveness analysis

The efficacy and safety of cabozantinib in adult patients who have received previous VEGF-targeted therapy for advanced RCC is provided by a single Phase 3 trial, the METEOR study. [9,10] METEOR a multicentre, open label, randomised controlled trial directly compared the clinical efficacy and safety of cabozantinib with everolimus in adult patients with advanced RCC who had received at least one prior VEGFR-TKI.

The primary efficacy endpoint was duration of PFS (among the first 375 randomised subjects [Primary endpoint intent-to treat, PITT population]) as assessed by an Independent Review Committee (IRC).

Key secondary endpoints (assessed in all randomised patients, ITT population) included:

- Overall survival
- Objective response rate

The study met its primary endpoint of prolonging the duration of PFS as assessed by an IRC. PFS (PITT population) was significantly improved with treatment with cabozantinib compared with everolimus treatment, with a median PFS of: 7.4 months vs. 3.8 months respectively (HR 0.58; 95% CI: 0.45 - 0.75; p-value <0.001).

PFS results for the ITT population were consistent with those observed for the PITT population. Median PFS was 7.4 months in the cabozantinib arm vs. 3.9 months in the everolimus arm (HR 0.51; 95% CI: 0.41 - 0.62; p<0.0001).

Treatment with cabozantinib significantly increased median OS by 4.9 months compared with that seen in patients treated with everolimus. Median OS was 21·4 months (95% CI 18·7–not estimable) in the cabozantinib group compared with 16·5 months (14·7–18·8) in the everolimus group [HR 0·66; 95% CI 0·53–0·83; p=0·00026].

ORR was significantly improved with cabozantinib vs. everolimus. The number of patients who achieved an objective response (as per Independent Radiological Review) was 17% [95% CI 13–22] in the cabozantinib group and 3% [95% CI 2–6] in the everolimus group (p<0·0001).

All pre-specified subgroup analyses showed consistently greater OS and PFS for patients in the cabozantinib treatment group compared with those in the everolimus treatment group (HR < 1) including those presenting with poor prognosis at baseline and those receiving cabozantinib second or third-line. Results were consistent with those seen in the overall study population.

Quality of life in the cabozantinib treatment group was comparable to that observed in the everolimus treatment group.

NMA

In the absence of head-to-head data outside of METEOR the OS and PFS benefits of cabozantinib versus axitinib (the current standard of care), best supportive care (BSC) and nivolumab have been estimated using an NMA approach. Modelled estimates suggest that cabozantinib offers superior OS and PFS versus all comparators (axitinib, BSC and nivolumab).

As with all indirect estimates, there is uncertainty associated with these analyses but the approach taken was designed to minimise uncertainty, despite a paucity of available data and heterogeneity across trials, and all sensitivity analyses support trends observed in the base case analysis.

Adverse events

The adverse events observed with cabozantinib were consistent with those reported by other VEGFR-TKI treatment options for advanced RCC. In the case of cabozantinib, they were managed with supportive care and dose modifications, which were effective in limiting or preventing treatment-associated discontinuations.

The most common AEs in the cabozantinib treatment group compared with the everolimus treatment group were diarrhoea (75% vs. 28%), fatigue (59% vs. 47%), nausea (52% vs. 30%), decreased appetite (47% vs. 36%) and palmar-plantar erythrodysaesthesia syndrome (42% vs. 6%).

Serious adverse events of grade $\geq$ 3 had similar frequency as those observed with everolimus (39% vs. 40%), despite an almost two-fold longer exposure to cabozantinib. One treatment-related death occurred in the cabozantinib group (death not otherwise specified) and two occurred in the everolimus group (one aspergillus infection and one pneumonia aspiration).

1.4 Summary of the cost-effectiveness analysis

A de novo economic model was developed to assess the cost-effectiveness of cabozantinib for the treatment of advanced renal cell carcinoma (RCC) following prior VEGFR-targeted therapy. A partitioned survival model was used in line with previous NICE assessments in advanced RCC (TA219[12] and TA333[7]). The structure was designed to capture disease progression, the primary end point in the METEOR trial. The analysis is in line with the treatment pathway, enabling the analysis to capture all relevant costs and outcomes associated with each treatment and health state.

Patient level data from the pivotal Phase 3 trial, METEOR, were used to inform clinical effectiveness estimates for cabozantinib and everolimus. In the absence of head-to-head data a network meta-analysis was conducted to compare cabozantinib to axitinib, BSC and nivolumab. Health related quality of life assumptions were informed by ED-5D data from METEOR. Resource use and costs were obtained from published sources.

The model outputs were validated by UK clinical experts and were found to be in line with those observed in UK clinical practice and consistent with clinical expectations.

The results of the economic evaluation indicated that treatment with cabozantinib was associated with higher costs but also with additional quality adjusted life years (QALYs) versus both axitinib and best supportive care. The incremental cost per QALY gained was [redacted] versus axitinib and [redacted] versus BSC. In the scenario analysis versus nivolumab treatment with cabozantinib was not only more effective in terms of life years (LY) and QALYs gained but also less costly.

Conclusion

Cabozantinib is the first multi-targeted therapy to demonstrate significant improvement across all three key efficacy endpoints (OS, PFS, ORR) for patients with advanced RCC who have had prior VEGFR-targeted therapy versus an active comparator (everolimus).

As an oral, once-daily treatment, cabozantinib is easy to administer and offers convenience for both patients and clinicians as it can be taken at home, with any dose modifications managed remotely. No change in current management arrangements or infrastructure of units is required.

Cabozantinib provides patients and clinicians with an alternative effective treatment option in the advanced RCC second-line treatment setting with an ICER of [redacted] versus the current standard of care, axitinib.

Table 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
Cabozantinib*	[redacted]	[redacted]	[redacted]				
Axitinib (current standard of care)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib**	[redacted]	[redacted]	[redacted]				
Everolimus**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
*Cost-effectiveness results based on efficacy outputs from the NMA
**Cost-effectiveness results based on the efficacy outputs from the METEOR study

2 The technology

2.1 Description of the technology

Brand name: CABOMETYX®▼

UK approved name: Cabozantinib

Therapeutic class: Protein kinase inhibitor

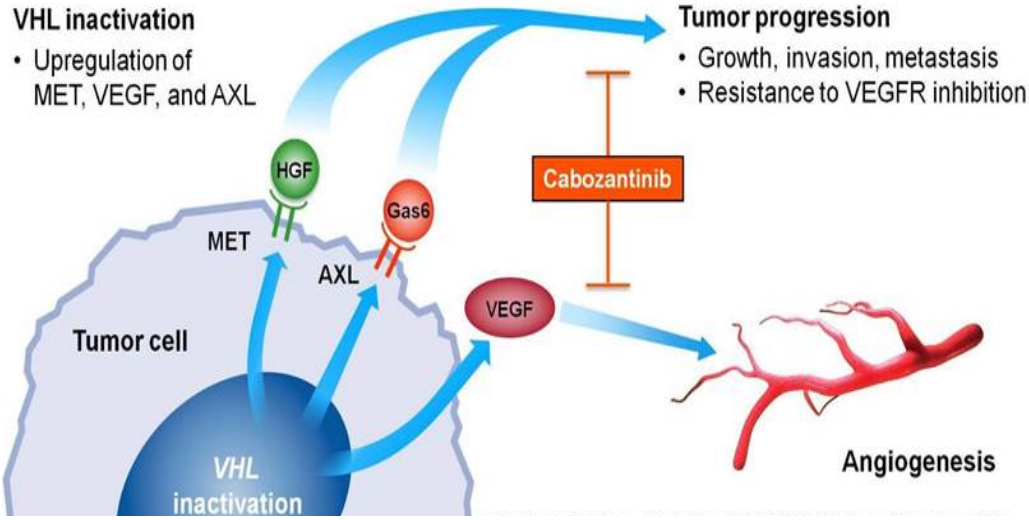
Brief overview of the mechanism of action:

Cabozantinib inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, drug resistance, and metastatic progression of cancer. In particular, cabozantinib inhibits the MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors (Figure 1).

Cabozantinib also inhibits a number of other receptor tyrosine kinases that have also been implicated in tumour pathobiology, including RET and AXL, and FLT amongst others.

By targeting more than just the VEGF pathway cabozantinib provides a multi-targeted approach to the treatment of RCC.

Figure 1: Cabozantinib mode of action



Sources: Shen et al 2013[13]; Zhou et al 2015[14]

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing Authorisation

CABOMETYX®▼ is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.

The indication is based on the results of a single, randomised, open-label, multicenter, pivotal Phase 3 study (METEOR study) which compared cabozantinib with everolimus in patients with advanced RCC who had previously received at least one VEGF receptor tyrosine kinase inhibitor (VEGFR-TKI) (See Section 4).

The Marketing Authorisation application was submitted to the European Medicines Agency (EMA) in January 2016. CHMP positive opinion, following an accelerated review procedure reserved for medicinal products expected to be of major public health interest, was received on 21 July 2016 and Marketing Authorisation granted on 9 September 2016.

Cabozantinib was granted PIM (Promising Innovative Medicine) designation by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in July 2016 meeting the PIM criteria of treatment of a life-threatening or seriously debilitating condition with high unmet need; likelihood of major advantage over current treatments; and reasonable expectation of a positive benefit risk profile.

A copy of the Summary of Product Characteristics (SmPC) is provided in Appendix 1 and a copy of the European Public Assessment Report (EPAR) in Appendix 2. The main issue discussed by the regulators related to the proposed indication, with the regulators requesting that the final indication specify that patients should have received treatment with a least one prior VEGFR-TKI.

Regulatory approvals outside of the UK

Cabozantinib received FDA approval for the treatment of advanced RCC in patients who have received prior antiangiogenic therapy on 25 April 2016.

Health Technology Assessments

In addition to the NICE single technology appraisal, submissions will also be made to the Scottish Medicines Consortium (SMC) Q4 2016 and the National Centre for Pharmacoeconomics (NCPE) in the Republic of Ireland Q1 2017.

2.3 Administration and costs of the technology

Details on the administration of cabozantinib are provided in Table 4.

Table 4: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Film coated tablet	SmPC
Acquisition cost (excluding VAT)	£5,143.00 for a 30 tablet pack	List price
Method of administration	Oral	SmPC
Doses	20 mg, 40 mg and 60 mg	SmPC
Dosing frequency	Once daily	SmPC
Average length of a course of treatment	Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Median duration of treatment with cabozantinib in the phase III pivotal trial (the METEOR study) was 8.3 months as of 31 December 2015.	SmPC METEOR study[10]
Average cost of a course of treatment	[redacted]	Economic model
Anticipated average interval between courses of treatments	Not applicable – retreatment is not anticipated	
Anticipated number of repeat courses of treatments	Not applicable – retreatment is not anticipated	
Dose adjustments	Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of cabozantinib therapy. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.	SmPC (Table 1)
Anticipated care setting	Therapy with cabozantinib should be initiated by a physician experienced in the administration of anticancer medicinal products. Once initiated patients can be managed remotely with dose interruptions/reductions managed by phone.	SmPC

Key: CTCAE, Common Terminology Criteria for Adverse Events; SmPC, Summary of Product Characteristics

2.4 Changes in service provision and management

It is anticipated that administration of cabozantinib will utilise existing NHS infrastructure and resources with no additional requirements.

There are no additional tests or investigations required for the selection of patients for cabozantinib treatment. Cabozantinib treatment should be initiated by a physician experienced in the administration of anticancer medicinal products and patients should be monitored closely during the first eight weeks of treatment for suspected adverse drug reactions which may require temporary dose interruption or reduction of cabozantinib therapy. In clinical practice the monitoring of adverse events is routine and no additional resources above those already in place will be required. Treatment emergent adverse events with cabozantinib can be managed with dose reductions, treatment interruptions and/ or supportive care. No specific concomitant therapies are required. Cabozantinib is an oral therapy and dose reductions and treatment interruptions can be managed remotely via the telephone.

2.5 Innovation

Cabozantinib is the first therapy for advanced RCC that has evidence versus an active comparator (everolimus) of significant improvement in all three key efficacy parameters: overall survival (OS), progression-free survival (PFS) and objective response rate (ORR).

In recognition of its innovative nature, cabozantinib was assigned PIM designation in July 2016 after meeting the PIM criteria of treatment of a life-threatening or seriously debilitating condition with high unmet need; likelihood of major advantage over current treatments; and reasonable expectation of a positive benefit risk profile.

While health-related benefits to patients will be captured in the economic model, which will use EQ-5D data from the METEOR trial and data from other literature sources and clinical trials, the impact on carers' quality of life will not

be captured. Advanced RCC can present a significant burden to carers as result of direct care requirements.[15]

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

3.1 Overview of renal cell carcinoma

Renal cell carcinoma

Renal cell carcinoma (RCC) is the collective name for a group of cancers that originate in the kidney within the epithelium of the proximal renal tubules. It accounts for approximately 80% of kidney cancer cases. [1]

There are several distinct histological subtypes of RCC, with clear cell RCC the most common subtype accounting for 75% of cases.[16,17]

Aetiology

RCC exists in both sporadic and hereditary forms. Approximately 2% to 3% of RCC are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being Von Hippel Lindau (VHL) disease.[1]

Although the aetiology and risk factors for sporadic RCC are not completely understood, several risk factors have been identified. Of these, smoking, obesity and hypertension are the most well-established risk factors.[1,18] In the UK, an estimated 42% of kidney cancers are linked to lifestyle factors including smoking (24%) and overweight and obesity (24%).[18]

Additional risk factors include end-stage renal disease, acquired cystic kidney disease, tuberous sclerosis and viral hepatitis, as well as environmental and occupational factors, such as use of analgesics, paracetamol and non-aspirin non-steroidal anti-inflammatory drugs, and exposure to asbestos. [19,20]

Disease staging and symptoms

Disease staging

RCC is divided into stages that describe how widespread the disease has become. Within the UK, the most commonly used staging system is the American Joint Cancer Committee (AJCC) Tumour Node Metastasis (TNM) system which classifies the size of the tumour (T), the involvement of regional lymph nodes (N) and the presence of distant metastases (M).

Symptoms

RCC is divided into stages that describe how widespread the disease has become. In the early stages of the disease RCC is relatively asymptomatic and often detected incidentally during medical investigation for other conditions.[1] Advanced RCC includes both locally advanced RCC that cannot be removed by surgery and metastatic RCC.

Due to the often indolent course of RCC, patients typically present with advanced disease. Approximately 35% of patients present with metastatic disease at initial diagnosis[2] and up to 40% of patients develop metastasis after surgery for initially localised disease.[3]

Metastatic symptoms frequently include airway obstruction, venous thromboembolism, bone pain, skeletal-related events (SREs) and hypercalcaemia[3] imposing significant morbidity and poor prognosis.

The symptoms of advanced disease and the generally poor prognosis for patients with advanced RCC can also significantly impact on all domains of patient health-related quality of life (HRQoL) including physical and psychosocial function.[4]

3.2 Life expectancy, prevalence and incidence

Life expectancy

There are two main scoring systems used to specifically assess prognosis in individual patients with advanced RCC: the Memorial Sloane Kettering Cancer Centre (MSKCC) score and a slightly modified version, known as the International Metastatic RCC Database Consortium (IMDC) or Heng criteria.[1]

Survival is dependent on the stage of the disease and the relative 5-year survival rate for advanced RCC is approximately one in ten.[5,21] Using the Heng criteria to assess patient risk the median OS for patients with advanced RCC ranges from approximately 5 months (high risk patients) to 3 years (favourable risk patients).[22]

Prevalence and incidence in the UK

In the United Kingdom (UK) in 2013, there were 11,873 new cases of kidney cancer, making kidney cancer the seventh most common cancer in the UK and accounting for 3% of all new cancer cases. Overall in the UK in 2014, there were 4,421 deaths due to kidney cancer, the thirteenth most common cause of cancer-related deaths in the UK.[18]

In the UK, kidney cancer incidence rates have increased by 38% over the last decade, with a greater increase evident in females (40%) than in males (35%).[23] There is a higher incidence in men than in women (1.5:1), with a peak in incidence rates between the ages of 60 and 70 years.[19]

With an ageing population and increasing prevalence of risk factors such as obesity, the burden of advanced RCC is predicted to increase.[4]

Population estimates for England

The incidence of kidney cancer in England in 2014 was 9,123.[24] The increased UK incidence rate of 38% translates into an annualised rate of 5.17%. Applying this rate to the 2014 incidence figure of 9,123 the total number of new kidney cancer cases in 2017 is predicted to be 10,613 patients. Assuming that 80% of all cases of kidney cancer are RCC and that 35.9% of all cases of RCC present

at advanced stages[2] the incidence of advanced RCC is estimated at 3,048 patients. Of these patients it is estimated that 68% would be eligible for first line systemic therapy[25] and upon failure of first line approximately 50% would go on to receive second-line treatment[26] resulting in a total number of eligible patients for second line advanced RCC of 1,037 patients.

3.3 Clinical pathway of care

There is no cure for advanced RCC and the goals of treatment are to extend life and delay disease progression while relieving physical symptoms and maintaining function.[6]

Advanced RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. The elucidation of the pathogenesis of RCC has played a key role in the development of targeted therapies focused on two pathways that are commonly de-regulated in RCC: the VEGF pathway which is targeted by tyrosine kinase inhibitors (TKIs) such as axitinib, sunitinib and pazopanib, and the mammalian target of rapamycin (mTOR) pathway which is targeted by mTOR inhibitors such as everolimus. More recently, nivolumab a programmed death 1 (PD-1) immune checkpoint inhibitor has become available for the treatment of RCC after prior therapy.

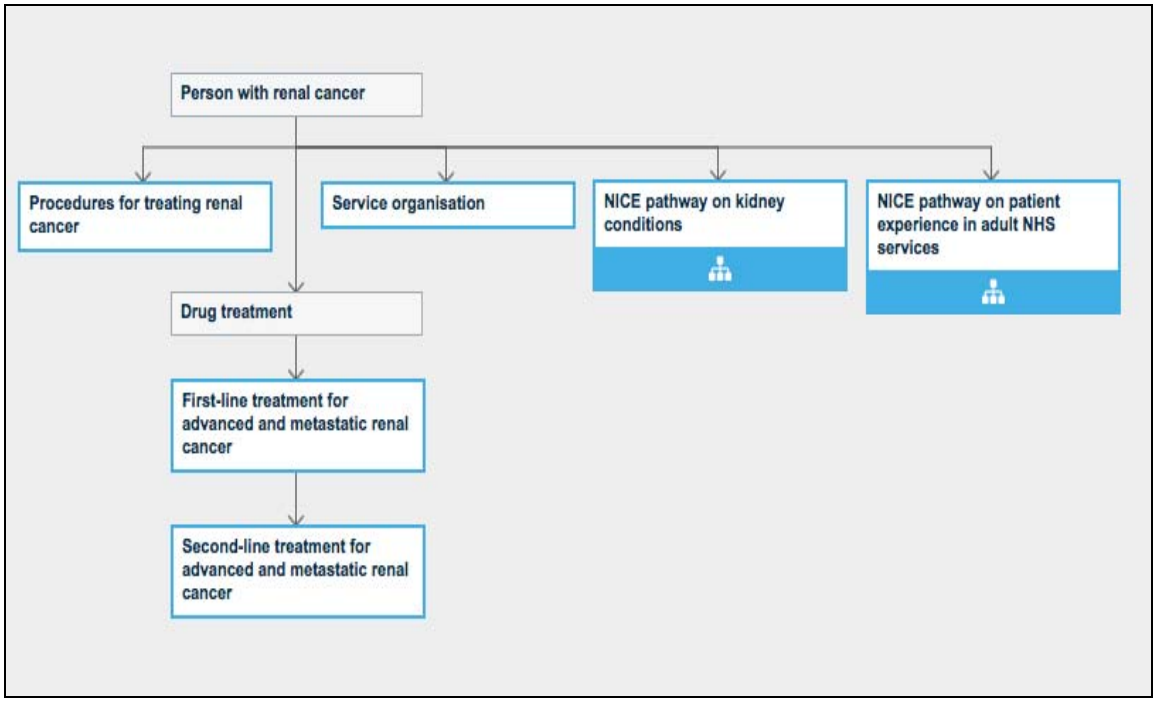
There are no recent UK specific treatment guidelines and the current treatment pathway is based on international guidelines taking into account NICE recommendations and medicines available via the Cancer Drugs Fund (CDF).

3.3.1 Clinical guidance and guidelines

NICE Pathway

A NICE pathway for renal cancer is available[27] and includes details of the NICE recommended treatments listed in Table 5 (Figure 2).

Figure 2: NICE pathway for renal cancer[27]



NICE Technology Appraisal Guidance

Details of current NICE guidance for RCC are provided in Table 5. In summary NICE recommends:

- Sunitinib or pazopanib for the first-line treatment of patients with advanced and /or metastatic RCC with an ECOG performance status of 0 or 1 (TA169[28] and TA215[29])
- Axitinib for use in patients with advanced RCC after failure of treatment with a first-line TKI or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme (TA333[7]).

While everolimus is not recommended by NICE (TA219[12]), it is available via the Cancer Drugs Fund (CDF) for:

- People with RCC who have had prior treatment with only one previous TKI, and
- Patients contraindicated to second line axitinib or excessive toxicity to axitinib necessitating discontinuation of axitinib within three months of

starting therapy and at which time there is no evidence of disease progression.

Everolimus is subject to ongoing NICE CDF transition review [ID1015].

A NICE single technology appraisal (STA) of nivolumab for previously treated advanced RCC is ongoing (as of 11 October 2016) [NICE GID-TA10037] with guidance anticipated November 2016.[30]

Table 5: NICE technology appraisal guidance

Date guidance issued	TA no.	Technology	Recommendation
February 2015	TA333[7]	Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment	Axitinib is recommended for use after failure of treatment with a first-line TKI or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme.
April 2011	TA219[12]	Everolimus for the second-line treatment of advanced renal cell carcinoma	Everolimus is not recommended for the second-line treatment of patients with advanced RCC
February 2011	TA215[29]	Pazopanib for the first-line treatment of advanced renal cell carcinoma	Pazopanib is recommended as a first-line treatment option for patients with advanced RCC who had not received prior cytokine therapy and with an ECOG performance status of 0 or 1 if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme
August 2009	TA178[6]	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	Bevacizumab, sorafenib or temsirolimus are not recommended for first line treatment Sorafenib or sunitinib are not recommended for the second-line treatment of advanced and/or metastatic RCC
March 2009	TA169[28]	Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma	Sunitinib is recommended for the first-line treatment of advanced and/or metastatic RCC in patients who are suitable for immunotherapy and with an ECOG performance status of 0 or 1

Clinical guidelines

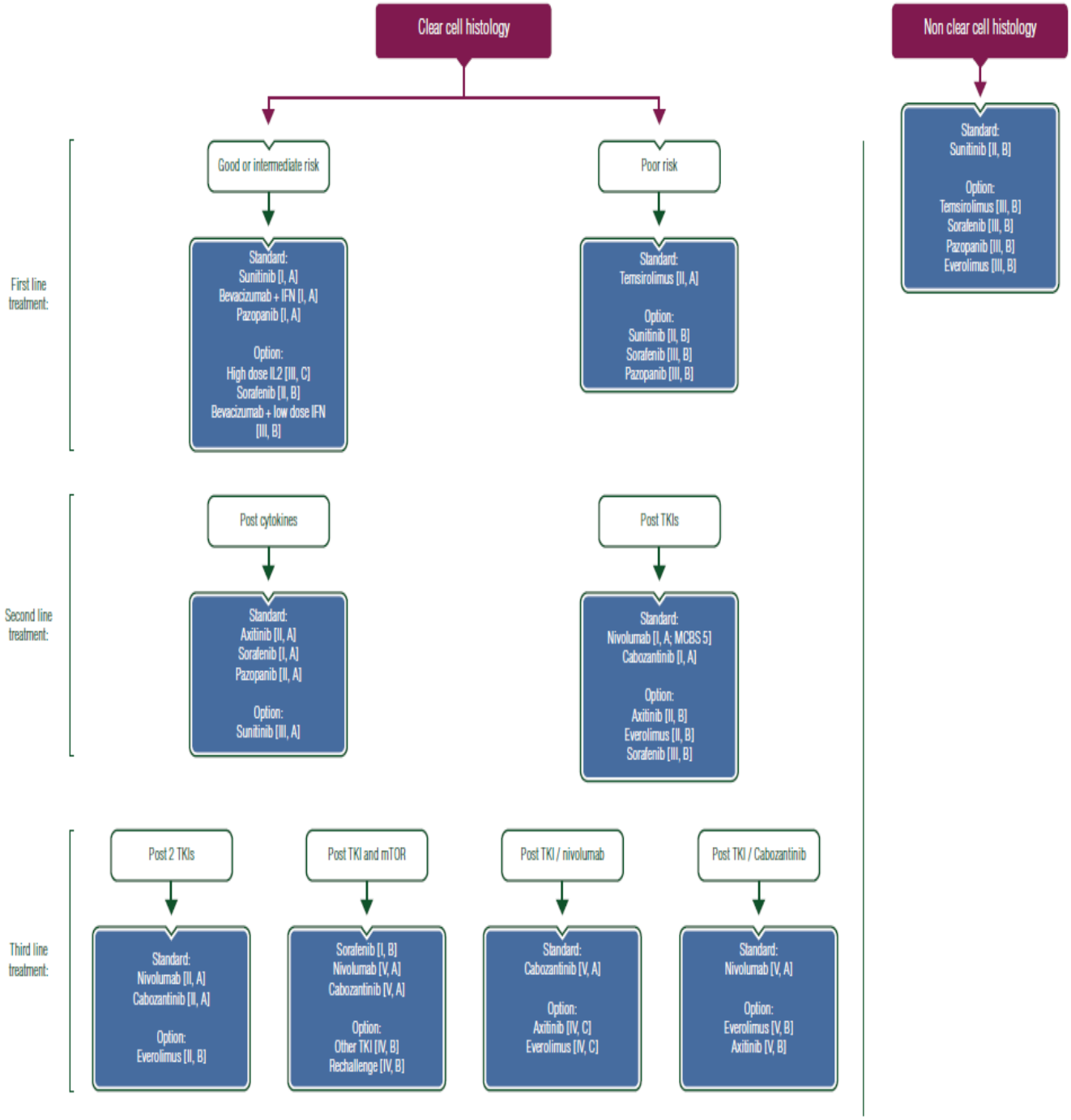
There are no UK-specific clinical guidelines for the treatment of RCC and current clinical practice in England and Wales reflects the following European and US guidelines whilst taking account of those medicines recommended by NICE:

- European Society of Medical Oncology (ESMO) Renal Cell Carcinoma: Clinical Practice Guidelines for diagnosis, treatment and follow-up (2016)[1]
- European Association of Urology (EAU) Renal Cell Carcinoma Guidelines (2016)[31]
- National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology, kidney cancer 2017[32]

The ESMO clinical practice guidelines recommend cabozantinib and nivolumab as preferred second-line treatments. Axitinib, everolimus and sorafenib are recommended as options but are not categorised as 'preferred' (Figure 3).[1]

Cabozantinib is also recommended in the third-line setting (Figure 3).

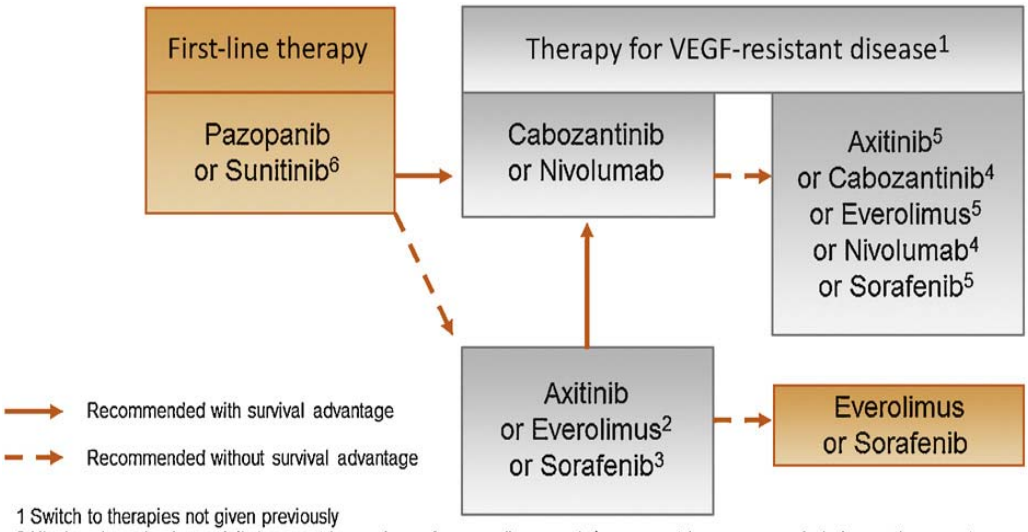
Figure 3 ESMO algorithm for systemic treatment in metastatic RCC



Source: Escudier et al 2016[1]
mRCC, metastatic renal cell carcinoma, IFN, interferon; IL2, interleukin 2; TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; MCBS, ESMO Magnitude of Clinical Benefit Scale v1.0

The EAU updated their guidelines in 2016, in response to the results of the METEOR study, to include cabozantinib as second-line therapy for metastatic RCC in patients who have failed one or more lines of VEGFR targeted therapy (Figure 4).[31]

Figure 4: EAU evidence based recommendations for systemic therapy in patients with metastatic RCC



1 Switch to therapies not given previously
2 Nivolumab and cabozantinib have not been given after everolimus and thus cannot be recommended above other agents
3 Sorafenib has an inferior progression free survival to axitinib
4 These drugs have shown a survival advantage in VEGF-resistant disease but not in this specific setting.
5 These drugs were given after progression in the pivotal cabozantinib or nivolumab trials
6 Sunitinib and pazopanib can be recommended in all MSKCC risk groups. Bevacizumab/interferon (favourable and intermediate-risk disease) and temsirolimus (poor-risk disease) have not been widely used as first line therapy in the pivotal VEGF-resistant trials and therefore recommendations are not possible

Source: Powles et al 2016[31]
MSKCC, Memorial Sloan Kettering Cancer Centre; VEGF, vascular endothelial growth factor;

In the most recent update to the NCCN guidelines 2017, and again in response to the results of the METEOR study, cabozantinib is recommended as a preferred second-line treatment after angiogenic therapy to treat advanced RCC patients. [32]

3.3.2 Current treatment pathway

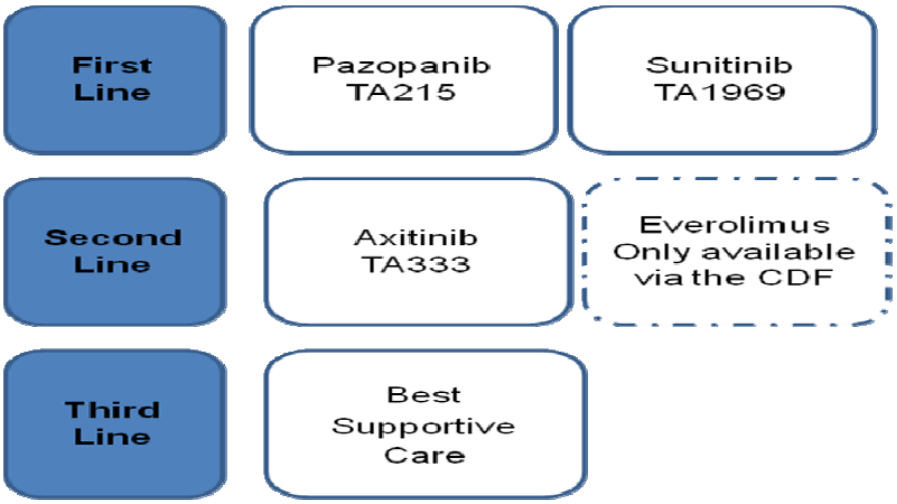
In the absence of UK-specific clinical guidelines, current clinical practice in England and Wales reflects the European and US guidelines relating to RCC, taking account of NICE recommendations.

Patients with advanced RCC move from first- to second-line treatment and subsequently to third-line treatment as their disease progresses. Current treatments used are documented in Figure 5 and the pathway has been validated with clinical experts during a roundtable meeting.[33]

The current established standard of care in the second-line setting is axitinib and while, as stated above, everolimus is available in England for metastatic RCC through the CDF, feedback from clinicians is that it is rarely used in this setting and is reserved for third-line use.[33] Feedback from clinicians is that nivolumab is also used in the second-line setting and, as stated above, is undergoing a NICE STA(GID-TA10037).[30]

The current standard of care in the third-line setting is best supportive care (BSC).

Figure 5: Current clinical pathway of care for advanced RCC in England



Place of cabozantinib in the existing treatment pathway

Figure 6 illustrates the anticipated place of cabozantinib in the current treatment pathway. In clinical practice and as validated with clinical experts[33] cabozantinib will offer:

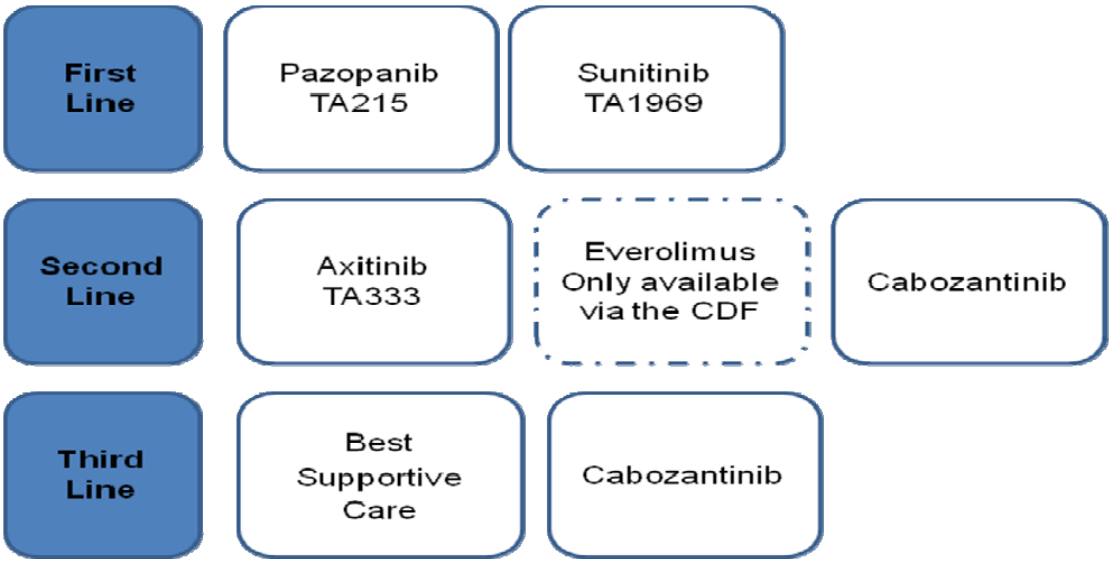
- An oral treatment in the second-line setting (post TKI – pazopanib or sunitinib). In the second-line setting it is anticipated that cabozantinib will displace axitinib. In the event nivolumab is recommended by

NICE cabozantinib will sit alongside nivolumab and clinicians will choose oral cabozantinib or intravenous (IV) nivolumab based on a range of factors including their clinic infrastructure and patient choice.[33]

As an oral, once-daily treatment, cabozantinib is easy to administer and offers convenience for both patients and clinicians as it can be taken at home, with any dose modifications managed remotely. No change in current management arrangements or infrastructure for units is required.

- A third-line treatment option - clinical expert feedback is that in clinical practice cabozantinib can be used after any of the current second-line treatments.[33]

Figure 6: Position of cabozantinib in the current treatment pathway



Source: Ipsen Roundtable meeting. September 2016[33]

As stated in 3.3.1, the place of cabozantinib in the treatment pathway is already recognised by ESMO[1] and EAU[31], who based on the results of the METEOR study, updated their guidelines to include cabozantinib as second-line therapy for metastatic RCC in patients who have failed one or more lines of VEGFR targeted therapy (see Section 3.3).

3.4 Issues relating to current practice

Metastatic RCC is one of the most treatment-resistant cancers (Gupta 2008). Almost all patients with advanced RCC experience disease progression on first-line therapies.[34]

Despite the advances in targeted therapies for RCC, few treatments have shown an overall survival benefit, and none have shown a significant improvement in all three efficacy endpoints of OS, progression-free survival (PFS) and objective response rate (ORR) when compared with standard-of-care treatment in a randomised Phase 3 trial in previously treated patients with renal cell carcinoma.[10]

Furthermore, median PFS with current treatments after initial VEGFR targeted therapy is a relatively modest 3 to 5 months.[35]

There is a need for more effective therapy options for advanced RCC following failure of first-line VEGF treatment that have proven OS benefits as well as PFS and ORR benefits and which provide a further treatment option for clinicians and patients.

3.5 Assessment of equality issues

Not applicable - there are no equality issues related to the use of cabozantinib.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

A systematic literature review designed to identify studies of cabozantinib in second-line treatment of advanced RCC was undertaken in August 2016.

The literature search was conducted using a range of relevant bibliographic databases (Table 6).

Table 6: Resources searched

Database / information source	Interface / URL
MEDLINE, MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print	Ovid SP
Embase	Ovid SP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library / Wiley
Health Technology Assessment Database (HTA Database)	Cochrane Library / Wiley
NHS Economic Evaluation Database (NHS EED)	Cochrane Library / Wiley
FDA webpages	http://www.fda.gov/

The search strategy used to identify studies in Ovid MEDLINE is presented in Figure 7. Full strategies (including search dates) for all sources searched are included in Appendix 3.

Figure 7:Search strategy for MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE

1 (cabozantinib$ or cabometyx$ or cometriq$ or 849217-68-1 or 1C39JW444G or XL184 or XL-184 or BMS907351 or BMS-907351).ti,ab,kf,rn. (329)
2 exp animals/ not humans/ (4283633)
3 (comment or letter or case reports).pt. (2861095)
4 1 not (2 or 3) (297)
5 limit 4 to english language (284)

Key to Ovid symbols and commands

$	Truncation symbol
ti,ab,kf, rn	Searches are restricted to the Title, Abstract, Keyword Heading Word, or Registry Number fields
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field

In addition, the following relevant conferences were checked for the last three years (2013 to 2016) to ensure that their proceedings were indexed by Embase and that relevant abstracts could have been retrieved by the search of Embase.

Any conferences that were not included in Embase for the relevant dates were hand-searched where the abstracts were freely available online:

- American Society of Clinical Oncology (ASCO) Annual Meeting. Proceedings from 2015, 2014 and 2013 were included in Embase. Proceedings from 2016 were hand-searched
- ASCO Genito-Urinary Symposium. Proceedings from 2013-2016 were included in Embase and therefore no hand-searching was required
- ESMO Congress. Proceedings from 2013 (joint meeting with ECCO) and 2015 (joint meeting with ECCO) were included in Embase. Proceedings from 2014 were hand-searched. The 2016 Congress was held on 7 October 2016 after the review had been completed
- ESMO Multidisciplinary Meeting on Urological Cancers. Proceedings from 2013 and 2014 were included in Embase. Proceedings from 2015 were hand-searched. The 2016 Meeting will be held in November 2016 and could not yet be searched
- European Cancer Organisation - European Cancer Congress (ECC/ECCO). Proceedings from 2013 and 2015 were included in Embase (these were both joint meetings with ESMO). No Congress was held in 2012, 2014 or 2016 and, therefore no hand-searching was required.

Reference lists of relevant studies were scanned to identify other relevant additional studies that might have been missed in the database searches.

Study Selection

The full eligibility criteria applied to the identified evidence base are presented in Table 7.

Table 7: Summary of the review eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	• 80% or more of the study population must be adults (≥18 years of age) • Previously treated metastatic renal cell carcinoma (patients who had received prior systemic therapy)	• Non-human subjects; • Patients aged under 18 years of age • Patients with non-metastatic RCC • Patients with early stage RCC If a study included groups of eligible and ineligible patients, the study was included if data for the eligible patient group were presented separately
Intervention	Cabozantinib	
Comparators	For comparative studies: • Axitinib • Everolimus • Nivolumab • Best supportive care Single-arm prospective studies were also eligible	For comparative studies: • Radiotherapy, surgery and other non-relevant comparators
Outcomes	**Efficacy** • OS • PFS • TTP • ORR (complete or partial response) • Proportion of patients with stable disease • Duration of response • Time to response • Symptom assessments • Time to deterioration (composite/individual endpoint) **Safety** • Incidence and severity (grade) of all reported AEs • Withdrawals due to AEs • Incidence of serious AEs Quality of life or any other global patient-reported outcomes	• Studies not investigating efficacy, safety or quality of life • Studies not providing sufficient data on outcomes
Study design	• Prospective randomised controlled trials • Cross-over RCTs • Non-RCT studies; • Systematic reviews	• Duplicate publications of the same trial • Case reports • Commentaries and letters • Recommendations/ guidelines • Non-systematic reviews
Language restrictions	English language only	Non-English language
RCC, renal cell cancer; OS, overall survival; PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; AE, adverse event, RCT, randomised controlled trial		

The search results were rapidly assessed according to their relevance in providing information on advanced RCC. Irrelevant records, such as animal studies, commentaries and news items, and records on issues other than advanced RCC, were removed.

The initial record selection, based on the screening of title and abstracts against the review eligibility criteria, was undertaken by two reviewers independently.

The eligibility criteria were assessed in the following order so that the first 'no' response was used as the primary reason for exclusion of the record and the remaining criteria did not need to be assessed:

- Population
- Study design
- Intervention
- Comparator (for comparative studies)

Records were not excluded based on lack of outcomes information if there was any possibility that the publication might report efficacy, safety or quality of life outcomes.

Decisions for each paper assessed were saved in a central database. Any disagreements on eligibility were resolved by consulting a third independent reviewer.

Electronic or paper copies of studies that seemed likely to meet the eligibility criteria or where information on eligibility could not be fully ascertained from the title and abstract were obtained.

A full assessment of the eligibility of each full text document was made by two independent reviewers. Eligibility was decided in the same way as detailed above, with the addition of "outcomes" to the end of the list.

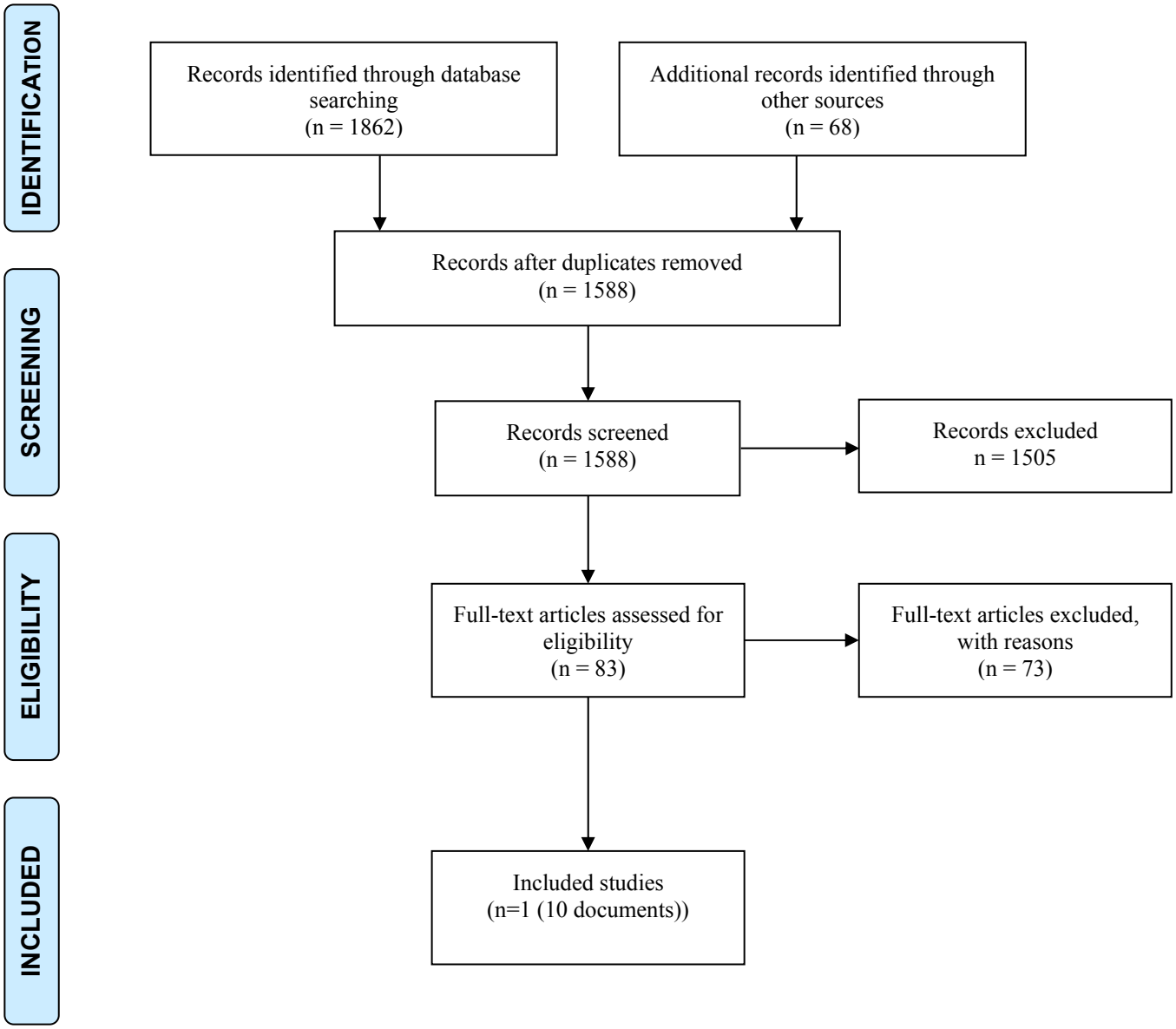
- Population
- Study design
- Intervention
- Comparator (for comparative studies)
- Outcomes

The eligibility decisions for each document were saved in a central database, and any disagreements on eligibility resolved by consulting a third independent reviewer. Studies excluded at the full text stage of the selection process are listed in Appendix 4.

Since results for trials can be reported in more than one paper, all related papers were grouped together. This minimised the chances of double counting participants and meant that all sources of outcome data could be assessed.

A PRISMA flow chart detailing the number of studies included and excluded at each stage of the review is shown in Figure 8.

Figure 8: PRISMA flow diagram of the literature search process



The literature search identified 1930 records. Following removal of duplications, a total of 1588 unique records were retained for eligibility assessment (Table 8).

Table 8: Number of records retrieved from each information source

Resource	Records identified
MEDLINE, MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print	284
Embase	1529
Cochrane Database of Systematic Reviews (CDSR)	2
Cochrane Central Register of Controlled Trials (CENTRAL)	43
Database of Abstracts of Reviews of Effects (DARE)	0
Health Technology Assessment Database (HTA Database)	4
NHS Economic Evaluation Database (NHS EED)	0
FDA webpages	43
American Society of Clinical Oncology (ASCO) Annual Meeting.	19
European Society for Medical Oncology (ESMO) Congress	6
European Society for Medical Oncology (ESMO) Multidisciplinary Meeting on Urological Cancers	0
Total number of records retrieved	**1930**
Total number of records following duplication	**1588**

Following title and abstract selection, 83 records were taken through to assessment of full text. After obtaining and assessing the full documents for each of these records, 10 were included (Table 9) and 73 were excluded; the excluded records are recorded in Appendix 4 with the reasons for exclusion. Only one RCT, the METEOR study, was identified.

Table 9: Eligible records

Study name	Record
METEOR	Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917-27[10]
	Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015;373(19):1814-23[9]
	Choueiri T, Escudier B, Powles T, Mainwaring P, Rini B, Donskov F, et al. Cabozantinib versus everolimus in patients with advanced renal cell carcinoma: Results of the randomized phase 3 METEOR trial. Eur J Cancer. 2015;51:S708-S09[36]
	Powles T, Escudier B, Mainwaring PN, Rini BI, Donskov F, Hammers HJ, et al. METEOR: Results from the randomized phase 3 trial of cabozantinib versus everolimus in pts with advanced renal cell carcinoma (RCC). BJU Int. 2015;116(Suppl 5):19[37]
	Choueiri TK, Powles T, Escudier BJ, Tannir NM, Mainwaring P, Rini BI, et al. Overall survival (OS) in METEOR, a randomized phase 3 trial of cabozantinib (Cabo) versus everolimus (Eve) in patients (pts) with advanced renal cell carcinoma (RCC) [abstract]. J Clin Oncol. 2016;34(Suppl):A4506[38]
	Escudier B, Powles T, Motzer R, Olencki T, Aren OR, Oudard S, et al. Efficacy of cabozantinib (C) vs everolimus (E) in patients (pts) with advanced renal cell carcinoma (RCC) and bone metastases (mets) from the phase III METEOR study [abstract]. J Clin Oncol. 2016;34(Suppl):A4558[39]
	Escudier BJ, Motzer RJ, Powles T, Tannir NM, Davis ID, Donskov F, et al. Subgroup analyses of METEOR, a randomized phase 3 trial of cabozantinib versus everolimus in patients (pts) with advanced renal cell carcinoma (RCC) [abstract]. J Clin Oncol. 2016;34(2 Suppl 1):A499[40]
	Powles T, Motzer R, Escudier B, Pal S, Kollmannsberger C, Pikiel HG, et al. Outcomes based on prior VEGFR TKI and PD-1 checkpoint inhibitor therapy in METEOR, a randomized phase 3 trial of cabozantinib (C) vs everolimus (E) in advanced renal cell carcinoma (RCC) [abstract]. J Clin Oncol. 2016;34(Suppl):A4557[41]
	U.S. Food and Drug Administration. Cabozantinib (CABOMETYX) [webpage]. Silver Spring, MD: U.S. Food and Drug Administration; 2016. Last updated 04/25/2016. [cited August 11 2016]. Available from: http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm497483.htm[42]
	U.S. Food and Drug Administration. Patient Information: CABOMETYX™ (cabozantinib) tablets, for oral use. Silver Spring, MD: U.S. Food and Drug Administration; 2016. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208692s000lbl.pdf[43]

4.2 List of relevant randomised controlled trials

The efficacy and safety of cabozantinib in adult patients who had received previous VEGF-targeted therapy for advanced RCC is provided by a single Phase 3 RCT, the METEOR study; see Table 10.

METEOR directly compared the clinical efficacy and safety of cabozantinib with everolimus.

At the time the study was initiated everolimus was the only active treatment licensed for advanced RCC patients who had received prior therapy and as a consequence was the appropriate active comparator (see Appendix 2). No head-to-head data are available comparing cabozantinib with axitinib, nivolumab or BSC and a network meta-analysis (NMA) was performed to estimate comparative efficacy (see Section 4.10).

Table 10: Relevant RCT

Trial name (NCT Number)	Population	Intervention	Comparator	Primary study references
METEOR NCT01865747	Adult patients with advanced RCC that has progressed after prior VEGFR tyrosine kinase inhibitor therapy	Oral cabozantinib 60 mg once daily	Everolimus 10 mg once daily	Choueiri *et al.* 2016

4.3 Summary of methodology of the relevant randomised controlled trials

The efficacy and safety of cabozantinib in adult patients with advanced RCC who had received previous VEGFR-targeted therapy is provided by a single Phase 3 study, the METEOR study.

A total of 658 subjects were randomised to receive either cabozantinib or everolimus. The primary end point was PFS assessed in the first 375 patients randomised. Secondary efficacy end points were OS and ORR assessed in all 658 randomised patients. Subjects received treatment for as long as they continued to experience clinical benefit in the opinion of the investigator

(including after progression), or until there was unacceptable toxicity or the need for subsequent anticancer treatment, or any other reasons for treatment discontinuation listed in the protocol. Treatment was allowed to continue after radiographic progression per RECIST 1.1 if the investigator believed that the subject was still receiving clinical benefit from study treatment and that the potential benefit of continuing treatment outweighed potential risks. Crossover between treatment arms was not allowed.

A summary of the trial design is provided in Figure 9 with further details provided in Table 11.

Figure 9: Schematic of the METEOR Study

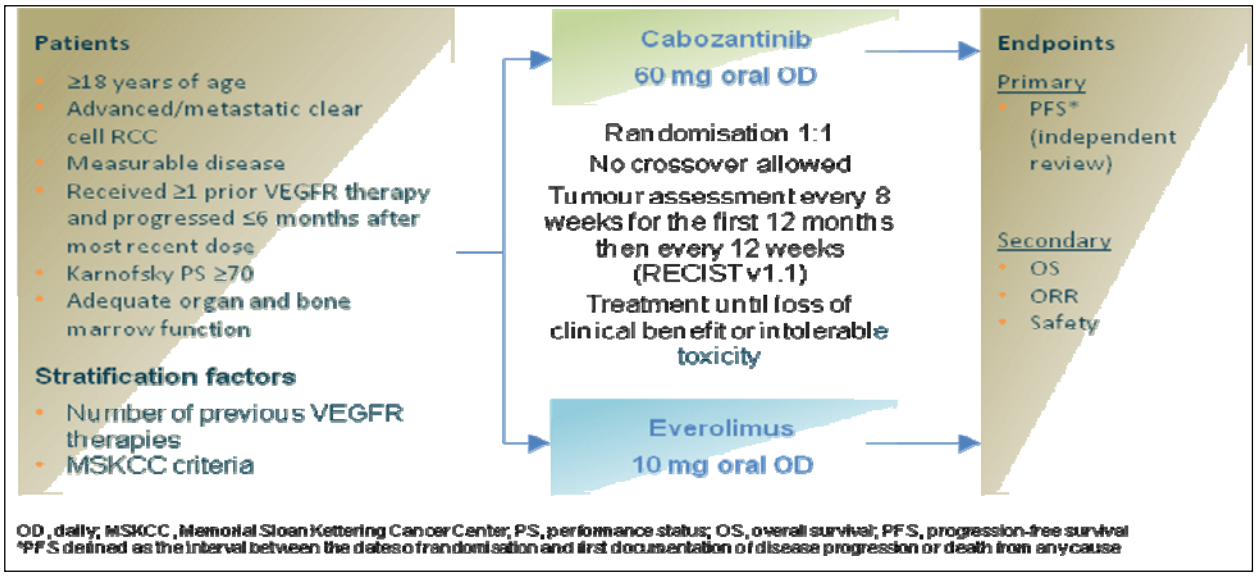


Table 11: Summary of the METEOR study

	METEOR
Study objectives	To evaluate the effect of cabozantinib compared with everolimus on progression-free survival and overall survival in subjects with advanced RCC that had progressed after prior VEGFR-TKI therapy.
Location	A total of 658 subjects were randomised in 25 countries: 36% were enrolled in North America, 49% in Europe, 13% in Asia Pacific/Australia and 1.8% in Latin America.
Trial design	Phase 3 multicentre, international, 1:1 randomised, active-controlled, open-label study 3 sequential periods: • Pre-treatment (screening) period. • Treatment Period. Subjects received treatment for as long as they continued to experience clinical benefit in the opinion of the investigator (including after progression) or until there was unacceptable toxicity or the need for subsequent anticancer treatment. • Post-Treatment Period (30 days + 14 days after the date of the decision to permanently discontinue study treatment subject returned for a Post-Treatment Follow up Visit). In addition patients were contacted every 8 weeks [±7 days] after the Post-Treatment Follow-up Visit to assess survival status and document receipt of subsequent cancer therapy.
Eligibility criteria for participants	Eligible patients were 18 years of age or older with advanced or metastatic RCC with a clear-cell component and measurable disease. Patients must have received prior treatment with at least one VEGFR-targeting TKI and must have had radiographic progression during treatment or within 6 months after the most recent dose of the VEGFR inhibitor. Patients with known brain metastases that were adequately treated and stable were eligible. There was no limit to the number of previous anticancer therapies, which could include cytokines, chemotherapy, and monoclonal antibodies, including those targeting VEGFR, the programmed death 1 (PD-1) receptor, or its ligand PD-L1. Eligible patients also had a Karnofsky performance-status score of at least 70% (on a scale from 0 to 100%, with higher scores indicating better performance status) and adequate organ and bone marrow function. Key exclusion criteria were previous therapy with an mTOR inhibitor or cabozantinib or a history of uncontrolled, clinically significant illness. A list of all inclusion and exclusion criteria is provided in Appendix 5.
Setting and locations where the data were collected	The study was conducted in hospital and outpatient clinics

Duration of study	Study period: 8 August 2013 (first subject enrolled) to 31 December 2015 (data cut off). Subjects received treatment for as long as they continued to experience clinical benefit in the opinion of the investigator (including after progression), or until there was unacceptable toxicity or the need for subsequent anticancer treatment, or any other reasons for treatment discontinuation listed in the protocol. Treatment was allowed to continue after radiographic progression per RECIST 1.1 if the investigator believed that the subject was still receiving clinical benefit from study treatment and that the potential benefit of continuing treatment outweighed potential risks. Crossover between treatment arms was not allowed.
Trial drugs	Oral cabozantinib 60 mg once daily (n= 330) Oral everolimus 10 mg once daily (n= 328)
Methods of randomisation	Patients were randomly assigned (1:1) to receive either cabozantinib or everolimus. Randomisation was stratified by the number of previous VEGFR TKI treatments (1 or ≥2) and Memorial Sloan Kettering Cancer Center (MSKCC) risk group (number of risk factors 0,1, 2 or 3) for previously treated patients. Study treatment was assigned centrally with an interactive voice and web response system. Study personnel did not have access to the master list of blocks or block sizes. Patients and investigators were not masked to study treatment to allow appropriate management of adverse events.
Dose reduction	Cabozantinib could be dose reduced to 40 mg and then 20 mg, and everolimus could be dose reduced to 5 mg and then 2.5 mg. Dose reductions for cabozantinib were allowed for unacceptable toxicity, and doses may have been modified at any time. First dose level reduction to 40 mg, second dose reduction to 20 mg. Dose interruption and reduction criteria recommendations for cabozantinib in order to manage treatment-related AEs were according to toxicity criteria (CTCAE v4). Dose reductions for everolimus were allowed for management of severe or intolerable adverse reactions. If dose reduction was required, the suggested dose was approximately 50% lower than the daily dose previously administered; investigators were instructed to refer to the most recent product package insert/drug label for detailed instructions.
Permitted and disallowed concomitant medications	<u>Disallowed medications</u> • Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor or cabozantinib. • Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before randomisation. • Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before randomisation. • Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before randomisation. Systemic treatment with radionuclides within 6 weeks before

	randomisation. • Concomitant anticoagulation at therapeutic doses with oral anticoagulants or platelet inhibitors. • Chronic treatment with corticosteroids or other immunosuppressive agents (with the exception of inhaled or topical corticosteroids or corticosteroids with a daily dosage equivalent ≤ 10 mg prednisone if given for disorders other than renal cell cancer).
Discontinuation of study drugs	Patients withdrew from the study for the following reasons: • Death • Unacceptable toxicity • Protocol deviation • Pregnancy • Patient choice to withdraw from treatment • Withdrawal of patient consent
Primary outcomes	The primary efficacy variable was duration of PFS (among the first 375 randomised subjects) as assessed by the IRC per RECIST 1.1 and was defined as the time from randomisation to the earlier of the following events: documented PD per RECIST 1.1 or death due to any cause. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.
Secondary outcomes	• Overall survival: Survival status was determined at scheduled visits and every 8 weeks (± 7 days) after the Post-Treatment Follow-up Visit. Subjects were followed until death, consent withdrawn or Sponsor decision to no longer collect these data. • Objective response rate: The ORR was defined as the proportion of subjects for whom the best overall response at the time of data cut-off was complete response (CR) or partial response (PR) as assessed by the IRC per RECIST 1.1, which was confirmed by a subsequent visit ≥ 28 days later. Secondary endpoints were assessed on all randomised patients (ITT population).
Additional endpoints	<u>Quality of life</u> • *Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-19)* The FKSI-19 instrument is a 19-item self-reported questionnaire that assesses the most important disease-related symptoms (DRS), treatment side effects, and function/well-being associated with advanced kidney cancer. It queries symptom severity and interference in activity and general health perceptions. Each symptom was scored on a 5-point scale. The symptom scores were converted into a score for the total and four subscales. • *EQ-5D-5L* The EQ-5D-5L is a standardised measure of health status which assesses five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.

	Subjects were to complete the questionnaires prior to each clinic visit or, if completed on the day of the visit, before seeing the study site personnel. <u>Safety and tolerability</u> Safety analyses were performed using the Safety population (those that received at least one dose of study treatment). New or worsening AEs from informed consent through 30 days after the date of the decision to permanently discontinue study treatment (related SAEs at any time) were documented. Adverse event information was collected at study visits and may also have been collected at any time over the phone or by spontaneous subject report. Adverse event seriousness, severity grade, and relationship to study treatment were assessed by the investigator. Severity grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4. An event was assessed as related to study treatment when there was a reasonable possibility that the study treatment caused the event. <u>Other</u> • Duration of response (DOR) • Changes in bone scans • Characterisation of the pharmacokinetics of cabozantinib • Proportion of patients with post-randomisation skeletal-related events • Relationship of baseline and changes in plasma biomarkers, serum bone markers, serum calcium and circulating tumour cells with treatment and/or clinical outcome • Health care resource utilisation
Pre-planned subgroups	Pre-planned subgroup analyses assessing the effects of a range of baseline characteristics on PFS and OS were performed. These included analyses on the following: • MSKCC Risk Factors (favourable [0], intermediate [1], poor [2 or more]) • Heng Criteria (favorable [0], intermediate [1-2], poor [3-6]) • Number of prior VEGFR-TKI agents (1, ≥ 2) • Treatment Duration on first VEGFR-TKI ((< 3 months, ≥ 3 months; < 6 months, ≥ 6 months; < 9 months, ≥ 9 months)
Sources: Choueiri et al 2015[9], METEOR Clinical Study Report[44] Key: IRC, independent review committee; MSKCC, The Memorial Sloan Kettering Cancer Centre; ORR, objective response rate, OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1; VEGFR-TKI, vascular endothelial growth factor tyrosine kinase inhibitor	

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

Sample size

The study was designed to provide adequate power for both PFS and OS analyses.

For the primary endpoint of PFS, assuming exponential PFS, proportional hazards, and a 1:1 treatment allocation ratio, 259 events were required to provide 90% power to detect an HR of 0.667 (5 months in the everolimus arm vs. 7.5 months in the cabozantinib arm) using the log-rank test and a 2-sided significance level of 5%. Under this design, the minimum observed effect that would result in statistical significance for PFS was a 27.8% improvement (HR 0.783) in PFS from 5 to 6.39 months when 259 events were observed in the first 375 subjects randomised into the study.

For the key secondary efficacy endpoint of OS, assuming a single interim analysis at the 33% information fraction (at the time of the primary analysis of PFS) and a subsequent primary analysis, 408 deaths were required to provide 80% power to detect a HR of 0.75 (15 months in the everolimus arm vs. 20 months in the cabozantinib arm) using the log-rank test and a 2-sided significance level of 4%. Under this design, the minimum observed effect that would result in statistical significance for the primary analysis of OS was a 22.5% improvement (HR 0.816) in OS from 15 to 18.38 months.

Using an average accrual rate of 32 subjects per month and a 1:1 treatment allocation ratio, a total of 650 subjects (325 per treatment arm) were required to observe the required number of events within the planned study duration (21 months accrual; approximately 17 months to observe the required PFS events among 375 subjects and approximately 36 months to observe the required deaths for OS among 650 subjects).

As the total sample size of 650 required to evaluate OS was much larger than needed to assess the primary endpoint of PFS there was the possibility that

patients with earlier onset of radiographic progression would be over-represented (and those with later onset of radiographic progression under-represented) among the planned 259 PFS events. To reduce this potential bias, the primary analysis of PFS was pre-specified to occur when the required 259 events were observed in the first 375 randomised patients, the size the study would have been without the overall survival endpoint. Supportive analyses of PFS among all randomly assigned patients were also planned.

Populations analysed

The following populations were defined for statistical analyses:

Primary Endpoint Intent-to-Treat Population

The Primary Endpoint Intent-to-Treat (PITT) population consisted of the first 375 randomised subjects. The PITT population was used to determine the primary endpoint (PFS) of the study. Analyses were performed according to the randomisation assignment.

Intent-to-Treat Population

The Intent-to-Treat (ITT) population, defined as all randomised subjects, was used for efficacy analyses (other than for the primary analysis of PFS), with analyses according to the randomisation assignment.

Safety Population

The Safety population consisted of all subjects who received any amount of study treatment. Analyses based on the Safety population were performed according to the treatment received.

Statistical analysis

Hypothesis testing of OS and PFS was done with the stratified log-rank test with the randomisation stratification factors. Median duration of PFS and OS, corresponding 95% confidence intervals, and landmark proportions were estimated by the Kaplan-Meier method. Hazard ratios (HRs) were estimated with a Cox regression model adjusted for the randomisation stratification

factors. The proportional hazards assumption was evaluated by visual inspection of log-log plots. A post-hoc sensitivity analysis of PFS per independent radiology review committee among the 283 patients randomised after the first 375 was conducted using the same methods as the primary analysis. Post-hoc analysis of patients who continued on study treatment for at least 2 weeks after radiographic progression as determined by the investigator evaluated post-progression changes in tumour status by two criteria: the proportion with at least one assessment of stable disease or partial response (from randomisation) after progression; and the proportion with at least one assessment in which the sum of target lesion diameters was lower than the pre-randomisation baseline value.

The primary analysis of ORR used the ITT population. Hypothesis testing was performed using the 2-sided chi-squared test at the 0.01 α level. Point estimates of ORR, the difference in response rates between the two treatment arms, and associated confidence intervals were provided. Confidence intervals were calculated using exact methods.

All subgroup analyses of PFS and OS were prespecified except for the subgroups based on receiving sunitinib or pazopanib as the only previous VEGFR-TKI. ECOG performance status was converted from Karnofsky status using ECOG 0 for Karnofsky status of 100% and 90%, or ECOG 1 for Karnofsky status of 80% and 70%. Confidence intervals and p values for subgroup analyses are considered descriptive. HRs reported for subgroup analyses are unadjusted.

Safety analyses were limited to patients who received any amount of study treatment and analysed per protocol. All analyses were done with SAS (version 9.1 or higher).

Data management, patient withdrawals

For patients who were alive at the time of data cutoff or who were permanently lost to follow up, duration of OS was censored at the date the subject was last known to be alive.

For PFS patients who had received subsequent anti-cancer therapy before experiencing an event or had not experienced an event at the time of data cutoff were censored on the date of last tumour assessment. Patients who had missed two or more scheduled tumour assessments followed by an event were censored on the date of their most-recent tumour assessment prior to the missing assessments.

PFS censoring triggers also applied to ORR.

Handling of multiplicity

The multiplicity issue resulting from analysis of one primary endpoint (PFS), two key secondary efficacy endpoints (ORR and OS), and performing one interim analysis (of OS) was addressed by employing a fixed-sequence testing procedure, applying a modified Bonferroni procedure (dividing the alpha between the secondary endpoints), and implementing an alpha spending function.

OS – interim analyses

The planned interim analysis of overall survival (done at the time of the primary PFS analysis with a data cut-off date of May 22 2015; minimum follow-up of 6 months) at that time did not meet the boundary for significance (HR 0·67; 95% CI 0·51–0·89; p=0·005; 49% information fraction: critical p value ≤0·0019) defined by the Lan-DeMets O'Brien-Fleming alpha spending function.

The decision to conduct an unplanned second interim analysis was made by the manufacturer in consultation with the FDA and EMA. As a result, the analysis plan was revised to include an unplanned second interim analysis of OS with a prospectively defined cut-off date of 31 December 2015, to provide a minimum of 13 months of follow-up from the last patient enrolled. At this analysis, the critical p value to achieve significance from the alpha spending function was 0·0163 or lower.

4.5 Participant flow in the relevant randomised controlled trials

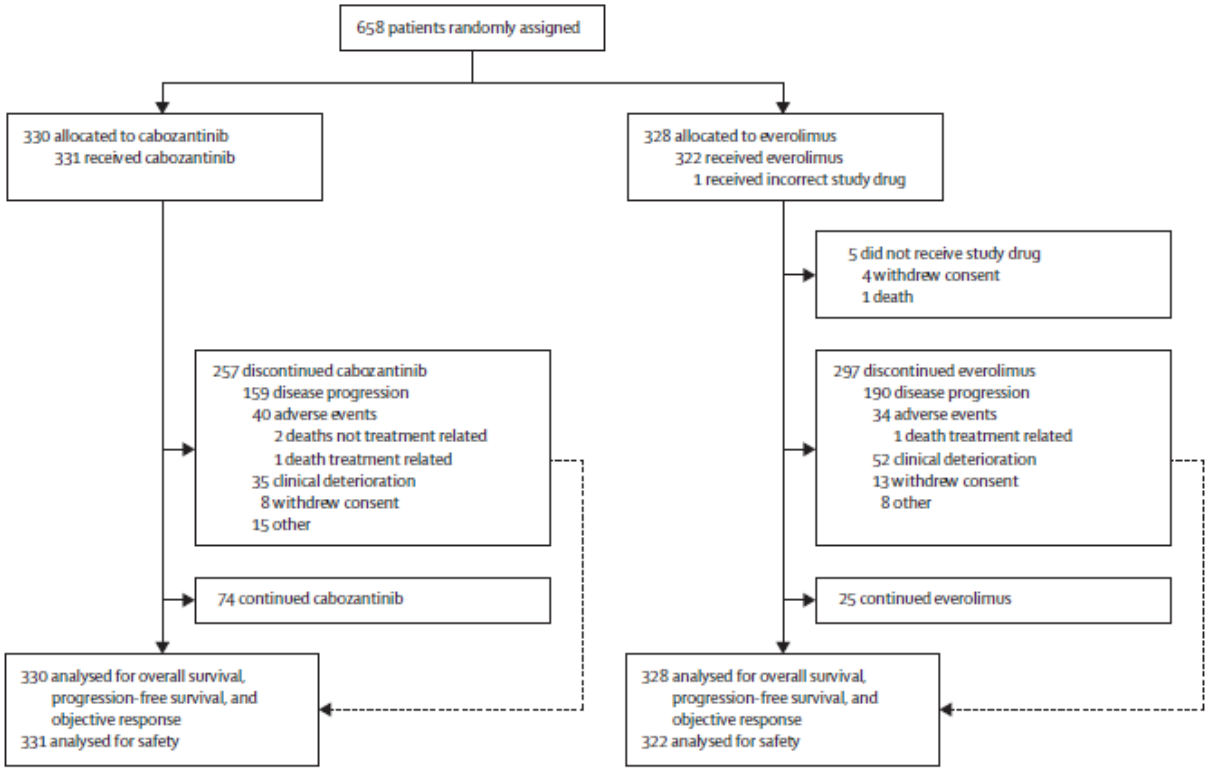
Participant flow

Participant flow is presented in Figure 10. Between 8 August 2013, and 24 November, 2014 a total of 658 subjects (ITT population) were randomised to receive cabozantinib (n=330) or everolimus (n=328).

Two hundred and fifty seven patients in the cabozantinib treatment group and 297 patients in the everolimus treatment group discontinued treatment.

As of 31 December 2015 22% of cabozantinib patients and 8% of everolimus patients remained on study treatment.

Figure 10: CONSORT diagram of participant flow in METEOR



Source: Choueiri et al 2016[10]

Patient characteristics

Baseline characteristics for both the PITT and ITT populations are provided in Table 12.

Demographic and baseline characteristics were balanced between the treatment arms and were representative of the population of patients with advanced RCC who will be treated with cabozantinib in UK clinical practice.

As most subjects were enrolled in North America and Europe, prior anticancer therapies reflected the current standard of care in these regions, with sunitinib the most frequently reported treatment. Approximately 50% (320) of patients were enrolled in Europe. The majority of subjects had received only one prior VEGFR-TKI. Sunitinib and pazopanib were the most frequent prior systemic therapies. Over 50% of patients had a poor or intermediate prognostic risk score at baseline.

Table 12: Baseline Demographic and Clinical Characteristics

Characteristic	PITT		ITT	
	Cabozantinib N= 187	Everolimus N= 188	Cabozantinib N= 330	Everolimus N= 328
Age — yr				
Median (range)	62	61	63	62
Range	36–83	31-84	32-86	31–84
Sex — no. (%)				
Male	142 (76)	130 (69)	253 (77)	241 (73)
Female	45 (24)	57 (30)	77 (23)	86 (26)
Not reported	0	1 (<1)	0	1 (<1)
Geographic region — no. (%)				
Europe*	83 (44)	84 (45)	167 (51)	153 (47)
North America	76 (41)	64 (34)	118 (36)	122 (37)
Asia–Pacific	25 (13)	36 (19)	39 (12)	47 (14)
Latin America	3 (2)	4	6 (2)	6 (2)
Race — no. (%)†				
White	157 (84)	147 (78)	269 (82)	263 (80)
Asian	12 (6)	20 (11)	21	26
Black	4 (2)	2	6 (2)	3 (<1)
Other	10 (5)	6	19	13
Not reported	4 (2)	12	15	22
Missing data	0	1 (<1)	0	1 (<1)
ECOG performance-status score — no. (%)‡				
0	129 (69)	116 (62)	226 (68)	217 (66)
1	58 (31)	72 (38)	104 (32)	111 (34)
MSKCC prognostic risk category — no. (%)§				
Favourable	80 (43)	83 (44)	150 (45)	150 (46)

Intermediate	80 (43)	75 (40)	139 (42)	135 (41)
Poor	27 (14)	30 (16)	41 (12)	43 (13)
Prior VEGFR tyrosine kinase inhibitors — no. (%)				
1	137 (73)	136 (72)	235 (71)	229 (70)
≥2	50 (27)	52 (28)	95 (29)	99 (30)
Previous systemic therapy — no. (%)				
Sunitinib	114 (61)	113 (60)	210 (64)	205 (62)
Pazopanib	87 (47)	78 (41)	144 (44)	136 (41)
Axitinib	28 (15)	28 (15)	52 (16)	55 (17)
Sorafenib	11 (6)	19 (10)	21	31
Bevacizumab	1 (<1)	7	5 (2)	11
Interleukin-2	11 (6)	13	20	29
Interferon alfa	6 (3)	13	19	24
Nivolumab	9 (5)	11	17	14
Radiotherapy — no. (%)	56 (30)	61 (32)	110 (33)	108 (33)
Nephrectomy — no. (%)	156 (83)	153 (81)	282 (85)	279 (85)
Source: Choueiri et al 2015[9]				

* Statistical testing of differences in baseline characteristics between groups was not included in the statistical analysis plan. VEGFR denotes vascular endothelial growth factor receptor.
† Race was self-reported.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.
§ The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk category was determined by the number of three factors (anaemia, hypercalcemia, and poor performance) that were present. Patients with zero factors had a favourable prognosis, patients with one factor had an intermediate prognosis, and patients with two or three factors had a poor prognosis.

4.6 Quality assessment of the relevant randomised controlled trials

METEOR was conducted in compliance with Good Clinical Practice (GCP) and the Declaration of Helsinki. Outcome assessments were all conducted in accordance with trial validated methodology.

Selection bias

Patients were randomised to treatment in a 1:1 ratio to receive cabozantinib or everolimus. Randomisation was stratified by the number of previous VEGFR-TKI treatments (1 or ≥2) and Memorial Sloan Kettering Cancer Center (MSKCC) risk group (favourable, intermediate, or poor) for previously treated patients.

Study treatment was assigned centrally with an interactive voice and web response system. Study personnel did not have access to the master list of blocks or block sizes. Patients and investigators were not masked to study treatment to allow appropriate management of adverse events.

Baseline characteristics of the two treatment groups were closely matched (see Table 12) supporting the fact that there was no bias in the selection of patients.

Performance bias

While the study used an open-label design, specific measures were taken to ensure that PFS and OS were rigorously evaluated:

- For the purposes of determination of the study endpoints of PFS and ORR a central Independent Review Committee (IRC) reviewed all available radiographic studies. The IRC was blinded to treatment identity and to clinical data that may lead to inadvertent unblinding.
- For the purpose of robust documentation of radiographic progression per IRC, investigators were encouraged, if any doubt or ambiguities existed, to continue study treatment, to repeat radiographic studies at the next scheduled time, and to delay determination of progression until the findings indicating progression were unequivocal per investigator assessment.
- Treatment in both study arms could continue beyond investigator-determined progression if the subject was receiving clinical benefit in the opinion of the investigator. Radiographic tumour assessments continued if treatment continued beyond investigator assessed progression. This had the benefit of providing radiographic studies for IRC review beyond investigator-determined progression, which helped reduce missing data arising from discordance between the investigator and the IRC about the date of progression.

Drop outs

There were no unexpected imbalances in the drop-outs between the groups.

Analysis

Analysis was performed using the following populations:

Primary Endpoint Intent-to-Treat Population

The Primary Endpoint Intent-to-Treat (PITT) population consisted of the first 375 randomised subjects. The PITT population was used to determine the primary endpoint (PFS) of the study. Analyses were performed according to the randomisation assignment.

Intent-to-Treat Population

The Intent-to-Treat (ITT) population, defined as all randomised subjects, was used for efficacy analyses (other than for the primary analysis of PFS), with analyses according to the randomisation assignment.

Quality Assessment in accordance with the NICE recommended checklist for RCT assessment of bias is provided in Table 13. Full details are provided in Appendix 6.

Table 13: Quality Assessment - METEOR study

	METEOR
Was randomisation carried out appropriately	Yes. Patients were randomised 1:1 ratio to receive cabozantinib or everolimus. Randomisation was stratified.
Was concealment of treatment allocation adequate?	Yes. Treatment allocation was concealed using an interactive voice and web response system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were care providers, participants and outcome assessors blind to treatment allocation?	No. This was an open-label study. Patients and investigators were not masked to study treatment to allow appropriate management of adverse events.
Were there any unexpected imbalances in drop-outs between groups?	No
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
How closely do the RCT(s) reflect routine clinical practice?	The baseline characteristics of patients in the trial reflect those patients likely to receive cabozantinib in clinical practice. The outcomes measured are relevant to clinical practice.
Source: Choueiri et al 2015[9]	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

The endpoints of the METEOR study relevant to the scope and decision problem are presented in this section. For PFS results for the PITT (first 375 randomised subjects) and ITT populations (all 658 randomised subjects) are presented. OS and ORR results are for the ITT population only.

Data cut offs are: 22 May 2015 for PFS and OR and 31 December 2015 for OS.

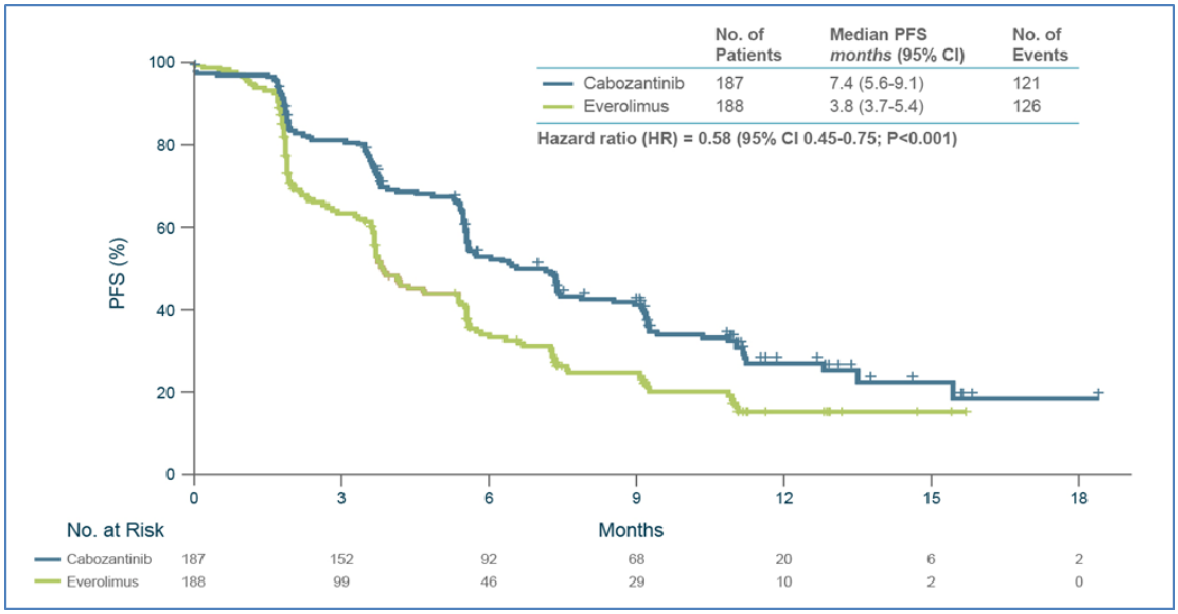
PFS - Primary Endpoint

PITT population

The study met its primary endpoint of prolonging the duration of PFS as assessed by an IRC.

PFS was significantly improved with cabozantinib compared to everolimus treatment with a median PFS of: 7.4 months vs. 3.8 months respectively (HR 0.58; 95% CI: 0.45 - 0.75; p-value <0.001) (Figure 11).

Figure 11: Kaplan-Meier estimates of PFS (PITT)

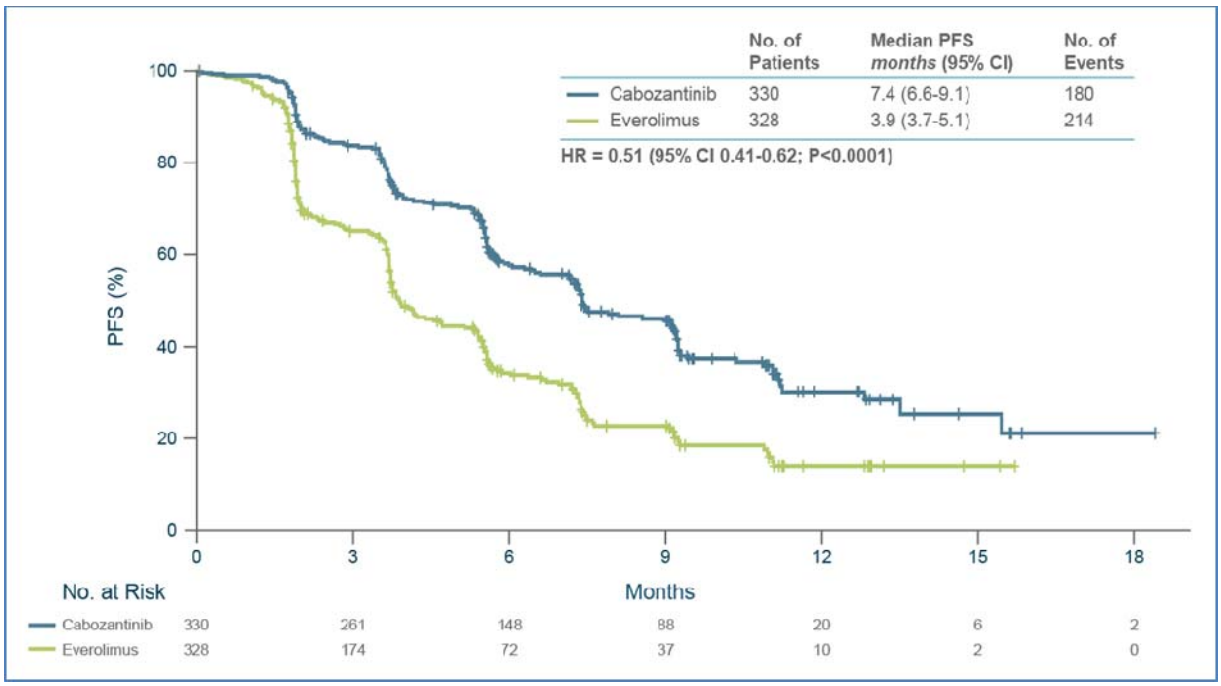


Source: Choueiri et al 2015[9]

ITT population

PFS results for the ITT population were consistent with those observed for the PITT population. Median PFS was 7.4 months in the cabozantinib arm vs. 3.9 months in the everolimus arm (HR 0.51; 95% CI: 0.41 - 0.62; p<0.0001) (Figure 12).

Figure 12: Kaplan-Meier estimates of PFS (ITT)



Source: Choueiri et al 2016[10]

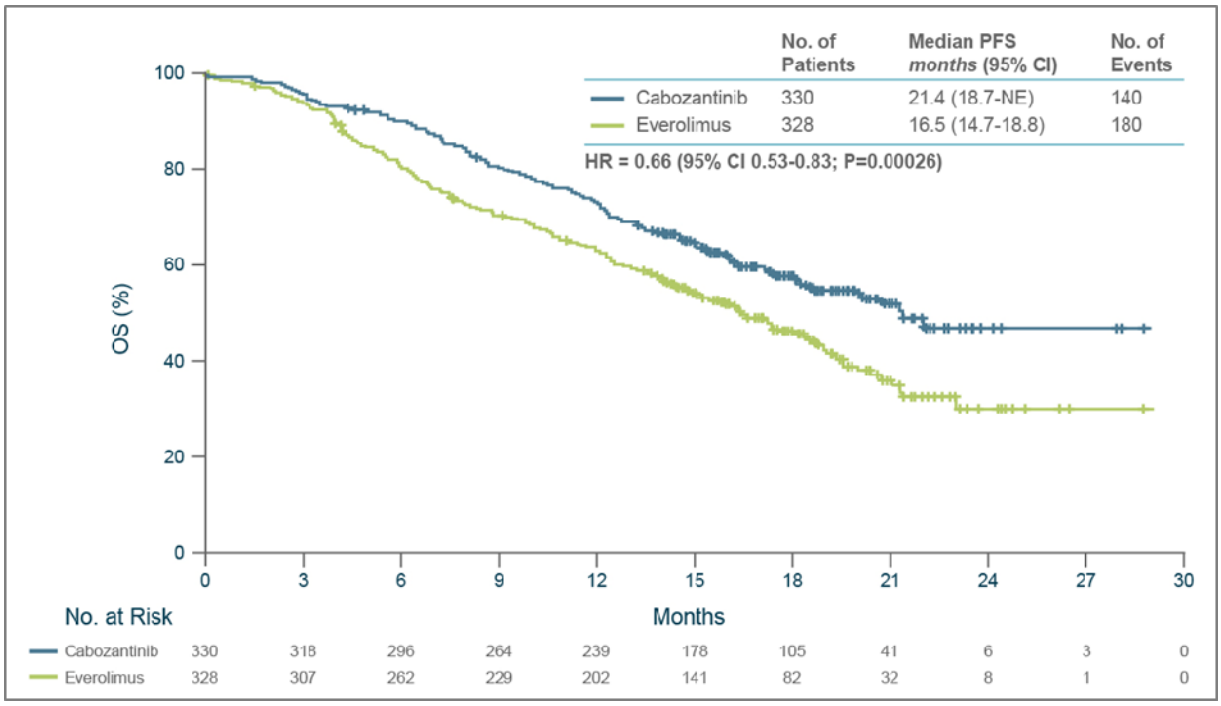
Secondary endpoints

Overall survival

As of 31 December 2015 the median duration of follow-up for OS was 18·7 months (interquartile range [IQR] 16·1–21·1) in the cabozantinib group and 18·8 months (IQR 16·0–21·2) in the everolimus group.

Treatment with cabozantinib significantly increased median OS by 4.9 months compared with that seen in patients treated with everolimus. Median OS was 21·4 months (95% CI 18·7–not estimable) in the cabozantinib group compared with 16·5 months (14·7–18·8) in the everolimus group [HR 0·66; 95% CI 0·53–0·83; p=0·00026] (Figure 13).

Figure 13: Kaplan-Meier estimates of overall survival (ITT)



Source: Choueiri et al 2016[10]

Kaplan-Meier landmark estimates at 6, 12, 18, and 24 months showed that at each timepoint the proportion of patients estimated to be alive was greater in the cabozantinib group compared with the everolimus group (48% versus 31% at 24 months) (Table 14).

Table 14: Kaplan-Meier landmark estimates

Landmark	Estimate of % of patients alive (95% CI)	
	Cabozantinib N=330	Everolimus N=328
6 months	91 (87-93)	81 (76-85)
12 months	73 (68-79)	63 (58-78)
18 months	58 (53-64)	47 (41-52)
24 months	48 (38-55)	31 (23-39)
Source: Choueiri et al 2016 (supplementary appendix)[45]		

Objective response rate

ORR was significantly improved with cabozantinib vs. everolimus. The number of patients who achieved an objective response (as per Independent Radiological Review) was 17% [95% CI 13–22] in the cabozantinib group and 3% [95% CI 2–6] in the everolimus group (p<0·0001) (Table 15).

Progressive disease was seen as best response in 12% of patients in the cabozantinib group and 27% of patients in the everolimus group (Table 15).

Median time to objective response (as per Independent Radiological Review) was 1.91 months (95% CI 1.6 - 11) in the cabozantinib treatment group compared with 2.14 months (95% CI 1.9 - 9.2 months) in the everolimus group.

Table 15: Tumour Response

	Cabozantinib N=330	**Everolimus N= 328**
ORR, % (95% CI)	17 (13-22)*	3 (2-6)
Complete response, n (%)	0	0
Partial response, n (%)	57 (17)	11 (3)
Stable disease, n (%)	216 (65)	203 (62)
Progressive disease, n (%)	41 (12)	88 (27)
Not evaluable or missing n (%)	16 (5)	26 (8)
Source: Choueiri et al 2016[10,45] p<0.001 compared to Everolimus		

Additional endpoint - Health related quality of life

Quality of life in the cabozantinib treatment group was comparable to that observed in the everolimus treatment group. Results for the specific quality of life questionnaires are provided below.

FKSI-19

Overall, there were no notable differences between treatment arms in the FKSI-total and three subscales of Disease-Related Symptoms (DRS)-Physical, DRS-Emotional, and Function/Well-Being (Table 16).

The FKSI-19 total score was similarly sustained in each arm over time: estimated mean change from baseline -3.48 cabozantinib vs. -2.21 everolimus

(Effect size [ES] difference -0.13). Scores at end of treatment (which were mainly due to progression) were ~7 points lower than baseline in each arm. On the Treatment Side Effects subscale, diarrhoea and nausea were worse for cabozantinib (ES -0.77 and -0.34, respectively) and shortness of breath was worse for everolimus (ES +0.30). Diarrhoea and nausea are frequent AEs for VEGFR-TKIs. No treatment differences were observed for the other three FKSI subscales (DRS-Physical, DRS-Emotional, Function/Well Being).

EQ-5D-5L

There were no clinically significant treatment differences in EuroQol (EQ)-visual analogue scale (VAS) or EQ-Index scores between the two treatment groups (**Error! Reference source not found.** and Table 17).

Table 16: Changes from Baseline in FKSI-19, Repeated Measures Analysis (ITT Population)

	Cabozantinib N = 330			Everolimus N = 328			Difference in Mean Change[a]	Pooled SD	p-value[a]	Effect Size[b]
	n	LSMean	SD	n	LSMean	SD				
DRS-Physical	[redacted]	-1.093	[redacted]	[redacted]	-1.386	[redacted]	[redacted]	[redacted]	[redacted]	0.046
Lack of energy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Short of breath	[redacted]	0.029	[redacted]	[redacted]	-0.271	[redacted]	[redacted]	[redacted]	[redacted]	0.295
Fevers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coughing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weak all over	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood in my urine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Good appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleeping well	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DRS-Emotional	[redacted]	0.398	[redacted]	[redacted]	0.393	[redacted]	[redacted]	[redacted]	[redacted]	0.004
Worry condition will worsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Side Effects (TSE)	[redacted]	-2.416	[redacted]	[redacted]	-0.814	[redacted]	[redacted]	[redacted]	[redacted]	-0.621
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.340

Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.767
Side effects of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Function/Well-Being (FWB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Able to work	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enjoy life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Content with quality life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Score	[redacted]	**-3.483**	[redacted]	[redacted]	**-2.214**	[redacted]	[redacted]	[redacted]	[redacted]	**-0.130**

Source: METEOR Clinical Study Report [44]
DRS, disease-related symptoms; FKSI, Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index; ITT, intent-to-treat; LSMean, least squares mean; SD, standard deviation.
A positive mean change (higher score) indicates improved health-related quality of life status.
[a] Derived from the prespecified repeated-measures mixed-effects model analysis of covariance for all measures.
[b] Effect size ≥ 0.5 (if applicable) is deemed clinically meaningful (Sloan et al 2005). Effect size = (treatment difference in mean change from baseline scores) / (pooled SD for both groups for baseline values).

Table 17: EQ VAS and EQ-5D-5L Index Scores: Change From Baseline, Repeated Measures Analysis

	Cabozantinib (N = 330) n LSMeans SD	Everolimus (N = 328) n LSMeans SD	Difference in Mean Change[a]	Pooled SD	p-value[a]	Effect Size[b]
VAS	[redacted] -1.32 [redacted]	[redacted] -1.27 [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Index Score	[redacted] -0.02 [redacted]	[redacted] -0.02 [redacted]	[redacted]	[redacted]	[redacted]	-0.009

Source: METEOR Clinical Study Report[44]
A higher score indicates better health-related quality of life.
[a] Derived from the prespecified repeated-measures mixed-effects model analysis of covariance for all measures.
[b] Effect size ≥ 0.5 (if applicable) is deemed clinically meaningful (Sloan et al 2005). Effect size = (treatment difference in mean change from baseline scores) / (pooled SD for both groups for baseline values).

4.8 Subgroup analysis

All pre-specified subgroups analysed showed consistently greater OS and PFS for patients in the cabozantinib treatment group compared with those in the everolimus treatment group (HR < 1) including those presenting with poor prognosis at baseline and those receiving cabozantinib second or third line. Further details for OS and PFS for subgroups specified in the scope are provided below with results for all the subgroups considered provided in Appendix 7.

Number and duration of prior VEGFR-TKI therapies.

Pre-specified analysis showed consistently greater OS compared with everolimus for patients in the cabozantinib treatment group who had received prior VEGFR-TKI treatment irrespective of the duration of the first VEGFR-TKI (Figure 14).

[redacted]

[redacted]

An additional post-hoc ITT subgroup analysis demonstrated OS benefit in the subgroup of subjects with:

- sunitinib as their only prior VEGFR –TKI (Median OS cabozantinib vs. sunitinib 21.4 months vs.16.5 months; HR 0.66, 95% CI: 0.47 - 0.93)
- pazopanib as their only prior VEGFR-TKI (Median OS cabozantinib vs. pazopanib 22.0 months vs.17.5 sunitinib; HR 0.66, 95% CI: 0.42 - 1.04)

Prognostic Score

The observed OS benefit was applicable to patients regardless of MSKCC or Heng risk category at baseline Table 18.

Table 18: OS by baseline risk group

	Cabozantinib		Everolimus		Median OS Cabozantinib vs. everolimus	HR (95% CI)
	n	**events**	**n**	**events**		
MSKCC Risk group						
0 (Favourable)	150	48	150	66	[redacted]	0.66 (0.46, 0.96)
1 (Intermediate)	139	64	135	79	[redacted]	0.67 (0.48, 0.94)
2 or 3 (Poor)	41	28	43	35	[redacted]	0.65 (0.39, 1.07)
IMDC (Heng) risk group						
0 (Favourable)	66	14	62	17	[redacted]	0.70 (0.34, 1.41)
1-2 (Intermediate)	210	89	214	121	[redacted]	0.65 (0.49, 0.85)
3-6 (Poor)	54	37	52	42	[redacted]	0.74 (0.48,1.15)

Key: NE, not estimable MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic RCC Data Consortium
Source: Choeuiri et al 2016[10], METEOR Clinical Study Report[44]

4.9 Meta-analysis

Not applicable. The evidence supporting the efficacy and safety of cabozantinib for the treatment of advanced RCC is provided by the METEOR study (see Sections 4.3 to 4.8 and Section 4.12).

4.10 Indirect and mixed treatment comparisons

In the absence of any head-to-head trials a NMA was conducted to compare cabozantinib with axitinib, nivolumab, and BSC in patients with advanced RCC who have progressed after previous VEGFR-TKI treatment. Nivolumab was included in the NMA in order that inputs could be generated for inclusion in the economic model and scenarios provided for cost-effectiveness analysis in the event of nivolumab receiving a positive NICE recommendation and as a result of this being available and used in clinical practice at the time cabozantinib is considered by the Appraisal Committee in January 2017.

4.10.1 Identification and selection of studies

A systematic literature review was designed to identify studies on cabozantinib and all other possible comparators in advanced RCC including everolimus, axitinib and nivolumab. The review was conducted from a global perspective and consequently included additional comparator treatments not specified in the decision problem.

The literature search was conducted on 3 June 2016 using the following relevant bibliographic databases:

- Medline (includes Medline in Process and other non-indexed citations with status: publisher, in-data review or Pubmed-not-Medline)
- Embase
- Cochrane Library (includes Cochrane Central Register of Controlled Trials, Cochrane Reviews, DARE, HTA Database, NHSEED)

The eligibility criteria applied to the initial systematic literature search are presented in Table 19. A copy of the search protocol is presented in full in Appendix 8.

Table 19: Summary of the review eligibility criteria

Category	Details
Population	Patients with renal cell cancer (advanced / metastatic, previously treated)
Intervention	Cabozantinib
Comparators	Everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib
Outcomes	• PFS • OS • Response rates • Drug discontinuation • Any other efficacy outcomes • Safety outcomes • Quality of life and other Patient-reported Outcomes • Biomarkers for efficacy and safety
Study Design	RCT
Language restrictions	None
OS – overall survival, PFS – progression-free survival, RCT – randomised controlled trial	

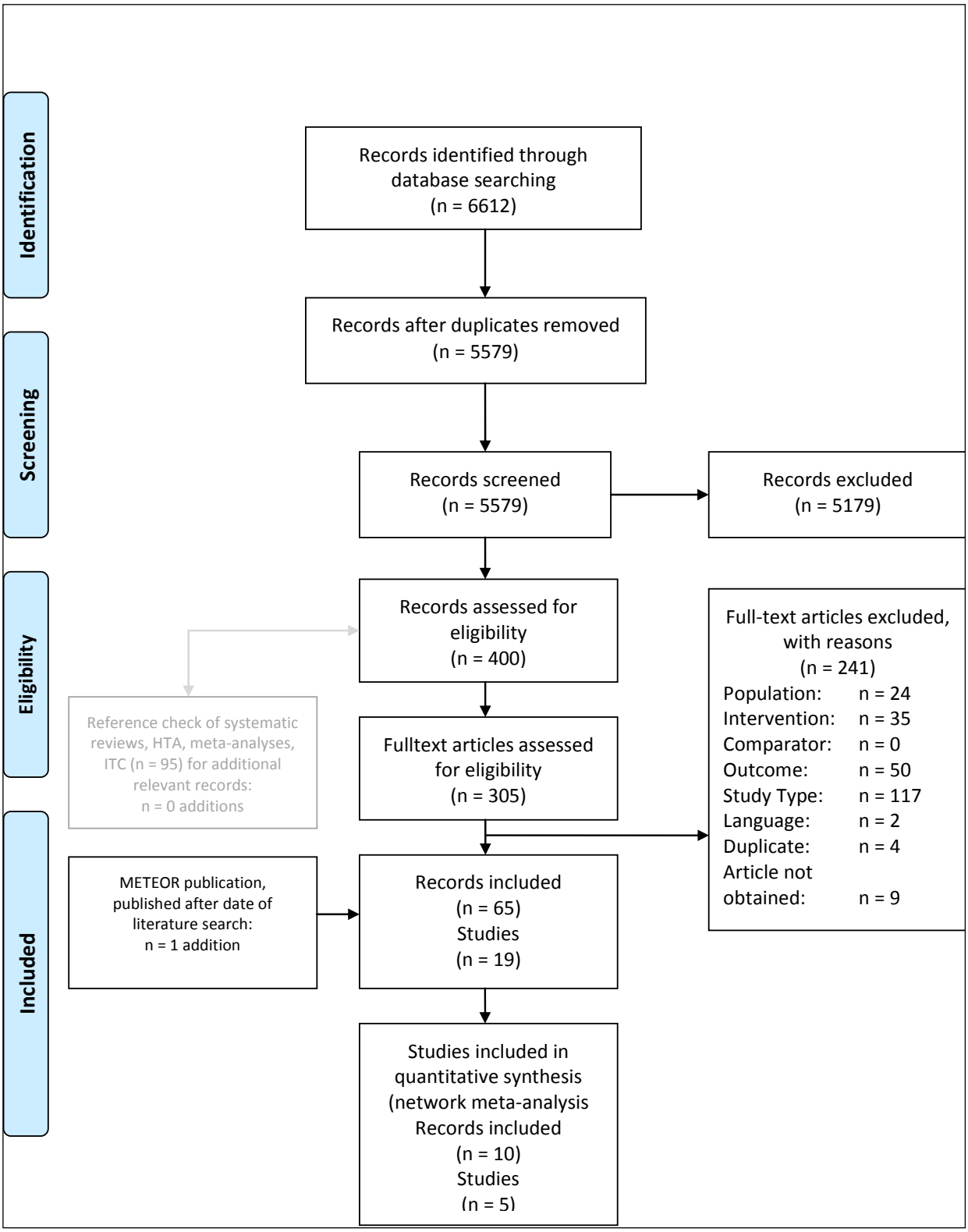
Each of the records identified during the initial search were assessed for relevance against predefined inclusion and exclusion criteria (Table 20). Copies of potentially relevant full papers were obtained and further selection was undertaken based on full text review. Double independent record selection was undertaken during the screening of titles/abstract as well as full texts, and discrepancies were resolved after discussion between reviewers or by a third reviewer.

Table 20: Summary of review inclusion and exclusion criteria

Clinical effectiveness	Inclusion Criteria	Exclusion Criteria
Population	Patients with previously treated advanced or metastatic renal cell carcinoma	Patients <18 years of age Healthy subjects Animal studies
Intervention	The following interventions in the second- (and further-) line setting: • Cabozantinib (Cabometyx®▼) • Axitinib (Inlyta®) • Everolimus (Afinitor®) • Sorafenib (Nexavar®) • Sunitinib (Sutent®) • Lenvatinib (Lenvima®) • Nivolumab (Opdivo®)	Interventions in the first-line setting
Comparators	Any, including placebo and BSC	Radiotherapy, surgery and other non-pharmaceutical treatments
Outcomes	• OS • PFS	• Patient-reported outcomes • Biomarker results • Safety results
Trial Design	• RCT • Systematic reviews, meta-analyses, HTAs were screened for bibliographies only	• Non-RCT • Comments, letters, editorials • Non-systematic reviews
Timeframe	All publication years	
Language restrictions	• English • French • German • Italian • Spanish	Publications with abstract in English but full text in language other than listed in inclusion criteria will not be included but listed.
OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial		

A PRISMA flow chart detailing the number of studies included and excluded at each stage of the review is shown in Figure 16.

Figure 15: PRISMA flow diagram of the literature search process



The systematic literature search retrieved 6,612 citations. After excluding duplicates (n=1,033) and screening against inclusion/exclusion criteria 5,179 titles/abstracts were excluded. Four hundred citations were found eligible for the screening on full-text level. Reference lists of these studies were checked for any further relevant studies. This process did not yield any additions. Of the 305 full-text articles 241 publications were excluded (Figure 16). In total, 65 publications, referring to 19 different studies, were included to be considered for potential inclusion into the NMA. Multiple publications reporting the same study were identified and grouped as associated references.

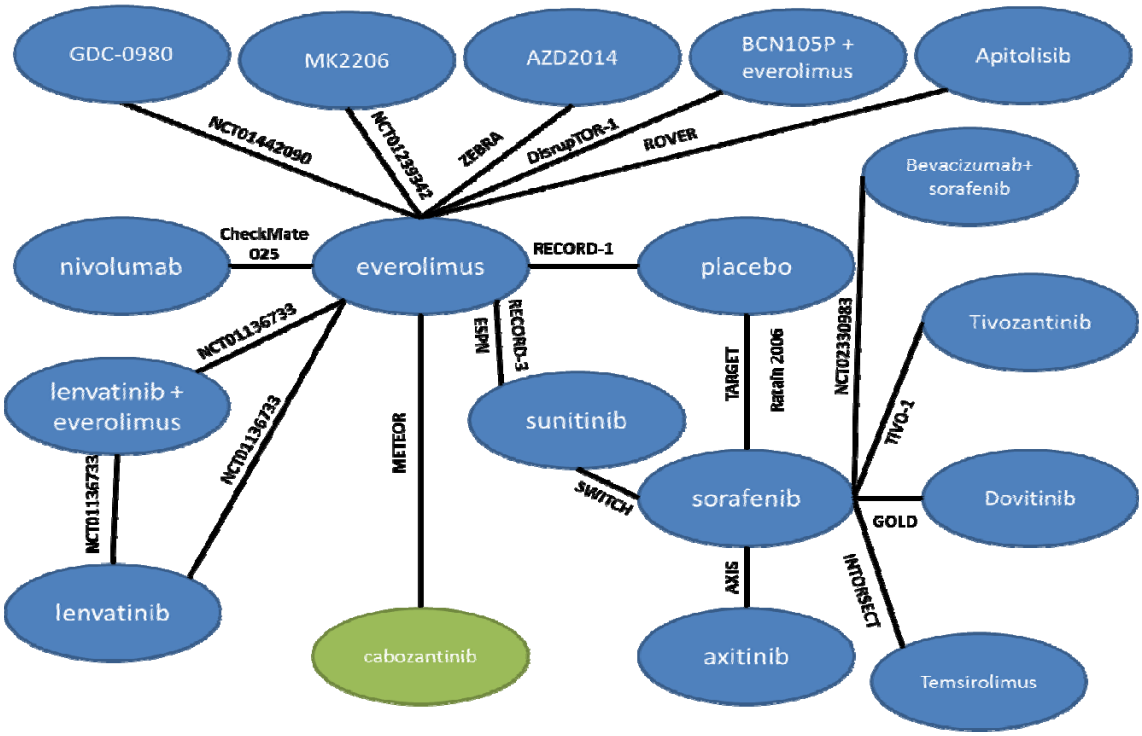
Summary of trials

In total 19 studies were identified for potential inclusion in the NMA, including studies on medicines outside of scope of the NICE appraisal (Table 21). The potential network developed from these studies is shown in Figure 16.

Table 21: Primary RCT data sources included in the network evidence base

Trial name	Treatment arms	Primary data source
METEOR	Cabozantinib vs. everolimus	Choueiri et al. 2016[10]
RECORD-1	Everolimus vs placebo/BSC	Motzer et al. 2010[46]
CheckMate025	Nivolumab vs everolimus	Motzer et al. 2015[8]
TARGET	Placebo vs sorafenib	Escudier et al. 2009[47]
AXIS	Axitinib vs sorafenib	Rini et al. 2011[48]
NCT01136733	Everolimus vs lenvatinib vs lenvatinib + everolimus	Motzer et al. 2015[49]
RECORD-3	Everolimus vs sunitinib	Motzer et al. 2014[50]
SWITCH	Sorafenib vs sunitinib	Eichelberg et al. 2012[51]
TIVO-1	Tivozanib vs sorafenib	Motzer et al. 2013[52]
DisrupTOR-1	Everolimus vs BNC105P+everolimus	Pal et al. 2015[53]
ESPN	Everolimus vs sunitinib	Tannir et al. 2014[54]
GOLD	Dovitinib vs sorafenib	Motzer et al. 2014[55]
INTORSECT	Temsirolimus vs sorafenib	Hutson et al. 2014[56]
ROVER	Apitolisib vs everolimus	Powles et al. 2016[57]
ZEBRA	AZD2014 Versus Everolimus	Powles et al. 2016[58]
NCT01239342	MK2206 versus everolimus	Jonasch et al. 2013[59]
NCT01442090	GDC-0980 versus everolimus	Powles et al. 2014[60]
NCT02330783	Bevacizumab+sorafenib vs sorafenib	Guo et al. 2015[61]
Ratain 2006	Sorafenib followed by sorafenib vs placebo	Ratain et al. 2006[62]
Key: BSC, best supportive care; vs, versus		

Figure 16: Primary evidence network for potential network meta-analysis



Since the NMA for this appraisal of cabozantinib only needed to include the comparators relevant to the decision problem: axitinib, everolimus, BSC and nivolumab, studies which did not include these comparators were therefore excluded unless they provided an intermediate link.

The following trials which did not contribute to the network were excluded: NCT01442090[60], NCT01239342 [59] ZEBRA[58] ,DusrupTOR-1[53], ROVER[57], NCT02330783[61], TIVO-1[52], GOLD[55], INTORSET[56], NCT01136733.[49]

A further four studies: RECORD-3[50] , SWITCH[51], ESPN[54] and a study reported by Ratain et al. 2006[62] were excluded for a number of methodological and /or reasons including sequential study design (Table 22).

Table 22: Key methodological and clinical reasons for further exclusions

Study	Key methodological and clinical parameters supporting exclusion
RECORD-3[50]	• Sequential design and hence randomisation only for first-line treatment • No PFS or OS data available for second line only
SWITCH[51]	• Sequential design and hence randomisation only for first-line treatment • Second line baseline characteristics not reported • No OS data for second line
ESPN[54]	• Only non-clear cell patients included • No blinding details available
Ratain 2006[62]	• No information on prior VEGFR therapies
PFS, progression-free survival; OS, overall survival; VEGFR, vascular endothelial growth factor receptor	

The studies included in the final evidence base utilised for the NMA are summarised in Table 23. Quality assessments of each study are provided in Appendix 9.

Table 23: Studies included in the final evidence base for indirect treatment comparison

Study name	Design	Population	Treatment arms	Primary endpoint
RECORD-1[46]	Phase 3 RCT Double-blind Cross over	Adult patients with clear cell mRCC who had documentation of progressive disease during or within 6 months of stopping sunitinib and/or sorafenib (prior therapy with cytokines and/or VEGF inhibitors also permitted)	Everolimus Placebo	PFS
CheckMate[8]	Phase 3 RCT Open-label Parallel group	Adult patients with clear cell mRCC who had progressed after one or two previous regimens of antiangiogenic therapy	Nivolumab Everolimus	OS
TARGET[47]	Phase 3 RCT Double-blind Cross over	Adult patients with clear cell mRCC which had progressed after one systemic treatment within the previous 8 months not including VEGFR pathway inhibitors	Sorafenib Placebo	OS
AXIS[48]	Phase 3 RCT Double blind Parallel group	Adult patients with clear cell mRCC who had progressed despite first-line systemic therapy (Sunitinib, bevacizumab plus interferon-alfa, temsirolimus or cytokines)	Axitinib Sorafenib	PFS
Key: RCT, randomised controlled trial; mRCC, metastatic renal cell carcinoma; PFS, progression-free survival; OS, overall survival				

4.10.2 Network meta-analysis

Clinical efficacy

The NMA was planned primarily on two efficacy endpoints: OS and PFS. These represent key outcomes of interest to clinicians and patients and are consistently selected as primary and secondary efficacy endpoints in RCC trials. The outputs of the NMA for these efficacy endpoints are utilised in the health economics analysis presented in Section 5.

In order to assess the feasibility of performing an NMA, data availability for OS and PFS HRs and Kaplan-Meier curves were first assessed (see Table 24).

For OS ITT and cross-over results (in those trials where cross-over was present) were identified.

PFS as measured by an independent review committee (IRC) was prioritised over investigator assessment of disease progression. Investigator assessed PFS was only considered when IRC-assessed PFS was not available.

Time to treatment discontinuation

The cost-effectiveness model described in Section 5 also required time to treatment discontinuation (TTD) estimates. Due to this requirement the identified trials were screened to identify median treatment duration data and TTD Kaplan-Meier (KM) curves.

Manufacturer submissions for previous NICE STAs for RCC (see Table 5) were also reviewed for TTD data, as often KM curves are not available in published clinical literature identified through systematic literature searches. The results for TTD endpoint are shown in Table 25.

Table 24: Availability of OS and PFS HR and KM plots

	OS ITT		OS Cross-over adjusted		PFS Independent review committee		PFS Investigator assessed	
	HR (95% CI)	**KM source in reference**	**HR (95% CI)**	**KM source in reference**	**HR (95% CI)**	**KM source in reference**	**HR (95% CI)**	**KM source in reference**
RECORD-1	0.87 (0.65, 1.15) [46]	Figure 6A [46]	0.60 (0.22, 1.65)	Figure 5	0.30 (0.22, 0.40)	Figure 2	Not applicable, IRC PFS available	Not applicable, IRC PFS available
CheckMate025	0.73 (0.57, 0.93)[8]	Figure 1[8]	Not applicable	Not applicable	Not available	Not available	0.88 (0.75, 1.03)[8]	Figure 2B
TARGET	0.88 (0.74, 1.04)[47]	Figure1A[47]	0.78 (0.62, 0.97)[47]	Figure 1B[47]	0.44 (0.35, 0.55)[63]	Figure 2C [63]	Not applicable, IRC PFS available	Not applicable, IRC PFS available
AXIS**	0·997 (0.78, 1.27)[11]	Figure 2B[11]	Not applicable	Not applicable	0.741 (0.573-0.958)[48]	Figure 2C[48]	Not applicable, IRC PFS available	Not applicable, IRC PFS available

Key: OS, overall survival; ITT, intent to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier.
Note: ** prior-sunitinib group results reported.
Sources: [46] Motzer et al. 2010, [64] Korhonen et al. 2012, [35] Motzer et al. 2008, [8]Motzer et al. 2015, [47]Escudier et al. 2009, [63] Escudier et al. 2007, [11]Motzer et al. 2013, [48]Rini et al. 2011,

Table 25: Availability of time on treatment data

	Time on treatment	
	Median treatment duration	**KM source in reference**
RECORD-1	Everolimus: 141 days[46] Placebo: 60 days[46]	Not available
CheckMate025	Nivolumab: 5.5. months[8] Everolimus: 3.7 months[8]	Figure 39 [26]
TARGET	Sorafenib: 25.6 weeks[47] Placebo: 15.7 weeks[47]	Not available
AXIS**	Axitinib: 6.4 months[11] Sorafenib: 5.0 months[11]	Not available
Key: OS, overall survival; ITT, intent to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier. **Note**: ** prior-sunitinib group results reported. **Sources**: [46] Motzer et al. 2010, [8] Motzer et al. 2015, [47] Escudier et al. 2009, [11] Motzer et al. 2013, [26] NICE STA in development [GID-TA10037] Manufacturer submission. 2016.		

Included trial populations

A key consideration for any NMA is whether the studies identified are suitably homogeneous to facilitate a reliable comparison. This similarity comparison is achieved by comparing selected data from candidate studies (with covariates that act as relative treatment effect modifiers needing to be similar across trials).[65] The similarity of the studies in each network was assessed based on:

- Study design
- Prior therapies and prognostic score at baseline (Table 26)

In addition the availability of subgroup results for PFS and OS endpoints was also assessed Table 26.

Table 26: Assessment of similarity between identified studies and availability of outcomes and subgroup results

	Study type	Prior therapies	Prognostic score (MSKCC)	Subgroup results available by
METEOR[10]	Phase 3 RCT Double blind Open-label Parallel group	1 prior VEGFR Cabozantinib: 71% Everolimus: 70% 2+ prior VEGFR Cabozantinib: 29% Everolimus: 30%	Favourable: 43-44% Intermediate: 40-43% Poor: 14-16% Missing: 0%	Patient level data available
RECORD-1[46]	Phase 3 RCT Double blind Cross-over	1 prior VEGFR Everolimus: 74% Placebo: 74% 2+ prior VEGFR Everolimus: 26% Placebo: 26%	Favourable: 28-29% Intermediate: 56-57% Poor: 14-15% Missing: 0%	Prognostic score: Yes Type of prior therapies: Number of prior therapies: No Cross-over adjusted: Yes
CheckMate025[8]	Phase 3 RCT Double blind Open-label Parallel group	1 prior VEGFR[28] Nivolumab: 72% Everolimus: 72% 2 prior VEGFR Nivolumab: 28% Everolimus: 28%	Favourable: 35-36% Intermediate: 49% Poor: 15-16% Missing: 0%	Prognostic score: Yes Type of prior therapies: No Number of prior therapies: Yes* Cross-over adjusted: NA
TARGET[47]	Phase 3 RCT Double blind Cross-over	No prior VEGFR therapy was received among patients.	Favourable: 45-53%[29] Intermediate: 47-55%[29] Poor: NR Missing: NR	Prognostic score: No Type of prior therapies: No Number of prior therapies: No Cross-over adjusted: Yes
AXIS[48]	Phase 3 RCT Double blind Parallel group	1 prior treatment**	Favourable: 28% Intermediate: 36-37% Poor: 33% Missing: 2-3%	Prognostic score: No Type of prior therapies: Yes*** Number of prior therapies: No Cross-over adjusted: NA

Key: BSC, best supportive care; RCT, randomised controlled trial; PFS, progression free survival; IRC, independent review committee assessed; INV; investigator assessed; vs, versus; NA, not applicable; NR, not reported.

*KM plot available in Nivolumab NICE appraisal, Company response to clarification questions.Appendix A8, Figure 2-5 on page 301-304.
**All patients received one previous systemic first-line regimen (sunitinib-based, bevacizumab plus interferon-alfa-based, temsirolimus-based, or cytokine based regimen) prior to study drug. 35% of patients received cytokine-based regimes.
***Subgroup is available by type of prior therapy (e.g. Sunitinib as first line treatment).

The final networks utilised in the NMA, based on the review of available data, are presented in Figure 17 and Figure 18.

Figure 17: Evidence network for OS, PFS

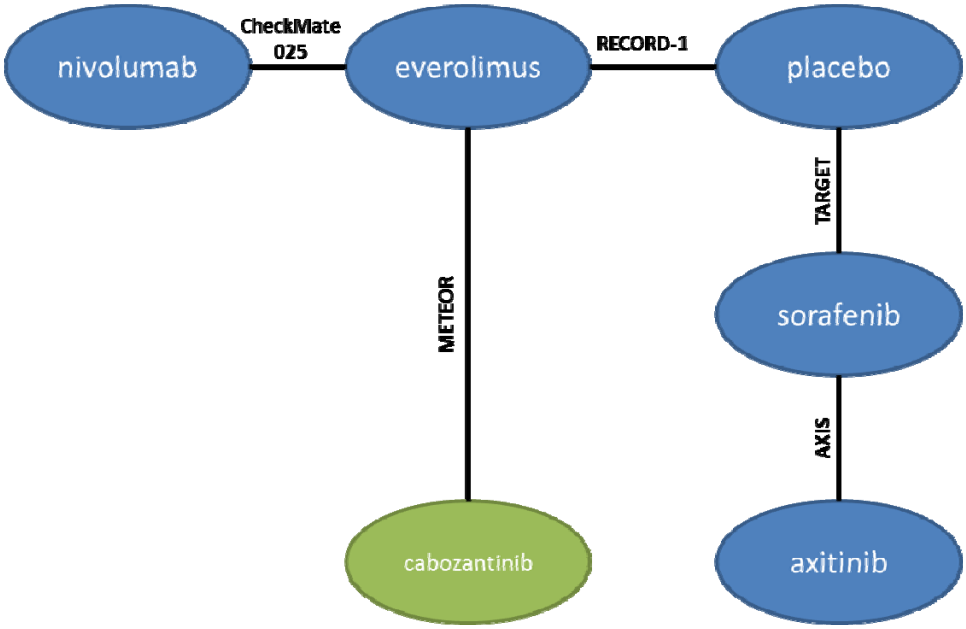
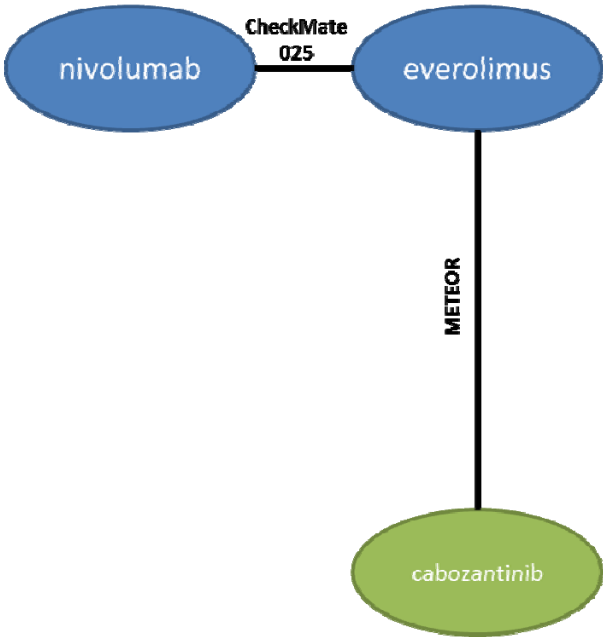


Figure 18: Evidence network for TTD



Differences between included trial populations

There were considerable differences between the included trials. The main sources of difference were presence/absence of cross-over design, number/type of prior therapies and baseline prognostic scores (Table 26). Each of these factors is discussed in more detail below. Summary tables with information on study design, and OS and PFS results are provided in Appendix 9.

Cross-over study design

In both the RECORD-1 and TARGET trials cross-over was allowed.

In the RECORD-1 trial, the OS HR for everolimus vs. placebo (BSC) was estimated at 0.87 [0.65, 1.17] in the ITT population and 0.60 [0.22, 1.65] once adjusted for cross-over using the rank-preserving structural failure time (RPSFT) model published by Korhonen et al.[66] The RPSFT model relies on assumption of constant effect of active treatment (everolimus) in terms of relative survival time; hence the effect does not depend on when active treatment was initiated. Since this method requires additional censoring of patient data the precision of the HR estimate is lower than that for the ITT estimate. However, the method was shown to be preferable to simple adjustments, such as censoring of patients at time of crossover. [66] It should be noted that one other possible approach to adjust for study cross-over was considered by Hollaender in the RECORD-1 trial, using inverse probability of censoring weights and multivariate Cox models (HR = 0.47 [0.27, 0.82]).[67] This method however relies on a strong (and un-testable) assumption of no unmeasured confounders, therefore for the purpose of the NMA the estimated HR using the RPSFT model were chosen.

In the TARGET study, an analysis with censoring of placebo-assigned patients who crossed over to sorafenib at the start of cross-over was conducted in addition to the ITT analysis. [47] The adjustment methodology is simple censoring of all cross-over patients.

Use of cross-over adjusted OS was deemed feasible for the NMA as data is available from both the RECORD-1 and TARGET studies and was used in the base case analysis in line with the DSU Technical Support Document 16 (Treatment Switching)[68] which recommends the use of treatment switching adjustment methods. ITT population results for OS were used in a scenario analysis.

Type and number of prior therapies

Trials included in the NMA varied with regard to the number of allowed prior therapies, the distribution of previous therapies in patient cohorts and also the availability of results for subgroups of patients by prior therapy (Table 26).

Previous therapies

In the METEOR study patients were included in the study if they had received at least one previous VEGFR-TKI (there was no limit to the number of previous treatments). In CheckMate025 patients were eligible to participate if they had received one or two previous regimens of antiangiogenic therapy. In RECORD-1, previous therapy with sorafenib, sunitinib or both was allowed. The TARGET study included patients if they had progressed after one systemic treatment within the previous 8 months. AXIS study patients had received one previous systemic first line regimen with a sunitinib-based, bevacizumab plus interferon-alfa-based, temsirolimus-based, or cytokine based regimen, which reflected regimens with regulatory approvals at the time of the study design. In the NMA the prior-sunitinib population was included as this was considered more comparable than prior cytokine-based regimens.

For CheckMate025, results stratified by number of prior therapies received were reported in the ongoing nivolumab NICE STA although results were not reported by type of prior therapies.[26] For RECORD-1 stratified estimates were available for PFS, but not OS. In the TARGET study publication no subgroup data were identified that stratified results by number/type of prior therapies. The AXIS study reported results by type of first-line therapy.

Evidence available on the number of previous therapies received from the METEOR, CheckMate025, RECORD-1, and AXIS studies are reported in Table 27, Table 28, Table 29, and Table 30.

Table 27: Subgroup results – number of previous therapies received (METEOR)

Number of VEGFR-TKIs	PFS Choueiri et al. 2016[10]		OS Choueiri et al. 2016[10]	
	HR	95% CI	HR	95% CI
1	0.52	0.41–0.66	0.65	0.50–0.85
≥2	0.51	0.35–0.74	0.73	0.48–1.10

Table 28: Subgroup results – number of previous therapies received (CheckMate025)

Number of VEGFR-TKIs	PFS		OS Motzer et al. 2015[8]	
	HR	95% CI	HR	95% CI
1	-	-	0.71	0.56–0.90
2	-	-	0.89	0.61–1.29

Table 29: Subgroup results – number of previous therapies received (RECORD-1)

Number of VEGFR-TKIs	PFS Motzer et al. 2008[35]		OS	
	HR	95% CI	HR	95% CI
Sorafenib only	0.29	-	-	-
Sunitinib only	0.30	-	-	-
Both	0.28	-	-	-

Table 30: Subgroup results – number of previous therapies received (AXIS)

Number of VEGFR-TKIs	PFS Rini et al. 2011[48]		OS Motzer et al. 2013[11]	
	HR	95% CI	HR	95% CI
Sunitinib-containing regimen	0.741	0.574–0.958	0.997	0.782–1.270
Bevacizumab-containing regimen	1.147	0.573–2.295	Not reported	Not reported
Temsirolimus-containing regimen	0.595	0.188–1.886	Not reported	Not reported
Cytokine-containing regimen	0.462	0.318–0.673	0.813	0.555–1.191

Due to lack of consistency and availability of results across all trials in the network, was is not possible to analyse results by prior therapy.

Initial prognosis as a potential modifier of relative efficacy

Within the identified trials MSKCC prognosis was commonly used to stratify PFS (METEOR, RECORD-1 and AXIS) or OS (METEOR and CheckMate025) estimates. The TARGET trial did not include any patients with poor MSKCC prognosis and no subgroup analysis was presented by MSKCC prognosis. No subgroup result was identified for initial prognosis from the AXIS study.

An overview of identified HRs by prognosis is shown in Table 31 and availability of HR and Kaplan-Meier data across clinical studies is provided in Appendix 9.

Availability of HR and Kaplan-Meier data across the studies did not allow for recreating a NMA for particular prognosis (poor/intermediate/favourable) based on HRs or Kaplan-Meier plots.

Study quality assessment

Complete quality assessments of each clinical trial carried out by two assessors are provided in Appendix 9.

Table 31: Subgroup results – availability of HR results by prognostic score

End point	Study	Comparator	Baseline	HR for poor prognosis [95% CI]	HR for intermediate prognosis [95% CI]	HR for favourable prognosis [95% CI]
OS	CheckMate025[8]	Nivolumab	Everolimus	0.47 [0.30, 0.73]	0.76 [0.58, 0.99]	0.89 [0.59, 1.32]
OS	METEOR[10]	Cabozantinib	Everolimus	0.65 [0.39, 1.07]	0.67 [0.48, 0.94]	0.66 [0.46, 0.96]
PFS	AXIS[48]	Axitinib	Sorafenib	0.68 [0.49, 0.94]	0.80 [0.58, 1.10]	0.50 [0.33, 0.76]
PFS	RECORD-1[46]	Everolimus	Placebo	0.44 [0.22, 0.85]	0.32 [0.22, 0.44]	0.31 [0.19, 0.50]
PFS	METEOR[10]	Cabozantinib	Everolimus	0.70 [0.42, 1.16]	0.47 [0.35, 0.62]	0.51 [0.38, 0.69]

Key: OS, overall survival; PFS, progression free survival, CI, confidence interval

Sources: [8]Motzer et al 2015, [10]Choueiri et al 2016, [48]Rini et al 2011, [46]Motzer et al 2010

Risk of bias

Demographic and baseline characteristics were assessed to be balanced between the treatment arms in all included studies. Randomisation was carried out appropriately in two of the five studies (METEOR and AXIS) while for the remaining studies (TARGET, RECORD-1 and CheckMate025) there was insufficient information available to conclude that randomisation was carried out appropriately.

None of the studies reported unexpected dropouts between study groups. All five studies reported ITT analysis and appropriate methods to account for missing data.

A potential risk of bias arises from investigators, participants and outcome assessors not being blind to treatment allocation in all studies. Blinding is not always possible, however. There were studies that were not double blinded:

- METEOR: Patients and investigators were not blinded to study treatment. A masked independent radiology committee assessed progression-free survival, overall survival, tumour response, duration of response, and changes on bone scans.
- AXIS: This was an open-label study. Progression-free survival and objective response rate were assessed by a masked independent radiology review.
- CheckMate025: This was an open-label study.

Blinding of outcome assessors can be especially important for assessment of subjective outcomes.

4.10.3 Network meta-analysis methodology

Choice of method

In the NMA two potential methods were considered for comparing OS and PFS endpoints: one based on the HRs and the other on the parametric curves (Kaplan-Meier). Data availability for the identified studies showed that an NMA based on both the HR and parametric curves would be feasible (Table 24). However, an NMA based on the HRs would need to assume that the

proportional hazard (PH) assumption holds for each pair of comparators. When the PH assumption is violated the HR parameters change over time and the use of constant HR is not preferable in such cases. The first step in confirming the best method to use in the NMA was to digitally extract the information from the relevant Kaplan-Meier plots applying the algorithm from Guyot et al [70] and re-generating the patient-level data to test whether the proportional hazards assumption was violated.

NMAs based on parametric curves do not assume proportional hazards between the pairwise comparators and as such this method can be applied to any survival function for which transitivity of treatment effects in the NMA model can be shown.

Tests for proportional hazards

For time-to-event outcomes such as PFS and OS, typically a NMA based on the HR is employed. The proportional hazards assumption is often implausible, and for this reason an assessment of proportional hazards assumption was carried out. The Kaplan-Meier curves in the five selected studies were digitally extracted with DigitizeIt software.[69] For each treatment, the patient level data including event or censor time, the number of patients at that time, the number of deaths and the number of patients censored during the time interval were re-created by applying the method published in Guyot et al. 2012.[70] The reconstructed data were then used as inputs for the NMA models. The data regeneration was executed in programming language R.[71]

Table 32 shows the Kaplan-Meier plots that were digitalised for each study for the PFS and OS endpoints. The proportional hazards assumption only held across the pairwise comparisons in METEOR, RECORD-1 and AXIS.

For the TTD analysis, Figure 39 from the manufacturer submission for the ongoing NICE appraisal of nivolumab for the treatment of metastatic RCC [GID-TA10037][26] was digitalised (see Figure 19).

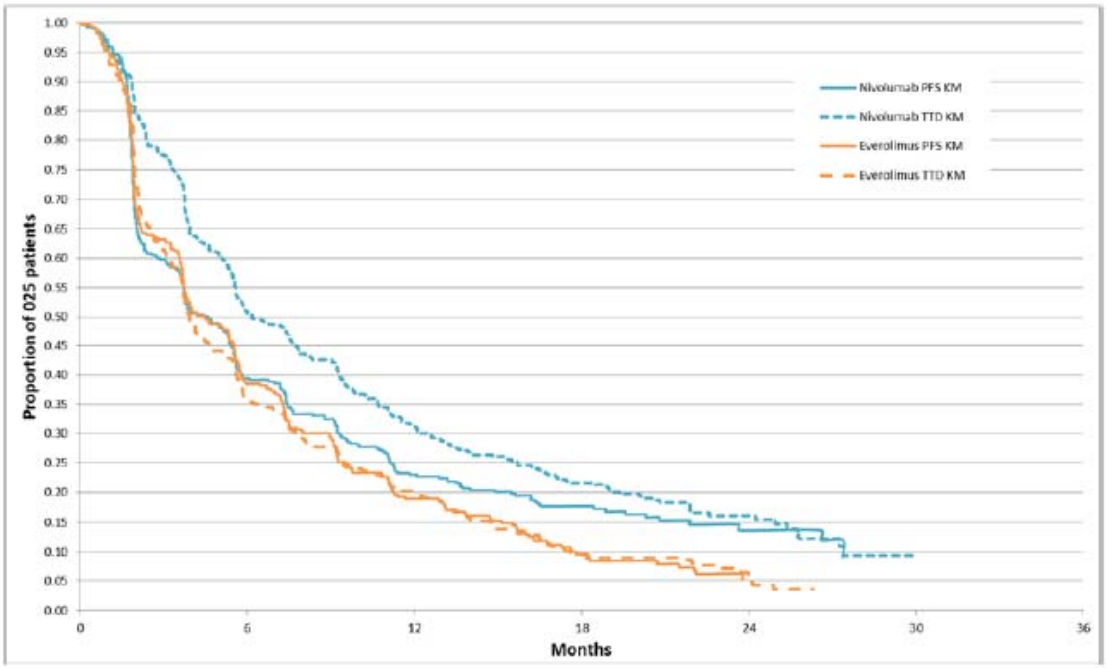
Details of the programming code for testing proportional hazards assumption and associated results are provided in Appendix 10.

Table 32: Sources of digitalised curves for each study (OS, PFS)

	Base case cross-over adjustment		Sensitivity analysis ITT		Proportional hazards assumption holds?		
Study Name	**OS**	**PFS**	**OS**	**PFS**	**OS**	**PFS**	**Comments**
METEOR	Patient level data				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).
RECORD-1	Figure 5 [64]	Figure 2 [35]	Figure 6A [46]	Figure 2 [35]	Yes	Yes	
CheckMate025	Figure 1 [8]	0.88 (0.75, 1.03) [8]	Figure 1 [8]	Figure 2B [8]	No	No	
TARGET	Figure 1B [47]	Figure 2C [63]	Figure 1A [47]	Figure 2C [11]	No	No	
AXIS	Figure 2B [11]	Figure 2C [48]	Figure 2B [11]	Figure 2C [48]	Yes	Yes	

[64]Korhonen 2012, 46·Motzer et al 2010, [8]. Motzer et al 2015, [47]. Escudier 2009, [48]. Rini et al 2011, [35]. Motzer et al 2009, [11]. Motzer et al 2013

Figure 19: Nivolumab KM PFS and TTD data, CheckMate025



Key: KM, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

Source; Figure 39 from BMS submission. Nivolumab NICE appraisal [GID-TA10037][26]

4.10.4 Network meta-analysis of parametric survival curves

Rationale for choice of method

Based on the results of the PH test, it was concluded that an NMA based on parametric curves was a more suitable method than that based on HRs given that the PH assumption does not hold for the TARGET and CheckMate025 studies. For this reason, an NMA method based on parametric survival models was chosen and implemented as described by Ouwens et al. 2010.[72]

Introduction to method

The Bayesian NMA was implemented with five parametric survival functions: log-normal, log-logistic, Weibull, Gompertz and exponential distributions, on the PFS or OS data. Generalised gamma distribution was not implemented due to the inaccessibility of the incomplete gamma function, required to compute the hazard rate function, under Winbugs.

Consistency and transitivity test

In the analysis, transitivity was used as an underlying model assumption to ensure both direct and indirect comparisons of survival curves across trials based on a common comparator. The transitivity property was tested for each survival distribution, as detailed in Appendix 11.

Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method using WinBUGs[73] run for 50,000 iterations with the first 25,000 iterations discarded as “burn-in”. Convergence of the chains was checked with help of the Gelman-Rubin statistic. [74]

Fixed and random effects models were considered for this analysis. Random effects models were tested for the purpose of heterogeneity checking.

Programming code

Appendix 12 includes the codes used in the programming of the parametric survival curve NMA.

Presentation of analysis

After digitally extracting the Kaplan-Meier curves for PFS and OS, the patient level data including survival probabilities over time and median survival times for each treatment were re-created applying the method published in Guyot et al. (2012)[70].

Each survival function used a specific underlying hazard function over time, h(t), as follows:

$$h(t) = \begin{cases} \lambda\gamma t^{\gamma-1}, & \text{for Weibull model,} \\ a\,exp(bt), & \text{for Gompertz model,} \\ \dfrac{abt^{b-1}}{1+at^{b}}, & \text{for log-logistic model,} \\ \dfrac{\varphi\left[-\dfrac{log(t)-\alpha}{\beta}\right]}{\beta t\Phi\left[-\dfrac{log(t)-\alpha}{\beta}\right]}, & \text{for log-normal model,} \\ \lambda, & \text{for Exponential model.} \end{cases}$$

where φ and Φ are the density and the cumulative distribution of standard normal distribution.

The digitised PFS or OS curves, S(t), from the identified studies were parameterised using the following five underlying survival functions over time:

$$S(t) = \begin{cases} \exp(-\lambda t^{\gamma}), & \text{for Weibull distribution,} \\ \exp\left(-\dfrac{a}{b}(\exp(bt)-1)\right), & \text{for Gompertz distribution,} \\ \dfrac{1}{1+at^{b}}, & \text{for log-logistic distribution,} \\ \Phi\left[-\dfrac{\log(t)-\alpha}{\beta}\right], & \text{for log-normal distribution,} \\ \exp(-\lambda t), & \text{for Exponential distribution,} \end{cases}$$

where Φ is the cumulative distribution of the standard normal distribution.

The algorithm of the NMA, presented in equation (1) in Appendix 12 could be programmed since the explicit formulas for hazard functions were available. The MCMC algorithm, presented in Appendix 12 was applied to estimate the parameters of the NMA model, i.e. parameters μ for the "baseline" treatment as well as those μ+δ for the other treatments relative to the "baseline" treatment.

The survival functions were then estimated based on the posterior mean/median of those parameters, specific for treatments.

4.10.5 Results of the analysis

Heterogeneity

Given the limitation in the available data, heterogeneity could not be tested specifically by contrast, but only at the network level. Additional random effects (RE) models were run for both OS and PFS and compared with the fixed effects (FE) models for data fitting in terms of DIC and residual deviance. RE models provided almost identical results to the FE models (Table 33 and Table 34). Full details of the RE models are provided in Appendix 13.

Table 33: Model fit statistics with OS

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Residual deviance (*Dbar)*	4364.9	4364.8	4443.8	4344.0	4314.5	4314.3	4293.8	4293.4	4535.8	4536.3
Effective number of parmeters (p^D)	20.0	19.7	19.6	20.1	20.0	19.9	20.2	19.8	9.8	10.2
Deviance information criteria (*DIC*)	4384.9	4384.5	4463.4	4464.1	4334.5	4334.2	4314.0	4313.2	4545.6	4546.5
Key: FR, fixed effects; RE, random effects										

Table 34: Model fit statistics with PFS

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Residual deviance (*Dbar)*	6355.8	6355.3	6456.8	6456.3	6047.7	6047.9	5987.3	5987.0	6599.7	6600.1
Effective number of parmeters (p^D)	19.7	20.0	19.8	19.8	19.9	19.9	20.2	19.9	9.9	10.2
Deviance information criteria (*DIC*)	6375.5	6375.3	6476.6	6476.1	6067.6	6067.8	6007.5	6006.9	6609.6	6610.3
Key: FE, fixed effects; RE, random effects										

Choice of model

Fixed-effects models were considered for this analysis due to lack of heterogeneity on pairwise comparisons. There was only one trial comparing the same two treatments and, therefore, the estimation of between trial heterogeneity was confounded with the estimation of treatment effect. It was not possible to investigate measures of heterogeneity in this treatment network. Furthermore, when RE models were estimated, these gave almost identical results to the FE model.

In conclusion fixed effect models provided as good estimates as random effect models but were more stable, faster to run and provided good data fit.

Parameter estimates from the NMA

Estimates of parameters of each survival curve (Weibull, Gompertz, log-logistic, log-normal and exponential) based on the FE model are presented in Table 35 and estimations for the parameter for the TTD curve based on the FE model are presented in Table 36. Model fit statistics are presented in Table 37 and Table 38, with deviance information criterion (DIC) used to indicate the best fitting model. Networks are adjusted to the baseline of the METEOR study.

Expected OS curves and expected PFS curves in the following 24 months based on the estimated parameters are provided in Appendix 14.

Table 35: Parameter estimates of Weibull, Gompertz, log-logistic, log-normal and Exponential distributions for fixed effects NMA

		OS		PFS	
Weibull	**Distribution parameters**	**Scale λ**	**Shape γ**	**Scale λ**	**Shape γ**
	Everolimus	0.015	1.365	0.087	1.317
	Cabozantinib	0.007	1.498	0.036	1.418
	Nivolumab	0.005	1.628	0.100	1.168
	Placebo	0.014	1.635	0.208	1.635
	Sorafenib	0.016	1.388	0.053	2.088
	Axitinib	0.015	1.427	0.043	2.015
Gompertz	**Distribution parameters**	**Shape a**	**Scale b**	**Shape a**	**Scale b**
	Everolimus	0.029	0.041	0.140	0.027
	Cabozantinib	0.018	0.048	0.065	0.060
	Nivolumab	0.017	0.067	0.151	-0.013
	Placebo	0.026	0.143	0.279	0.249
	Sorafenib	0.027	0.085	0.104	0.364
	Axitinib	0.028	0.083	0.079	0.364
Log-logistic	**Distribution parameters**	**Scale a**	**Shape b**	**Scale a**	**Shape b**
	Everolimus	0.011	1.631	0.057	1.968
	Cabozantinib	0.005	1.725	0.024	1.825
	Nivolumab	0.003	1.982	0.064	1.778
	Placebo	0.014	1.761	0.095	3.033
	Sorafenib	0.013	1.586	0.011	3.373
	Axitinib	0.010	1.698	0.010	2.875
Log-normal	**Distribution parameters**	**Location μ**	**Scale σ**	**Location μ**	**Scale σ**
	Everolimus	2.792	1.077	1.482	0.858
	Cabozantinib	3.130	1.030	2.058	0.942
	Nivolumab	3.033	0.918	1.620	0.933
	Placebo	2.442	1.032	0.851	0.591
	Sorafenib	2.760	1.131	1.310	0.572
	Axitinib	2.756	1.029	1.594	0.660
Exponential	**Distribution parameters**	**Rate λ**		**Rate λ**	
	Everolimus	0.042		0.155	
	Cabozantinib	0.029		0.086	
	Nivolumab	0.032		0.130	
	Placebo	0.057		0.372	
	Sorafenib	0.041		0.234	
	Axitinib	0.041		0.173	

Table 36: Parameter estimates of TTD for fixed effects NMA

		TTD	
Weibull	**Distribution parameters**	**Scale λ**	**Shape γ**
	Everolimus	0.115	1.087
	Cabozantinib	0.03558511	1.297
	Nivolumab	0.079	1.061
Gompertz	**Distribution parameters**	**Shape a**	**Scale b**
	Everolimus	0.149	-0.010
	Cabozantinib	0.064	0.025
	Nivolumab	0.1000	-0.012
Log-logistic	**Distribution parameters**	**Scale a**	**Shape b**
	Everolimus	0.056	1.850
	Cabozantinib	0.020	1.7840
	Nivolumab	0.038	1.6550
Log-normal	**Distribution parameters**	**Location μ**	**Scale σ**
	Everolimus	1.602	0.8912153
	Cabozantinib	2.194	0.943
	Nivolumab	1.995	1.0000
Exponential	**Distribution parameters**	**Rate λ**	
	Everolimus	0.141	
	Cabozantinib	0.077	
	Nivolumab	0.091	

The model fit statistics for the fixed effects model are presented in Table 37 and Table 38. The goodness-of-fit of the model prediction to the observed IPD was measured by computing the posterior mean residual deviance, Dbar.[75] The DIC was used to compare different fixed effects models and provided a measure of model fit that penalised model complexity according to Spiegelhalter et al., 2002[73].

$$\begin{cases} DIC = Dbar + pD \\ pD = Dbar - Dhat \end{cases}$$

pD is the effective number of parameters and Dhat is the deviance evaluated at the posterior mean of the model parameters.

Table 37. Model fit statistics (PFS and OS)

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS
Residual deviance (*Dbar*)	4364.9	6355.8	4443.8	6456.8	4314.5	6047.7	4293.8	5987.3	4535.8	6599.7
Effective number of parameters (*pD*)	20.0	19.7	19.6	19.8	20	19.9	20.2	20.2	9.8	9.9
Deviance information criteria (*DIC*)	4384.9	6375.5	4463.4	6476.6	4334.5	6067.6	4314	6007.5	4545.6	6609.6

Table 38. Model fit statistics (TTD)

Model fit statistics	Weibull	Gompertz	Log-logistic	Log-normal	Exponential
Residual deviance (*Dbar*)	2761.2	2767.1	2638.9	2597.5	2775.6
Effective number of parameters (*pD*)	7.6	7.7	7.8	7.8	4.0
Deviance information criteria (*DIC*)	2768.8	2774.8	2646.7	2605.3	2779.6

The model with the lowest DIC in this case the log-normal fixed effects model provided the best data fit (Figure 20 to Figure 22). Modelled estimates suggest that cabozantinib offers superior OS and PFS benefits compared to axitinib, BSC (represented by placebo) and nivolumab. Median PFS and OS figures based on the log-normal functions are provided in Table 39. The results demonstrate that cabozantinib compared with each of the comparators improves OS and PFS.

Figure 20: Averaged OS adjusted to the baseline from METEOR study, fixed effects (Log-normal)

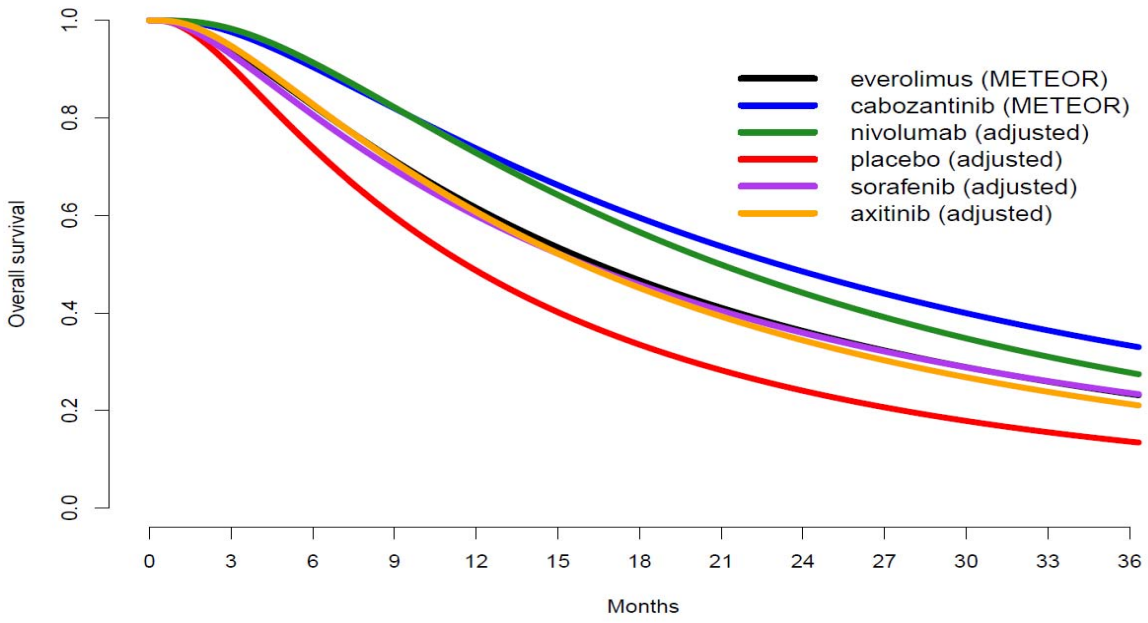


Figure 21: Averaged PFS adjusted to the baseline from METEOR study, fixed effects (Log-normal)

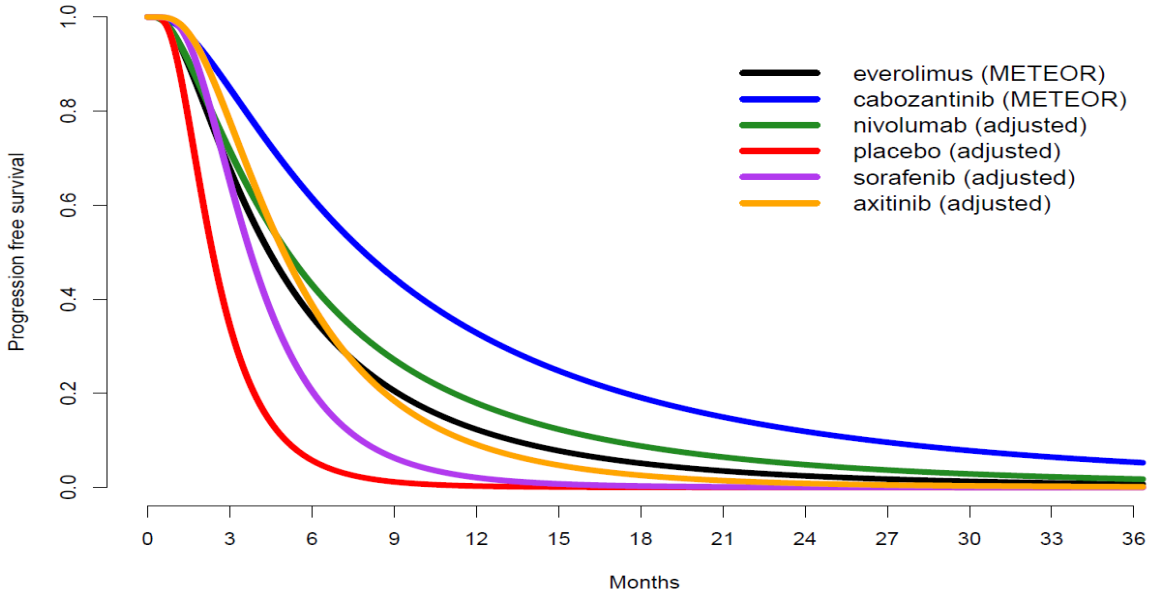


Table 39: Median OS and PFS results based on the Log-normal function

	NMA result - lognormal function	
	Median OS (months)	**Median PFS (months)**
Cabozantinib	22.9	7.8
Axitinib	15.7	4.9
Everolimus	16.3	4.4
BSC	11.5	2.4
Nivolumab	20.8	5.1
Key: OS, overall survival; PFS, progression free survival; BSC, best supportive care		

Results for TTD are provided in Figure 23 and Table 40. TTD was longer with cabozantinib compared with everolimus and nivolumab (9 months vs. 5 months and 7.4 months respectively).

Figure 22: Averaged TTD adjusted to the baseline from METEOR study, fixed effects (lognormal)

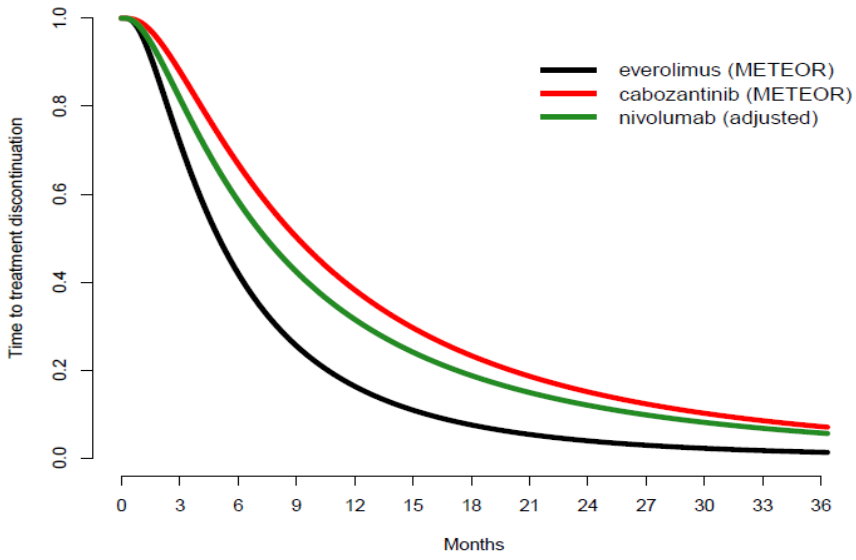


Table 40: Median TTD results based on the Log-normal function

	Median TTD (months)
Cabozantinib	9.0
Everolimus	5.0
Nivolumab	7.4
Key: TTD, time to treatment discontinuation	

The model parameter estimates and their estimates of covariance for fixed effects NMA are shown in Appendix 15.

Sensitivity analyses

Analyses on the ITT (un-adjusted) OS population has been conducted and the results are presented in Appendix 16.

4.11 Non-randomised and non-controlled evidence

Not applicable.

4.12 Adverse reactions

Safety data are presented from the METEOR study for the 31 December 2015 data cut-off.

Treatment exposure

The median duration of exposure was 8·3 months in patients given cabozantinib and 4·4 months in patients given everolimus (Table 41). Dose reductions occurred for 62% of patients in the cabozantinib group and 25% of patients in the everolimus group. The median daily dose was 43 mg for cabozantinib and 9 mg for everolimus.

Table 41: Exposure and dose reductions (safety population)

	Cabozantinib N=331	Everolimus N=322
Median duration of exposure, months	8.3 (IQR 4.2-14.6)	4.4 (IQR 1.9-86)
Median average daily dose	43 mg (IQR 36-56)	9 mg (IQR 7-10)
Any dose reduction % (n)	62 (206)	25 (80)
Discontinuation due to adverse event not associated with RCC, %(n)	12 (40)	11 (34)
Source: Choueiri et al 2016[10] IQR, Interquartile range		

Adverse events

The adverse events observed with cabozantinib were consistent with those reported by other VEGFR-TKI treatment options for advanced RCC. In the case of cabozantinib, they were managed with supportive care and dose modifications, which were effective in limiting or preventing treatment-associated discontinuations.

The most common AEs in the cabozantinib treatment group compared with the everolimus treatment group were diarrhoea (75% vs. 28%), fatigue (59% vs. 47%), nausea (52% vs. 30%), decreased appetite (47% vs. 36%) and palmar-plantar erythrodysaesthesia syndrome (42% vs. 6%) (Table 42). The majority of these events were manageable by reducing treatment dose. The most frequent adverse reactions leading to permanent discontinuation in patients treated with cabozantinib were decreased appetite and fatigue.

AEs of grade 3 or 4 were reported in 71% and 60% of the cabozantinib and everolimus patients, respectively (Table 42). The most common grade 3/4 AEs (cabozantinib vs. everolimus) were hypertension (15% vs. 4%), diarrhoea (13% vs. 2%), fatigue (11% vs. 7%), PPES (8% vs. 1%), while anaemia was reported more frequently with everolimus (6% vs. 17%) (Table 42).

Table 42: Adverse events reported as Grade 1-2 in ≥10% in either treatment arm

	Cabozantinib (N=331)			Everolimus (N=322)		
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Any adverse event	70 (21%)	210 (63%)	25 (8%)	103 (32%)	167 (52%)	26 (8%)
Diarrhoea	206 (62%)	43 (13%)	0	85 (26%)	7 (2%)	0
Fatigue	159 (48%)	36 (11%)	0	130 (40%)	24 (7%)	0
Nausea	158 (48%)	15 (5%)	0	92 (29%)	1 (<1%)	0
Decreased appetite	146 (44%)	10 (3%)	0	111 (35%)	3 (1%)	0
Palmar-plantar erythrodysaesthesia syndrome	115 (35%)	27 (8%)	0	16 (5%)	3 (1%)	0
Vomiting	106 (32%)	7 (2%)	0	44 (14%)	3 (1%)	0
Weight decreased	105 (32%)	9 (3%)	0	42 (13%)	0	0
Constipation	89 (27%)	1 (<1%)	0	64 (20%)	1 (<1%)	0
Dysgeusia	80 (24%)	0	0	30 (9%)	0	0
Hypothyroidism	76 (23%)	0	0	1 (<1%)	1 (<1%)	0

Hypertension	73 (22%)	49 (15%)	0	14 (4%)	12 (4%)	0
Dysphonia	68 (21%)	2 (1%)	0	16 (5%)	0	0
Cough	67 (20%)	1 (<1%)	0	107 (33%)	3 (1%)	0
Stomatitis	65 (20%)	8 (2%)	0	71 (22%)	7 (2%)	0
Mucosal inflammation	60 (18%)	5 (2%)	0	64 (20%)	10 (3%)	1 (<1%)
Dyspnoea	56 (17%)	10 (3%)	0	82 (26%)	11 (3%)	3 (1%)
Aspartate aminotransferase increased	55 (17%)	5 (2%)	0	19 (6%)	1 (<1%)	0
Back pain	54 (16%)	8 (2%)	0	41 (13%)	7 (2%)	0
Rash	52 (16%)	2 (1%)	0	92 (29%)	2 (1%)	0
Asthenia	49 (15%)	15 (5%)	0	46 (14%)	8 (2%)	0
Abdominal pain	48 (15%)	12 (4%)	0	27 (8%)	5 (2%)	0
Alanine aminotransferase increased	47 (14%)	7 (2%)	1 (<1%)	20 (6%)	1 (<1%)	0
Pain in extremity	46 (14%)	5 (2%)	0	31 (10%)	1 (<1%)	0
Muscle spasms	45 (14%)	0	0	17 (5%)	0	0
Arthralgia	43 (13%)	1 (<1%)	0	46 (14%)	4 (1%)	0
Headache	43 (13%)	1 (<1%)	0	42 (13%)	1 (<1%)	0
Anaemia	42 (13%)	19 (6%)	0	73 (23%)	53 (17%)	0
Dizziness	41 (12%)	1 (<1%)	0	21 (7%)	0	0
Dyspepsia	40 (12%)	1 (<1%)	0	15 (5%)	0	0
Oedema peripheral	39 (12%)	0	0	70 (22%)	6 (2%)	0
Hypomagnesaemia	38 (12%)	6 (2%)	10 (3%)	5 (2%)	0	0
Dry skin	37 (11%)	0	0	35 (11%)	0	0
Proteinuria	37 (11%)	8 (2%)	0	28 (9%)	2 (1%)	0
Flatulence	33 (10%)	0	0	7 (2%)	0	0
Insomnia	32 (10%)	0	0	33 (10%)	1 (<1%)	0
Pyrexia	31 (9%)	3 (1%)	0	57 (18%)	2 (1%)	0
Pruritus	27 (8%)	0	0	48 (15%)	1 (<1%)	0
Blood creatinine increased	17 (5%)	1 (<1%)	0	39 (12%)	0	0
Hypertriglyceridaemia	17 (5%)	4 (1%)	0	31 (10%)	7 (2%)	3 (1%)
Hyperglycaemia	15 (5%)	2 (1%)	1 (<1%)	46 (14%)	16 (5%)	0
Epistaxis	14 (4%)	0	0	46 (14%)	0	0

Source: Choueiri et al 2016[10]

Adverse events that were reported as grade 1–2 in at least 10% of the patients in either study group are shown, irrespective of whether the event was considered by the investigator to be related to the study treatment.

Serious AEs

The incidence of serious AEs of grade 3 or higher was comparable between both treatment arms (39% for cabozantinib and 40% for everolimus) despite two-fold longer exposure to cabozantinib; none resulted in death (Table 43). Most common serious AEs reported in at least 2% of patients in either treatment group were abdominal pain, pleural effusion, diarrhoea, nausea, anaemia, dyspnoea, pneumonia, dehydration and pneumonitis (Table 43).

Deaths

A total of 51 deaths (Grade 5 AEs) were reported during the adverse event reporting period the majority of which were due to disease progression. Three deaths assessed as treatment-related occurred: one in the cabozantinib treatment arm and two in the everolimus treatment arm (Table 43).

Table 43: Grade ≥ 3 serious adverse events

	Cabozantinib (n=331)	**Everolimus (n=322)**
Grade ≥3 serious adverse events, n (%)	130 (39)	129 (40)
Most common Grade ≥3 serious adverse events, n (%)		
Abdominal pain	9 (3)	3 (1)
Pleural effusion	8 (2)	7 (2)
Pneumonia	7 (2)	13 (4)
Pulmonary embolism	7 (2)	1 (<1)
Anaemia	5 (2)	10 (3)
Dyspnoea	4 (1)	10 (3)
Deaths during the adverse event reporting period, n (%)*	26 (8)	25 (8)
Deaths assessed as treatment-related	1 (not otherwise specified)	2 (one aspergillus infection and one pneumonia aspiration)
Source: Adapted from Choueiri et al 2016[10] * Grade 5 AEs were classified as deaths		

4.13 Interpretation of clinical effectiveness and safety evidence

Cabozantinib is the first multi-targeted therapy to demonstrate significant improvement, versus an active comparator (everolimus), across all three key efficacy endpoints (OS, PFS, ORR) for patients with advanced RCC who have had prior VEGFR-targeted therapy

The evidence base consists of a single Phase 3, international, randomised, active-controlled study, the METEOR study, which compared cabozantinib with everolimus in patients with advanced RCC who had received at least one prior VEGFR-TKI.

The study population enrolled is reflective of the broader patient population eligible to receive cabozantinib in clinical practice.

In METEOR, cabozantinib significantly improved median OS by 4.9 months (OS 21.4 months vs. 16.5 months, cabozantinib vs. everolimus, HR 0.66; 95%CI 0.53-0.83; p=0.00026).

Cabozantinib treatment also resulted in improved median PFS (HR 0·51; 95% CI 0·41–0·62; p<0·0001) and ORR (17% [13–22] with cabozantinib vs. 3% [2–6] with everolimus, p<0·0001).

Efficacy (OS and PFS) in pre-specified subgroups was consistent with that observed for the whole population, including the subgroups defined by the pre-stratification factors: MSKCC risk group and number of previous VEGFR-TKIs.

Although the METEOR study was not blinded, the study results are robust and did not arise from bias. The primary PFS endpoint and the secondary ORR endpoint were assessed by an IRC blinded to study treatment. In addition, OS is an objective endpoint that is not subject to investigator or independent interpretation.

Quality of life

Quality of life was maintained with cabozantinib compared with everolimus. No clinically significant differences in health related quality of life measures (EQ-5D-5L) or in FKSI treatment side-effect scores were seen.

Side effect profile

The adverse events observed with cabozantinib were consistent with those reported by other VEGFR-TKI treatment options for advanced RCC. In the case of cabozantinib, they were managed with supportive care, dose interruptions and dose modifications, which were effective in limiting or preventing treatment-associated discontinuations. Furthermore, the serious adverse events of grade $\geq$ 3 had similar frequency as those observed with everolimus (39% vs. 40%), despite an almost two-fold longer exposure to cabozantinib.

As an oral, once-daily treatment, cabozantinib is easy to administer and offers convenience for both patients and clinicians as it can be taken at home, with any dose modifications managed remotely. No change in current management arrangements or infrastucture for units is required.

Indirect comparison data

In order to compare cabozantinib with the other comparators included in the decision problem and in the absence of direct head-to head trials a NMA was conducted. The NMA demonstrated a superior OS and PFS benefit of cabozantinib compared with axitinib (standard of care), everolimus and BSC. A superior OS and PFS benefit of cabozantinib compared with nivolumab was also demonstrated. Accepting that there is uncertainty associated with the NMA due to heterogeneity across the trials and paucity of available data for all the endpoints considered (OS, PFS and TTD) the approach taken was designed to minimise uncertainty.

Strengths and limitations of the clinical evidence base

Strengths

The METEOR study provides a robust evidence base for the efficacy and safety of cabozantinib for treatment of patients with advanced RCC who have received prior VEGFR-TKI therapy in clinical practice.

The trial is well designed with recognised and accepted endpoints.

- PFS is an acceptable endpoint in situations where it is expected that further lines of treatment with an effect on OS may hamper the detection of a relevant treatment effect on OS.

- OS is considered to be the most reliable endpoint in late-stage oncology trials.

- ORR is also an accepted endpoint and a measure of antitumour activity.

The open-label design enabled appropriate dose modifications for AEs in both arms. To prevent bias, the IRC was blinded to treatment and to clinical data that may lead to inadvertent unblinding.

The trial population is reflective of patients presenting for subsequent-line treatment for advanced RCC in UK clinical practice. Approximately 50% (320) of patients were enrolled in Europe.

Significant improvement across all three key efficacy endpoints (OS, PFS and ORR) was demonstrated for cabozantinib compared with everolimus for patients with advanced RCC with prior VEGFR-targeted therapy with this benefit observed across all pre-determined subgroups. Cabozantinib is the first multi-targeted therapy to demonstrate significant improvement across all three key efficacy endpoints (OS, PFS, ORR) versus an active comparator in patients with advanced RCC who have had prior VEGFR-targeted therapy.

Limitations

There are no direct head-to-head studies comparing cabozantinib with the other comparators listed in the scope and as a result a NMA was performed. As stated above the approach taken was designed to minimise uncertainty.

The NMA results were presented to clinical experts who validated the findings for cabozantinib compared with axitinib and BSC.

End of life treatment considerations

The life expectancy of patients with advanced RCC is historically poor and the relative 5-year survival rate is approximately one in ten[5]. The current standard of care treatment options of axitinib and everolimus are associated with median OS estimates of approximately 16 months (15.7 months for axitinib based on NMA outputs and 16.5 months for everolimus based on the METEOR clinical trial)

Head-to-head trial data from the METEOR study demonstrate an extension to life of over 4.9 months with cabozantinib treatment compared with everolimus (HR for death: 0.66; 95% CI 0.53 - 0.83; p<0.00026). Superior OS benefit is estimated in the NMA with results demonstrating that cabozantinib extends life by:

- 7.2 months compared with axitinib
- 6.6 months compared with everolimus
- 11.4 months compared with BSC
- 2.1 months compared with nivolumab

The expected number of patients with advanced RCC is 3,048 of whom 34% are eligible for second line treatment (see Section 3.2).

Table 44: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median life expectancy: <24 months with axitinib the established standard of care[11] and everolimus[35] 11.5 months with BSC (From NMA see Section 4.10.5, Table 39)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median survival times Cabozantinib: 21.4 months (METEOR)[10] Axitinib: 15.7 months (NMA) Everolimus: 16.5 months (METEOR)[10] Difference: 4.9 to 5.7 months
The treatment is licensed or otherwise indicated for small patient populations	Anticipated advanced RCC population 2017:3,048 Number of patients who have failed on prior treatment:1,037

4.14 Ongoing studies

No additional evidence to support the use of cabozantinib for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGFR)-targeted therapy is anticipated within the next 12 months.

5 Cost effectiveness

In line with the final scope, the economic model includes nivolumab; however at the decision problem meeting Ipsen were advised that, as the appraisal of nivolumab is still ongoing and nivolumab is not yet established standard of care, it is not a current or relevant comparator. As stated in Section 1.1 nivolumab has been retained in the decision problem with the view that, if recommended, nivolumab will be used in clinical practice at the time cabozantinib is considered by the Appraisal Committee.

5.1 Published cost-effectiveness studies

A systematic review of previous cost-effectiveness analyses in advanced RCC was performed.

Identification of studies

The following databases were searched on 7 July 2016:

- Medline (includes Medline in Process and other non-indexed citations with status: publisher, in-data review or Pubmed-not-Medline)
- Embase
- NHS Economic Evaluation Database, HTA Database

All searches were conducted for the 2006 – 2016 publication period. The timeframe of the search was restricted to start from 2006 based on an HTA report published by the Peninsula Technology Assessment Group (PenTAG) in 2008 in which they did not identify any publications with relevant information before 2006.[76.77] In addition, the NICE website was searched for Evidence Review Group reports, manufacturer submissions and other relevant documents for appraisals of medicines for second-line metastatic RCC. See Appendix 17 for details of the search strategy. Details of inclusion and exclusion criteria are provided in Table 45.

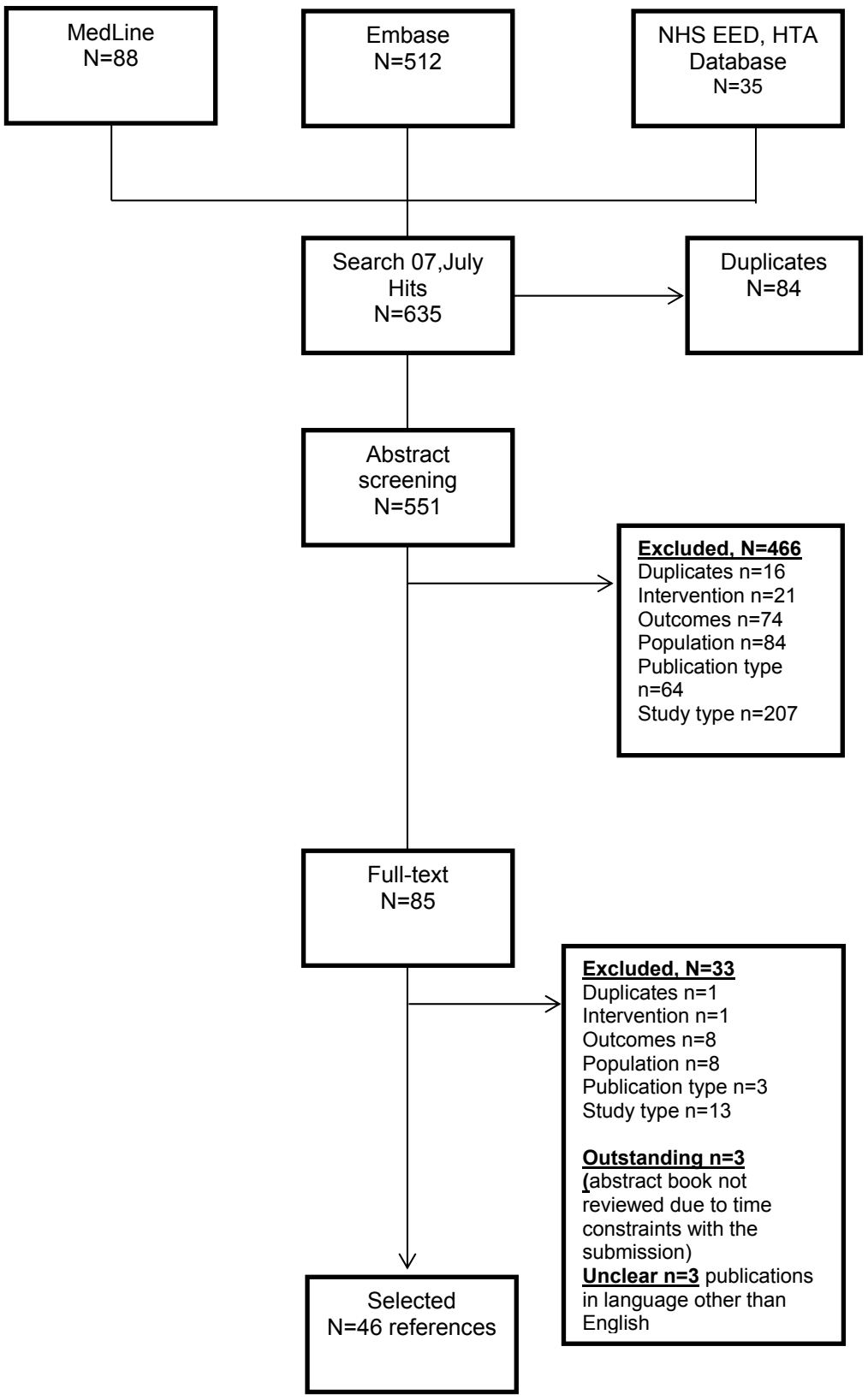
Table 45: Cost effectiveness search inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients with RCC (advanced / metastatic, previously treated)	Animal studies, paediatric population and other indications
Intervention	Cabozantinib, everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib, BSC	Other non-pharmacological therapies
Comparator	Cabozantinib, everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib, BSC	As above
Outcomes	Cost-effectiveness Methods and Results (e.g. total costs, costs per life year gained, costs per QALY gained, ICER, ICUR)	Other outcomes
Study design	Cost-effectiveness /cost-utility studies	-
Language	No restrictions. English, German, French, Spanish and Italian (publications in other languages will be listed, and only abstracts in English included)	-
Publication type	Full-text publications, conference proceedings	Mere animal studies Letter, Editorial, Notes, Historical article
Key: BSC, best supportive care; QALY quality adjusted life year; ICER, incremental cost effectiveness ratio, ICUR, incremental cost utility ratio		

Data were extracted into the summary tables by a reviewer. Uncertainties were resolved following discussion with a second reviewer.

In total, 635 papers were identified through the electronic searches. Upon removal of 84 duplicates, 551 abstracts were reviewed. Of these, 466 were excluded and 85 included on abstract level. Review of the full-text publication resulted in exclusion of 33 studies, with 46 publications included in final selection, 3 publications were published in languages other than English and 3 were abstract books (Figure 23). Out of the 46 included publications, there were 20 European studies (9 full-text articles, 8 conference abstracts and 3 HTA reports), 9 systematic reviews and 17 analyses for countries not in Europe.

Figure 23: Flow diagram for the systematic review of published cost-effectiveness studies



Description of identified studies

Out of the 46 included publications, there were 20 European studies (8 full-text articles, 8 conference abstracts and 4 HTA reports). The rest were either systematic reviews or analyses conducted outside of Europe. Data from the full-text European articles (8) were extracted. The 8 extracted full-text publications assessed various interventions, included assessments of zoledronic acid, sunitinib for second-line treatment, sorafenib, everolimus and axitinib in comparison with placebo or BSC in the treatment of mRCC patients. Three of the studies were original assessments from a UK perspective.[77,78,79] Further details on these studies are provided below with summary details of the eight publications and the three HTA reports provided in Appendix 18.

Botteman et al. found in 2011 that the bisphosphonate zoledronic acid (ZOL) saved costs and increased quality-adjusted life years (QALYs) compared to placebo in French, German, and UK RCC patients with bone metastases. ZOL improved QALYs gained by 0.1575 compared to placebo with an increment of costs of €2,636 in the UK. The cost per QALY was estimated to be -€4,566. [78]

Hoyle et al. (2010)[79] used a Markov model to conclude in 2010 that compared to BSC, sorafenib treatment resulted in a QALY gain but costs were well above the willingness-to-pay (WTP) threshold of £30,000 per QALY:

- Gain of 0.27 QALYs per patient, at an additional cost of £20,063
- Incremental cost per QALY gained of £75,398
- Zero probability that sorafenib is cost-effective compared to BSC at a willingness to pay threshold of £30,000 per QALY

Thompson Coon et al. (2010)[77] carried out a systematic review comparing any interventions with any comparator in participants with advanced and/ or metastatic RCC. Phase II studies and conference abstracts of sufficient quality were also included. Results were synthesised narratively and a Markov model was developed to simulate disease progression and estimate the cost-effectiveness of the interventions under consideration. The results indicated that cost in first-line sunitinib was £21,116 per life-year (LY) gained and

£28,546 per QALY gained, and in second-line sunitinib £29,061 per LY gained and £37,510 per QALY gained.

Quality assessment of identified studies

Quality assessment of identified studies is available in Appendix 17.

5.2 De novo analysis

5.2.1 Patient population

Cabozantinib is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior VEGFR-targeted therapy. This economic analysis evaluates the cost-effectiveness of cabozantinib in this patient group.

The key clinical data source is the METEOR study a Phase 3, RCT of cabozantinib versus everolimus in subjects with advanced RCC that has progressed after prior VEGFR-TKI therapy.[10] This study is explained in detail in Sections 4.2 to 4.8. Data from the METEOR study was used to inform the cost-effectiveness comparison of cabozantinib versus everolimus. Comparisons to axitinib, BSC and nivolumab are supported by results from the NMA described in Section 4.10.

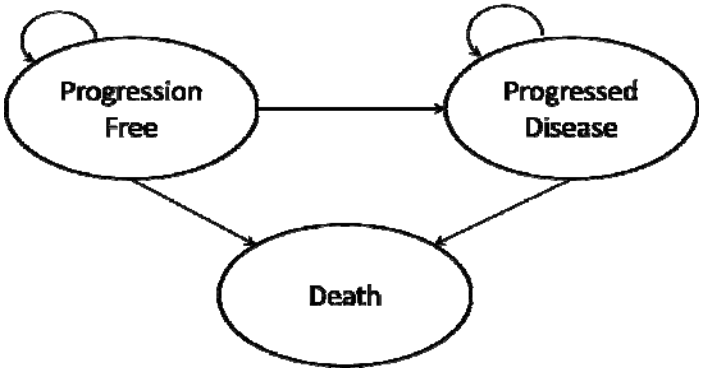
In the METEOR study participants had received at least one prior VEGFR - TKI and there was no limit to the number of previous treatments received. The evidence in the economic model is based on the ITT population of the METEOR study and is intended to reflect the use of cabozantinib in patients with at least one prior treatment. Given that the PFS and OS benefit of cabozantinib was observed regardless of the number of prior VEGFR-TKI agents (see Section 4.8), it is considered that the economic model results are also reflective of second-line treatment.

Patient populations in trials informing efficacy and safety of axitinib, nivolumab and BSC are described in Table 26 to Table 30.

5.2.2 Model structure

The partitioned survival (area under the curve) model was used as the model structure in line with previous health economic analyses, including NICE technology assessments in metastatic RCC: TA219[12], TA333[7] and at the time of this submission the ongoing nivolumab STA GID-TA10037. The model has three health states of progression-free, progressed and death (see Figure 24). The health states of a cohort of patients are modelled at each discrete model cycle. All patients enter the model in the progression free health state, having progressed on a previous VEGFR treatment for advanced RCC. Patients remain in the progression free health state until they experience disease progression or die. Once patients enter the progressed disease (PD) state, they remain there until death.

Figure 24: Structure of economic model



The structure was designed to capture disease progression, the primary end point in the METEOR study. The analysis is in line with the treatment pathway, enabling the analysis to capture all relevant costs and outcomes associated with each treatment and health state. Treatment duration in the model is captured independently from disease progression, enabling treatment times longer and shorter than PFS. This feature was included in the model because in the trials cabozantinib, everolimus and nivolumab treatments could be continued if patients were believed by the investigator to be experiencing clinical benefit and tolerating treatment; this is reflective of actual clinical practice.

The model structure is appropriate to capture differences in health-related quality of life (HRQoL) experienced by patients during different health states (progression-free and progression), and the utility decrement for experiencing adverse events.

A cycle length of 28 days (4 weeks) is applied in the model, which reflects the frequency of physician visits in the METEOR study. In addition, half-cycle correction is implemented to obtain a more accurate estimation of PFS, OS and TTD. This structure is regarded as appropriate for capturing the health effects and costs in patients with advanced RCC. The cycle length parallels the measurement time points and clinical follow-up visits in the METEOR study.

Summary details on the model structure are provided in Table 46 with summary features of the de novo analysis in Table 47.

Table 46: Summary of the model structure

	Approach	Source / Justification
Model	Partitioned survival model.	Can be considered as one of the standard methods for population-based cancer patient survival analysis. Method is in line with previous health economic analyses [7, 12,80]
Health states	Three health states: progression-free, progressed disease and death.	The model structure and the health states utilised reflect the natural history of the disease. Additionally they are typical of modelling in metastatic oncology and have been utilised in previous NICE STAs and MTAs (including GID-TA10037, TA219 and TA333)[7, 12, 80]
Adverse events	Included in the model as a one off time event. Adverse events are associated with additional cost and disutility.	Based on observed treatment-emergent grade 3/4 AEs (TEAE) with occurrence in more than 5% of the population in any of the pivotal trials, and judged by clinical expert to have implication for resource use. Adverse events for nivolumab and axitinib were obtained from SmPCs. No TEAEs were identified for nivolumab and treatment-related AEs (TRAE) were used instead. For the BSC group no TEAEs were assumed.[81-83]
Health related quality of life	Health states specific utility values were estimated. Before and after progression utilities were assumed to be independent of treatment.	Utilities are based on EQ-5D-5L as administered in the METEOR trial. All treatments were assumed to have health state specific utilities with reductions associated with adverse events experienced by patients.
Resource utilisation and costs	• Treatment cost • Cost of adverse events • Progression-free survival health state costs • Progressed health state costs • Terminal care cost	Based on UK reference costs, literature and expert opinion.
STA, single technology appraisal; MTA, multiple technology appraisal, TEAE, treatment emergent adverse event; EMA, European Medicines Agency; TRAE, treatment-related adverse event; BSC, best supportive care		

Table 47: Summary of features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	30 years	Mean age of patients in the METEOR study was 61 years; 100% of patients in any model arm are dead at 30 years. The time horizon of 30 years is long enough to reflect all important differences in costs and outcomes among patients with advanced RCC.
Comparator	• Axitinib • Everolimus • BSC • Nivolumab	In line with the decision problem.
Cycle length	4 weeks	Aligned with the METEOR study measurement periods and clinical follow-up visits.
Half-cycle correction	Yes	NICE reference case[84]
Measurement of health effects	QALYs	NICE reference case[84]
Discount (costs/effects)	3.5% per annum	NICE reference[84]
Perspective	NHS/PSS	NICE reference case[84]
Key: PSS, personal social services; QALYs, quality-adjusted life years		

5.2.3 Intervention technology and comparators

The main comparators are axitinib, everolimus and nivolumab in line with the decision problem. Comparison to BSC is also included as an option in the model for patients unsuitable for axitinib, everolimus and nivolumab. The comparators are included in the model as per their marketing authorisation (see Table 48).

Table 48: Marketing authorisations

Treatment	Indication	Line of therapy in trial
Cabozantinib	Treatment of advanced renal cell carcinoma (RCC) in adults following prior VEGF-targeted therapy (SmPC)	One or more prior therapies
Axitinib	Treatment of advanced renal cell carcinoma (RCC) in adults after treatment with sunitinib or a cytokine[82]	One prior therapy
Everolimus	Treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy[81]	One or two prior therapies
Nivolumab	Treatment of advanced renal cell carcinoma after prior therapy in adults[83]	One or two prior therapies

Cabozantinib and everolimus are implemented in the model as per the dosing schedule observed in the METEOR study, and as described in Table 11. Cabozantinib was given orally once a day at 60 mg. Treatment modifications, including interruptions and dose reductions, were used in the METEOR study to manage adverse events. Cabozantinib could be dose reduced to 40 mg and then 20 mg. Everolimus was given orally once a day at 10 mg. Everolimus could be dose reduced to 5 mg and then 2.5 mg. Dose reductions occurred for 206 (62%) patients in the cabozantinib group and 80 (25%) patients in the everolimus group (Table 41). The median daily dose was 43 mg for cabozantinib and 9 mg for everolimus (Table 41). Patients were allowed to continue study treatment beyond radiographic progression at the discretion of the investigator. On-study crossover between treatment groups was not permitted.[19] The standard daily dose for axitinib was 10 mg/day (5 mg twice daily). [48] Nivolumab is administered at a dose of 3 mg/kg by intravenous infusion every two weeks. [8] Everolimus, axitinib and nivolumab total cost per patient were adjusted for dose intensity.

Treatment continuation rule

Time to treatment discontinuation (TTD) data from METEOR study was used in the model to inform the comparison of cabozantinib and everolimus. Parametric survival curves estimated from the METEOR patient level data show the duration of treatment to be different to PFS across both study arms, and particularly on the cabozantinib arm, where treatment continued beyond progression for some patients. TTD for nivolumab was estimated from the ongoing NICE STA for nivolumab (See Figure 19).[26] No TTD curves were identified for axitinib from the literature and the PFS distribution generated from the NMA was used instead as a proxy for TTD. Based on the evidence from the METEOR trial (where treatment beyond progression continued for both cabozantinib and everolimus patients) and also from feedback from clinical experts consulted it is expected that in clinical practice some patients will continue treatment with axitinib beyond progression.

5.3 Clinical parameters and variables

5.3.1 Incorporation of Clinical Data in the Model

The pivotal study to inform the economic model was the METEOR study, described in detail in Section 4. The OS and PFS data from the METEOR study were used to calculate the proportion of patients in each treatment arm at any time point after starting treatment. The proportion of patients in the post-progression health state at any given time was calculated as the difference between OS and PFS. Because there are no head-to-head trials comparing cabozantinib with axitinib, nivolumab or BSC, a NMA was performed (see Section 4.10). Table 49 summarises the key inputs for efficacy data in the model.

Table 49: Summary of key efficacy model input parameters

	Model input	
	Cabozantinib vs. axitinib **Cabozantinib vs. nivolumab** **Cabozantinib vs. BSC**	**Cabozantinib vs. everolimus**
Efficacy	Regenerated data from the CheckMate025, RECORD-1, TARGET and AXIS studies and adjusted efficacy curves of axitinib, nivolumab and BSC to METEOR study	Patient-level data in METEOR study
Distributions fitted efficacy data (PFS, OS, TTD)	• Exponential • Gompertz • Loglogistic • Lognormal • Weibull	• Exponential • Gompertz • Loglogistic • Lognormal • Weibull • Generalized gamma
Best fitted distributions for PFS, OS and TTD	• PFS: lognormal • OS: lognormal • TTD: lognormal	• PFS: loglogistic • OS: loglogistic • TTD: lognormal
BSC, best supportive care; PFS, progression-free survival; OS, overall survival, TTD, time to treatment discontinuation		

5.3.2 Overall Survival

Patient level data from the METEOR study were used to estimate OS in the cabozantinib and everolimus arms of the model. Figure 25 shows the Kaplan-Meier OS data from the METEOR study, including the number of patients who were at risk or were censored over time. Parametric survival models (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised Gamma) were fitted to the patient level data from the METEOR study. Treatment was also tested as a covariate in these parametric models. To select the best survival model fit the algorithm (SMEEP) as described in the NICE DSU Technical Support Document 14[85] was followed. This included the use of statistics: the Akaike's information Criteria (AIC) and Bayesian Information Criteria (BIC) statistics (Table 50 and Table 51), visual inspection of the curves and anchoring i.e. comparison of extrapolation estimates with external data sources, including a long-term follow-up study in second-line advanced RCC long-term follow-ups. [85,86] Ruiz-Morales reported a median OS of 13.1 and 11.0

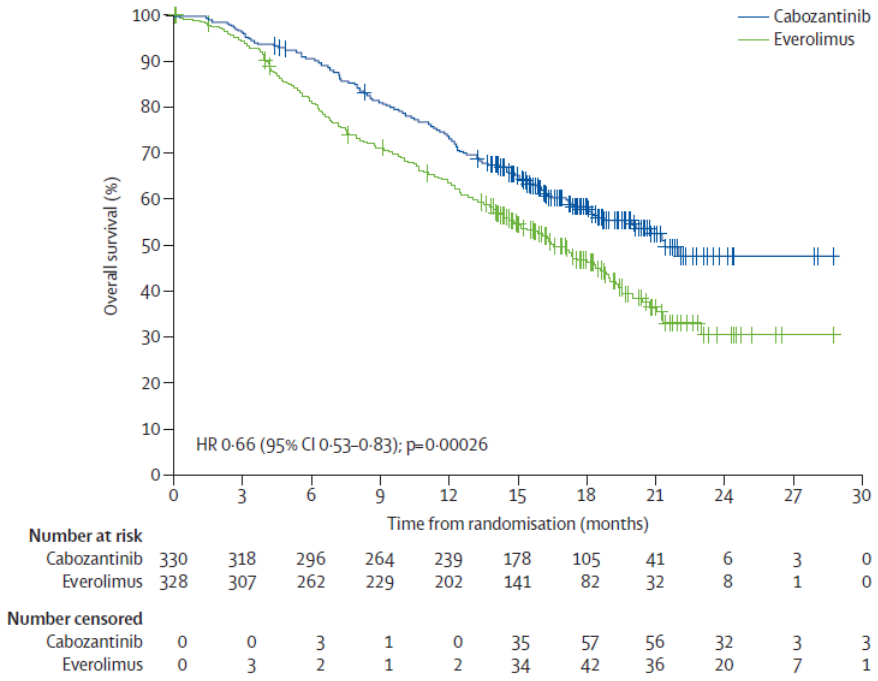
months for second line treatment with sunitinib and pazopanib, respectively.[86] The plausibility of different extrapolations was also assessed by oncologists currently practising within the NHS in England by visual inspection. The most appropriate model was selected based on a combination of all these factors.

The results from the NMA were used to inform OS estimates of axitinib, BSC and nivolumab comparisons (see Section 4.10). The statistical fitness tests for the re-generated data for axitinib, BSC and nivolumab are reported in Table 33 and Table 34. In line with the NICE DSU Technical Support Document 16[68], cross-over adjusted OS was used for the base case, as described in Section 4.10. Exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma were planned to be included in the NMA. However, generalised gamma distribution was not implemented due to the inaccessibility of the incomplete gamma function, called by the hazard rate function, under Winbugs. The assumption of proportional hazards (PH) and accelerated failure time were tested, to assess whether survival analysis stratified by treatment group was appropriate. Patient level data generated from publications of included studies suggest that proportional hazards assumption does not hold throughout all the pairwise comparisons included in the NMA. Although joint fit for OS data from the METEOR study would have been possible, it was decided that separate fits were to be used, as the choice of NMA method does not require proportional hazard assumption to hold. The separately fitted loglogistic model is the best fit for cabozantinib in the METEOR patient level data while Weibull model is the best fit to everolimus, closely followed by loglogistic. Considering that fitting cabozantinib and everolimus into different curves results in differently shaped distributions, which is not recommended,the loglogistic distribution was chosen in the base case for OS efficacy data for the comparison between cabozantinib and everolimus. The oncologists consulted agreed that the loglogistic would provide the best fit for both cabozantinib and everolimus. [33]

Based on the statistical fit of DIC in the curve NMA, the lognormal distribution provided the best fit for the METEOR, AXIS, TARGET, RECORD-1 and CheckMate025 re-generated data. Therefore, lognormal models were used for

the comparisons between cabozantinib and axitinib, BSC or nivolumab, Other models were tested in scenario analyses (see Section 4.10).

Figure 25: Kaplan-Meier plot of overall survival (ITT)



Source: Choueiri et al 2016

Table 50: AIC and BIC statistics for independently fitted OS data from the METEOR study – cabozantinib

Model	AIC	Model	AICC	Model	BIC
Loglogistic	1254.15	Loglogistic	1254.19	Loglogistic	1261.75
Weibull	1256.13	Weibull	1256.17	Weibull	1263.73
Gamma	1256.53	Gamma	1256.60	Lognormal	1267.93
Lognormal	1257.92	Lognormal	1257.95	Gamma	1265.52
Gompertz	1264.42	Exponential	1264.455	Exponential	1272.017
Exponential	1274.41	Gompertz	1274.43	Gompertz	1278.21

Table 51: AIC and BIC statistics for independently fitted OS data from the METEOR study – everolimus

Model	AIC	Model	AICC	Model	BIC
Weibull	1487.54	Weibull	1487.57	Weibull	1495.12
Loglogistic	1487.61	Loglogistic	1487.65	Loglogistic	1495.20
Gamma	1488.23	Gamma	1488.30	Gamma	1499.60
Lognormal	1492.45	Lognormal	1492.49	Lognormal	1500.04
Gompertz	1493.90	Exponential	1493.94	Exponential	1501.49
Exponential	1503.30	Gompertz	1503.31	Gompertz	1507.09

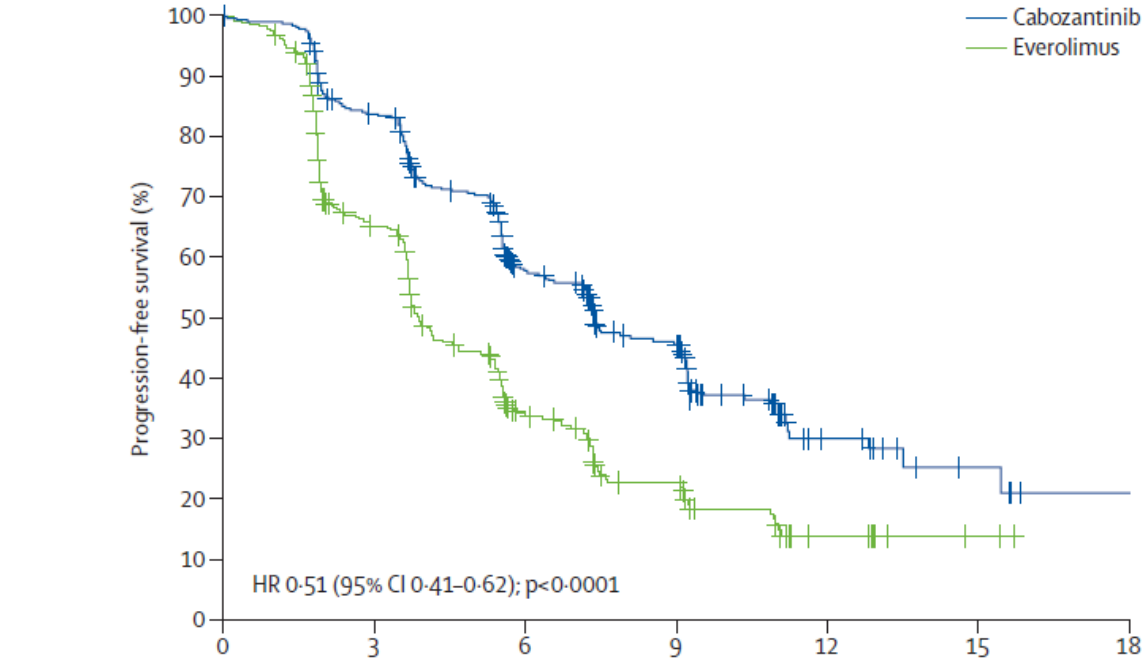
5.3.3 Progression Free Survival

Similarly to the OS endpoint, patient level data from the METEOR study was used to inform PFS in the cabozantinib and everolimus arms of the model. Figure 26 shows the Kaplan-Meier PFS data for METEOR patients, including the number of patients who were at risk or were censored over time. Parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised Gamma) were fitted to the patient level data from the METEOR study. Treatment was also tested as a covariate in these parametric models. To select the best survival model, the algorithm (SMEEP) as described in the NICE DSU Technical Support Document 14 was followed. [85] The AIC and BIC statistics are shown in Table 52 and Table 53. By AIC, AICC and BIC statistics, the Loglogistic model provide the best fit to the cabozantinib METEOR data and the log normal to the everolimus data (see Table 52 and Table 53). As with OS the plausibility of different extrapolations was assessed by oncologists currently practising within the NHS in England by visual inspection.[33] The most appropriate model was identified based on a combination of statistics and visual inspection. The NMA was used to inform PFS estimates of nivolumab, axitinib and BSC comparisons (see Section 4.10).

The statistical fitness tests for re-generated data for axitinib, BSC and nivolumab are reported in Table 33 and Table 34. Exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma were planned to be included in the NMA. However, generalised gamma distribution was not implemented due to the inaccessibility of the incomplete gamma function, called by the hazard rate function, under Winbugs. The assumption of PH and accelerated failure time were tested, to assess whether survival analysis stratified by treatment group was appropriate (Appendix 10). Patient level data generated from publications of included studies suggest that proportional hazards assumption does not hold throughout all the pairwise comparisons included in the NMA (see Section 4.10). Separate fits were used, as the choice of NMA method does not require the proportional hazard assumption to hold. Separately fitted loglogistic provided the best fit to cabozantinib PFS data,

followed by gamma distribution. For everolimus PFS data, the best fits are lognormal, followed by loglogistic and gamma distribution as measured by Akaike information criterion (AIC), corrected Akaike information criterion (AICC) and Bayesian information criterion (BIC). Considering that fitting cabozantinib and everolimus into different curves results in differently shaped distributions, which is not recommended within the NICE DSU Technical Support Document 14[85], the loglogistic distribution was chosen in the base case analysis for PFS efficacy data for the comparison between cabozantinib and everolimus. Lognormal models provided good fits to the METEOR patient level data and AXIS, TARGET, RECORD-1 and CheckMate025 re-generated data compared to other distributions. The lognormal model was used in the base case for the comparisons between cabozantinib and axitinib, BSC or nivolumab. Other models were tested in scenario analyses.

Figure 26: Kaplan-Meier plot of PFS (ITT)



Number at risk							
Cabozantinib	330	261	148	88	20	6	2
Everolimus	328	174	72	37	10	2	0
Number censored							
Cabozantinib	0	17	37	32	47	12	3
Everolimus	0	51	24	13	16	8	2

Source: Choueiri et al 2016[10]

Table 52: AIC and BIC statistics for independently fitted PFS data from METEOR study - cabozantinib

Model	AIC	Model	AICC	Model	BIC
Loglogistic	1205.81	Loglogistic	1205.85	Loglogistic	1213.41
Weibull	1213.37	Weibull	1213.41	Weibull	1220.97
Gamma	1209.01	Gamma	1209.08	Lognormal	1220.40
Lognormal	1212.02	Lognormal	1212.05	Gamma	1219.61
Gompertz	1229.14	Exponential	1229.17	Exponential	1236.74
Exponential	1238.40	Gompertz	1238.41	Gompertz	1242.20

Table 53: AIC and BIC statistics for independently fitted PFS data from METEOR study - everolimus

Model	AIC	Model	AICC	Model	BIC
Lognormal	1165.83	Lognormal	1165.87	Lognormal	1173.42
Gamma	1167.55	Loglogistic	1167.61	Loglogistic	1175.16
Loglogistic	1167.58	Gamma	1167.62	Gamma	1178.93
Weibull	1197.33	Weibull	1197.37	Weibull	1204.92
Gompertz	1219.26	Exponential	1219.30	Gompertz	1224.42
Exponential	1220.63	Gompertz	1220.64	Exponential	1226.85

5.3.4 Time to discontinuation

In the economic model TTD determined the proportion of patients on treatment at each point in time. For cabozantinib and everolimus treatment duration was based on TTD data from the METEOR trial. For the other comparators TTD was obtained from publications. In absence of TTD data, PFS curves derived from the NMA were used as an approximation for TTD. No TTD Kaplan-Meier data was identified for axitinib, and hence the PFS curve from the NMA was used as an estimate for TTD. The TTD survival curve for nivolumab was identified and extracted from the literature and fitted using the NMA methods as described in Section 4.10.

Parametric models were fitted independently using the models recommended in the DSU Technical Support Document 14; exponential, Weibull, Gompertz, log-logistic, log-normal and generalised Gamma.[85] To select the best survival model, the algorithm (SMEEP) as described in the NICE DSU Technical Support Document 14 was followed.[85] To determine the best model fit, the following criteria were considered: AIC and BIC statistics and visual inspection and the plausibility of different extrapolations was also assessed by oncologists

currently practising within the NHS in England by visual inspection.[33] The most appropriate model was identified based on a combination of these two factors.

According to the AIC, AICc or BIC statistics, the loglogistic and lognormal models provide the best fit to the cabozantinib METEOR data and everolimus METEOR data, respectively (see Table 54 and Table 55).

Table 54: AIC and BIC statistics for independently fitted TTD data from METEOR study - cabozantinib

Model	AIC	Model	AICC	Model	BIC
Loglogistic	1793.71	Loglogistic	1793.75	Loglogistic	1801.32
Gamma	1793.82	Gamma	1793.89	Gamma	1805.22
Lognormal	1792.67	Lognormal	1792.71	Lognormal	1800.28
Weibull	1805.85	Weibull	1805.88	Weibull	1813.45
Gompertz	1820.54	Gompertz	1820.58	Gompertz	1828.14
Exponential	1824.54	Exponential	1824.55	Exponential	1828.34

Table 55: AIC and BIC statistics for independently fitted TTD data from METEOR study - everolimus

Model	AIC	Model	AICC	Model	BIC
Lognormal	1701.25	Lognormal	1701.28	Lognormal	1708.80
Gamma	1701.76	Gamma	1701.83	Gamma	1713.08
Loglogistic	1707.81	Loglogistic	1707.85	Loglogistic	1715.36
Weibull	1747.55	Weibull	1747.58	Weibull	1755.09
Exponential	1753.65	Exponential	1753.66	Exponential	1757.42
Gompertz	1755.60	Gompertz	1755.64	Gompertz	1763.15

Separately fitted loglogistic and lognormal models provided good fits to the METEOR patient level data. Lognormal model that has lowest AIC, AICC and BIC was used in the base case for cabozantinib and everolimus. For nivolumab the TTD data were extracted from the nivolumab manufacturer STA submission[26] and a lognormal distribution was fitted to the data. Lognormal distribution was used as one of the models recommended by the Evidence Review Group in the nivolumab STA, instead of the complex spline-model originally submitted by the nivolumab manufacturer.[87] For axitinib and BSC, the PFS curves were used as the estimations of the TTD data as these data were not available.

5.3.5 Changes to transition probabilities over time

The relative effectiveness between treatments is based on head-to-head comparison for cabozantinib and everolimus, and on the NMA for axitinib, BSC and nivolumab. The curves are used beyond the clinical trial duration, until the end of the model time horizon. This is associated with uncertainty. Different distribution types were tested in scenario analyses.

5.4 Measurement and valuation of health effects

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

Disease symptoms and symptoms resulting from metastatic disease impact patients' health-related quality-of-life (HRQoL). Changes in mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and global health were measured in the METEOR study via the EuroQol Health questionnaire instrument (EQ-5D-5L). Patients completed the questionnaire prior to each clinic visit and up to 30 days after final administration of study drug. The EQ-5D-5L was converted into a single index value normalized across all the patients using the UK algorithm. Index values range from 0 to 1, and a higher index score indicates better health.

To analyse how patient HRQL differed, regression analyses by treatment arm, progression status, and adverse events were performed using patient level data from the METEOR study. A repeated-measure mixed-effect model was fitted to the METEOR EQ-5D-5L data. Table 56 displays results of the analysis. The data suggest that the effect on patient's utility was not significantly different between the treatment arms. A regression model controlling for only the progression status and adverse events was run and the results are shown in Table 56. Descriptive statistics of METEOR utility values are shown in Table 57.

Table 56: Mixed procedure model – progression status and adverse events

Effect	Planned Treatment	Progress	AE	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				0.2498	0.0259	609	9.64	<.0001
BASE				-0.3400	0.0302	2175	-11.27	<.0001
Progress		Yes		-0.0399	0.0066	2175	-6.05	<.0001
Progress		No		0	.	.	.	.
AE			Yes	-0.0552	0.0068	2175	-8.09	<.0001
AE			No	0	.	.	.	.

Table 57: Descriptive statistics of utility values

Analysis Visit	N	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum
BASELINE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 56	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 64	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WEEK 88	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-DAY POST-TREATMENT FOLLOW-UP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]							

The average EQ-5D index score for patients without disease progression was 0.817 (standard error 0.003) in the METEOR study. The decrement experienced by patients who experience disease progression was 0.040 (standard error 0.007). This results in post-progression health state utility value of 0.777 (0.817-0.040).

5.4.2 Published HRQoL studies

A systematic literature review was conducted to compare the utility values derived from the METEOR study with published estimates (Appendix 19). This was considered especially important given that the last measurement in the METEOR trial was conducted 30 days after final dose of study drug, and hence the possibility that the short follow-up with HRQoL assessments after stopping the study drug may over-estimate patients' utility during disease progression.

The systematic literature review focused on evidence from published original QoL/clinical studies. The review found that patient-reported EQ-5D data in previously treated RCC are relatively scarce.[88-92] Studies that were identified reported utility values by treatment at various time points[88,89] throughout a study by treatment arm, for a specific adverse event [90], or for a specific patient population[92]. The QoL publication of the CheckMate025 study reported baseline utility values of 0.78 across the two treatment arms (nivolumab and everolimus).[93] A study on elicitation of health state utilities in metastatic RCC by Swinburn et al. 2010 was also identified.[91] In this study health state descriptions were developed based on a literature review and in-depth interviews with clinical experts. The states included description of stable disease, progressive disease, and toxicities that may be experienced by patients receiving treatments for their advanced RCC. The general public rated the health states using the time-trade off (TTO) method.

Additionally, NICE submissions for key comparators (axitinib, everolimus and nivolumab) were checked. EQ-5D data were recorded in the AXIS[7] and CheckMate025 study.[26] The RECORD-1 trial did not use EQ-5D or any other generic preference based measure to estimate utilities and hence EQ-5D estimates were not included in the everolimus NICE single technology submission for advanced RCC (TA219).[12] Instead, utility values for patients receiving second-line advanced RCC treatment were taken from a Health Technology Assessment Report for the NICE technology appraisal of advanced RCC drug interventions from 2009.[77] The extracted utility values of key

studies/HTA submissions that were identified in the systematic literature review are reported below.

Comparison of HRQL studies

The values reported in the literature are reported in Table 58 to Table 61.

Table 58: TA333 (Axitinib) - AXIS study[7]

State	Utility value	Comments
Progression free	0.692	Average EQ5D index score for those visits without progression, SD 0.275
Progressed	0.610	Mean utility at the end of treatment for all patients, SD 0.316

Table 59: TA219 everolimus[12]

State	Utility value	Comments
Progression free without AE	0.758	Peninsula Technology Assessment Group (2008). SD 0.03
Progression free with AE	0.708	-0.05 disutility associated with dyspnoea health state utility in advanced non-small cell lung cancer (Doyle et al, 2008)
Progressed disease	0.683	Peninsula Technology Assessment Group (2008). SD 0.04

Table 60: GID-TA10037 nivolumab[26]

State	Utility value	Comments
Progression free_nivolumab	0.800	CheckMate025 study
Progressed_nivolumab	0.730	CheckMate025 study
Progression free_everolimus	0.760	CheckMate025 study
Progressed_everolimus	0.700	CheckMate025 study
Progression free_BSC	0.690	Assumption from TA333
Progressed_BSC	0.610	Assumption from TA333
Pneumonitis	-0.150	Medical oncologist opinion
Diarrhoea	-0.100	Medical oncologist opinion
Anaemia	-0.081	Medical oncologist opinion
Pneumonia	-0.130	Medical oncologist opinion

Table 61: Stand-alone utility study by Swinburn et al. 2010[91]

State	Utility value	Lower CI	Upper CI
Stable with no AE	0.795	0.761	0.830
Progressive	0.355	0.299	0.412
Stable with anaemia grade III	0.676	0.630	0.722
Stable with diarrhoea grade I/II	0.690	0.641	0.738
Stable with diarrhoea grade III	0.534	0.482	0.586
Stable with fatigue I/II	0.751	0.710	0.792
Stable with fatigue grade III	0.591	0.543	0.639
Stable with PPE grade III	0.469	0.414	0.524
Stable with mucositis grade I/II	0.726	0.681	0.771
Stable with mucositis grade III	0.526	0.476	0.575
Stable with nausea grade I/II	0.635	0.587	0.683
Stable with nausea III	0.540	0.486	0.593
Stable with hypertension grade III	0.642	0.594	0.690

Key differences of utility values

The progression free utility values identified varied between 0.692 and 0.800. The lower estimate comes from the AXIS trial and was used in the axitinib NICE single technology appraisal (TA333).[7] However the utility values estimated seem to have been obtained using the US EQ-5D tariff which might not be generalisable to a UK population. In the NICE axitinib appraisal, the utility values were applied to both the BSC and axitinib arms and this assumption was considered the most plausible by the Appraisal Committee because it was considered that the disease symptoms experienced by BSC patients may balance against the toxicity profile of axitinib (TA333).[7]

The higher estimate of 0.800 comes from the CheckMate025 trial which included EQ-5D as an exploratory endpoint.[8] The base-case utility values were higher for patients treated with nivolumab (0.80) than for patients treated with everolimus (0.76) before progression. Although the EQ-5D utility index showed significant benefit with nivolumab from weeks 8 through 12, weeks 24 through 44, weeks 52 through 68 and week 80, the Evidence Review Group noted that for both treatment groups, the median change from baseline was smaller than 0.000 until week 96.[87] Additionally, the Appraisal Committee noted that nivolumab is administered intravenously and that in other appraisals patient

experts have advised that quality of life is higher for patients who take oral medication.[80]

The PFS utility values estimated from the AXIS trial and the CheckMate025 trial provide the lowest and highest utility estimates for progression free health state identified in literature. The clinical experts consulted as part of the nivolumab single technology appraisal advised that the difference between the utility estimates was probably due to differences in trial populations, rather than the treatments received.[80]

The post-progression utility values varied between 0.355 and 0.730. The lowest value of 0.355 is reported in a publication by Swinburn et al. 2010.[91] The estimated value is substantially different from values estimated directly from patients participating in clinical trials. This is likely to be due to a different utility elicitation methodology used (Time Trade Off). Again, the highest values were reported in the nivolumab NICE single technology appraisal. Table 62 provides a summary of possible utility values to be considered in the economic model.

Table 62: Summary of available utility values for PFS and progressed health states and reduction due to AEs

State	METEOR	TA333 Axitinib	TA219 Everolimus	GID-TA10037 nivolumab	Swinburn et al. 2010
Progression free	0.817	0.692	0.758	0.800	0.795
Progressed	0.777	0.610	0.683	0.730	0.355
AE disutility	-0.055	NA	-0.050	See data details in Table 63	

5.4.3 Adverse reactions

The literature review identified a range of disutility values used in previous RCC NICE HTA submissions (see Table 63).

Table 63: Summary of available disutility values

Source	Disutility	Details
METEOR study	0.055	Patient level analyses
TA219	0.05	-0.05 disutility associated with dyspnoea health state utility in advanced non-small cell lung cancer (Doyle et al, 2008)
TA333	0.728	The HRQL estimates included in the AXIS trial reflect the adverse event profile associated with axitinib. BSC patients were assumed to have the same utility values as axitinib patients.
GID-TA10037	0.150	Pneumonitis. Clinical validation of TA215 estimates
	0.100	Diarrhoea. Clinical validation of TA215 estimates
	0.081	Anaemia. Clinical validation of TA215 estimates
	0.130	Pneumonia. Clinical validation of TA215 estimates
Swinburn et al. 2010	0.676	Stable with anaemia grade III
	0.534	Stable with diarrhoea grade III
	0.591	Stable with fatigue grade III
	0.540	Stable with nausea grade III
	0.642	Stable with hypertension grade III
	0.469	Stable with PPE grade III

To capture the effect of the AEs on HRQoL, assumptions about the durations of AEs were required. In the analyses it was assumed that duration of an AE was 4 weeks. This assumption is based on the fact that in the METEOR study the average adverse event duration was approximately 19 days in both the cabozantinib and everolimus arms. Given that it was not possible to estimate the exact duration of adverse events for each comparator due to lack of patient level data, an assumption was made that each AE would last for one model cycle. This approach was used as it could easily be extended to comparators where no direct evidence existed (axitinib, BSC and nivolumab). Table 64 shows the duration of disutility and the QALY decrements associated with each AE.

Table 64: Inputs of adverse events in the cost-effectiveness model

State	Duration of adverse events	Number of episodes experienced per patient	QALY decrement	Source
TEAE, grade 3/4	4 weeks – assumption	1.16	-0.055	METEOR study
Key; QALY, quality adjusted life year; TEAE, treatment emergent adverse event				

5.4.4 HRQL data used in cost-effectiveness analysis

Given the difficulties in combining utility estimates from different sources, including differences in trial populations and/or elicitation methods the base case analysis uses utility values derived directly from the METEOR trial for all comparisons. A scenario analysis is provided using alternative post-progression utility estimates. The average decrement across published estimates derived directly from patients using EQ-5D was used in this scenario.

Changes to HRQoL over course of disease

Although it is possible that the patient's utility might vary during progression a single mean value is used in this analysis to represent the whole health state. However utility values in the cost-effectiveness model changes between health states (i.e. separate utility values for PFS and Progression health states).

Baseline utility values

Baseline quality of life was not directly assumed in the economic evaluation as all patients start in the PFS health state, and are in the progression-free state or progressed disease state throughout the model.

Adjustment of utility values

No adjustments were required for the health state utility values used in the cost-effectiveness analysis.

Excluded health effects

No other health effects found in the literature or identified in clinical trials were intentionally excluded from the cost-effectiveness analysis.

Summary of utility values in cost-effectiveness analysis

The utility values used in the base case analysis are shown in Table 65.

Table 65: Summary of utility values for cost-effectiveness analysis – base case

State	Mean utility value	Standard error	Reference in submission (section and page number)	Justification
Progression-free Survival	0.817	0.003	Section 5.4.2 Page 133	Average EQ-5D index score for those visits without progression in the METEOR study data
Utility decrement due to progression	-0.040	0.007	Section 5.4.2 Page 133	Average decrement from METEOR study data
Post Progression Survival	0.777	-	Section 5.4.2 Page133	Derived value from METEOR study data
Treatment-emergent adverse event, grade 3 & 4	-0.055	0.007	Section 5.4.2 Page 133	METEOR study data decrement due to adverse event

Table 66: Summary of utility values for cost-effectiveness analysis – scenario

State	Mean utility value	Standard error	Reference in submission (section and page number)	Justification
Progression-free Survival	0.817	0.003	Section 5.4.2 Page 133	Average EQ-5D index score for those visits without progression in the METEOR study data
Post Progression Survival	0.745	0.007	Section 5.4.2 Page 133	Average decrement derived from published progression decrements. Standard error is ±10% of point estimate.
Treatment-emergent adverse event, grade 3 & 4	-0.055	0.007	Section 5.4.3 Page 133	METEOR study data decrement due to adverse event

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Cost and healthcare resource use parameters

Drug and Treatment Costs

Table 67 displays the estimated 4-weekly drug costs used in the cost-effectiveness model for cabozantinib, everolimus, axitinib and nivolumab, based on the NHS list prices. In nivolumab drug acquisition cost the cost of an intravenous infusion is added. [94]. The cost-effectiveness model also allows for the inclusion of wastage for nivolumab due to the weight-based dosing regimen. The percent wastage was estimated to be 8.5% by comparing the exact recommended weight-based dosage for patients to the total drug acquisition required given the availability of the 40 mg or 100 mg nivolumab vials. The wastage estimate was obtained using the weight distribution of patients in the METEOR trial (average 80.19 kg).

For each treatment, drug cost per cycle is determined based on dosage after accounting for relative dose intensity. For cabozantinib, the relative dose intensity was set to 100% given that the cabozantinib has the same price for each dose (60, 40 and 20 mg). Nivolumab intravenous infusions are given twice per cycle whereas axitinib and everolimus are taken daily. For BSC, no drug costs were assumed.

Following initial treatment discontinuation, patients are administered subsequent lines of treatment. The estimated 4-weekly drug costs used in the model for sorafenib, sunitinib and pazopanib are based on NHS list prices (Table 68). The distribution of subsequent treatment according to initial treatment is shown in Table 69 while duration is presented in Table 70. In the base case, there is no delay between discontinuation of previous, and onset of subsequent treatment.

Data on the subsequent treatment line received by patients in the analysis are based on evidence from the pivotal studies for each comparator e.g. METEOR for cabozantinib and everolimus, AXIS for axitinib and CheckMate025 for

nivolumab. For axitinib the duration when used as subsequent treatment was taken from the axitinib NICE technology appraisal (TA333)[7] while the distribution of treatments following its discontinuation was derived from a clinical trial in second line treatment for advanced RCC.[11] In this study, of patients who discontinued axitinib, 16% received subsequent sorafenib and one patient received subsequent axitinib. Since 33% of patients discontinuing axitinib received VEGF or VEGFR inhibitors and 39% received mTOR inhibitors, it was assumed that patients were administered sunitinib, pazopanib and everolimus in the following respective proportions: 8.5%, 8.5%, and 39.0%. The remaining 28% of patients did not receive subsequent treatment and were assumed to receive BSC. For the nivolumab comparison, the distribution of treatment following discontinuation was obtained from the EMA Product Information for nivolumab.[95]

Table 67: Drug formulation, dose and total cost per 4-weeks model cycle for comparators

Drug	Formulation (mg)	Cost per pack, £	Vials/ tabs per admin	Vials/ tabs per pack	Dose, mg	Weekly frequency	Relative dose intensity, % (SE)	Total cost per cycle, £
Cabozantinib	20/40/60	4,800.00 (7)	1.00	28	60/40/20	7	100.0 (0.0)*	4,800.00
Everolimus	10	2,673.00 96	1.00	30	10	7	83.9 (1.1)44	2,093.41
Axitinib	5	3,517.08 96	1.00	56	10	7	102.0 (1.9)48	3,587.34
Nivolumab	40 100	439.00 1,097.00 26	1.00 2.00**	1 1	3 / kg	0.5	97.5 (9.8)26	5,146.15

Key: mg, milligrams.
Note:
* Dose intensity is set to 100% given the constant price for each dosing
** Based on an average weight of 80.2 kg
Sources:
96 BNF, NHS indicative price
44 METEOR CSR
26 NICE Single technology appraisal. Nivolumab for treated or metastatic renal cell carcinoma GID-TA10037. Company submission;
48 Rini et al. 2011.

Table 68: Drug formulation, dose and total cost per 4-weeks model cycle for subsequent treatments

Drug	Formulation (mg)	Cost per pack, £	Vials/ tabs per admin	Vials/ tabs per pack	Dose, mg	Weekly frequency	Relative dose intensity, % (SE)	Total cost per cycle, £
Sorafenib	200	2,980.47[96,97]	4.00	112	800	7	100.0 (0.0)**	2,980.47
Sunitinib	50	3,138.80[96]	1.00	28	50	4.7 *	100.0 (0.0)**	2,092.53
Pazopanib	400	1,121.00[96]	1.00	30	800	7	100.0 (0.0)**	2,092.53

Key: mg, milligrams.
Note:
* Sunitinib is given in 6 weeks cycles of 4 weeks of treatment followed by a rest period of 2 weeks;
** Assumed 100% for subsequent therapies
Sources:
96 BNF, NHS indicative price
97 MIMS, Monthly Index of Medical Specialities

Table 69: Distribution of subsequent treatments following treatment discontinuation

Treatment at entry	Subsequent Treatment					
	Axitinib	Everolimus	Sunitinib	Sorafenib	Pazopanib	BSC
Cabozantinib[10]	17.0%	29.0%	5.2%	0.0%	0.0%	49%
Axitinib[48]	0.5%	39.0%	8.5%	16.0%	8.5%	28%
Everolimus[10]	27.0%	0.0%	10.0%	9.5%	6.7%	47%
Nivolumab[8]	24.2%	25.6%	6.8%	6.3%	9.0%	28%
BSC[48]	0.0%	0.0%	0.0%	0.0%	0.0%	100%

Key: BSC, best supportive care.
Sources:
10 METEOR study (Choueiri et al 2016)
48 AXIS study (Rini et al 2011)
8 CheckMate025 study (Motzer et al 2015)

Table 70: Duration of subsequent treatments

Subsequent treatments	Duration (SE), days
Axitinib	220.8 (22.1) [7]
Cabozantinib	231.8 (23.2) [98]
Everolimus	167.6 (16.8) [98]
Sunitinib	118.7 (11.9) [56]
Sorafenib	180.7 (18.1) [7]
Pazopanib	109.6 (11.0) [99]

Key: SE, standard Error.
Sources:
7 NICE technology appraisal guidance [TA333]
98 METEOR Trial (Ipsen METEOR patient level data. 2016)
56 Hutson,T.E. et al. 2014
99 Rautiola,J. et al. 2014

5.5.2 Health-state unit costs and resource use

The base case resource use and unit cost estimates attributed to disease management are shown in Table 71. The health resource utilisation in the base case was estimated by clinicians currently practicing in the UK. Resource use assumptions mirror those in TA333[7] and GID-TA10037 [26]

Table 71: Disease management - Cost and resource use

Disease state	Resource	Frequency (SE) per cycle	Unit cost (SE), £
Progression-free	GP visit	0.50 (0.05)	54.00 (5.40) [100a]
	CT scan	0.33 (0.003)	Tariff RA14Z 129.00 (18.20) [94]
	Blood test	1.00 (0.10)	54.00 (5.40) [101]
	Consultant/ nurse (50:50)	0.67 (0.07)	Consultant (tariff WF01A): 93.00[94] Nurse specialist: 65.00[100b] 50:50: 79.00 (7.90)
Progression	GP visit	1.00 (0.10)	54.00 (5.40) [100a]
	Community nurse visit	1.00 (0.10)	65.00 (6.50) [100b]
	Blood test	0.67 (0.07)	54.00 (5.40) [101]
End of life costs	Various	One-off cost *	5,912.39 (7.55) [102,103]

Key SE, standard error.
Note: * Applied as a one-off cost during the last 4 weeks of life;
Sources:
[100a] General practitioner - unit costs. PSSRU (2015) Section 10.8 p177 ;
[94] NHS National Tariff Payment System 2016-17.
[101] NHS Trust and PCT combined Reference Costs: the main schedule 2014-15. Code DAPS05 (Haematology);
[100b] Nurse specialist (community), 1 hour patients time. PSSRU (2015) Section 10.4 p172;
[102] Georghiou T, Bardsley M. Exploring the cost of care at the end of life. 2014. Table 4: summary costs of hospital care;
[103] http://www.inflation.eu/inflation-rates/great-britain/historic-inflation/cpi-inflation-great-britain.aspx. Access on 9th Aug, 2016.

The model assumes one GP visit per two cycles at a cost of £54 per visit which corresponds to a patient contact lasting 17.2 minutes (including direct staff costs, excluding qualifications). The CT scan cost was obtained from the NHS National Tariff Payment System 2016-17 and assumes exams involving more than three areas (Code RA14Z). In the pre-progression phase, CT scans are performed once every three cycles. During the pre-progression phase, a blood test is performed at each cycle. The unit blood test cost (haematology, code DAPS05) was obtained from the NHS Trust and PCT combined Reference

Costs (£3).[101] The consultant visit is performed every six weeks (twice per three model cycles). This cost consists of 50% of nurse visit cost and 50% consultant visit cost. In the post-progression phase, the patients receive a GP visit, nurse visit and blood test. The corresponding frequencies are once per cycle, once per cycle and twice per three cycles. The model also allows for the inclusion of the end-of-life costs which occur in 4-week period preceding death.

Cost estimates were taken from a 2014 report on the cost of care at the end of life among patients who had been diagnosed with cancer within two years.[102]The 2014 hospital care costs were inflated to 2016 using the average inflation rate for the UK. [103]

The resource assumptions retrieved from TA333[7] and GID-TA10037[26] were tested in a scenario analysis, see Table 72.

Table 72: Disease management - Cost and resource use (scenario analysis)

Disease state	Resource	Frequency (SE) per cycle	Unit cost (SE), £
Progression-free	GP visit	1.00 (0.10)	54.00 (5.40)[100a]
	CT scan	0.33 (0.008)	129.00 (18.20) [94]
	Blood test	1.00 (0.10)	54.00 (5.40) [101]
Progression	GP visit	1.00 (0.10)	54.00 (5.40) [100a]
	Community nurse visit	1.5 (0.15)	65.00 (6.50)[100b]
	Pain medication	28	5.25 (0.53)[96]
End of life costs	Various	One-off cost*	5,912.39 (7.55) [102,103]

key: SE, standard error.
Note: * Applied as a one-off cost during the last 4 weeks of life;
Sources:

[100a] General practitioner - unit costs. PSSRU (2015) Section 10.8 p177;
[94] NHS National Tariff Payment System 2016-17. Code RA14Z; Computerised Tomography Scan, more than three areas;
[101] NHS Trust and PCT combined Reference Costs: the main schedule 2014-15. Code DAPS05 (Haematology);
[100b] Nurse specialist (community), 1 hour patients' time. PSSRU (2015) Section 10.4 p172;
[96] BNF, NHS indicative price (morphine sulfate 50mg/50 ml solution for infusion, NHS indicative price for 50-ml vial = £ 5.25)
[102] Georghiou T, Bardsley M. Exploring the cost of care at the end of life. 2014. Table 4: summary costs of hospital care;
[103] http://www.inflation.eu/inflation-rates/great-britain/historic-inflation/cpi-inflation-great-britain.aspx. Access on 9th Aug, 2016.

5.5.4 Adverse event unit costs and resource use

The health care utilisation costs for the most frequent (≥ 5%) grade 3 and 4 TEAEs experienced by cabozantinib and the comparators treatments were included in the cost-effectiveness analysis. The included AEs are described in Section 5.4.3. A systematic literature review revealed limited published data on resource use associated with treatment of adverse events included in the cost-effectiveness models (see Appendix 21). Resource use was estimated based on clinical opinion and published sources and HTA reports from previous NICE RCC appraisals.[12,7,26]

The unit costs identified are presented in Table 73. Inpatients and outpatients costs were obtained from England NHS PbR tariffs [104] and drug costs were taken from the British National Formulary [96] For the blood transfusion cost, the specific NICE costing statement was used (NICE costing statement for NG24 2015).[111] The total cost for each AE was obtained by summing the costs of each resource used in managing the AE (i.e. inpatient, day case, outpatients and medication costs (Table 73). Table 74 presents the cost estimates for AEs used in the base case analysis.

Table 73: Unit costs for health resource utilisation in management of adverse events

Cost types	Unit costs, £
Inpatient costs	
Anaemia	827 [104]
Diarrhoea	426 [105]
Fatigue	442[106]
Hypertension	1 863 [107]
Day-case costs	
Anaemia	288[108]
Outpatient costs	
Follow-up visit	93 [110]
Medication & other costs	
Blood transfusion	170[111]
Clobetasol 0.05% cream (100mg)	8 [96, 109]
Amlodipine for 4 weeks (5 mg per day)	0.73[96,111]

Sources:

[104] England NHS PbR tariffs, HRG code: SA04F.
[105] England NHS PbR tariffs, HRG code: FZ37F.
[106] England NHS PbR tariffs, HRG code: HD26C.
[107] England NHS PbR tariffs, HRG code: EB04I9.
[108] England NHS PbR tariffs, HRG code: SA04F.
[109] England NHS PbR tariffs, HRG code: JD02C.
[110] England NHS PbR tariffs, HRG code: WF01A
[111] NICE Costing statement: Blood transfusion.
[96] BNF, NHS indicative price

Table 74: Health resource utilisation cost for adverse events experienced in cabozantinib or comparator group (base case)

Adverse Event	Resource Use Assumption	Total Costs, £ *
Anaemia	• 25% inpatient hospitalisation • 75% day-case visit • 1 blood transfusion	593
Diarrhoea	• 1 inpatient hospitalisation	426
Fatigue	• 1 outpatient visit	93
Hypertension	• Amilodipine 5 mg once a day for 4 weeks • 5% inpatient hospitalisation + 95% outpatient visits(4 visits)	656
PPE	• 1 outpatient visits • corticosteroid cream (clobetasol) for 50 days	101

Key: PPE, Palmar-plantar erythrodysaesthesia syndrome
Note: * Obtained by adding unit costs for each health resource used see Table 73.

5.5.5 Miscellaneous unit costs and resource use

A systematic literature search was conducted to identify relevant studies on resource utilisation and cost in the management of advanced RCC from the published literature. The following databases were searched:

- Medline (includes Medline in Process and other non-indexed citations with status: publisher, in-data review or Pubmed-not-Medline) on July, 07, 2016;
- Embase on July, 07, 2016;
- NHS Economic Evaluation Database, HTA Database on July, 07, 2016.

All searches were conducted for 2006 – 2016. Electronic searches were supplemented by hand searching the relevant NICE submission/appraisal data. Details of the search strategy are provided in Appendix 20. Inclusion and exclusion criteria are shown in Table 75.

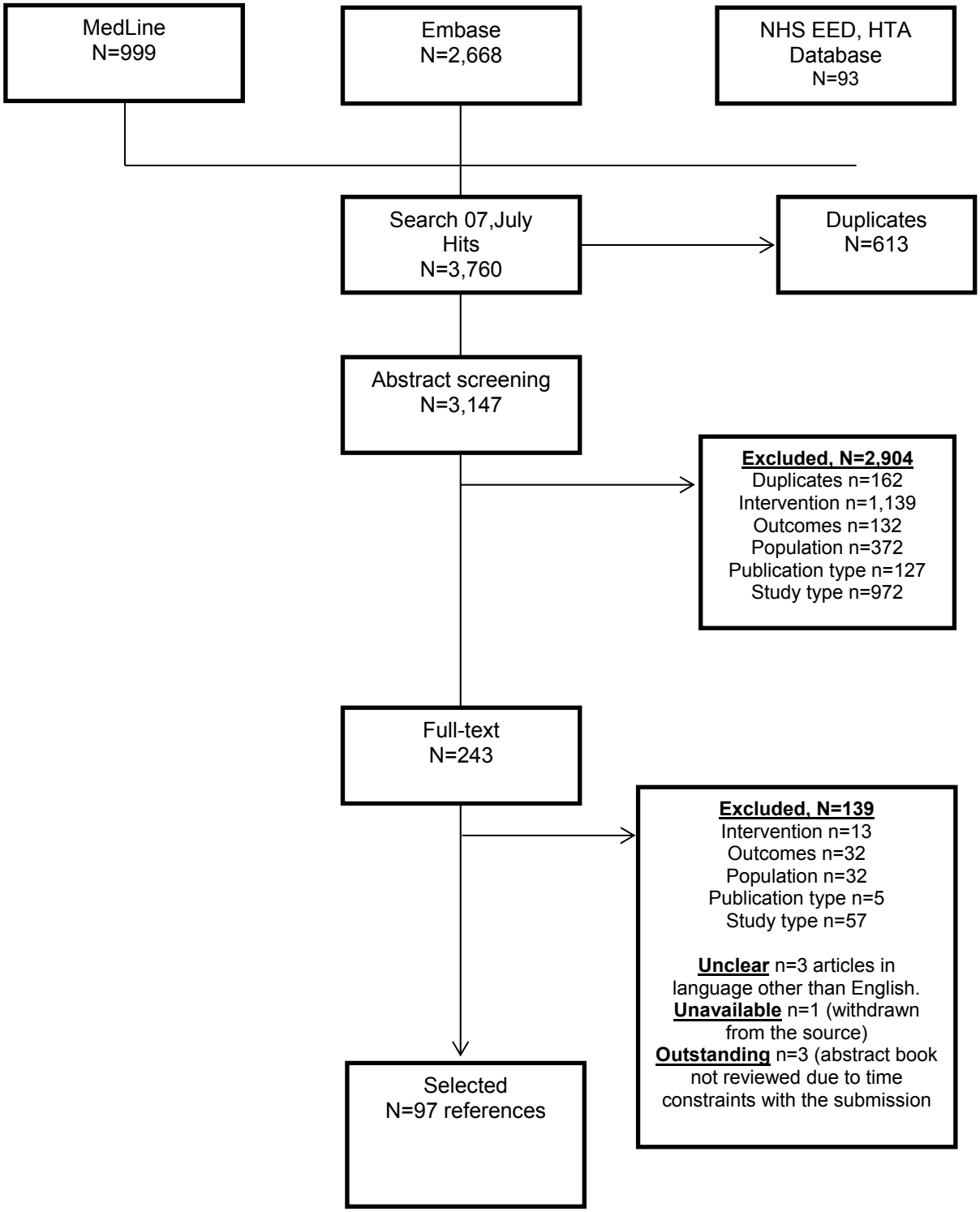
Table 75: Systematic literature search inclusion and exclusion criteria

Criteria	Include	Exclude
Population	Adult patients with RCC (advanced / metastatic, previously treated)	Animal studies, Paediatric population and other indications
Intervention	Not restricted	-
Comparator	Not restricted	-
Outcomes	Cost data: Direct medical cost (e.g. medication, physician visits, hospitalization, etc.) Direct non-medical cost (e.g. paid caregiver time, etc.) Indirect cost Resource utilisation data: Number of hospitalisations, rehabilitations, etc.	Other outcomes
Study design	Various study types	-
Language	English, German, French, Spanish and Italian (publications in other languages will be listed, and only abstracts in English included)	-
Publication type	Full-text publications, conference proceedings	Mere animal studies Letter, Editorial, Notes, Historical article

In total, 3,760 papers were identified through the electronic searches. Upon removal of 613 duplicates, 3,147 abstracts were reviewed of which 1,418 abstracts were excluded resulting in 243 publications selected for full-text screening. One study was withdrawn from the source and thus was unavailable. Three publications were published in languages other than English and a further 3 were large abstract books that were not searched due to time constraints (Figure 27). In total 97 publications were included. The full text European articles and HTA reports are summarised in Appendix 21 (n=10). Data were extracted into the summary tables by a reviewer. Uncertainties were resolved following discussion with a second reviewer.

Of the included studies six reported evidence on resource use and costs in the UK settings; two cost-effectiveness analysis, three technology appraisals and one retrospective cost attribution analysis. Reported treatments included: sunitinib, bevacizumab alone or with IFN, everolimus, axitinib, zoledronic acid, sorafenib and cabozantinib. Hoyle et al. 2010 reported medical management of 1 outpatient consultation per month, 1 CT scans per 3 months, and 1 blood test per month for the sorafenib arm prior to disease progression (PFS).[79] In the BSC arm the PFS medical management was 1 GP visit per month, 1 CT scan per 6 months and 1 blood test per month. After disease progression both sorafenib and BSC patients had the following disease management: 1 GP visit per month, 1.5 community nurse visit per month and pain medication each day. The cost-effectiveness model reported by Botteman et al. 2009 reported estimated cost of treatment for zoledronic acid in UK to be €270.86 per patient. [78] Liniker et al. 2013 provided detailed information on costs of therapy based on a retrospective analysis for the UK across different cancer types (including RCC) and various treatments.[112] All patients entered into oncology (non-haematology) clinical trials involving investigational medicinal products in 2009 and 2010 in a single UK institution were identified. The trial protocols on which they were treated were analysed to identify the treatment costs for the experimental arm(s) of the trial and the equivalent standard of care had the patient not been entered in the trial. The highest per patient per cycle costs were estimated for therapy with bevacizumab of £5,144.

Figure 27: Flow diagram for the systematic review of resource use and cost data



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

5.6.1 Summary of base-case de novo analysis inputs

Table 76 provides a summary of variables applied in the economic model. The efficacy parameter values are provided in Appendix 22 for both the METEOR patient level data analyses and results from the NMA. The OS, PFS, and TTD curve parameters are reported in Appendix 22.

Table 76: Summary of variables applied in the economic model

Variable	Value	SE	Distribution	Section
Treatment Costs (GBP)				
Baseline Weight (kg)	80.19	8.02	Normal	Section 5.5
Cost of Cabozantinib per day	171.43	0	No distribution	
Cost of Everolimus (per 10 mg)	89.10	8.91	Gamma	
Cost of Axitinib (per 10 mg)	125.61	12.56	Gamma	
Cost of Nivolumab (3mg)	32.91	3.29	Gamma	
Cost of Sorafenib (800mg)	106.45	10.65	Gamma	
Cost of BSC	0	0	No distribution	
Cost of Sunitinib (Sutent) (50mg)	112.10	11.21	Gamma	
Cost of Pazopanib (Votrient) (800 mg)	74.73	7.47	Gamma	
Relative dose intensity of Cabozantinib	1.00	0.00	No distribution	
Relative dose intensity of Everolimus	0.84	0.01	Normal	
Relative dose intensity of Axitinib	1.02	0.02	Normal	
Relative dose intensity of Nivolumab	0.98	0.10	Normal	
Wastage of Nivolumab	0.08		No distribution	
Single administration cost of Nivolumab	152.00	15.20	Gamma	
Adverse event costs (GBP)				
Total cost of Cabozantinib AE	237.56	23.76	Gamma	Section 5.5
Total cost of Everolimus AE	121.22	12.12	Gamma	
Total cost of Axitinib AE	246.02	24.60	Gamma	
Total cost of Nivolumab AE	0.00	0.00	Gamma	
Disease Management costs (GBP)				
Cost of GP visit	54.00	5.40	Gamma	Section 5.5
Cost of CT scan	129.00	18.20	Gamma	
Cost of Blood test	3.00	0.30	Gamma	
Cost of Specialist community nurse visit	65.00	6.50	Gamma	
Cost of Consultant	79.00	7.90	Gamma	

PFS: GP visit frequency	0.50	0.05	Gamma	
PFS: CT scan frequency	0.33	0.03	Gamma	
PFS: Blood test frequency	1.00	0.10	Gamma	
PFS: consultant visit frequency	0.67	0.07	Gamma	
OS: GP visit frequency	1.00	0.10	Gamma	
OS: community nurse visit frequency	1.00	0.10	Gamma	
OS: Blood test frequency	0.67	0.07	Gamma	
End-of-life costs (GBP)				
End-of-life cost	5912.39	7.55	Gamma	
Time on follow up treatment				
Time to third line treatment (days)	0	0	Normal	Section 5.5
Time on Axitinib - 3rd line (days)	220.8	22.1	Normal	
Time on Cabozantinib. - 3rd line (days)	231.8	23.2	Normal	Section 5.5
Time on Everolimus - 3rd line (days)	167.6	16.8	Normal	
Time on Sunitinib - 3rd line (days)	118.7	11.9	Normal	
Time on Sorafenib - 3rd line (days)	180.7	18.1	Normal	
Time on Pazopanib - 3rd line (days)	109.6	11.0	Normal	
Time on BSC - 3rd line (days)	0	0	Normal	
Utilities				
Utilities: Progression free state	0.82	0.00	Beta	
Utilities: Utility decrement due to progression	0.04	0.01	Normal	
Utilities: Progressed state	0.78		No distribution	Section 5.4
AE duration (weeks)	4.00	0.40	Normal	
AE average episodes per patient	1.16	0.02	Normal	
Utility decrement due to Grade 3/4 AEs	-0.06	0.01	Normal	
Key: CI, confidence interval; GP, general practitioner; HR, hazard ration; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; SA, survival analysis; TTD, time to treatment discontinuation.				

5.6.2 Assumptions

The base case analysis is subject to several key assumptions, described and discussed throughout Section 5. The key assumptions are:

Effectiveness

- OS and PFS curves for cabozantinib and everolimus fitted to the METEOR patient level data are best represented by loglogistic curves. Comparators modelled by using NMA are best represented by lognormal

curves fitted to re-generated patient level data of comparator studies (AXIS, RECORD-1, CheckMate025).

- The relative efficacy in the model is based on parametric survival curve NMA, which assumes that there are no significant imbalances in effect modifiers between different types of direct comparisons.
    - Given that there are differences in baseline prognostic scores and number/type of previous therapies, this assumption is discussed extensively. It was not possible to re-run the NMA for particular subgroups due to lack of data.
- Cross-over adjusted Kaplan Meier plots used in the NMA were assumed to be more appropriate than ITT data for those trials where cross-over was present (RECORD-1, TARGET).

Quality of life

- Quality of life is dependent on disease progression status and toxicity of treatments.
- The most suitable source to estimate utilities are the METEOR EQ-5D data for all comparators to avoid combining several sources/methods of preference elicitation together.

Resource use and costs

- Treatment duration is best characterised by lognormal curve for cabozantinib, everolimus and nivolumab. No TTD was identified for axitinib and PFS curve (lognormal) was used as an estimate i.e. axitinib patients are treated to progression.
- Vial sharing will not occur in practice in the administration of nivolumab.
- BSC is associated with no active treatment costs.
- Resource use and costs for disease management are dependent on RECIST-defined progression status.
- Management of grade 3 and 4 adverse events are associated with resource use validated by UK oncologists.[33]

5.7 Base-case results

5.7.1 Base-case incremental cost effectiveness analysis results

Base case results for pairwise analyses are shown in Table 77 and Table 78. Cabozantinib is shown to be an effective treatment for advanced RCC patients after prior therapy when compared to axitinib, with a predicted survival benefit of 0.81 years (0.65 QALYs). Cabozantinib is also an effective treatment compared to BSC, everolimus, and nivolumab.

Table 77: Base case results; pair-wise analysis of cabozantinib versus comparator (based on NMA outputs)

Drug	Total costs	Total QALYs	Total life-years	Incremental versus cabozantinib			ICER versus cabozantinib (QALYs)
				Costs	QALYs	Life years	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 78: Base case results; pair-wise analysis of cabozantinib versus everolimus (from METEOR study)

Drug	Total costs	Total QALYs	Total life-years	Incremental versus cabozantinib			ICER versus cabozantinib
				Costs	QALYs	Life years	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

In comparison versus nivolumab cabozantinib was found to be more effective and less costly Table 79.

Table 79: Base case results; pair-wise analysis of cabozantinib versus nivolumab

Drug	Total costs	Total QALYs	Total life-years	Incremental versus cabozantinib			ICER versus cabozantinib (QALYs)
				Costs	QALYs	Life years	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

5.7.2 Clinical outcomes from the model

The model estimated that cabozantinib is associated with longer survival, both progression free and after disease progression. QALY gains in cabozantinib were 2.26 while they were estimated to be 1.61 in the axitinib arm. Life-years, progression free life-years and QALYs were also consistently higher in the cabozantinib arm compared to everolimus, BSC and nivolumab. Table 80 shows comparisons of median OS, PFS, and TTD as predicted by the model and as observed in the clinical trials. When comparing the median survival data for axitinib, BSC and nivolumab from the trials with the predicted outputs from the model, the fact that the axitinib, BSC and nivolumab efficacy curves were adjusted to the everolimus curves from the METEOR study needs to be considered. For example, the time-varying HR function for the OS and PFS efficacy curves between nivolumab and everolimus were first estimated using with the curve NMA methodology. The time-varying HR was then applied to the efficacy curve of everolimus from the METEOR study to derive the efficacy data of nivolumab, at the same time ensuring that relative relationship between nivolumab and everolimus observed in CheckMate025 study was retained. As everolimus has distinct curves in the METEOR and CheckMate025 studies, the adjusted nivolumab efficacy data is different from the original median survival data, but the relative relation to everolimus is retained. Therefore, this adjustment factor needs to be taken fully consideration when making the comparison.

Table 80: Observed and modelled median PFS, TTD and OS from pivotal clinical studies, months (ITT)

	Predicted with NMA efficacy data				Predicted with METEOR efficacy data	
Outcome, median (months)	**Cabozantinib** (METEOR)	**Nivolumab** (CheckMate025) [8]	**Axitinib*** (AXIS) [48,11]	**BSC****	**Cabozantinib**	**Everolimus**
Observed OS	21.4	25.0	15.2	RECORD-1[46]: 14.4 (adjusted: 10 months)	21.4	METEOR: 16.5
				TARGET: 15.2 (adjusted:14.3 months)		RECORD-1[46]: 14.8
						CheckMate025: 19.6
Predicted OS	22.9	20.8	15.7	11.5	21.8	16.0
Observed PFS	7.4	4.6	4.8	RECORD-1[46]: 1.9 TARGET: 2.8	7.4	METEOR: 3.9 RECORD-1[46]: 4.9 CheckMate025: 4.4
Predicted PFS	7.8	5.1	5.0	2.4	7.5	4.2
Observed TTD	8.3	5.5	Overall: 8.2	-	8.3	METEOR: 4.4 RECORD-1[46]: 4.6 CheckMate025: 3.7
Predicted TTD	9.0	7.4	5.0	-	8.7	4.7

Key: PFS, progression-free survival; TTD, time to treatment discontinuation; OS, overall survival
Notes: independent review committee PFS used in network meta-analysis when available, otherwise investigator assessed PFS used. * subgroup previously treated with sunitinib used in NMA, **RPSFT adjusted median OS
Sources: [46] Motzer et al. 2010, [8] Motzer et al. 2015, [11] Motzer et al. 2013, [48] Rini et al. 2011

5.7.3 Proportion of cohort in health states over time

The proportion of patients in the cabozantinib and axitinib arms are shown in Figure 28. Treatment with cabozantinib is associated with visible pre- and post-progression survival benefit compared to axitinib in pre-treated patients with advanced RCC. Similar survival benefit is associated in comparison with other comparators (see Figure 30 to Figure 32).

Figure 28: Proportion of cohort in the health states over time – cabozantinib versus axitinib

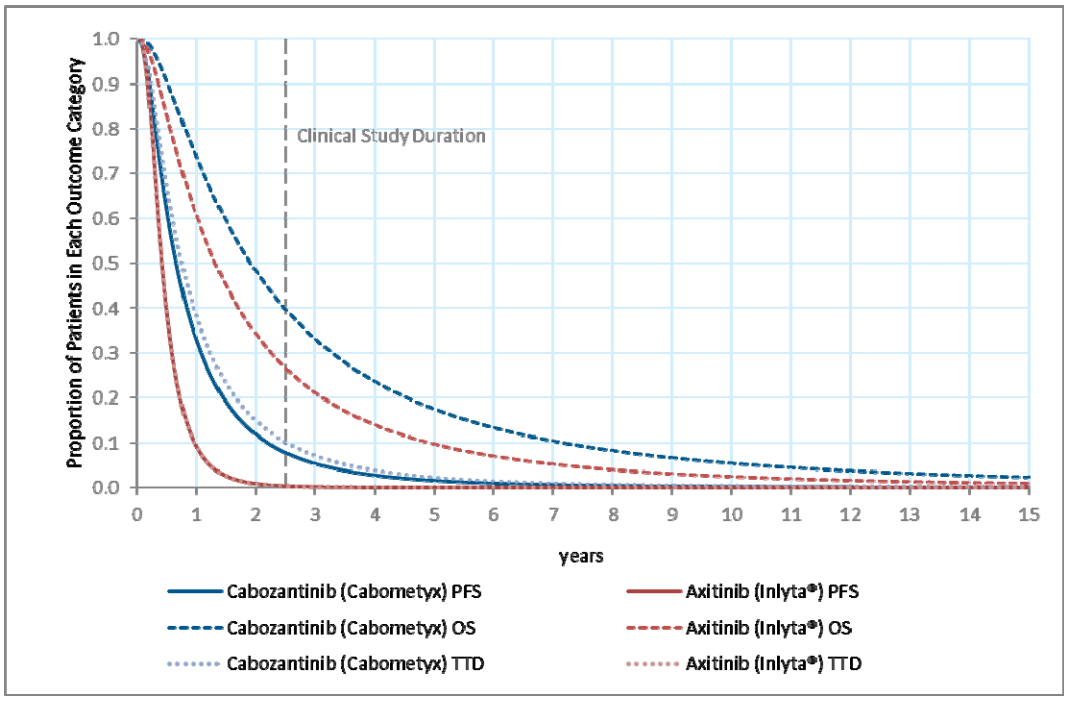


Figure 29: Proportion of cohort in the health states over time – cabozantinib versus everolimus

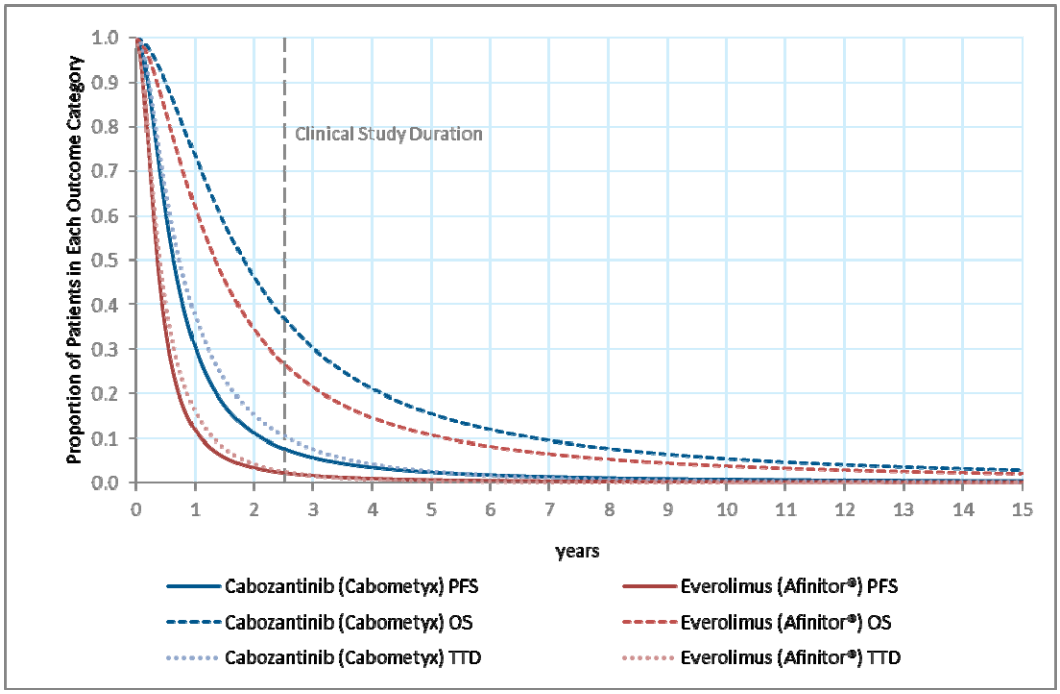


Figure 30: Proportion of cohort in the health states over time – cabozantinib versus BSC

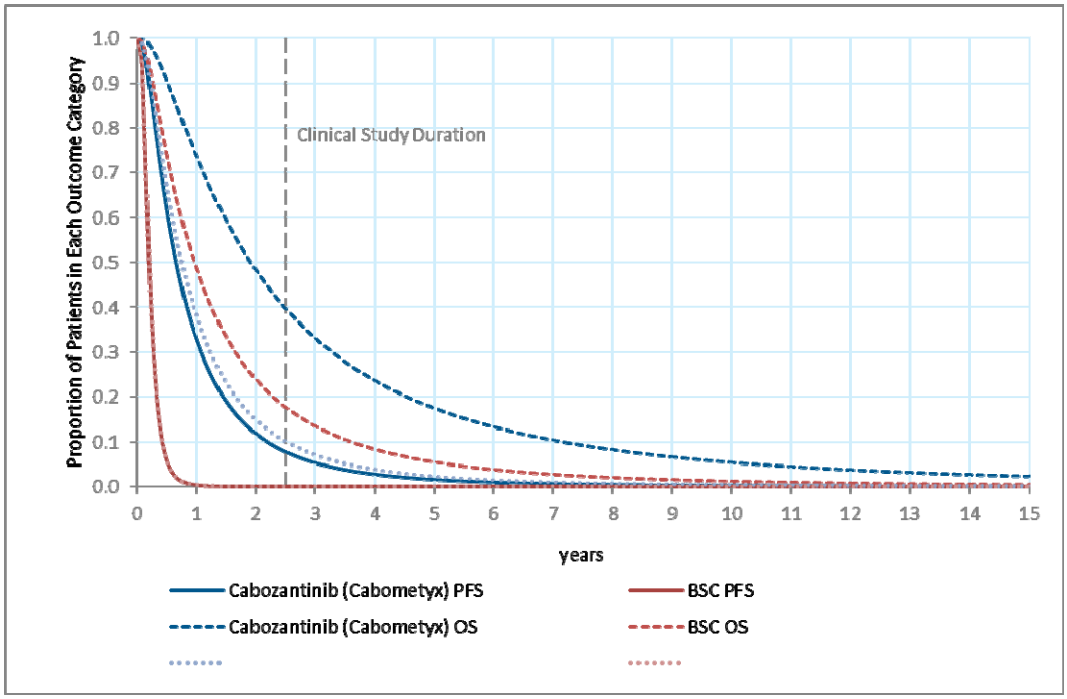
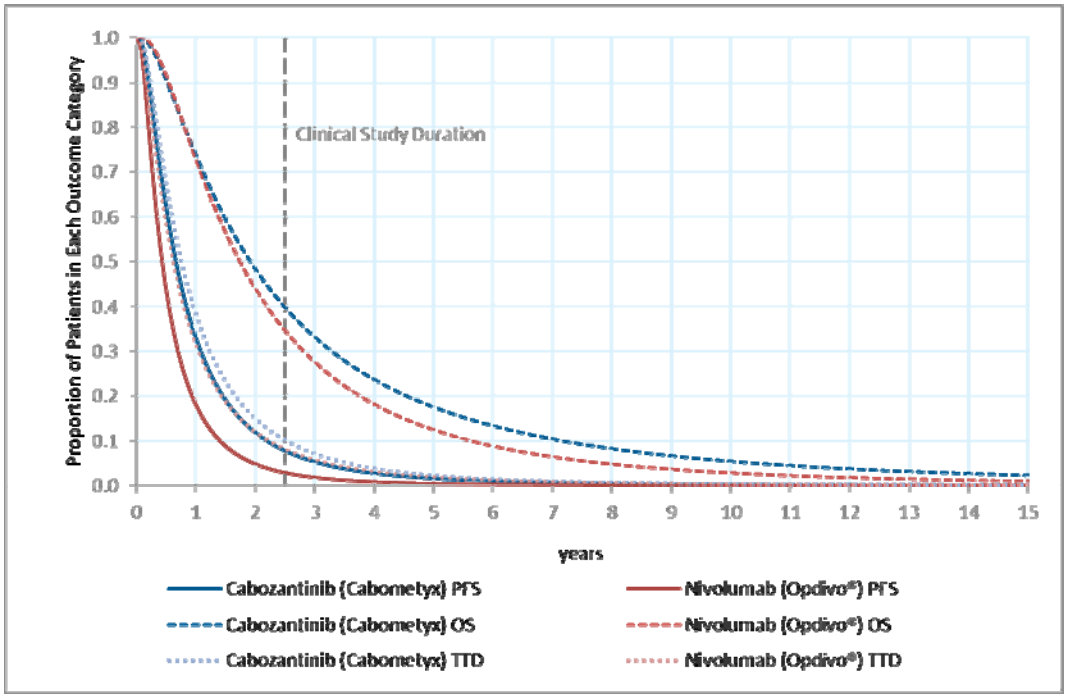


Figure 31: Proportion of cohort in the health states over time – cabozantinib versus nivolumab



5.7.4 QALY accrual over time

Figure 33 summarises the total QALYs for cabozantinib versus the key comparator axitinib for the base case; cabozantinib is predicted to produce more QALYs over time. These findings are consistent with the clinical benefit observed in the METEOR study in terms of OS, PFS and overall response.[10] The summary of QALY accruals is also shown in Figure 33 to Figure 35 and Table 81 to Table 83.

Figure 32: QALY accrual over time, cabozantinib vs. axitinib

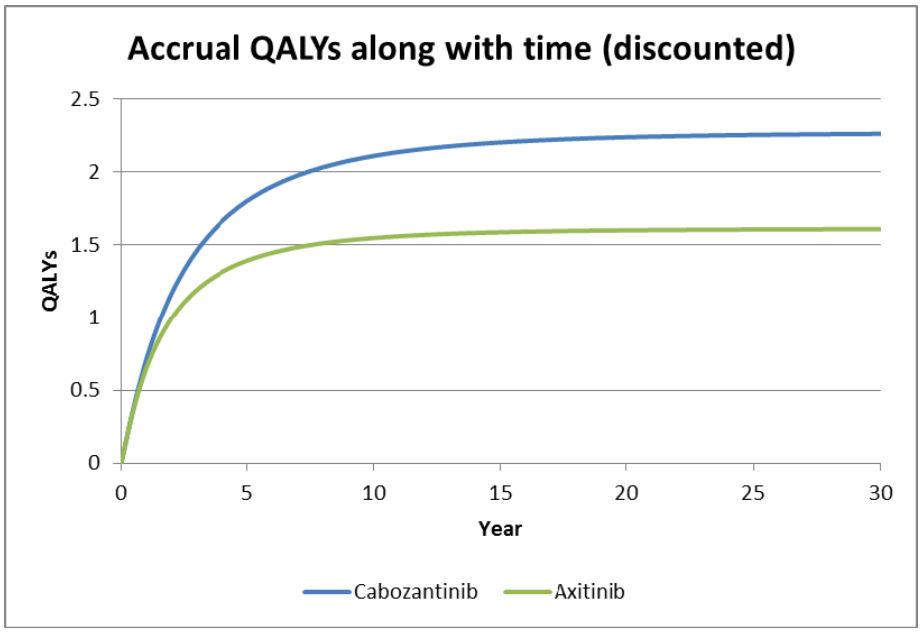


Table 81: Summary of QALY gain by health state, cabozantinib versus axitinib

Health state	QALY cabozantinib	QALY axitinib	Increment	Absolute increment	% absolute increment
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.					

Figure 33: QALY accrual over time, cabozantinib vs. everolimus

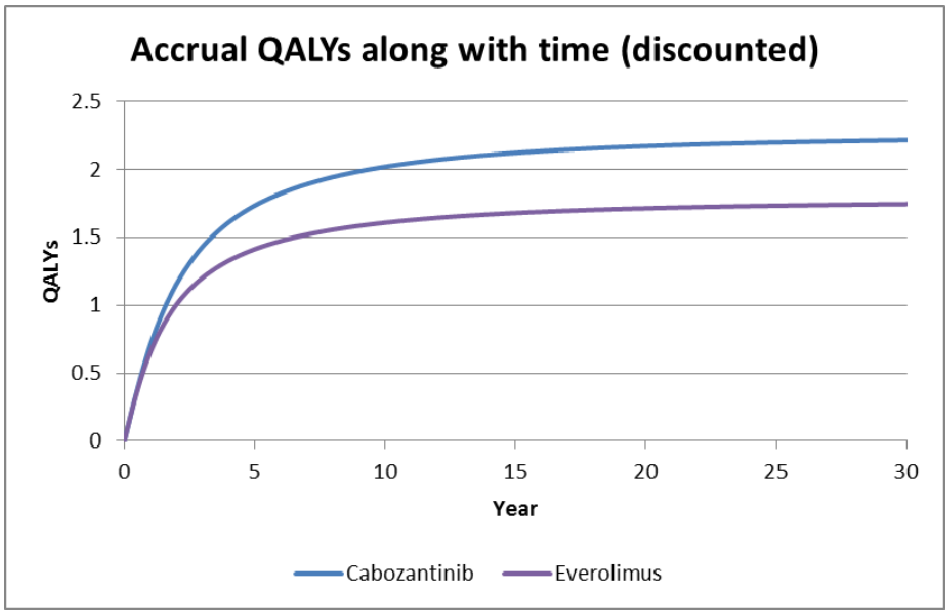


Table 82: Summary of QALY gain by health state, cabozantinib versus everolimus

Health state	QALY cabozantinib	QALY everolimus	Increment	Absolute increment	% absolute increment
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.					

Figure 34: QALY accrual over time, cabozantinib vs. BSC

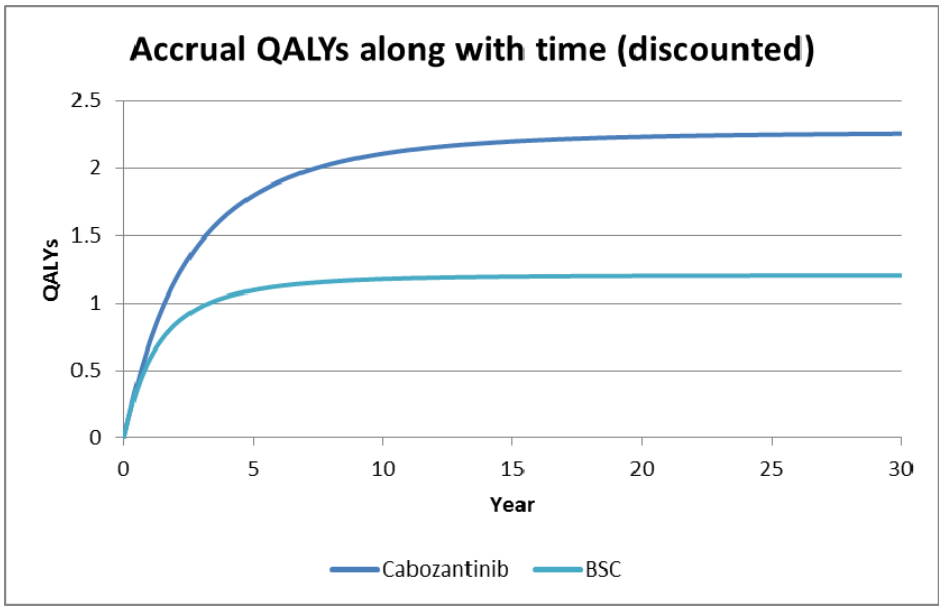


Table 83: Summary of QALY gain by health state, cabozantinib versus BSC

Health state	QALY cabozantinib	QALY BSC	Increment	Absolute increment	% absolute increment
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.					

Figure 35. QALY accrual over time, cabozantinib vs. nivolumab

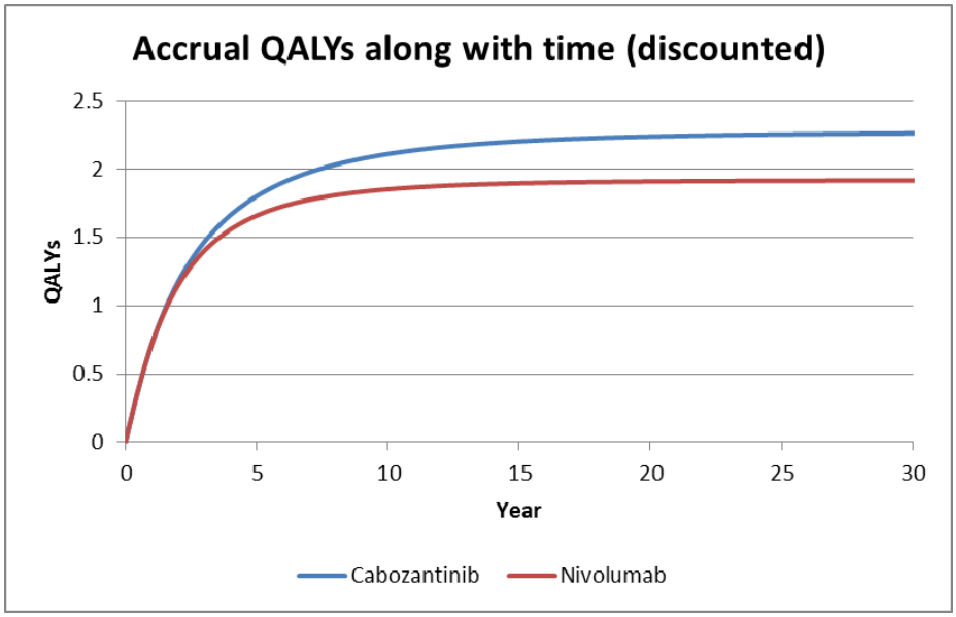


Table 84: Summary of QALY gain by health state, cabozantinib versus nivolumab

Health state	QALY cabozantinib	QALY nivolumab	Increment	Absolute increment	% absolute increment
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.

Table 85 to Table 87 show predicted total incremental costs for cabozantinib versus each of the four base case comparators, across health states, including separation by different resource use categories.

Table 85: Summary of costs by health state, cabozantinib versus axitinib

	Health state	Cabozantinib	Axitinib	Increment	Absolute increment	% absolute increment
PFS health state	Treatment acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total - PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS health state	Cost of subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End of life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total - PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.

Table 86: Summary of costs by health state, cabozantinib versus everolimus

	Health state	Cabozantinib	Everolimus	Increment	Absolute increment	% absolute increment
PFS health state	Treatment acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total - PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS health state	Cost of subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End of life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total - PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total			[redacted]	[redacted]	[redacted]	[redacted]

Key: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year

Table 87: Summary of costs by health state, cabozantinib versus BSC

	Health state	Cabozantinib	BSC	Increment	Absolute increment	% absolute increment
PFS health state	Treatment acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total – PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS health state	Cost of subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End of life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total - PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total			[redacted]	[redacted]	[redacted]	[redacted]

Key: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.

Table 88: Summary of costs by health state, cabozantinib versus nivolumab

	Health state	Cabozantinib	Nivolumab	Increment	Absolute increment	% absolute increment
PFS health state	Treatment acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Treatment administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total - PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS health state	Cost of subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End of life costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total - PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: PFS, progression-free survival; PPS, post-progression survival; QALY, quality-adjusted life year.

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to translate the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness model for the options being compared. The point estimates, standard errors/confidence intervals and distribution choices have been described for each parameter in Table 76. Uncertainties for distributions derived from the NMA were tested by sampling using variance-covariance matrix and random draws from the multivariate-normal distribution.

Figure 36 shows a PSA scatterplot and Figure 38 shows the cost-acceptability curve for the key comparison of cabozantinib versus axitinib for 5,000 PSA iterations. Table 89 to Table 92 report the mean probabilistic base case results for all four comparisons. Scatterplots show that there is some parameter

uncertainty around the mean ICER. The results suggest that the probability of cabozantinib being cost-effective versus axitinib at a willingness-to pay threshold of £50,000 per QALY gained is [redacted] Every effort has been made to ensure that parameter uncertainty was informed by data and not arbitrary assumptions for key parameters. PSA scatterplot and cost-acceptability curve diagrams for other comparisons are shown in Appendix 23.

Figure 36. PSA scatterplot, cabozantinib versus axitinib

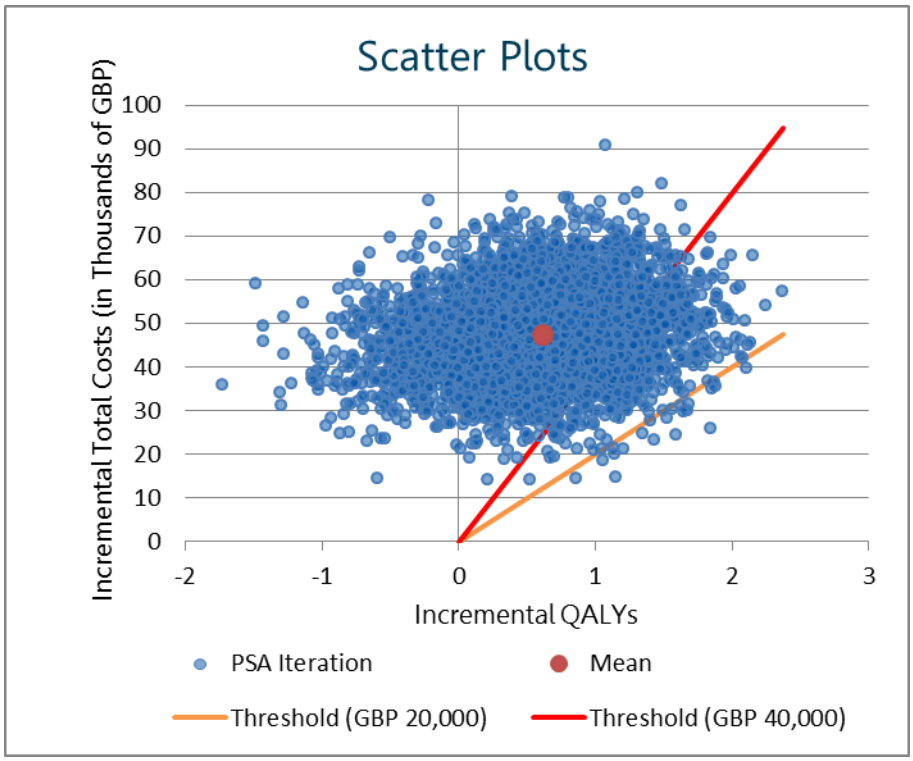


Figure 37: PSA cost-acceptability curve, cabozantinib versus axitinib

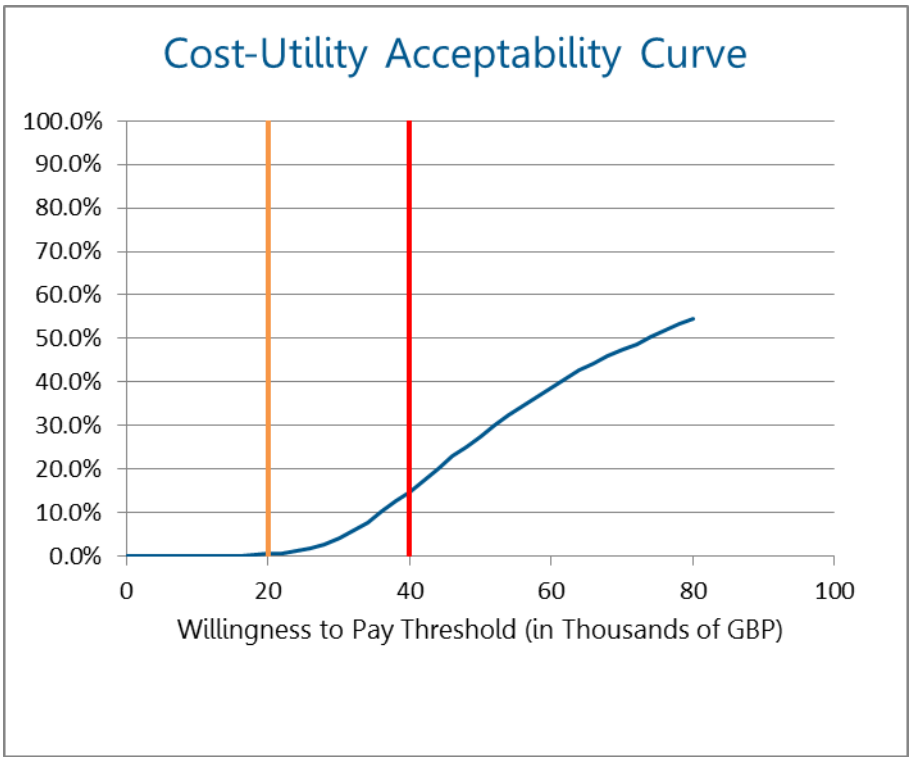


Table 89: Mean probabilistic base case results, cabozantinib vs. axitinib

				Incremental to cabozantinib			
	Total Costs	**QALYs**	**Life-Years**	**Costs**	**QALYs**	**Life Years**	**ICER**
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year							

Table 90: Mean probabilistic base case results, cabozantinib vs. nivolumab

				Incremental to cabozantinib			
	Total Costs	**QALYs**	**Life-Years**	**Costs**	**QALYs**	**Life Years**	**ICER**
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year							

Table 91: Mean probabilistic base case results, cabozantinib vs. everolimus (based on METEOR data)

				Incremental to cabozantinib			
	Total Costs	**QALYs**	**Life-Years**	**Costs**	**QALYs**	**Life Years**	**ICER**
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year							

Table 92: Mean probabilistic base case results, cabozantinib vs BSC

				Incremental to cabozantinib			
	Total Costs	**QALYs**	**Life-Years**	**Costs**	**QALYs**	**Life Years**	**ICER**
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life year							

5.8.2 Deterministic sensitivity analysis

An assessment of parameter uncertainty was also performed via deterministic sensitivity analysis. The model parameter values were individually varied to test the sensitivity of the model's results to specific parameters or sets of parameters. The inputs and the range tested are reported in Table 93.

Table 93: Summary of variables included in DSA

Variable	Base case	Min, max	Comment
General			
Cost discount	3.5%	0%, 5%	
Effect discount	3.5%	0%, 5%	
Time horizon (years)	30	15, 20	
Treatment Costs			
Baseline Weight (kg)	80.19	Normal	See Table 76
Cost of Cabozantinib for day	171.43	±10%	
Cost of Everolimus (per 10 mg)	89.10	±10%	
Cost of Axitinib (per 10 mg)	125.61	±10%	
Cost of Nivolumab (3mg)	32.91	±10%	
Cost of Sorafenib (800mg)	106.45	±10%	
Relative dose intensity of Cabozantinib	N/A	N/A	Not included (flat price)
Relative dose intensity of Everolimus	0.84	Normal	See Table 76
Relative dose intensity of Axitinib	1.02	Normal	See Table 76

Relative dose intensity of Nivolumab	0.98	Normal	See Table 76
Wastage of Nivolumab	N/A	N/A	Not included
Single administration cost of Nivolumab	152.00	±10%	
Adverse event costs			
Total cost of Cabozantinib AE	237.56	Gamma	See Table 76
Total cost of Everolimus AE	121.22	Gamma	See Table 76
Total cost of Axitinib AE	246.02	Gamma	See Table 76
Total cost of Nivolumab AE	0.00	Gamma	See Table 76
Disease Management costs			
Cost of GP visit	54.00	±10%	
Cost of CT scan	129.00	±10%	
Cost of Blood test	3.00	±10%	
Cost of Specialist community nurse visit	65.00	±10%	
Cost of Consultant	79.00	±10%	
PFS: GP visit frequency	0.50	Gamma	See Table 76
PFS: CT scan frequency	0.33	Gamma	See Table 76
PFS: Blood test frequency	1.00	Gamma	See Table 76
PFS: Consultant visit frequency	0.67	Gamma	See Table 76
OS: GP visit frequency	1.00	Gamma	See Table 76
OS: Nurse visit frequency	1.00	Gamma	See Table 76
OS: Blood test	0.67	Gamma	See Table 76
End-of-life costs			
End-of-life cost	5912.39	Gamma	See Table 76
Time on follow up treatment			
Time to third line treatment (days)	0	Normal	See Table 76
Time on Axitinib - 3rd line (days)	220.8	Normal	See Table 76
Time on Cabozantinib - 3rd line (days)	231.8	Normal	See Table 76
Time on Everolimus - 3rd line (days)	167.6	Normal	See Table 76
Time on Sunitinib - 3rd line (days)	118.7	Normal	See Table 76
Time on Sorafenib - 3rd line (days)	180.7	Normal	See Table 76
Time on Pazopanib - 3rd line (days)	109.6	Normal	See Table 76
Time on BSC - 3rd line (days)	0	Normal	See Table 76
Utilities			
Utilities: Progression free state	0.82	Beta	
Utilities: Utility decrement due to progression	0.04	Normal	
Utilities: Progressed state	N/A	N/A	Not included (calculated field, decrement tested)
AE duration (weeks)	4.00	Normal	
AE average episodes per patient	1.16	Normal	See Table 76
Utility decrement due to Grade 3/4 AEs	-0.06	Normal	See Table 76
Key: CI, confidence interval; GP, general practitioner; HR, hazard ration; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; SA, survival analysis; TTD, time to treatment discontinuation.			

Figure 39 shows a tornado diagram depicting the parameters which change ICER more than 10% compared to the base case. Tornado diagrams for comparisons to other comparators (everolimus, BSC and nivolumab) are included in Appendix 23. Results are robust to isolated parameter changes to the vast majority of variables in the model.

Figure 38: Tornado graph, cabozantinib versus axitinib

Table 94: Scenario analyses

		Total costs		Total QALYs		ICER
		Cabo.	Axit	Cabo.	Axit	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS curves: cross-over adjusted	OS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS=Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS unadjusted study population (ITT)	OS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	OS=Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility	Average decrement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease management cost (nivolumab TA submission)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key; Cabo, cabozantinib; axit, axitinib; PFS, progression-free survival; OS, overall survival, TTD, time to discontinuation

5.9 Subgroup analysis

Subgroup analyses of clinical outcomes in Section 4.8 showed the estimated clinical benefits of cabozantinib versus everolimus from METEOR data to be consistent across a range of subgroups. Further subgroup analysis was not explored in the economic model.

5.10 Validation

Validation of de novo cost-effectiveness analysis

Previous appraisals of advanced RCC treatments were reviewed and the economic approach was designed to be consistent. The aim was to analyse key clinical outcomes that impact NHS/PSS costs and patients' HRQoL.

The clinical outputs of the model were validated with UK clinical oncologists[33] whereas the model validation was carried out by economists who were not involved in the development of the original economic model. The list below gives an overview of the validation routines carried out:

- Input data validation
    - Rationale for inclusion of particular data sources
    - Data sources checked against original source
    - Distributions and parameters to represent uncertainty
    - Data adjustments:
        - Mathematical transformations, treatment of outliers, treatment of missing data, data synthesis, calibration, etc.
- Technical Validation
    - Detection of coding errors
    - Sheet by sheet testing, including macros
    - Check formulas on each input cell and how the linking of data to the variables/engines is done.
    - Check model parameters, testing of dropdown menus, names of cells, and all switches, including all sensitivity analyses
    - Check if any elements seem redundant

- Check intended functionality of macros versus actual functionality, and for interpretability
- Run model with extreme values
- Movement of patients through the model
- Additional checks:
    - Suggestions for optimisation for speed and accuracy, if relevant
    - Absence of bugs
    - Logical code structure
    - Appropriate transition of the conceptual model
    - Appropriateness of data and model

5.11 Interpretation and conclusions of economic evidence

Cabozantinib delivers clinically meaningful improvements in OS, PFS, and ORR, while maintaining a manageable toxicity profile. In previously treated advanced RCC patients, treatment with cabozantinib was more costly but also more effective in terms of LYs and QALYs gained than treatment with axitinib. Specifically, cabozantinib yielded overall ICER of [redacted] and [redacted] compared to axitinib the current standard of care. Cabozantinib also extended life by [redacted] life years and provided [redacted] incremental QALY gained compared to axitinib. The analysis was driven by the difference in PFS and OS between cabozantinib and axitinib, as well as the difference in treatment costs.

The results of the one-way sensitivity analyses demonstrated that the model was most sensitive to changes in: time horizon, drug cost (cost of cabozantinib) and the effect of discounting. Other inputs had little impact on the model results. The scenario analyses also showed the robustness of the base case results. The analysis that had the biggest impact on the results was the use of the OS curve based on the gompertz distribution in the unadjusted ITT population scenario analysis.

The results of the PSA demonstrated that cabozantinib had a [redacted] probability of being cost-effective at a threshold of £50,000. The key model drivers were identified from different sensitivity analyses: cost related model parameters and the choice of curve type for PFS and OS parametric modelling.

The key strength of this analysis was that it was based on evidence from a NMA comparing parametric survival curves, rather than HRs. This avoids the issue of violating the proportional hazards assumption as identified in the nivolumab NICE STA. In addition, resource use and cost inputs were populated using data reflecting UK clinical practices. Finally, the model concept, structure, and inputs were reviewed by oncologists actively treating RCC in the UK, thereby ensuring that the model assumptions were clinically relevant to the UK setting and that a comprehensive array of costs were accounted for.

This analysis is subject to limitations common to all models in that it combines data from numerous sources, requires structural and data assumptions, and that the model can be subject to bias. The first two limitations cannot be avoided since the primary motivation for creating any model is to assess comparative therapies in the absence of complete data. Assumptions were validated to ensure that they were justifiable on the basis of existing data and clinical opinion and were subjected to sensitivity analysis. The model used parametric curve extrapolation for both PFS and OS, based on a parametric curve NMA. The result of the model was impacted by the assumptions around curve extrapolation. In order to examine this impact, scenario analyses on time horizon were performed.

Time on treatment for axitinib was not identified in the published literature. For axitinib, PFS data was used as a proxy for treatment duration. This might not necessarily reflect clinical practice in the UK as some patients may receive treatment beyond progression. For nivolumab a TTD curve was identified and used in the analyses via indirect treatment comparison to METEOR data

The results of this analysis demonstrate that improvements in OS and PFS with cabozantinib translate into longer-term gains in LYs and QALYs compared to axitinib.

6 Assessment of factors relevant to the NHS and other parties

The same assumptions as those used in the population estimates for England presented in Section 3.2 are applied to derive the total number of advanced RCC patients eligible for second-line treatment in the budget impact calculations for Years 1 to 5.

In order to estimate new kidney cancer cases in years 2 to 5 the annual incidence rate of 5.17% observed in the UK between 2002-2004 and 2011-2013 for kidney cancer is applied to the projected incidence estimate for year 1 (10,613 patients in 2017) to estimate new cancer cases in years 2 to 5. In each year it is then assumed that 80% of all cases of kidney cancer are RCC and that 35.9% of all cases of RCC present at advanced stages (III and IV). Of these patients it is further estimated that 68% would be eligible for first-line systemic therapy and upon failure of first line approximately 50% would go on to receive second-line treatment. Table 95 presents the projected eligible patient population for Years 1 to 5.

Table 95: Projected second line advanced RCC cabozantinib eligible patient population for years 1 to 5

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated incidence of kidney cancer in England	10,613	11,162	11,739	12,346	12,985
Proportion of RCC in kidney cancer (80%)	8,490	8,930	9,391	9,877	10,388
Proportion of patients diagnosed in advanced stages (III and IV - 35.9%)	3,048	3,206	3,371	3,546	3,729
Proportion of patients eligible for first line treatment (68%)	2,073	2,180	2,292	2,411	2,536
Proportion of patients eligible for second line treatment (50%)	1,037	1,090	1,146	1,206	1,268

Table 96 presents the total number of patients estimated to be receiving treatment for second-line advanced RCC in England in Years 1 to 5 based on Ipsen market share data. 'Other' treatment includes patients who would be receiving either sunitinib or pazopanib in the second-line setting.

Table 96: Number of patients projected to be receiving treatment for second-line advanced RCC based on projected market share

	Year 1	Year 2	Year 3	Year 4	Year 5
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Assuming a positive NICE recommendation					

It is anticipated that the number of patients projected to be receiving cabozantinib based on Ipsen market share data would be [redacted] in year 1 rising to [redacted] in year 5. The number of patients anticipated to receive cabozantinib and all the other available treatments in each of the next 5 years is presented in Table 97.

Table 97: Number of patients projected to be receiving treatment for second-line advanced RCC based on anticipated market share

	Year 1	Year 2	Year 3	Year 4	Year 5
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Assuming a positive NICE recommendation					

The costs included in this analysis include all the direct costs to the NHS associated with the management of patients with advanced RCC. These include: drug costs, management costs (with and without progression), end of life costs and the costs of managing AEs.

The costs estimated for the purpose of this section are based on the inputs (and outputs) of the cost-effectiveness analysis as described in Section 5.0

There are no estimates of resource savings associated with the introduction of cabozantinib.

Estimated annual budget impact on the NHS in England

In order to estimate the annual budget impact to the NHS with the introduction of cabozantinib the annual cost per patient of each treatment option in Year 1 is multiplied by the total number of patients eligible for each treatment option in each of the years considered in the analysis. The total budget impact for cabozantinib is calculated as the difference between the total costs of treatment if cabozantinib is adopted minus the total cost of treatment if patients continued to receive existing therapies.

Table 98 reports the average annual cost per patient per year estimated from the cost effectiveness analysis for Year 1. Since the budget impact analysis only assumes that new incident cases would be treated in each year the average cost from year 1 of the cost effectiveness analysis is applied in each

year. The cost of “Other” are based on the weighted average annual cost per patient per year for sunitinib and pazopanib based on their projected market share.

Table 98: Average annual cost per patient per year as estimated in the cost-effectiveness analysis

	Cabozantinib	Axitinib	Nivolumab	Everolimus	Others	BSC
Average cost per year, £	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 98 reports the estimated annual budget impact to the NHS in England with the introduction of cabozantinib.

Table 99: Total annual budget impact to the NHS in England with the introduction of cabozantinib

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients eligible for treatment with cabozantinib in second-line advanced RCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients expected to receive cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost for total population without the introduction of cabozantinib (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost for total population with cabozantinib introduction (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental net budget Impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Main limitations within the budget impact analysis.

Since all resource use and costs used in the BIM were estimated directly from the cost effectiveness model, the same limitations as those discussed in the cost-effectiveness model section apply to the BIM estimates.

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8 Appendices

The following appendices have been provided in a separate document.

- Appendix 1: Cabozantinib SmPC
- Appendix 2: Draft EPAR
- Appendix 3: Clinical effectiveness literature review: Sources searched
- Appendix 4: Clinical effectiveness literature review: List of excluded studies
- Appendix 5: METEOR study: Inclusion/exclusion criteria
- Appendix 6: Quality assessment: METEOR Study
- Appendix 7: METEOR study: Forest plots of OS and PFS
- Appendix 8: NMA literature review: Search strategy
- Appendix 9: NMA: Results, outcomes and quality assessment of the relevant trials in the NMA
- Appendix 10: Assessment of proportional hazard assumption
- Appendix 11: Transitivity property test for each survival distribution
- Appendix 12 Programming code for parametric survival curve NMA
- Appendix 13: Random effects model
- Appendix 14: NMA expected OS and PFS curves based on estimated parameters
- Appendix 15: Model parameter estimates and their estimate covariance for fixed effects NMA
- Appendix 16: NMA sensitivity analysis on unadjusted OS population (ITT)
- Appendix 17: Cost-effectiveness studies literature review: Search strategy and quality assessment of identified studies

- Appendix 18: Summary lists of published cost-effectiveness studies
- Appendix 19: Measurement and valuation of health effects literature search: Search strategy
- Appendix 20: Cost and health care resource use literature review: Search strategy
- Appendix 21: Summary list of resource use and cost studies
- Appendix 22: Efficacy parameters from METEOR study and NMA
- Appendix 23: Sensitivity results for nivolumab, everolimus and BSC comparisons

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2016

Cabozantinib for previously treated advanced cell renal cell carcinoma [ID931)

IPSEN LTD

1 Introduction

The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2104) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company/ of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

Generic name: Cabozantinib
Brand name: CABOMETYX®
Licensed indication: For the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.

The scheme applies the above population.

3.2 Please outline the rationale for developing the Patient Access Scheme.

The PAS has been developed to enhance the cost effectiveness of cabozantinib for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy. It is anticipated that the proposed discount facilitate a positive NICE recommendation, resulting in access for RCC patients to a new treatment as per 3.1.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

A Simple Discount Scheme is proposed based on the agreed NHS List price with a discounted price which is applicable to all packs.

<u>Cabometyx® NHS List Price:</u>
20 mg 30-tab pack: £5,143.00
40 mg 30-tab pack: £5,143.00
60 mg 30-tab pack: £5,143.00

<u>Cabometyx® Discount:</u>
[redacted]

[redacted]

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The patient access scheme applies to the whole licensed patient population.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The patient access scheme will apply once a positive NICE recommendation has been received. As a proposed simple discount the scheme is not dependent on any criteria or measures.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All eligible patients defined within the licensed indication will benefit from the simple discount patient access scheme.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

A simple discount will be applied at the point of invoice. No rebates or other calculations will be necessary to manage the scheme.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

Ipsen Ltd will apply the simple discount at the point of Invoice, and no further management or additional information will be required to manage the scheme.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The discount is applied at the point of Invoice, no further processes or management of the scheme are required.

3.10 Please provide details of the duration of the scheme.

The scheme (once approved) will be available for the duration of any NICE recommendation.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

None identified

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

Not applicable.

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company/sponsor submission of evidence'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

Not applicable. All information on the population to whom the scheme applies is provided in the main Ipsen submission document.

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

Not applicable.

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

Data is as per the main Ipsen submission document.

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 5.5 of the 'Specification for manufacturer/sponsor submission of evidence'

Table 1: Costs associated with the implementation and operation of the patient access scheme (PAS)

	Calculation of cost	Reference source
Stock management	Zero	
Administration of claim forms	Zero	
Staff training	Zero	
Other costs…	Zero	
Total implementation/ operation costs	Zero	

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

There are no additional treatment-related costs incurred with implementing the scheme.

Table 2: Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Intervention without PAS		Intervention with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Interventions					
Monitoring tests					
Diagnostic tests					
Appointments					
Other costs…					
Total treatment-related costs	Zero	Zero	Zero	Zero	There are no incremental costs with a simple discount applied at Invoice

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 3).

The cost-effectiveness results without and with Patient Access Scheme are shown on Table 3 and Table 4 (NMA based analysis) and Table 5 and Table 6 (METEOR based analysis). Please note that the results are from the Ipsen

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

model which was updated during clarification stage and the corrected company base case results presented in Tables 95 and 96 of the ERG report.

Table 3 Base-case cost-effectiveness results without the Patient Access Scheme (NMA based)

	Cabozantinib	Axitinib	Everolimus	Nivolumab	BSC
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4 Base-case cost-effectiveness results with the Patient Access Scheme (NMA based)

	Cabozantinib	Axitinib	Everolimus	Nivolumab	BSC
Intervention cost (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER (£)	N/A	46,118	68,404	-49,561	57,019

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 5 Base-case cost-effectiveness results without the Patient Access Scheme (METEOR based)

	Cabozantinib	Everolimus
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 6 Base-case cost-effectiveness results with the Patient Access Scheme (METEOR based)

	Cabozantinib	Everolimus
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	N/A	78,557

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

The base-case cost-effectiveness results without and with Patient Access Scheme are shown on Table 7 and Table 8 (NMA based analysis) and Table 9 and Table 10 (METEOR based analysis).

Table 7 Base-case cost-effectiveness results for the intervention without the Patient Access Scheme (NMA based)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BSC	[redacted]							
Everolimus								
Axitinib								
Cabozantinib								
Nivolumab								

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 8 Base-case cost-effectiveness results for the intervention with the Patient Access Scheme (NMA based)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
BSC	[redacted]						N/A	N/A
Everolimus							45,354	N/A
Axitinib							74,597	29,243
Cabozantinib							57,019	-17,577
Nivolumab							108,759	51,740

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 9 Base-case cost-effectiveness results for the intervention without the Patient Access Scheme (METEOR based)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Everolimus	[redacted]							
Cabozantinib								

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 10 Base-case cost-effectiveness results for the intervention with the Patient Access Scheme (METEOR based)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	78,557	N/A

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The deterministic sensitivity analysis results with PAS are shown from Figure 1 to Figure 5.

Figure 1: Tornado graph, cabozantinib versus axitinib (NMA based)

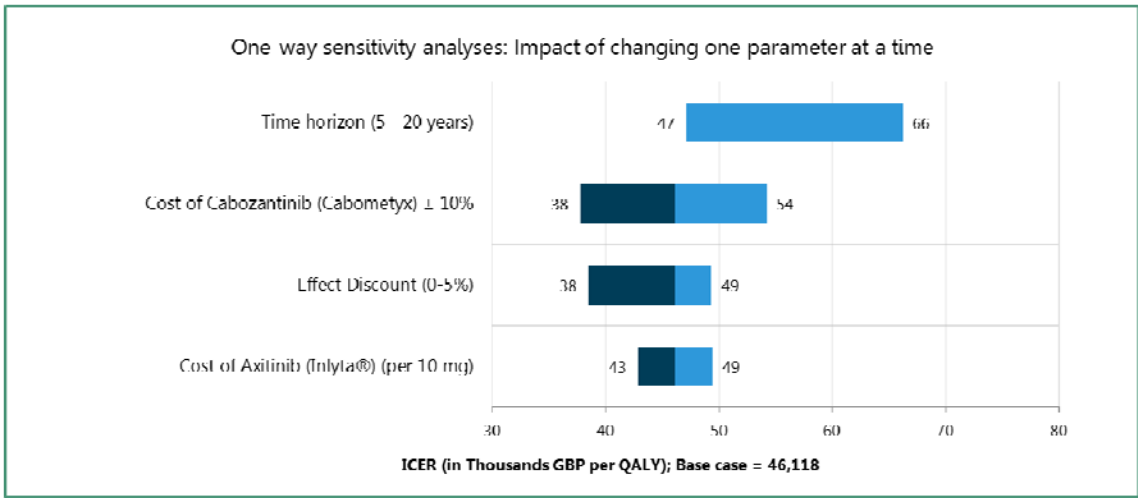


Figure 2: Tornado graph, cabozantinib versus everolimus (NMA based)

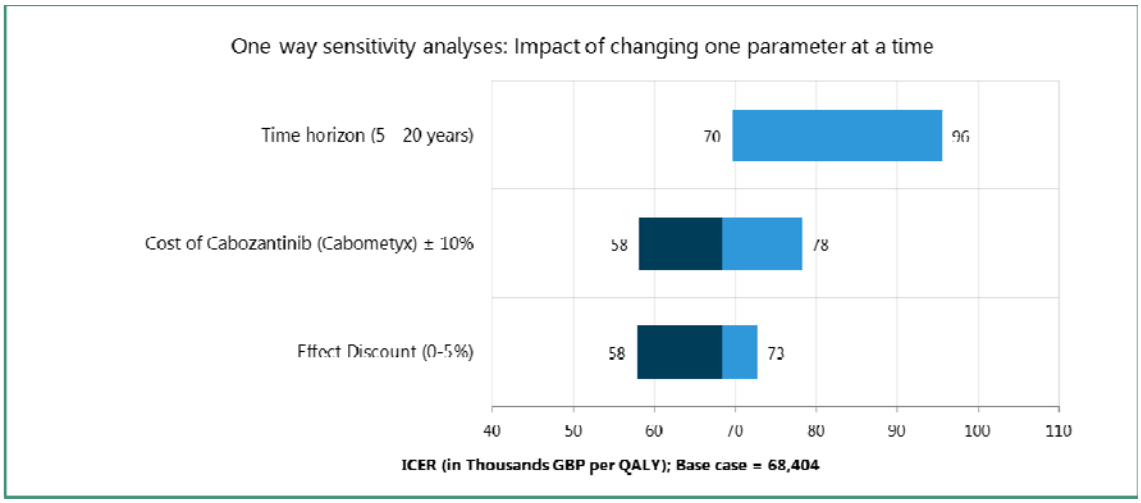


Figure 3: Tornado graph, cabozantinib versus nivolumab (NMA based)

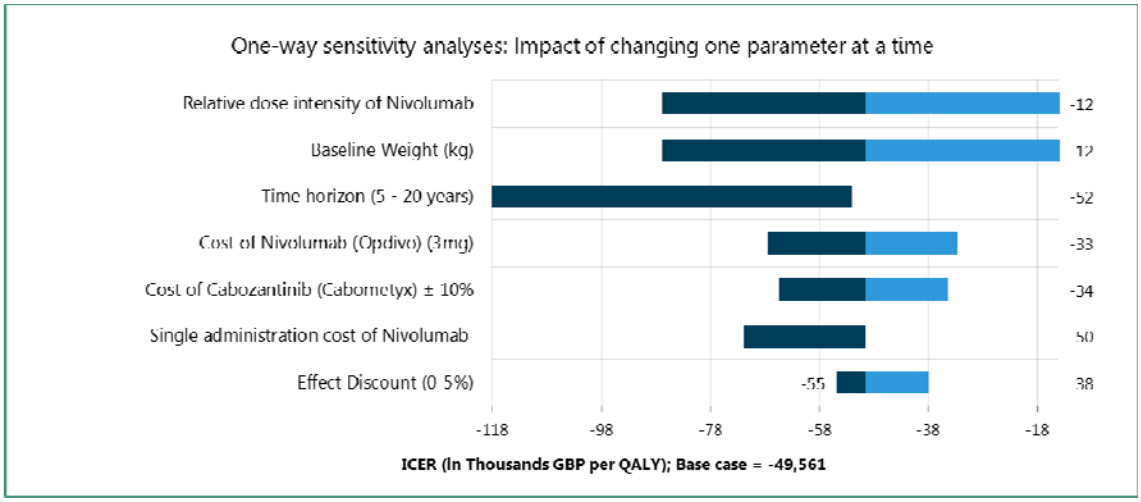


Figure 4: Tornado graph, cabozantinib versus BSC (NMA based)

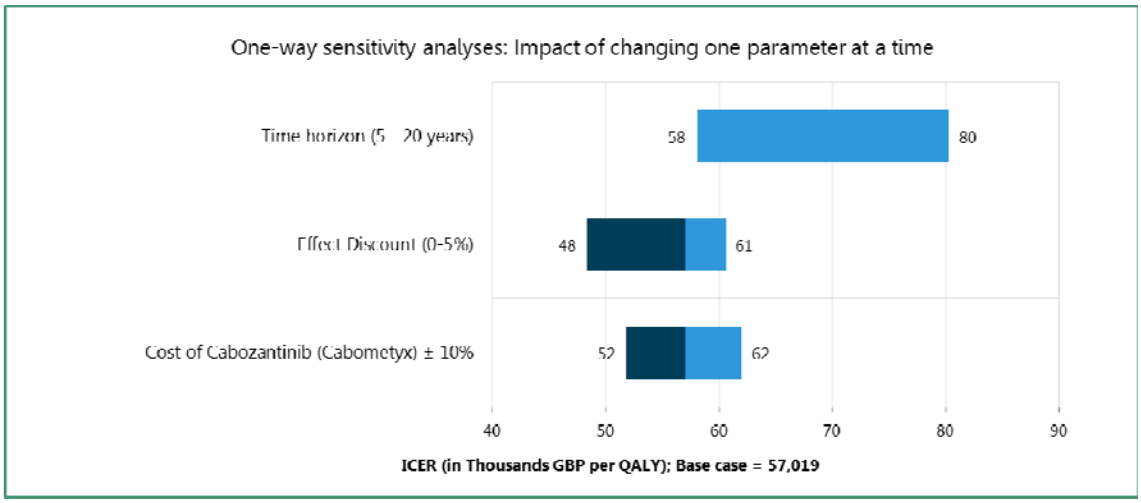
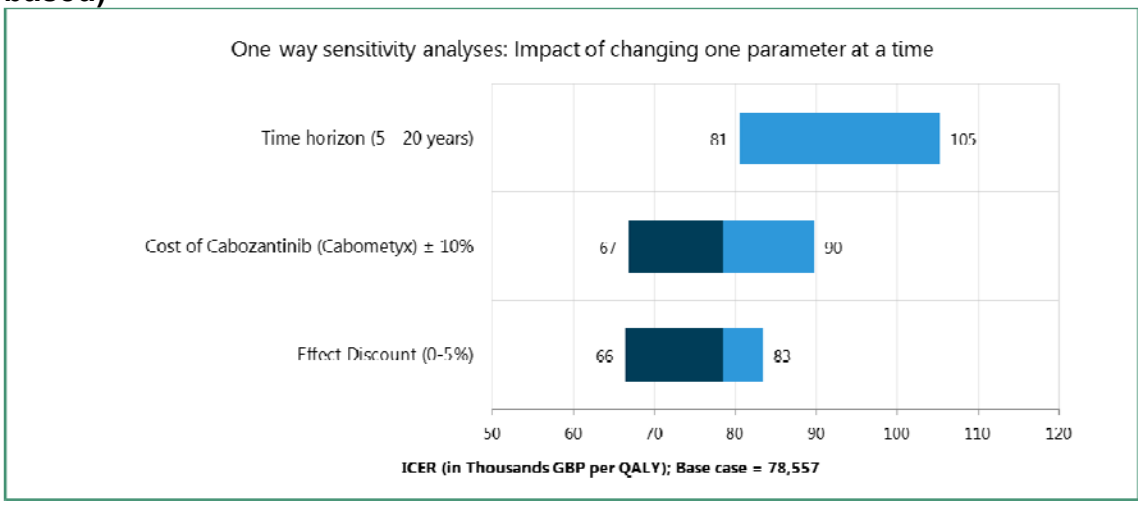


Figure 5: Tornado graph, cabozantinib versus everolimus (METEOR based)



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic sensitivity analysis results with PAS are shown from Figure 6 to Figure 15.

Figure 6: Scatter plot, cabozantinib versus axitinib (NMA based)

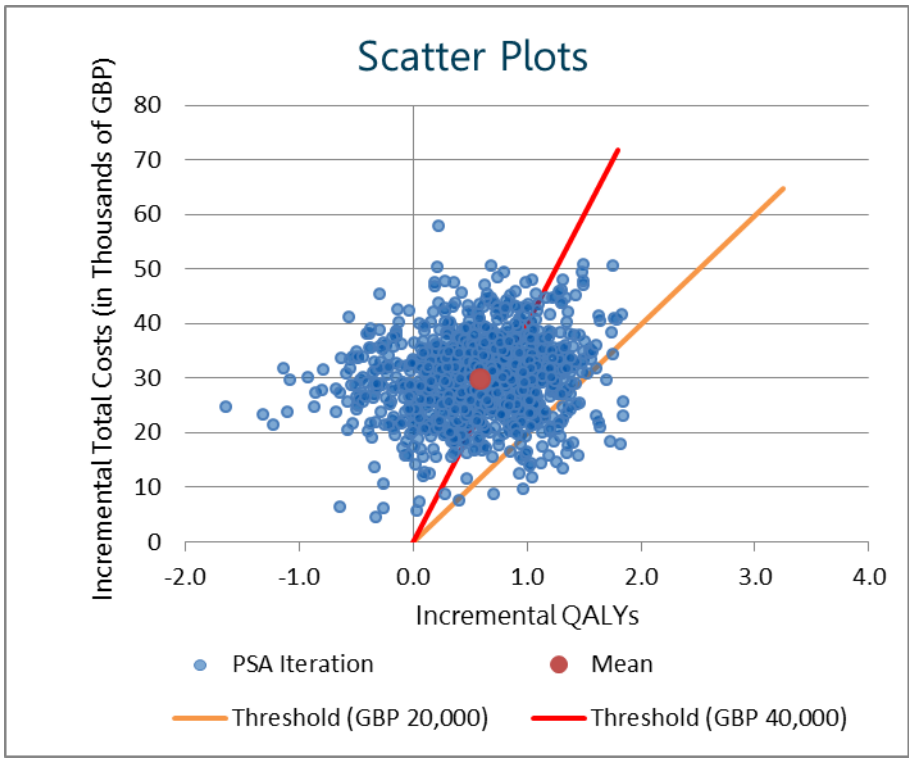


Figure 7: Cost-effectiveness acceptability curve, cabozantinib versus axitinib (NMA based)

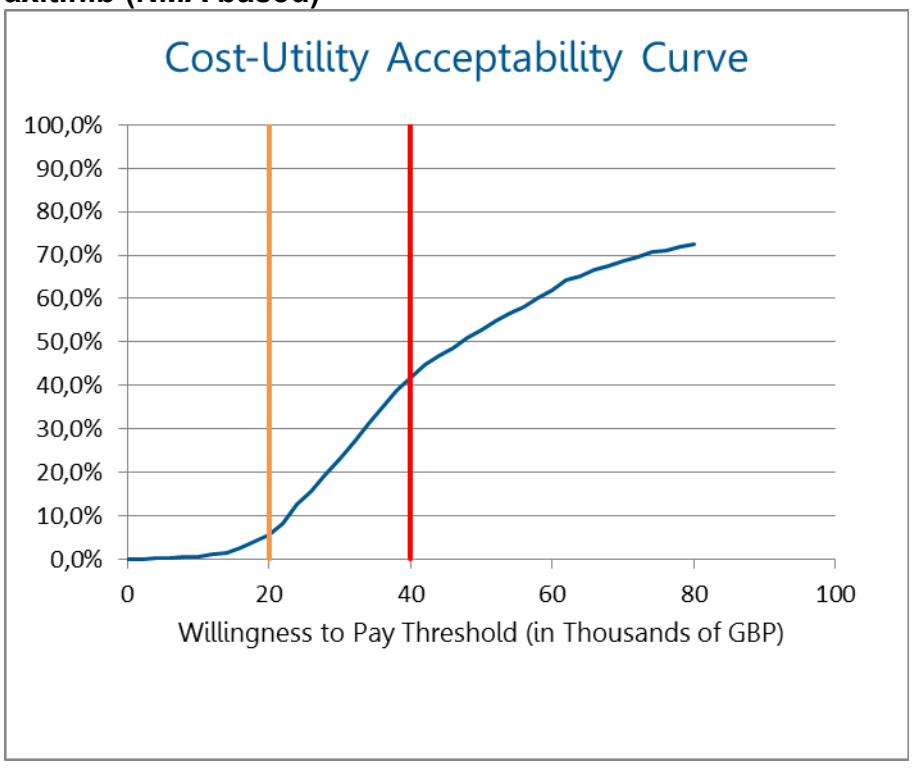


Figure 8: Scatter plot, cabozantinib versus everolimus (NMA based)

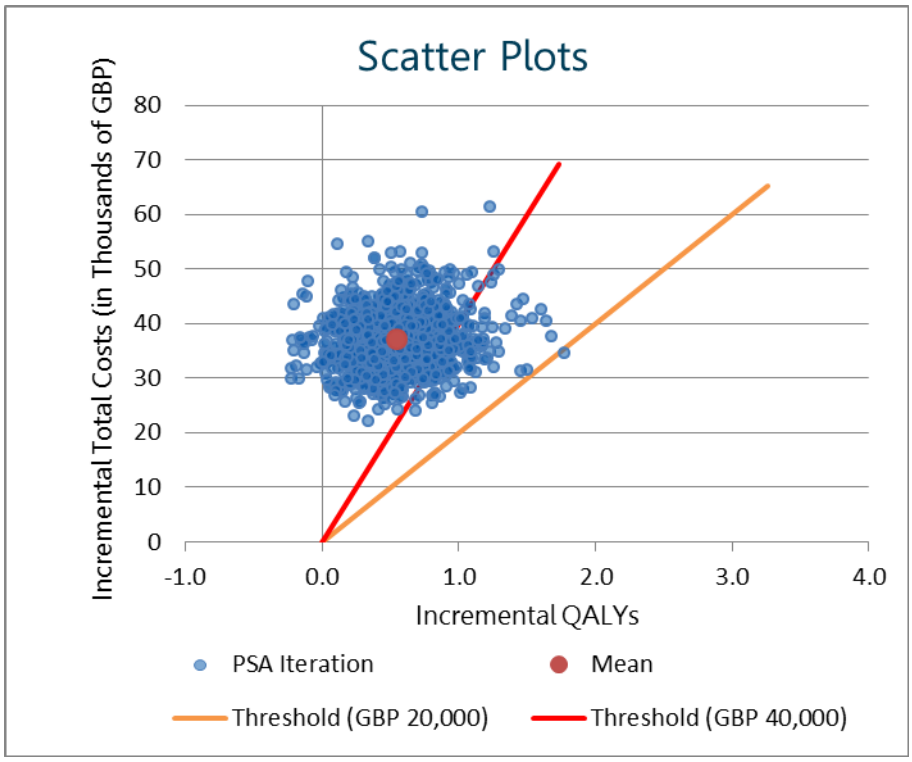


Figure 9: Cost-effectiveness acceptability curve, cabozantinib versus everolimus (NMA based)

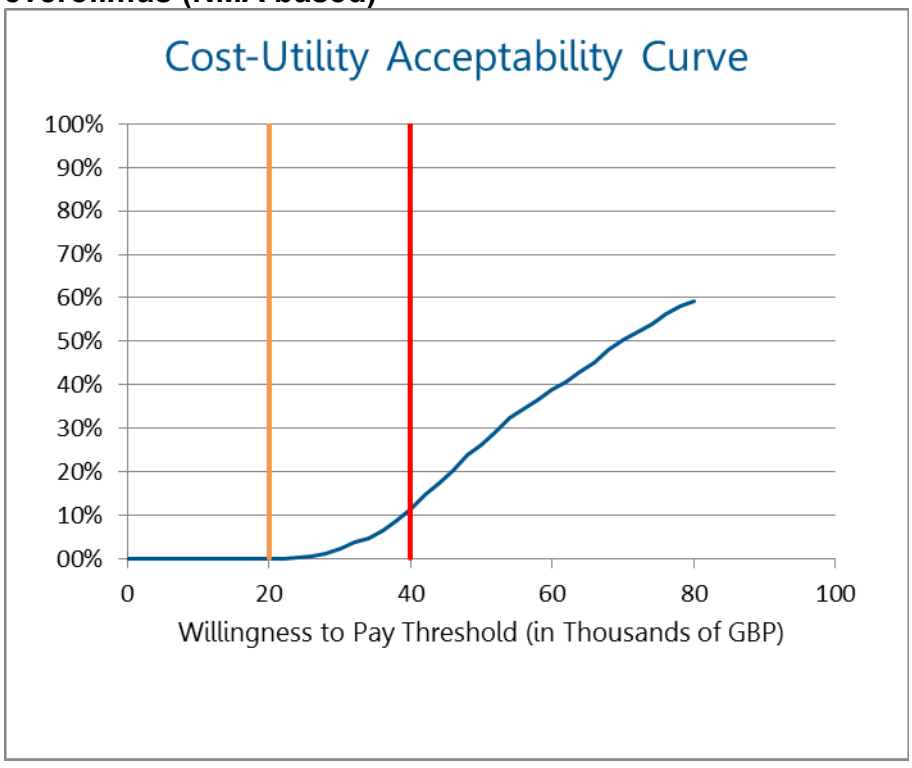


Figure 10: Scatter plot, cabozantinib versus nivolumab (NMA based)

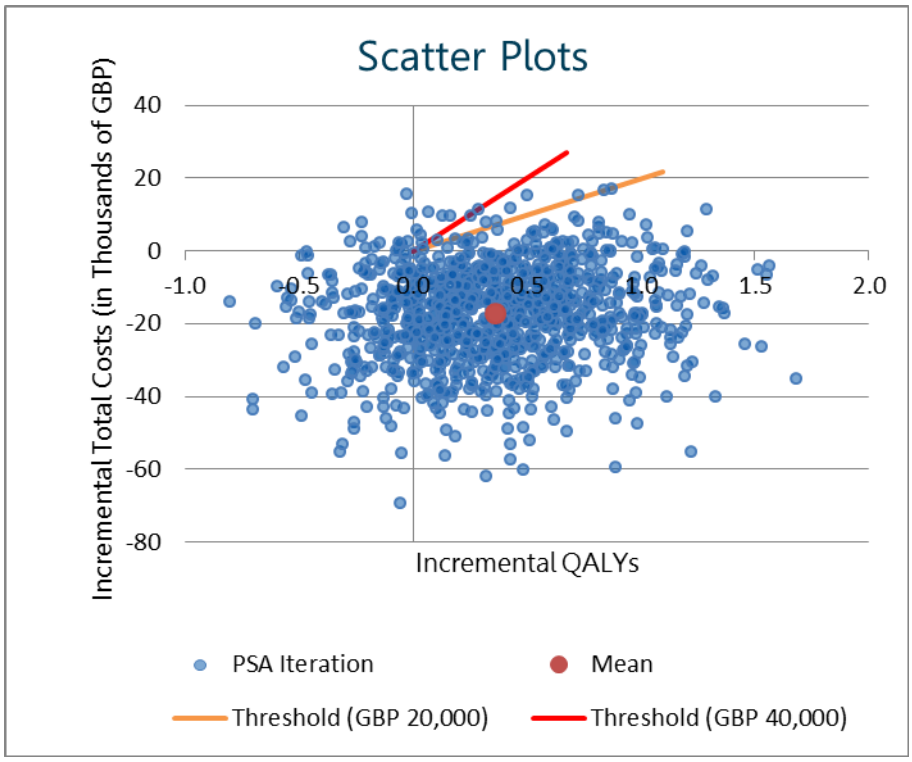


Figure 11: Cost-effectiveness acceptability curve, cabozantinib versus nivolumab (NMA based)

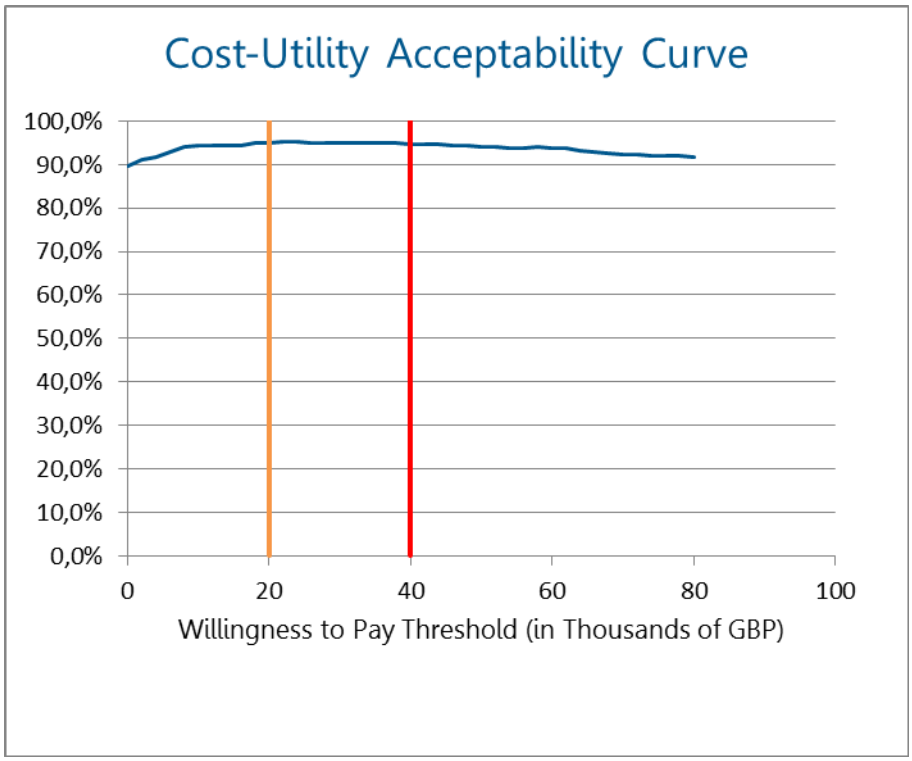


Figure 12: Scatter plot, cabozantinib versus everolimus (METEOR based)

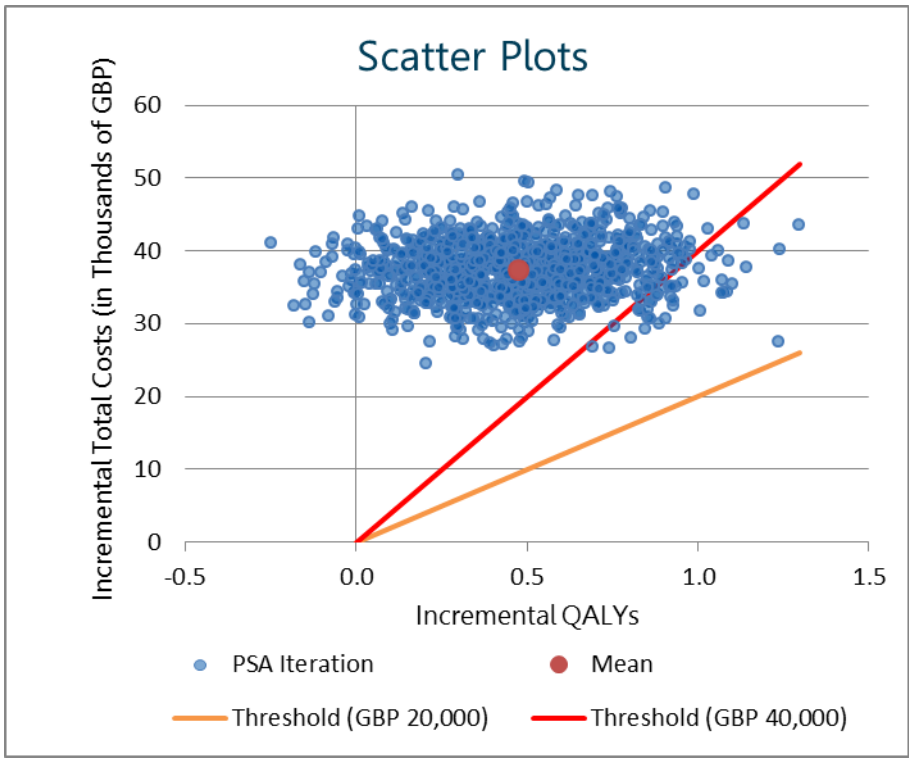


Figure 13: Cost-effectiveness acceptability curve, cabozantinib versus everolimus (METEOR based)

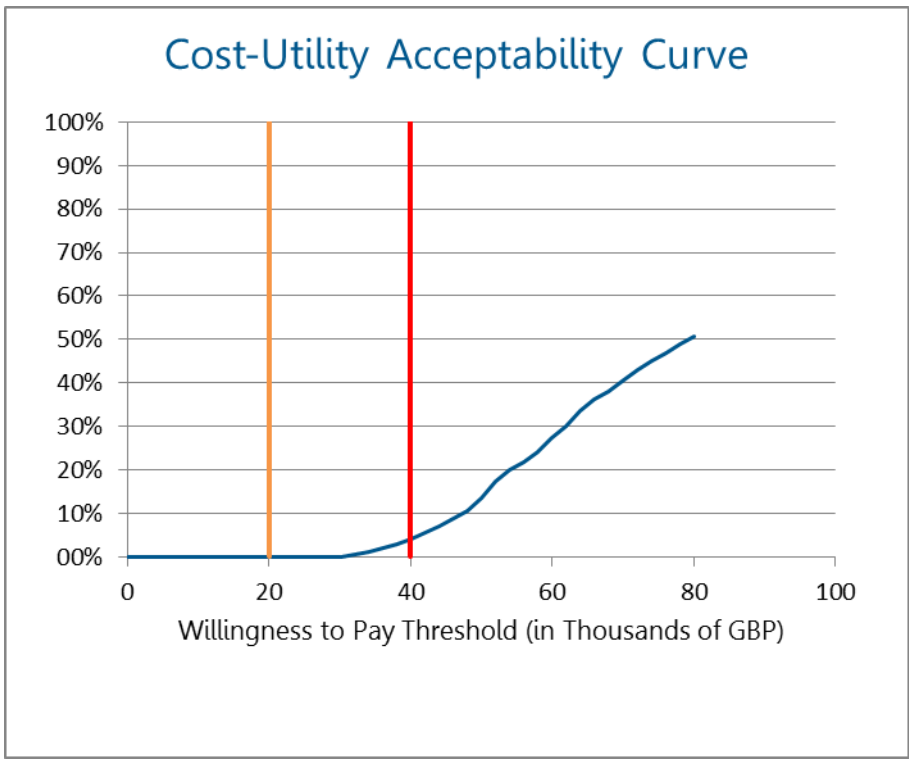


Figure 14: Scatter plot, cabozantinib versus BSC

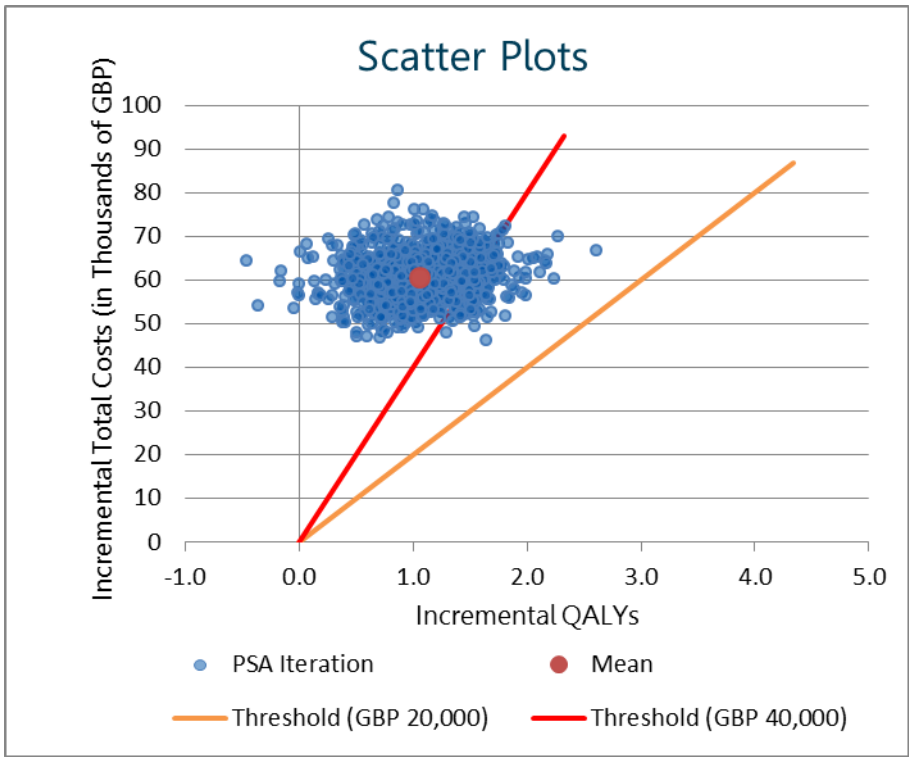
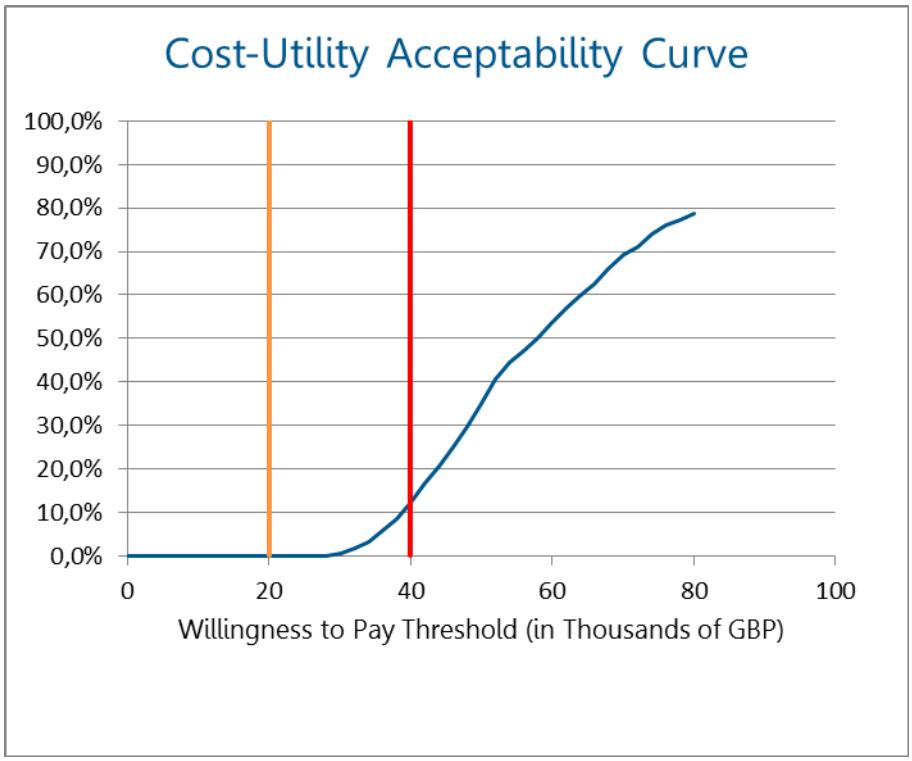


Figure 15: Cost-effectiveness acceptability curve, cabozantinib versus BSC



4.11 Please present scenario analysis results as described for the main company/sponsor submission of evidence for the technology appraisal.

The scenario analysis results are shown on Table 11.

Table 11 Scenario analysis results with the Patient Access Scheme

		Total costs		Total QALYs		ICER
		Cabo.	Axit	Cabo.	Axit	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	46,118
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	49,195
	0%	[redacted]	[redacted]	[redacted]	[redacted]	41,229
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	48,584
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	47,116
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	48,122
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	57,940
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	45,958
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	56,516
OS curves: cross-over adjusted	OS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	48,080
	OS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	48,387
	OS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	48,190
	OS=Weibull	[redacted]	[redacted]	[redacted]	[redacted]	59,044
OS unadjusted study population (ITT)	OS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	51,094
	OS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	111,384
	OS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	57,350
	OS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	52,394
	OS=Weibull	[redacted]	[redacted]	[redacted]	[redacted]	86,331
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	40,865
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	35,590
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	52,095
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	36,733
Utility	Average decrement	[redacted]	[redacted]	[redacted]	[redacted]	46,882
Cost	Disease management cost (nivolumab TA submission)	[redacted]	[redacted]	[redacted]	[redacted]	47,046
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	46,584
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	47,620
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	46,379

Key; Cabo, cabozantinib; axit, axitinib; PFS, progression-free survival; OS, overall survival, TTD, time to discontinuation

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable. The Patient Access Scheme does not depend on any clinical variable.

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 12 Results showing the impact of Patient Access Scheme on ICERs

	ICER for intervention versus:				
	Comparator 1		**Comparator 2**		**…**
	Without PAS	**With PAS**	**Without PAS**	**With PAS**	
Scenario 1 (base-case)					
Scenario 2					
Scenario 3					
Scenario 4					
…					

PAS: patient access scheme.

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable the scheme submitted is a simple discount scheme.

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection

- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

5.4 Please specify the period between the time points when the additional evidence will be considered.

Response

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Response

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

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Single technology appraisal

Cabozantinib for previously treated advanced renal cell carcinoma (ID931)

Dear Company,

The Evidence Review Group, BMJ Technology Assessment Group, and the technical team at NICE have looked at the submission received on 11th October from Ipsen. 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, 15th November 2016**. 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 Aminata Thiam, Technical Lead (Aminata.Thiam@nice.org.uk). Any procedural questions should be addressed to Jeremy Powell, Project Manager (Jeremy.Powell@nice.org.uk).

Yours sincerely

Melinda Goodall
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority Question:** Please provide the WinBUGS code files used for each of the outcomes in the network meta-analysis (NMA) presented in the submission, including the study data, and other model inputs.

A2. **Priority Question:** The submission states in section 4.10.5, page 94, that "networks are adjusted to the baseline of the METEOR study". Please provide details of all of the adjustments used in the NMA for each of the outcomes (OS, PFS and time to treatment discontinuation [TTD]) and the rationale for each adjustment. If this was done within WinBUGS, please provide the relevant code.

A3. **Priority Question:** Please complete the following table with the baseline characteristics of the population in METEOR based on treatment history for each trial arm (intent-to treat [ITT]and primary endpoint intent-to treat [PITT] population):

Baseline Characteristic		ITT Population		PITT Population	
		Cabozantinib N = 330	Everolimus N = 328	Cabozantinib N = 187	Everolimus N = 188
		n (%)	n (%)	n (%)	n (%)
Number of prior VEGFR-TKIs	1				
	2				
	≥3				
Number of prior systemic anti-cancer treatments for RCC	1				
	2				
	≥3				
Number of patients who received sunitinib as their first line therapy					
Number of patients who received pazopanib as their first line therapy					

A4. **Priority Question:** Please provide the results for PFS, OS, response rate and TTD for the subgroup of patients from METEOR with only 1 prior VEGFR-TKI therapy (i.e. in the proposed 2rd line treatment of advanced renal cell carcinoma [RCC]). Please also provide the baseline characteristics for each trial arm of METEOR for this subgroup.

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A5. **Priority Question**: Please provide the results for PFS, OS, response rate and TTD for the subgroup of patients from METEOR with 2 prior therapies including at least one VEGFR-TKI. (i.e. in the proposed 3rd line treatment of advanced RCC). Please also provide the baseline characteristics for each trial arm of METEOR for this subgroup.

A6. **Priority Question:** Please provide a comparison of cabozantinib, axitinib, everolimus, nivolumab and best supportive care using the subgroup of patients from METEOR with only 1 prior VEGFR-TKI therapy for PFS, OS and TTD (i.e. in the proposed 2nd line treatment of advanced RCC).

A7. **Priority Question**: Please provide a comparison of cabozantinib, everolimus, nivolumab and best supportive care using the subgroup of patients from METEOR with 2 prior therapies including at least one VEGFR-TKI for PFS, OS and TTD (i.e. in the proposed 3rd line treatment of advanced RCC).

A8. Please provide a figure for each of the comparators in the NMA showing both the resulting log-normal plot with the adjustments, and the log-normal plot without the adjustments to the baseline from the METEOR study applied for:

a) PFS
b) OS
c) TTD

A9. Please provide a rationale for why the OS and PFS seen in the everolimus arm of METEOR differ from the OS and PFS observed in Checkmate 025.

A10. For the outcome TTD in the NMA, please explain why it has been assumed that there is a relationship between TTD and the comparator intervention (i.e. why has it been assumed that the TTD for a treatment in one arm of a study has a relationship to the TTD for the alternative treatment arm in the same study?)

A11. The submission states in Table 13 on page 60 that METEOR was an open-label study and “Patients and investigators were not masked to study treatment to allow appropriate management of adverse events”. Please provide further details on the rationale for conducting METEOR as an open-label study.

A12. Please provide the appendices to the clinical study report (CSR) of METEOR as well as the tables referred to in the CSR that were not provided.

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Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide the regenerated Kaplan-Meier (KM) plots and KM data for OS, PFS and TTD for each of the interventions in the NMA.

B2. **Priority question**: Please provide the KM plots for TTD in the METEOR trial and the KM data for OS, PFS and TTD from the METEOR trial.

B3. **Priority question:** Please provide plots of KM data along with superimposed fitted curves for PFS, OS and TTD for both arms of the METEOR trial and the re-generated data for all treatments in the NMA. Please provide these for each of the parametric functions tested.

B4. **Priority question:** For OS, PFS and TTD in the METEOR trial data, please provide:

a) Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time)
b) Log(survival function / (1-survival function)) plots versus Log(time)
c) Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time)

B5. **Priority question:** For OS, PFS and TTD in the re-generated data used in the NMA, please provide:

a) Log(survival function / (1-survival function)) plots versus Log(time)
b) Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time)

B6. **Priority question**: On page 90 of the submission, table 32 outlines the studies included for the NMA and whether the proportional hazard (PH) assumption holds. Please:

a) Give further details on the justification used to determine whether this assumption holds for both PFS and OS in each of the trials;
b) Undertake the same assessment process with regards to a proportional odds and accelerated failure time assumption based on the plots requested in B4 and B5.

B7. **Priority question:** If a proportional odds assumption holds for PFS, OS and TTD, for any of the comparisons resulting to the response to question B4 and B5, please fit a proportional odds log-logistic model where relevant and report the results of the economic model as a scenario analysis.

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B8. **Priority question:** Given that a PH assumption holds for the METEOR trial data, please use a joint proportional hazards model to fit appropriate parametric curves for PFS, OS and TTD, and use these curves to perform a trial-based scenario analysis in the economic model.

B9. **Priority question**: Whether the relative treatment effect for cabozantinib in 2nd and 3rd line treatment for advanced RCC is equivalent or not, the baseline inputs in the economic model are likely to differ and therefore may result in different outcomes. Please provide separate base case analyses for the 2nd and 3rd line treatment for advanced RCC of cabozantinib compared with all relevant comparators using appropriate model inputs based on the subgroup analyses requested in questions A4 to A7.

B10. A flexible spline-based survival model approach was deemed appropriate in the ongoing nivolumab technology appraisal (ID853). Please explain why spline curves were not considered for the survival analysis in this appraisal.

B11. The model appears to calculate the cost of subsequent treatment for all patients whose disease progressed. However, the active treatment costs are calculated for all patients who have not yet discontinued treatment (based on the TTD data) but may have progressed. This results in a proportion of patients in the model receiving both active treatment and subsequent treatment, concurrently. Please amend this inaccuracy and provide the updated model results. Please also clarify any assumptions made following the amendments.

B12. The submission states that Table 56 on page 128 shows the results of the utility regression analyses with and without the treatment effect included as a covariate. However, only the results without the treatment effect appear to be presented. Please provide the results of the analysis that includes the treatment effect as a covariate.

B13. Please explain how the estimates in Table 56 on page 128 of the submission should be used to estimate the utility of a progression-free patient who has not experienced an adverse event, i.e. without applying the decrements for progression or adverse events.

B14. Please give further detail and justification on how the adverse events utility decrement has been estimated and applied.

B15. Please clarify why treatment-emergent adverse events were used in the model rather than treatment-related adverse events.

B16. Please clarify what the disutility value for axitinib, given in Table 63 on page 133 of the submission, relates to. It appears too high for a disutility.

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B17. Please clarify why an adverse event related disutility is not given in Table 62 on page 132 for axitinib.

B18. Please explain why the costs of adverse events were not considered for nivolumab in Table 76 on page 148.

B19. For the comparison of cabozantinib with nivolumab, the model results reported in the submission appear to be based on the model in which wastage was excluded. However, the submission implies that the base case includes wastage for nivolumab. Please clarify this discrepancy.

B20. Please clarify how events are defined in the TTD survival analysis, and in particular if patients who die are considered to discontinue treatment or are censored.

B21. Please provide the references for the studies listed in Appendix 21.

B22. The ERG found some discrepancies between the values reported in the submission and in the Excel model. Please clarify what are the correct values in Table 1 below.

Table 1. Discrepancies between the economic model and the company submission

Outcomes/Analysis	Reference in the model	Company submission	Correct values
QALYs for everolimus during PFS	'engine-e'!K8	Table 82, page 158	
QALY increment and absolute increment for everolimus during PFS	'engine-e'!K8-'engine-c'!K8	Table 82, page 158	
QALYS for nivolumab during PFS	'engine-n!K8	Table 84, page 160	
-Total costs for cabozantinib, and axitinib. -Increment, absolute increment and %absolute increment of cabozantinib compared to axitinib.	-'engine-c'!K8 and 'engine-a'!K8 -'engine-c'!K8 - 'engine-a'!K8	Table 85, page 160	
Treatment acquisition costs for everolimus	'engine-e'!E6	Table 86, page 161	
Treatment acquisition costs for cabozantinib	'engine-c'!E6	Table 86, page 161	
Disease management cost for cabozantinib	'engine-c'!E6	Table 86, page 161	
-Total costs for cabozantinib, and everolimus. -Increment, absolute	-'engine-c'!K8 and 'engine-e'!K8 -'engine-c'!K8 -	Table 86, page 161	

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increment and %absolute increment of cabozantinib compared to axitinib.	'engine-e'!K8		
-Total costs for cabozantinib, and BSC. -Increment, absolute increment and %absolute increment of cabozantinib compared to BSC.	-'engine-c'!K8 and 'engine-b'!K8 -'engine-c'!K8 - 'engine-b'!K8	Table 87, page 161	
-Treatment acquisition costs for nivolumab -Total PFS costs for nivolumab -Total costs for cabozantinib, and nivolumab. -Increment, absolute increment and %absolute increment of cabozantinib compared to nivolumab.	-'engine-n!' AF14 -'engine-n!' E4 -'engine-c'!K8 and 'engine-b'!K8 -'engine-c'!K8 - 'engine-b'!K8	Table 88, page 162	

Ipsen Ltd response to clarification questions – 15 November 2016

Single technology appraisal: **Cabozantinib for previously treated advanced renal cell carcinoma (ID931)**

Section A: Clarification on effectiveness data

A1. **Priority Question:** Please provide the WinBUGS code files used for each of the outcomes in the network meta-analysis (NMA) presented in the submission, including the study data, and other model inputs.

RESPONSE: Data is provided as a separate file.

A2. **Priority Question:** The submission states in section 4.10.5, page 94, that "networks are adjusted to the baseline of the METEOR study". Please provide details of all of the adjustments used in the NMA for each of the outcomes (OS, PFS and time to treatment discontinuation [TTD]) and the rationale for each adjustment. If this was done within WinBUGS, please provide the relevant code.

RESPONSE: The networks were adjusted to the baseline of the METEOR study by adding the same estimated "baseline" vector μ (from the METEOR study) to the estimated difference δ of each treatment relative to the "baseline". The adjustment to baseline was required to allow all treatments in the network to be comparable. Below are the details of the adjustments and the R code.

In the NMA, the parameter estimation was completed in two parts:

1. Model specific parameters μ for the "baseline" treatment A in study j
2. Study-specific difference δ for each treatment B relative to A in study j.

We have the following estimated parameters:

OS and PFS:

- METEOR study: vector μ1 for everolimus ("baseline" treatment) and vector δ1 for cabozantinib relative to everolimus;
- CheckMate025 study: vector μ2 for everolimus ("baseline" treatment) and vector δ2 for nivolumab relative to everolimus;
- RECORD-1: vector μ3 for everolimus ("baseline" treatment) and vector δ3 for placebo relative to everolimus;
- TARGET: vector μ4 for placebo ("baseline" treatment) and vector δ4 for sorafenib relative to placebo;
- AXIS: vector μ5 for sorafenib ("baseline" treatment) and vector δ5 for axitinib relative to sorafenib.

TTD:

- METEOR study: vector μ1 for everolimus (“baseline” treatment) and vector δ1 for cabozantinib relative to everolimus;
- CheckMate025 study: vector μ2 for everolimus (“baseline” treatment) and vector δ2 for nivolumab relative to everolimus.

The corresponding R code was extracted as follows:

```
### Log-normal fixed effects model
### WINBUGS  modelling
lognorm.fixed <- bugs(data = bugs_input_fixed, inits=bugs_inits, "BUGS run",
model.file="bugs_model_lognormal.txt", bugs.directory="C:/WinBUGS14",
parameters=c("mu", "d"), n.chains=4, n.iter=50000, n.burnin=25000, n.thin=10,
debug=FALSE)
### Using the direct output of the WINBUGS function
sm.lognorm <- lognorm.fixed$sims.matrix
### Estimated parameters with adjustment
### For OS/PFS:
  grlognorm1.esti <- lognorm.surv(xsim, sm.lognorm[,1:2]) # nu and theta for
everolimus (baseline treatment) in study METEOR
  grlognorm2.esti <- lognorm.surv(xsim, sm.lognorm[,3:4]) # nu and theta for
everolimus (baseline treatment) in study CheckMate025
  grlognorm3.esti <- lognorm.surv(xsim, sm.lognorm[,5:6]) # nu and theta for
everolimus (baseline treatment) in study RECORD-1
  grlognorm4.esti <- lognorm.surv(xsim, sm.lognorm[,7:8]) # nu and theta for placebo
(baseline treatment) in study TARGET
  grlognorm5.esti <- lognorm.surv(xsim, sm.lognorm[,9:10]) # nu and theta for
sorafenib (baseline treatment) in study AXIS
grlognorm6.esti <- lognorm.surv(xsim, sm.lognorm[,1:2]+sm.lognorm[,c(11,12)]) # nu
and theta for cabozantinib in study METEOR
 grlognorm7.esti <- lognorm.surv(xsim, sm.lognorm[,3:4]+sm.lognorm[,c(13,14)]) # nu
and theta for nivolumab in study CheckMate025 without adjustment
grlognorm7.adjusted.esti <- lognorm.surv(xsim,
sm.lognorm[,1:2]+sm.lognorm[,c(13,14)]) # nu and theta for nivolumab adjusted to
study METEOR
 grlognorm8.esti <- lognorm.surv(xsim, sm.lognorm[,5:6]+sm.lognorm[,c(15,16)]) # nu
and theta for placebo in study RECORD-1 without adjustment
grlognorm8.adjusted.esti <- lognorm.surv(xsim,
sm.lognorm[,1:2]+sm.lognorm[,c(15,16)]) # nu and theta for placebo adjusted to
study METEOR
 grlognorm9.esti <- lognorm.surv(xsim, sm.lognorm[,7:8]+sm.lognorm[,c(17,18)]) # nu
and theta for sorafenib in study TARGET without adjustment
grlognorm9.adjusted.esti <- lognorm.surv(xsim,
sm.lognorm[,1:2]+sm.lognorm[,c(17,18)]) # nu and theta for sorafenib adjusted to
study METEOR
```

```
 grlognorm10.esti <- lognorm.surv(xsim, sm.lognorm[,9:10]+sm.lognorm[,c(19,20)]) # nu and theta for axitinib in study AXIS  without adjustment
grlognorm10.adjusted.esti <- lognorm.surv(xsim, sm.lognorm[,1:2]+sm.lognorm[,c(19,20)]) # nu and theta for axitinib adjusted to study METEOR
```

For TTD:

```
  grlognorm1.esti <- lognorm.surv(xsim, sm.lognorm[,1:2]) #using nu and theta for everolimus (baseline treatment) in study METEOR
  grlognorm2.esti <- lognorm.surv(xsim, sm.lognorm[,3:4]) #using nu and theta for everolimus (baseline treatment) in study CheckMate025
grlognorm3.esti <- lognorm.surv(xsim, sm.lognorm[,1:2]+sm.lognorm[,c(5,6)]) #using nu and theta for cabozantinib in study METEOR
 grlognorm4.esti <- lognorm.surv(xsim, sm.lognorm[,3:4]+sm.lognorm[,c(7,8)]) #using nu and theta for nivolumab in study CheckMate025
 grlognorm4.adjusted.esti <- lognorm.surv(xsim, sm.lognorm[,1:2]+sm.lognorm[,c(7,8)]) #using nu and theta for nivolumab adjusted to study METEOR
```

A3. **Priority Question:** Please complete the following table with the baseline characteristics of the population in METEOR based on treatment history for each trial arm (intent-to treat [ITT]and primary endpoint intent-to treat [PITT] population):

Baseline Characteristic		ITT Population		PITT Population	
		Cabozantinib N = 330	Everolimus N = 328	Cabozantinib N = 187	Everolimus N = 188
		n (%)	n (%)	n (%)	n (%)
Number of prior VEGFR-TKIs	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	≥3	[redacted]	[redacted]	[redacted]	[redacted]
Number of prior systemic anti-cancer treatments for RCC	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
	≥3	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients who received sunitinib as their first line therapy		[redacted]			
Number of patients who received pazopanib as their first line therapy		[redacted]			
NOTE: Since information on the number of patients who received sunitinib or pazopanib as their first line therapy is not currently available Ipsen has provided the following additional information below.					
Types of prior VEGFR-TKI					
Number of patients who received sunitinib		[redacted]	[redacted]	[redacted]	[redacted]
Number of patients who received pazopanib		[redacted]	[redacted]	[redacted]	[redacted]
Prior VEGFR-TKI in patients receiving only 1 prior VEGFR-TKI					
Number of patients who received sunitinib		[redacted]	[redacted]	[redacted]	[redacted]
Number of patients who received pazopanib		[redacted]	[redacted]	[redacted]	[redacted]
Source: METEOR CSR and Data on file					

A4. **Priority Question:** Please provide the results for PFS, OS, response rate and TTD for the subgroup of patients from METEOR with only 1 prior VEGFR-TKI therapy (i.e. in the proposed 2rd line treatment of advanced renal cell carcinoma [RCC]). Please also provide the baseline characteristics for each trial arm of METEOR for this subgroup.

RESPONSE: The results for PFS, OS and response rates for the requested subgroups are provided below. It has not been possible to provide TTD results within the allowed timeframe.

Table 1: Baseline characteristics: Patients with only 1 prior VEGFR-TKI therapy

Characteristic	PITT		ITT	
	Cabozantinib N= 120	Everolimus N= 108	Cabozantinib N=203	Everolimus N=180
Age — yr				
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Sex — no. (%)				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Not reported				
Geographic region — no. (%)				
Europe*	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]
Asia–Pacific	[redacted]	[redacted]	[redacted]	[redacted]
Latin America	[redacted]	[redacted]	[redacted]	[redacted]
Race — no. (%)†				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC prognostic risk category — no. (%)				
Favourable	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]
Poor	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria — no. (%)§				
Favourable risk	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate risk	[redacted]	[redacted]	[redacted]	[redacted]
Poor risk	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy — no. (%)	[redacted]	[redacted]	[redacted]	[redacted]
Source: Data on file				

[redacted]

[redacted]

[redacted]

[redacted]

Landmark	Estimate of % of patients alive (95% CI)	
	Cabozantinib N=203	Everolimus N=180
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Source: Data on file		

[redacted]

	Cabozantinib N=203	Everolimus N=180
ORR, % (95% CI)	[redacted]	[redacted]
Complete response, n (%)	[redacted]	[redacted]
Partial response, n (%)	[redacted]	[redacted]
Stable disease, n (%)	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]
Not evaluable n (%)	[redacted]	[redacted]
Missing n (%)	[redacted]	[redacted]
Source: Data on file		

A5. **Priority Question**: Please provide the results for PFS, OS, response rate and TTD for the subgroup of patients from METEOR with 2 prior therapies including at least one VEGFR-TKI. (i.e. in the proposed 3rd line treatment of advanced RCC). Please also provide the baseline characteristics for each trial arm of METEOR for this subgroup.

RESPONSE: The results for PFS, OS and response rates for the requested subgroups are provided below. It has not been possible to provide TTD results within the allowed timeframe.

[redacted]

Characteristic	PITT		ITT	
	Cabozantinib N= 45	Everolimus N=51	Cabozantinib N=79	Everolimus N=92
Age — yr				
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
Sex — no. (%)				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Geographic region — no. (%)				
Europe	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]
Asia–Pacific	[redacted]	[redacted]	[redacted]	[redacted]
Latin America	[redacted]	[redacted]	[redacted]	[redacted]
Race — no. (%)†				
White	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]
Missing data	[redacted]	[redacted]	[redacted]	[redacted]
MSKCC prognostic risk category — no. (%)				
Favourable	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]
Poor	[redacted]	[redacted]	[redacted]	[redacted]
Heng prognostic criteria — no. (%)				
Favourable	[redacted]	[redacted]	[redacted]	[redacted]
Intermediate	[redacted]	[redacted]	[redacted]	[redacted]
Poor	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy — no. (%)	[redacted]	[redacted]	[redacted]	[redacted]

Source: Data on file

[redacted]

[redacted]

[redacted]

[redacted]

Landmark	Estimate of % of patients alive (95% CI)	
	Cabozantinib N= 79	Everolimus N= 92
6 months	[redacted]	[redacted]
12 months	[redacted]	[redacted]
18 months	[redacted]	[redacted]
24 months	[redacted]	[redacted]
Source: Data on file		

[redacted]

	Cabozantinib N=79	Everolimus N=92
ORR, % (95% CI)	[redacted]	[redacted]
Complete response, n (%)	[redacted]	[redacted]
Partial response, n (%)	[redacted]	[redacted]
Stable disease, n (%)	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]
Not evaluable (%)	[redacted]	[redacted]
Missing n (%)	[redacted]	[redacted]
Source: Data on file		

A6. **Priority Question:** Please provide a comparison of cabozantinib, axitinib, everolimus, nivolumab and best supportive care using the subgroup of patients from METEOR with only 1 prior VEGFR-TKI therapy for PFS, OS and TTD (i.e. in the proposed 2nd line treatment of advanced RCC).

RESPONSE: In the METEOR and RECORD-1 studies 1 or 2 (or more) prior treatments were allowed, whereas in CheckMate025 only up to 2 prior therapies were allowed at study entry. TARGET and AXIS studies only allowed 1 prior treatment (see Table 7). In order to perform a NMA for the subgroup of patients with only 1 prior VEGFR-TKI all studies in the network should have comparable populations. There is heterogeneity across the study populations in the network in terms of prior therapies and a lack of consistency and availability of evidence (i.e., no published KM for the 1 prior treatment subgroup for all trials in the network). However since the majority of patients in the RECORD-1 and CheckMate025 studies had received 1 prior treatment (>70%) and all of the patients in the TARGET and AXIS studies had received 1 prior treatment a NMA using the RECORD-1 and CheckMate025 full population KM might still provide a good proxy for the subgroup of patients with only 1 prior VEGFR-TKI therapy. A summary of prior therapies across the trials is provided in Table 2. The NMA results are provided from Figure 7 to Figure 21.

Table 2. Prior therapies in the studies included in the NMA

	Inclusion criteria	**% of prior therapies**
METEOR	Patients had received at least one previous VEGFR tyrosine-kinase inhibitor (there was no limit to the number of previous treatments).	1 prior VEGFR: Cabozantinib: 71%, Everolimus: 70% 2+ prior VEGFR: Cabozantinib: 29%, Everolimus: 30%
RECORD-1	Patients had progressed on stopping treatment with sunitinib or sorafenib, or both drugs. Previous therapy with bevacizumab, interleukin 2, or interferon alfa was also permitted.	1 prior VEGFR: Everolimus: 74%, Placebo: 74% 2+ prior VEGFR: Everolimus: 26%, Placebo: 26%
CheckMate 025	Patients had received one or two previous regimens of antiangiogenic therapy.	1 prior VEGFR[28]: Nivolumab: 72%, Everolimus: 72% 2 prior VEGFR: Nivolumab: 28%, Everolimus: 28%
TARGET	Patients had progressed after one systemic treatment within the previous 8 months.	No prior VEGFR therapy was received among patients.
AXIS	Patients had received one previous systemic first line regimen with a sunitinib-based, bevacizumab plus interferon-alfa-based, temsirolimus-based, or cytokine based regimen.	1 prior treatment

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

A7. **Priority Question**: Please provide a comparison of cabozantinib, everolimus, nivolumab and best supportive care using the subgroup of patients from METEOR with 2 prior therapies including at least one VEGFR-TKI for PFS, OS and TTD (i.e. in the proposed 3rd line treatment of advanced RCC).

RESPONSE: The network meta-analysis did not contain any studies with comparable populations in the 3rd line treatment setting (Table 7). In the RECORD-1 and CheckMate025 studies only around a quarter of patients had received 2 (or more) prior therapies, and in the TARGET and AXIS studies none of the patients had received 2 prior therapies. Due to the lack of consistency and availability of evidence (i.e., no published KM for the 2 prior therapies for all trials in the network) and heterogeneity in terms of prior therapies across all trials in the network Ipsen is of the opinion that it might not be feasible to perform a robust NMA in the 3rd line treatment setting and any outputs produced might be subject to substantial uncertainty.

A8. Please provide a figure for each of the comparators in the NMA showing both the resulting log-normal plot with the adjustments, and the log-normal plot without the adjustments to the baseline from the METEOR study applied for:

a) PFS
b) OS
c) TTD

RESPONSE: See log-normal plots provided from Figure 22 to Figure 30.

Figure 1. Comparison of PFS with and without adjustment to METEOR study – Axitinib

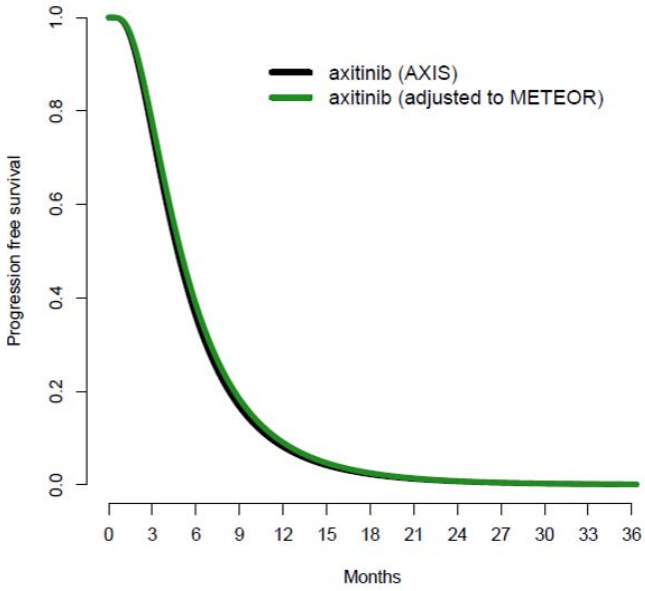


Figure 2. Comparison of PFS with and without adjustment to METEOR study – Nivolumab

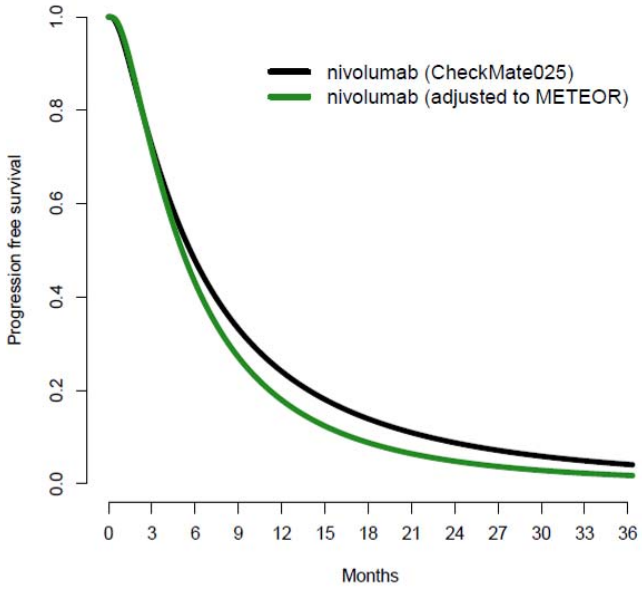


Figure 3. Comparison of PFS with and without adjustment to METEOR study – Placebo

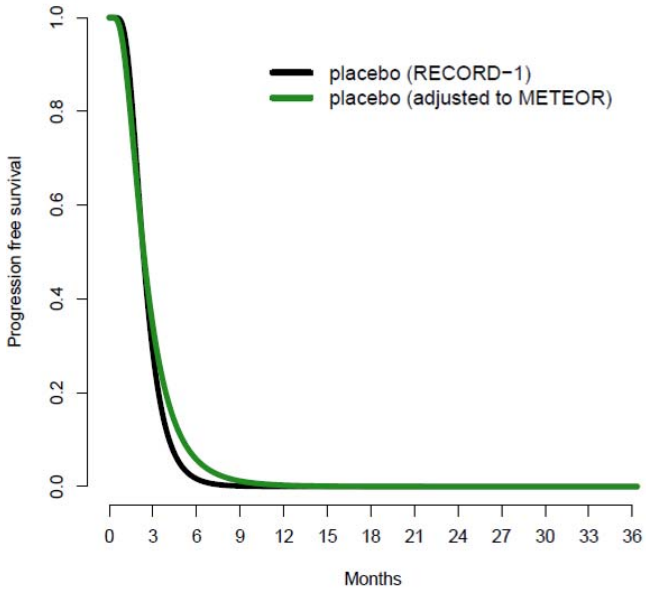


Figure 4. Comparison of PFS with and without adjustment to METEOR study – Sorafenib

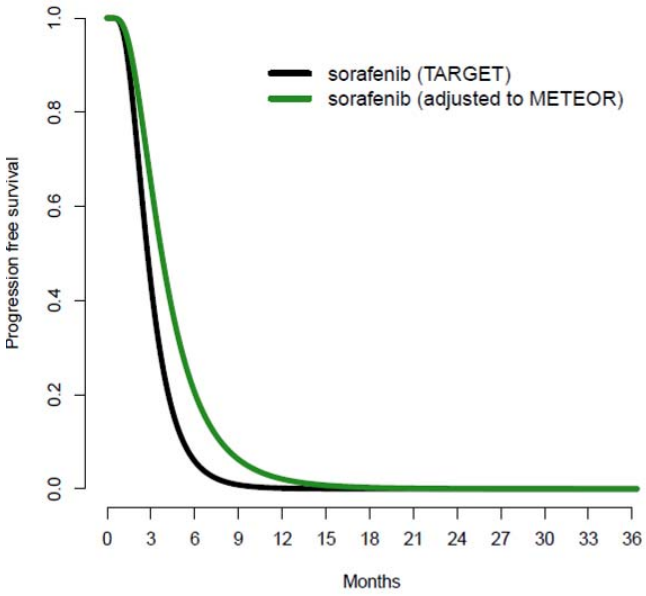


Figure 5. Comparison of OS with and without adjustment to METEOR study – Axitinib

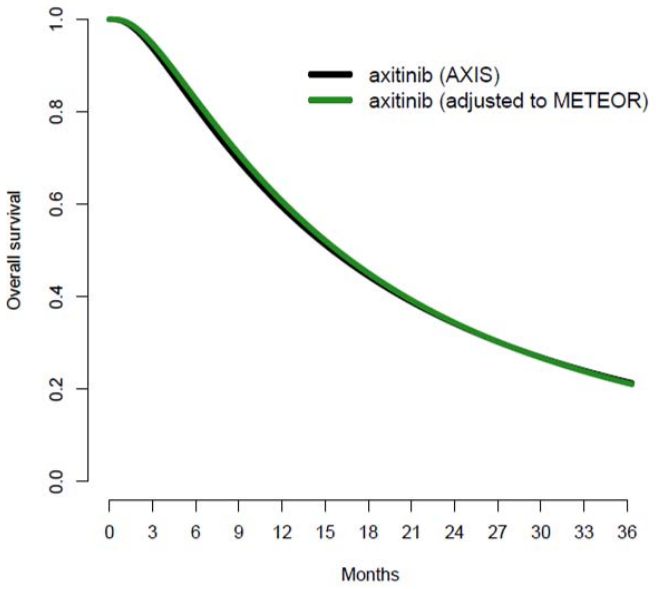


Figure 6. Comparison of OS with and without adjustment to METEOR study – Nivolumab

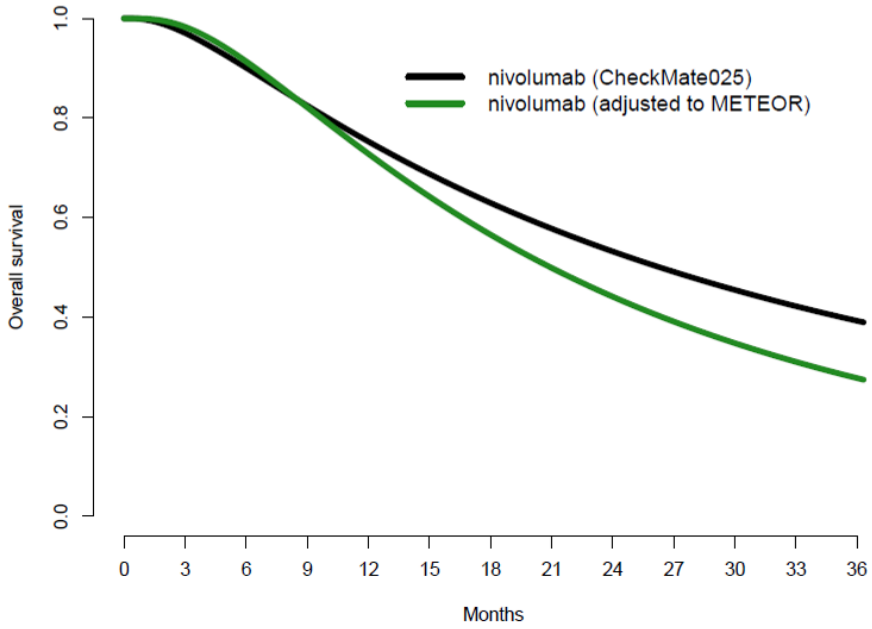


Figure 7. Comparison of OS with and without adjustment to METEOR study – placebo

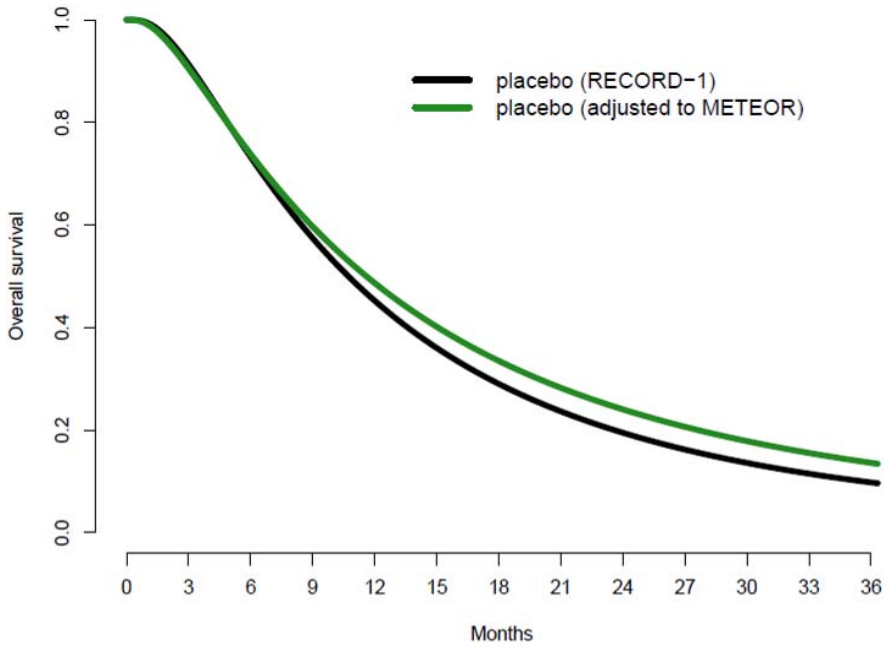


Figure 8. Comparison of OS with and without adjustment to METEOR study – sorafenib

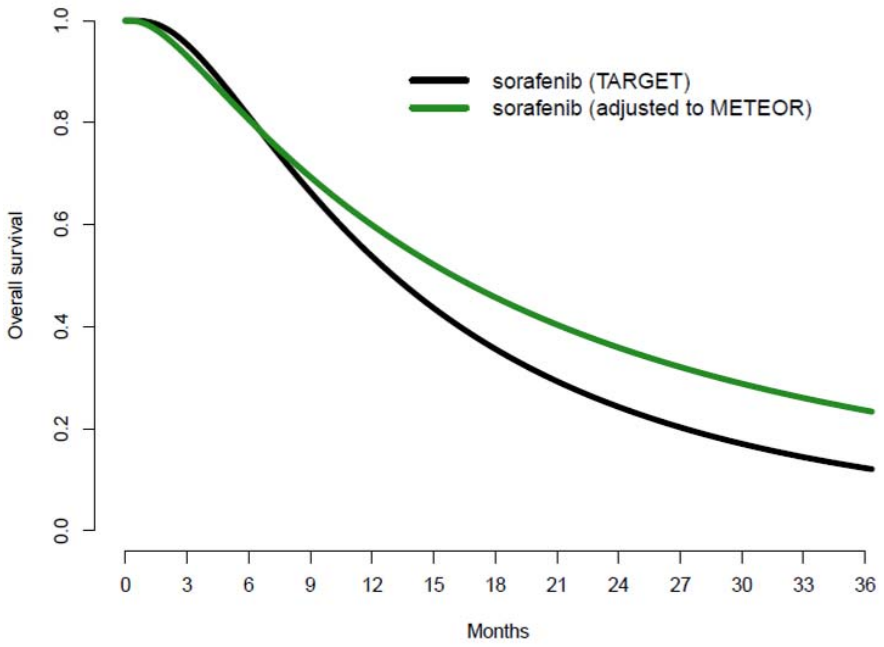
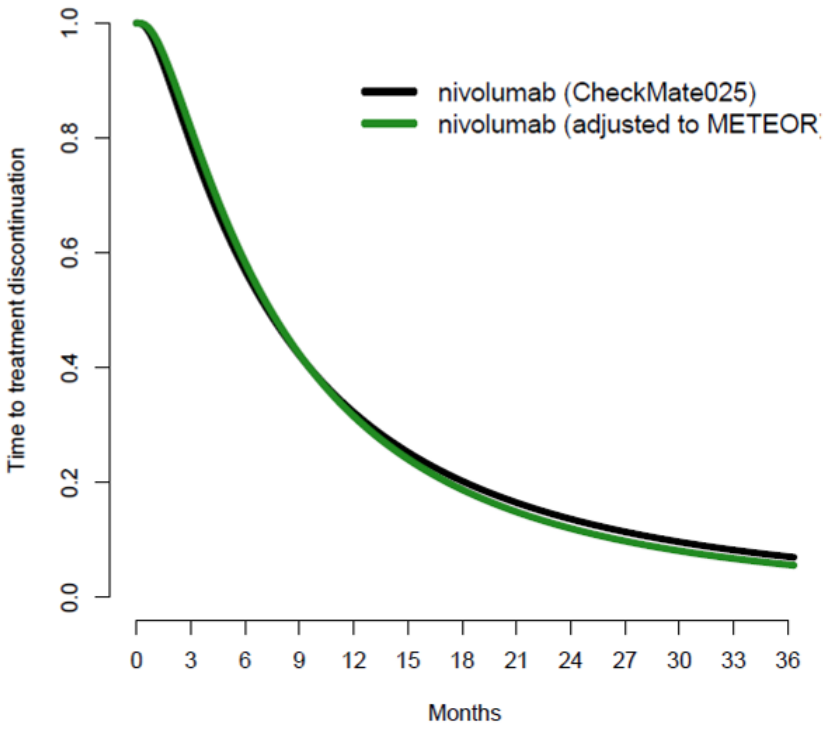


Figure 9. Comparison of TTD with and without adjustment to METEOR study – Nivolumab



A9. Please provide a rationale for why the OS and PFS seen in the everolimus arm of METEOR differ from the OS and PFS observed in Checkmate 025.

RESPONSE: The limits of publicly available data make it difficult to fully identify all factors to explain the difference in OS and PFS in the control groups of the two studies. From data available in the public domain, direct comparison of PFS and OS for these studies should be avoided because prognostic risk groups and number and type of previous treatments differed in the two trials. For these reasons it is not possible to provide a complete rationale for the difference in OS and PFS seen in the everolimus arms of the two studies.

A10. For the outcome TTD in the NMA, please explain why it has been assumed that there is a relationship between TTD and the comparator intervention (i.e. why has it been assumed that the TTD for a treatment in one arm of a study has a relationship to the TTD for the alternative treatment arm in the same study?)

RESPONSE: For the outcome of TTD in the NMA, a changing HR was assumed between any two of the comparators. In order to apply the changing HR, everolimus was chosen to be the reference treatment because it is the most often used treatment (as per METEOR, CHECKMATE025 and RECORD-1). Given the method of indirect treatment comparison described in the Ipsen submission the intermediate parameters were first derived based on the changing HR and then the final parameters for each distribution were calculated based on the intermediate parameters. The differences of the intermediate parameters between everolimus and

other comparators were obtained when fitting the data and further were converted into the final parameters used to generate the survival curves.

A11. The submission states in Table 13 on page 60 that METEOR was an open-label study and "Patients and investigators were not masked to study treatment to allow appropriate management of adverse events". Please provide further details on the rationale for conducting METEOR as an open-label study.

RESPONSE: The open-label design was selected as it enabled appropriate dose modifications for adverse events in both study arms. With the different dosage presentations and dose modification guidelines for both drugs an open study was the only feasible design.

Although the study used an open-label design, bias was minimised for the primary endpoint of progression-free survival and secondary endpoint of objective response by evaluation of radiographic assessments by a masked central independent radiology review committee. Additionally, radiographic assessments were continued beyond investigator-determined progression to reduce missing data arising from discordance between the investigator and the independent radiology review committee about the date of progression. An advantage of the open-label design is that it allowed for the appropriate management of adverse effects in both study groups.

A12. Please provide the appendices to the clinical study report (CSR) of METEOR as well as the tables referred to in the CSR that were not provided.

RESPONSE: Appendices 16.1.9, 14.1.8.1 and 14.1.8.2 are provided as requested.

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Please provide the regenerated Kaplan-Meier (KM) plots and KM data for OS, PFS and TTD for each of the interventions in the NMA.

RESPONSE: Please see KM plots from Figure 31 to Figure 48. KM data is provided in Table 8 to Table 25.

Figure 10. KM Plot - OS axitinib AXIS study

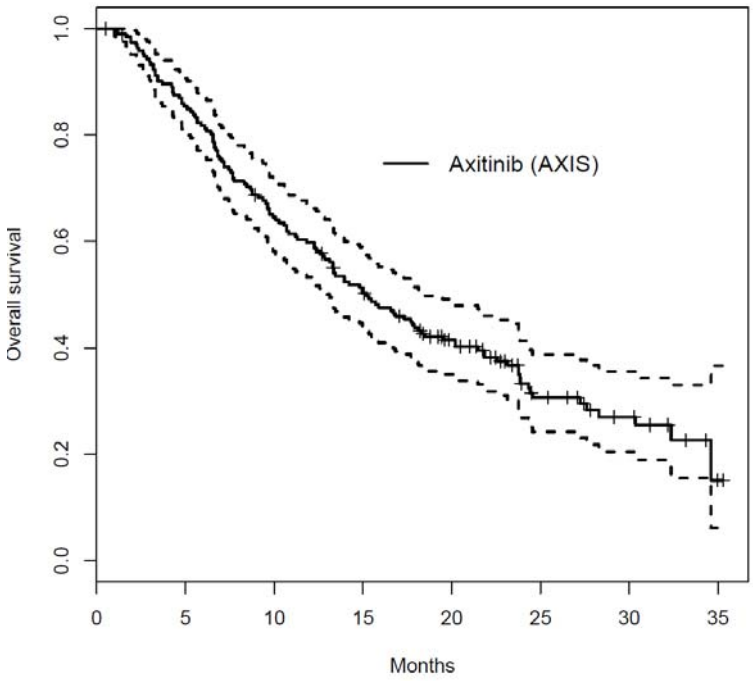


Figure 11. KM Plot - OS everolimus CheckMate025 study

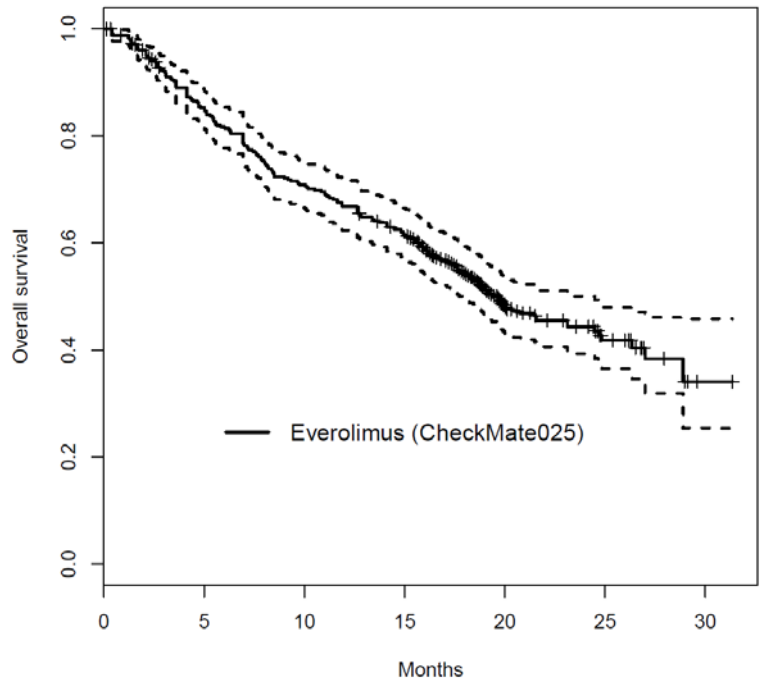


Figure 12. KM Plot - OS everolimus RECORD-1 study

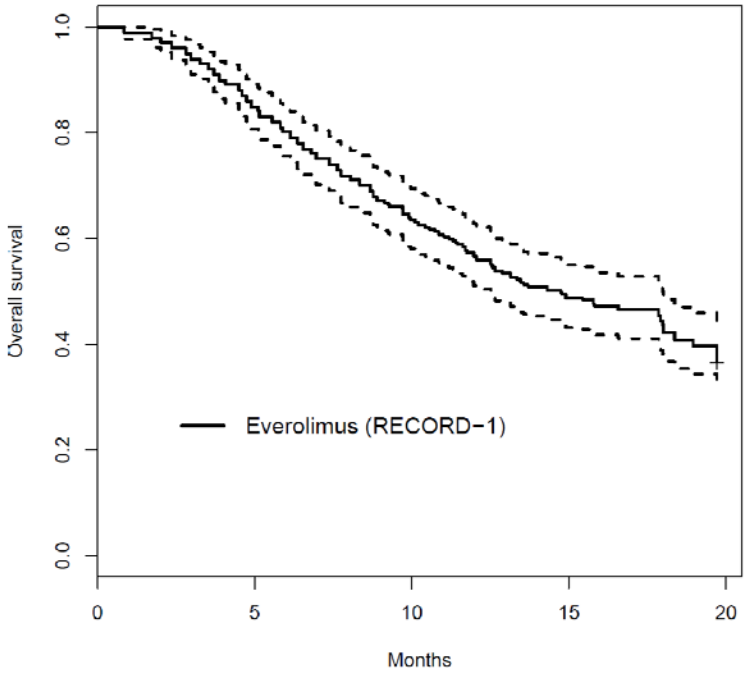


Figure 13. KM Plot - OS nivolumab CheckMate025 study

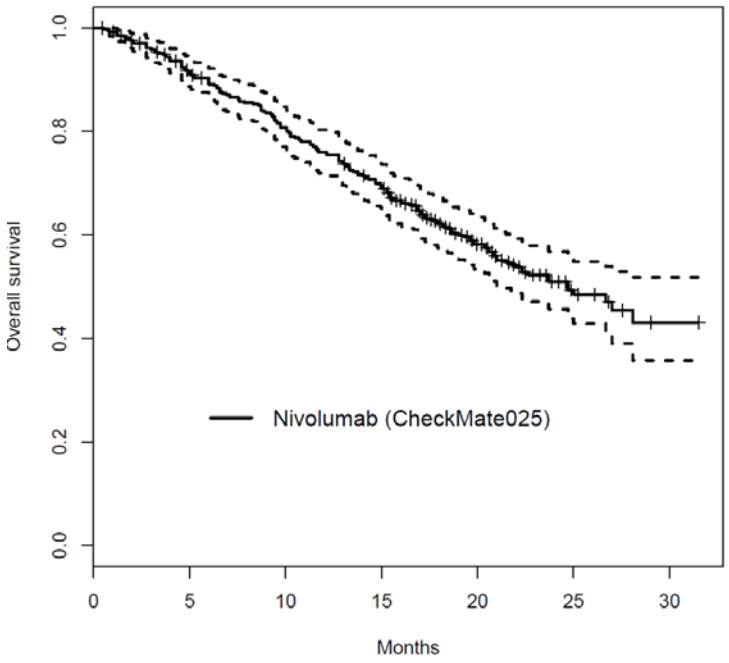


Figure 14. KM Plot - OS placebo RECORD-1 study

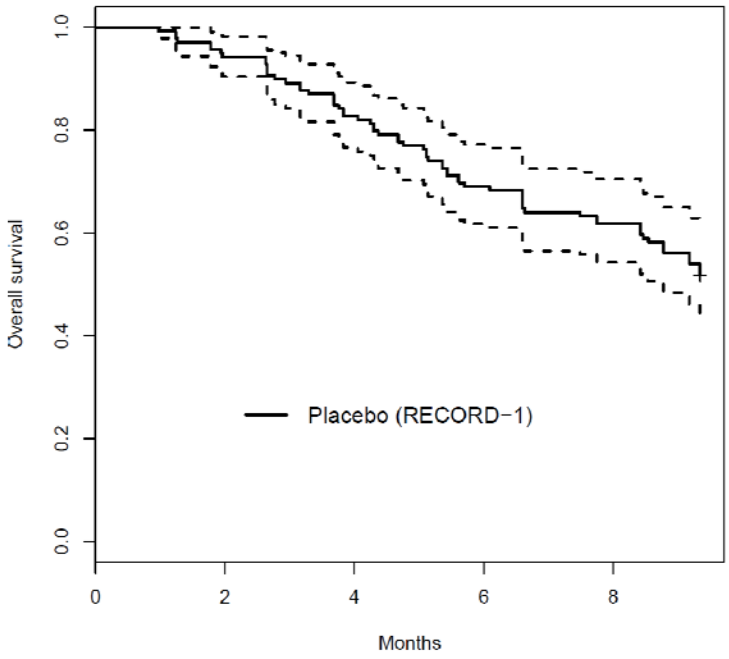


Figure 15. KM Plot - OS placebo TARGET study

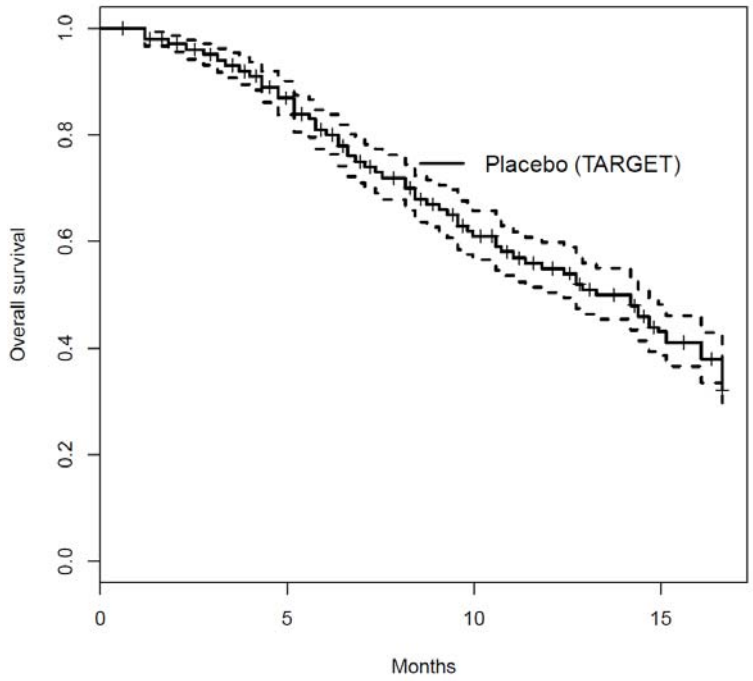


Figure 16. KM Plot - OS sorafenib AXIS study

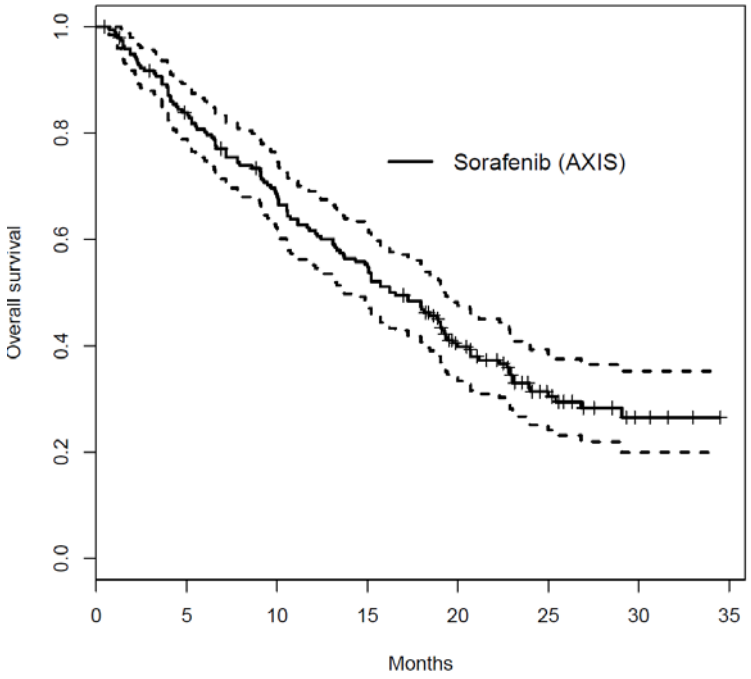


Figure 17. KM Plot - OS sorafenib TARGET study

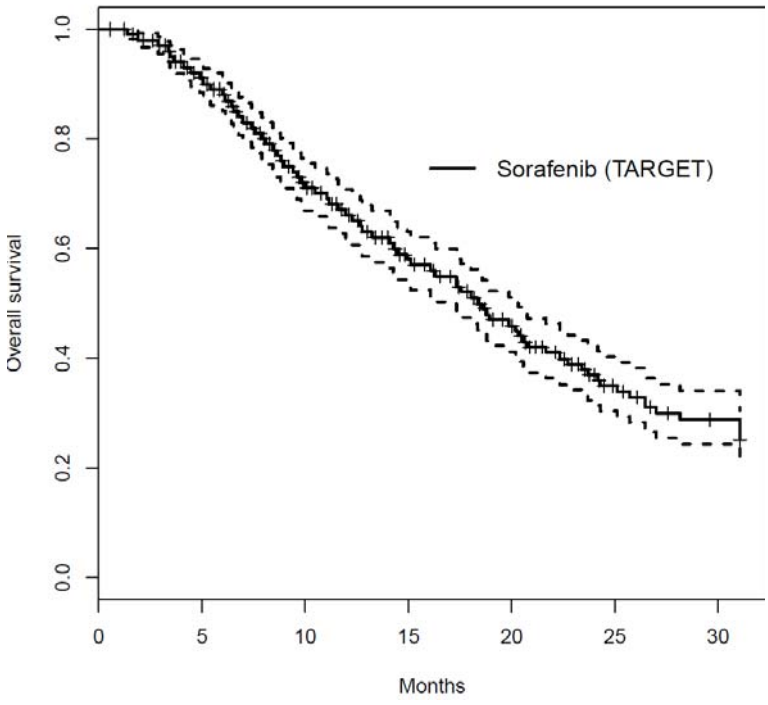


Figure 18. KM Plot - PFS axitinib AXIS study

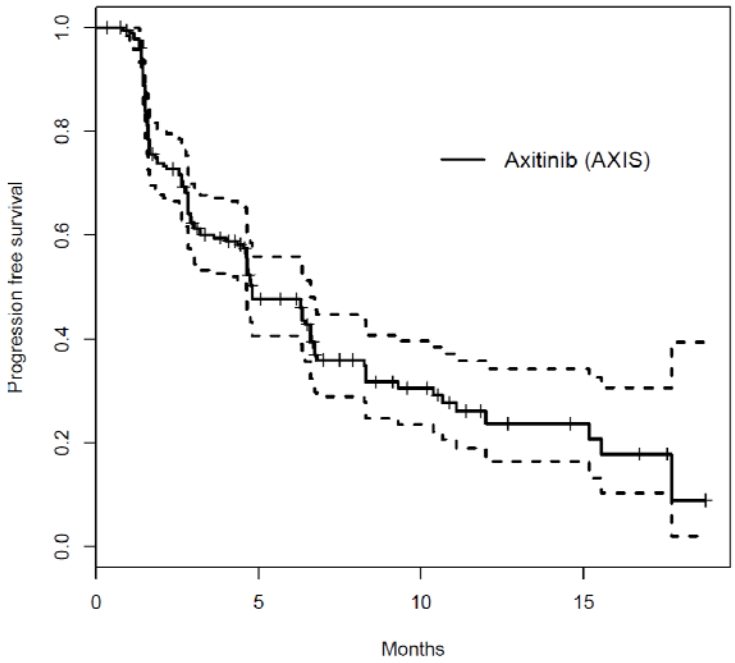


Figure 19. KM Plot - PFS everolimus CheckMate025 study

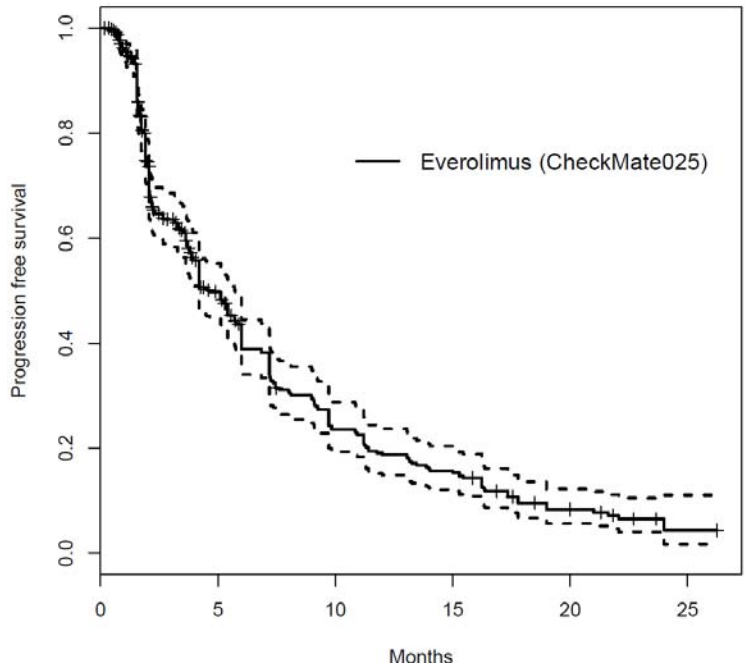


Figure 20. KM Plot - PFS everolimus RECORD-1 study

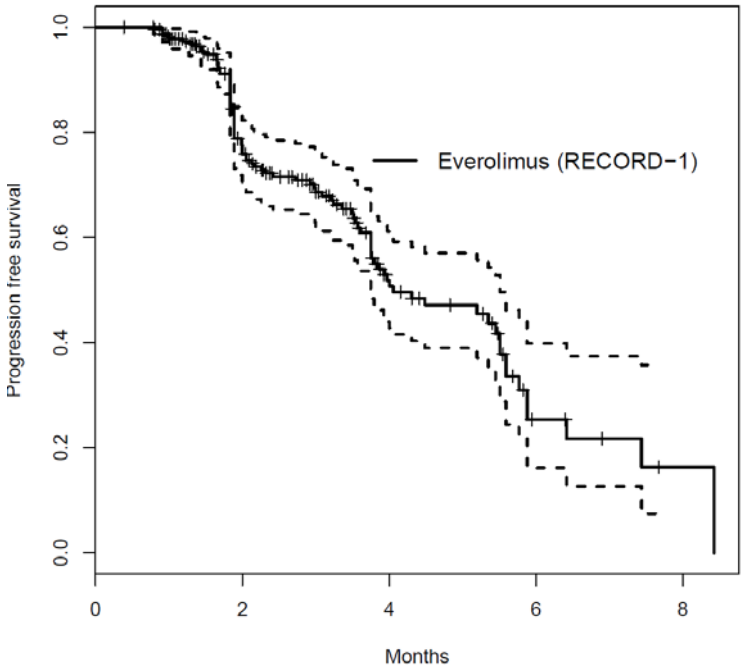


Figure 21. KM Plot - PFS nivolumab CheckMate025 study

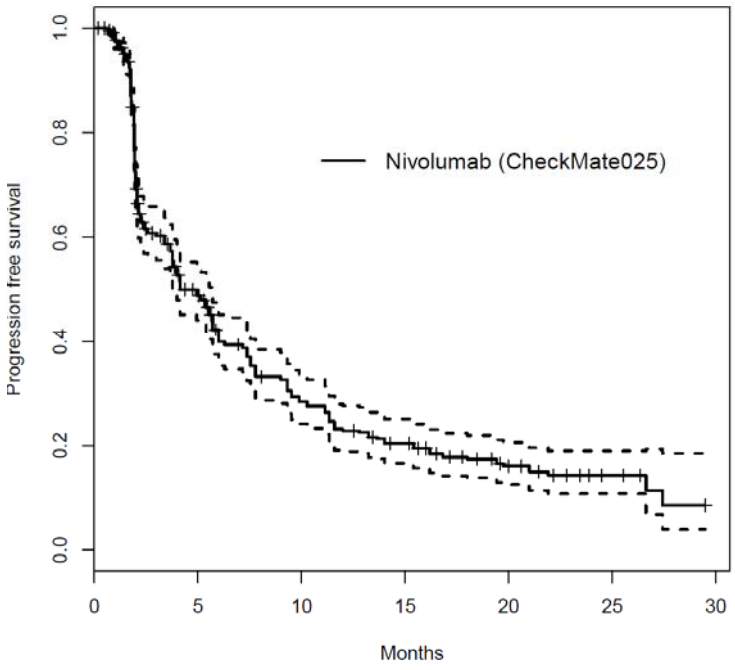


Figure 22. KM Plot - PFS placebo RECORD-1 study

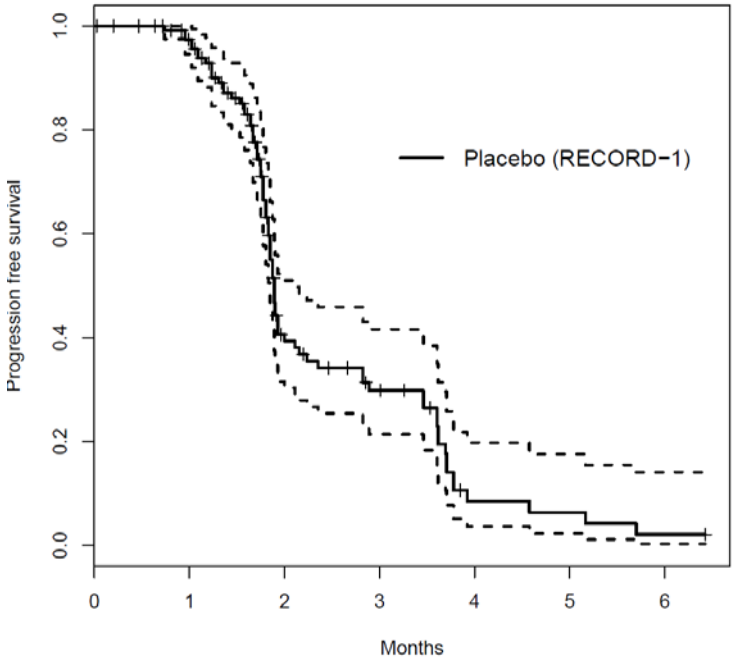


Figure 23. KM Plot - PFS placebo TARGET study

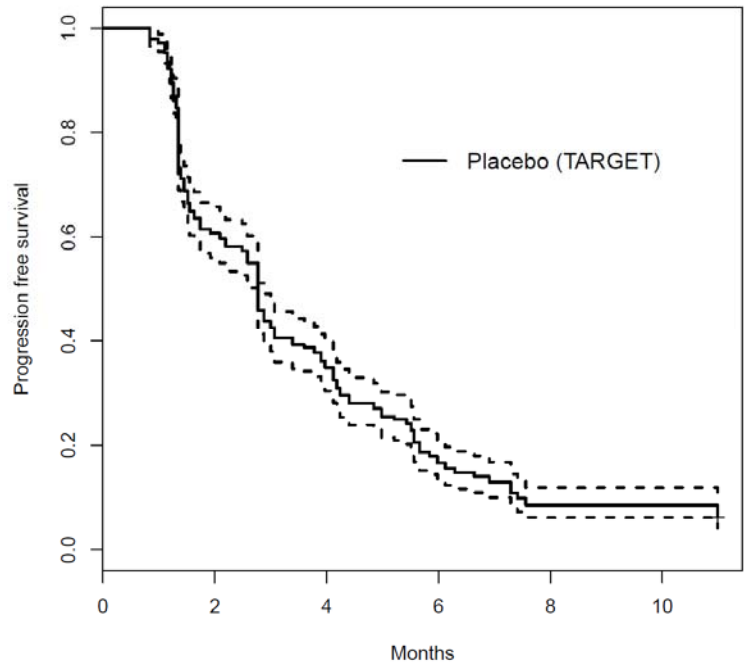


Figure 24. KM Plot - PFS sorafenib AXIS study

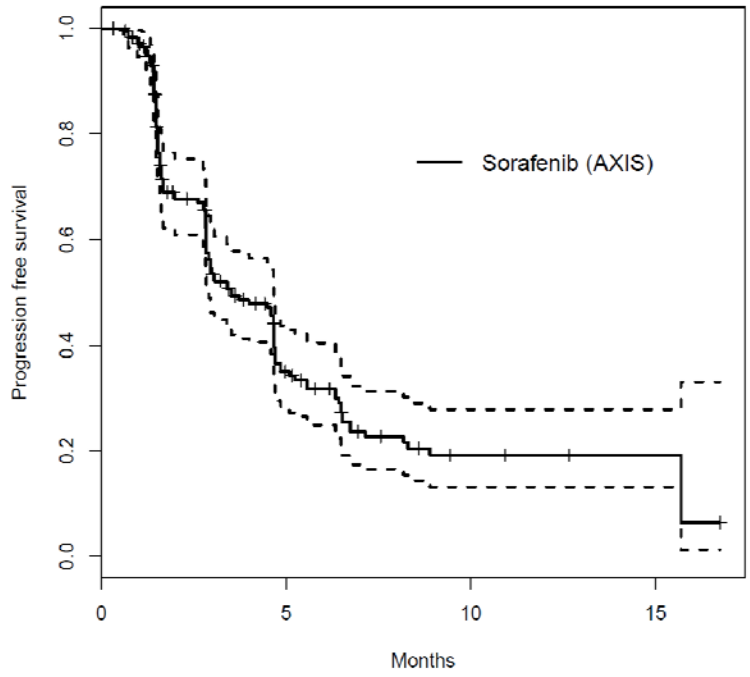


Figure 25. KM Plot - PFS sorafenib TARGET study

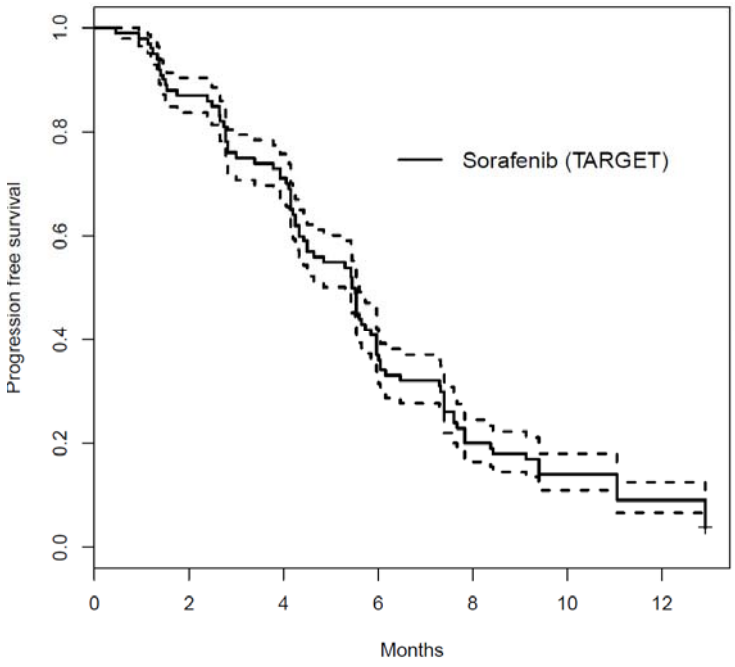


Figure 26. KM Plot - TTD everolimus CheckMate025 study

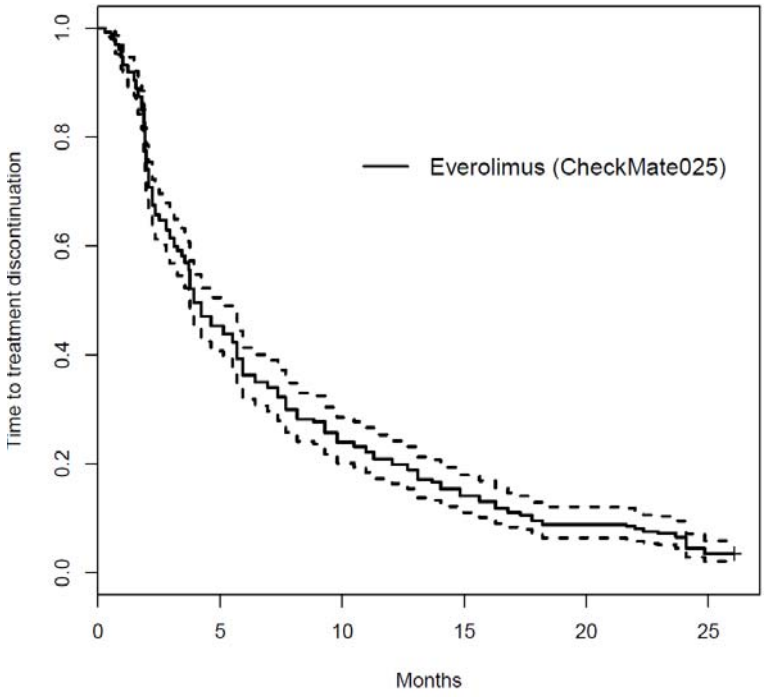


Figure 27. KM Plot - TTD nivolumab CheckMate025 study

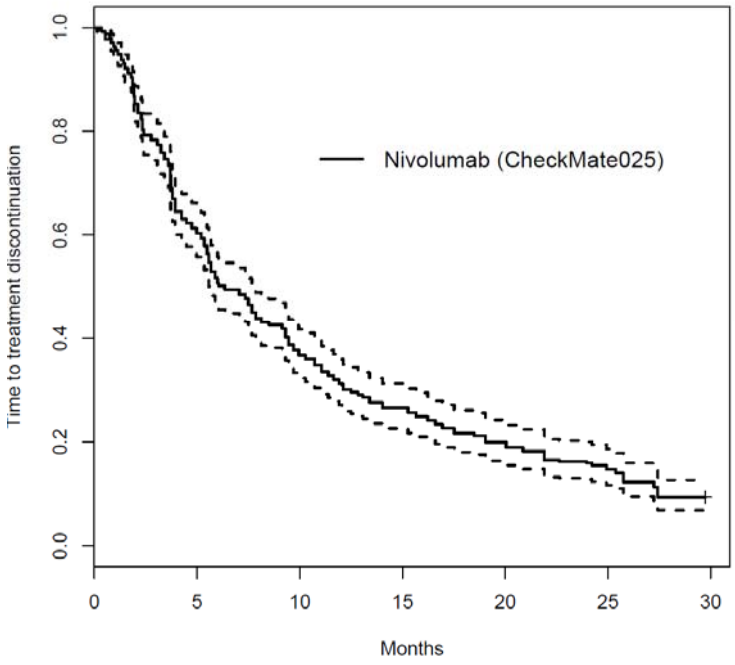
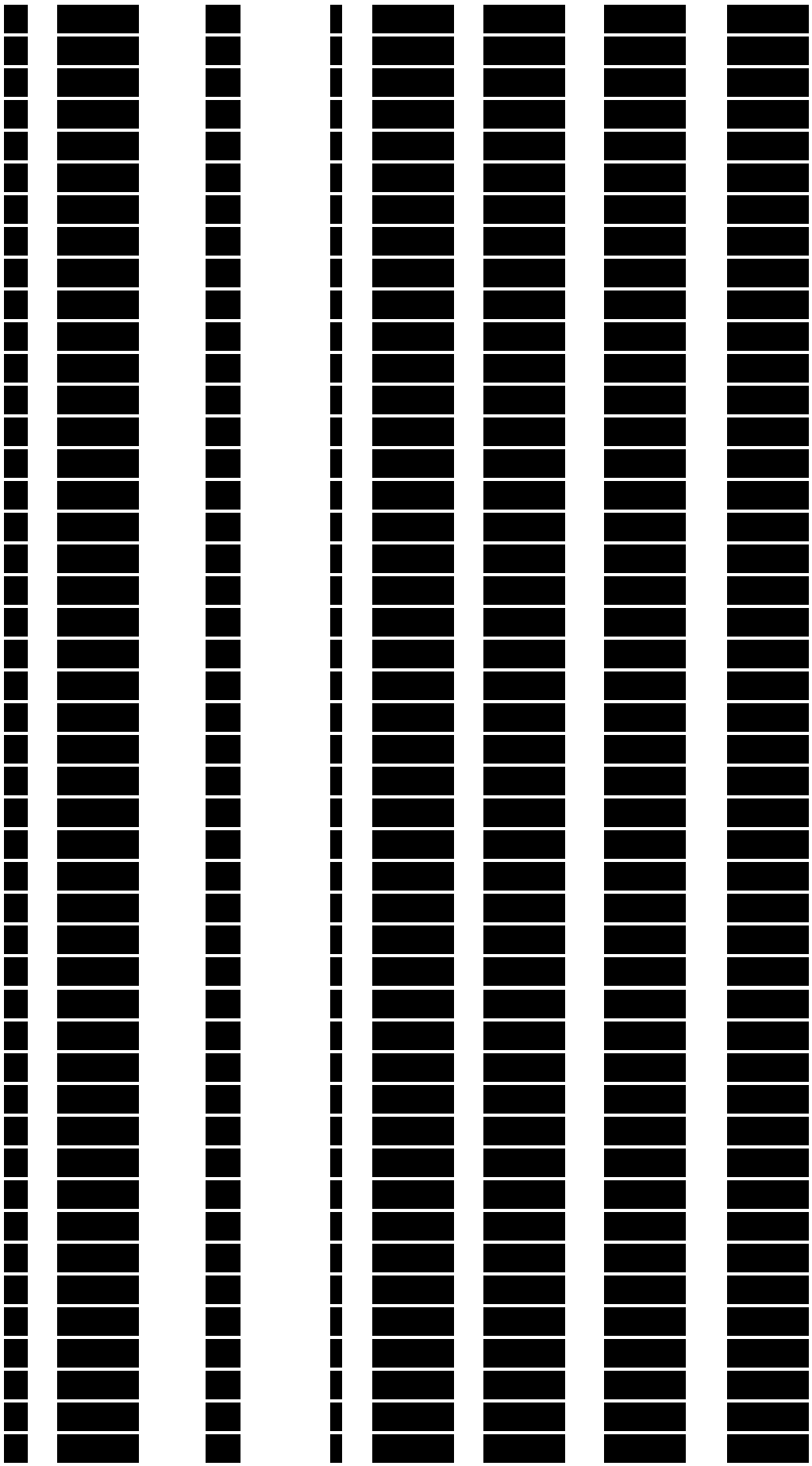


Table 3. KM Data - OS axitinib AXIS study

	time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]							



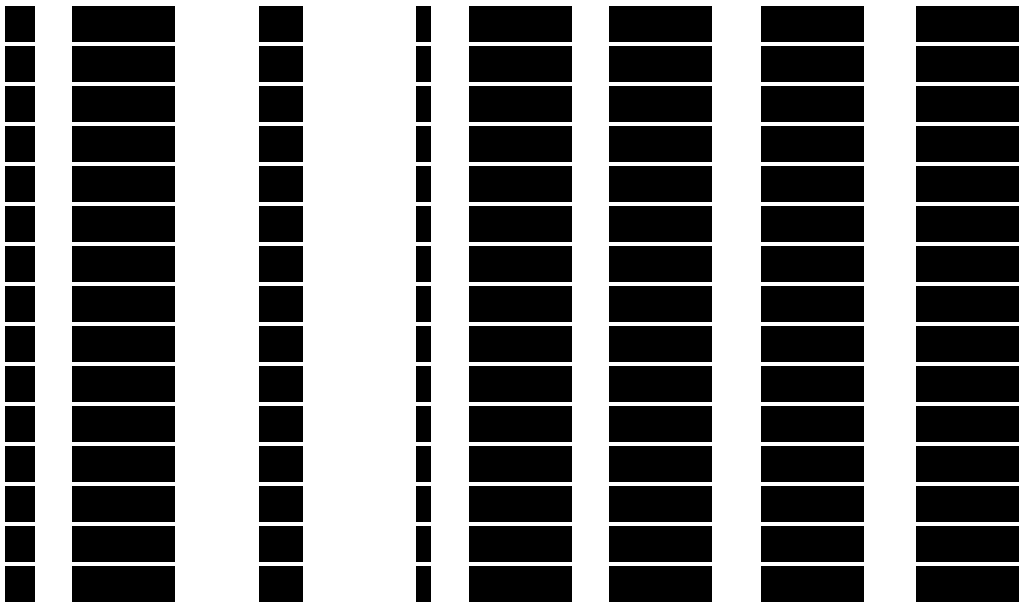
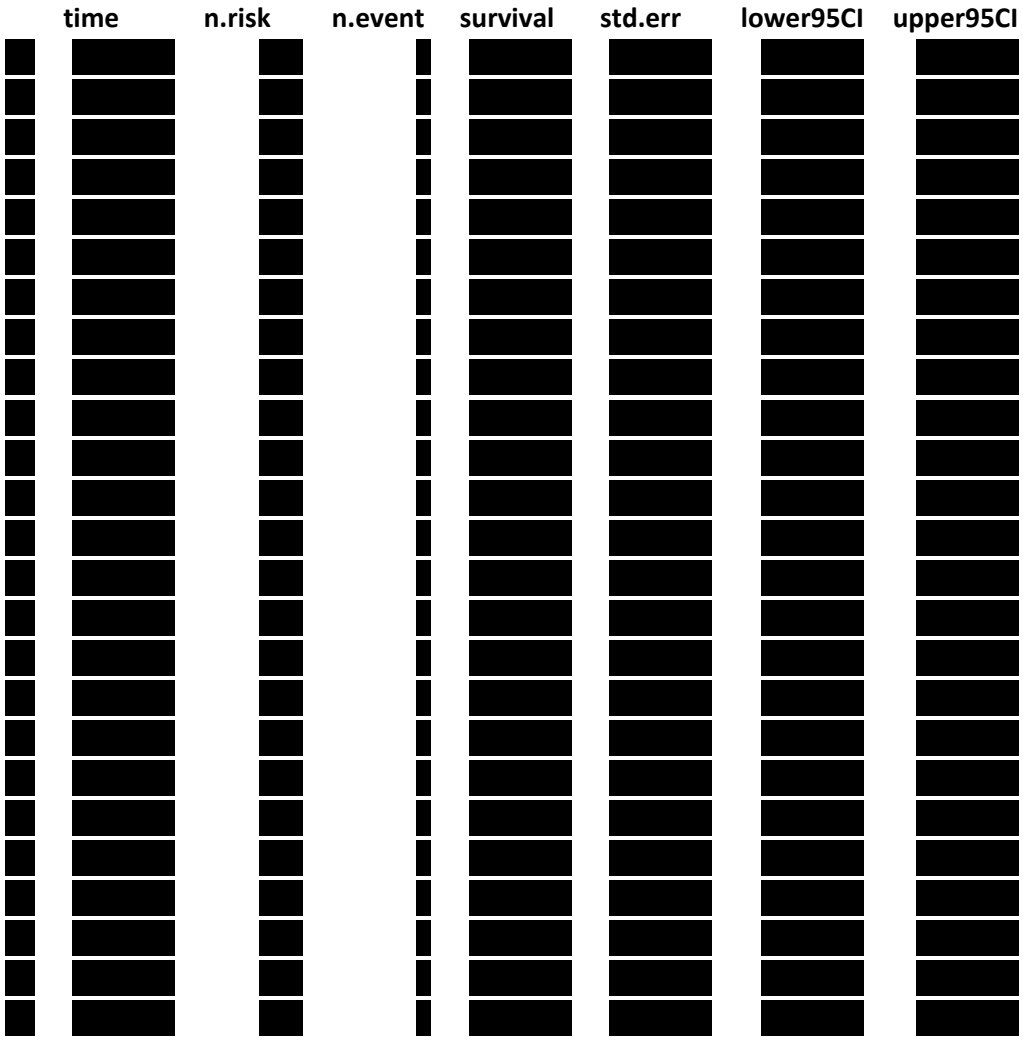
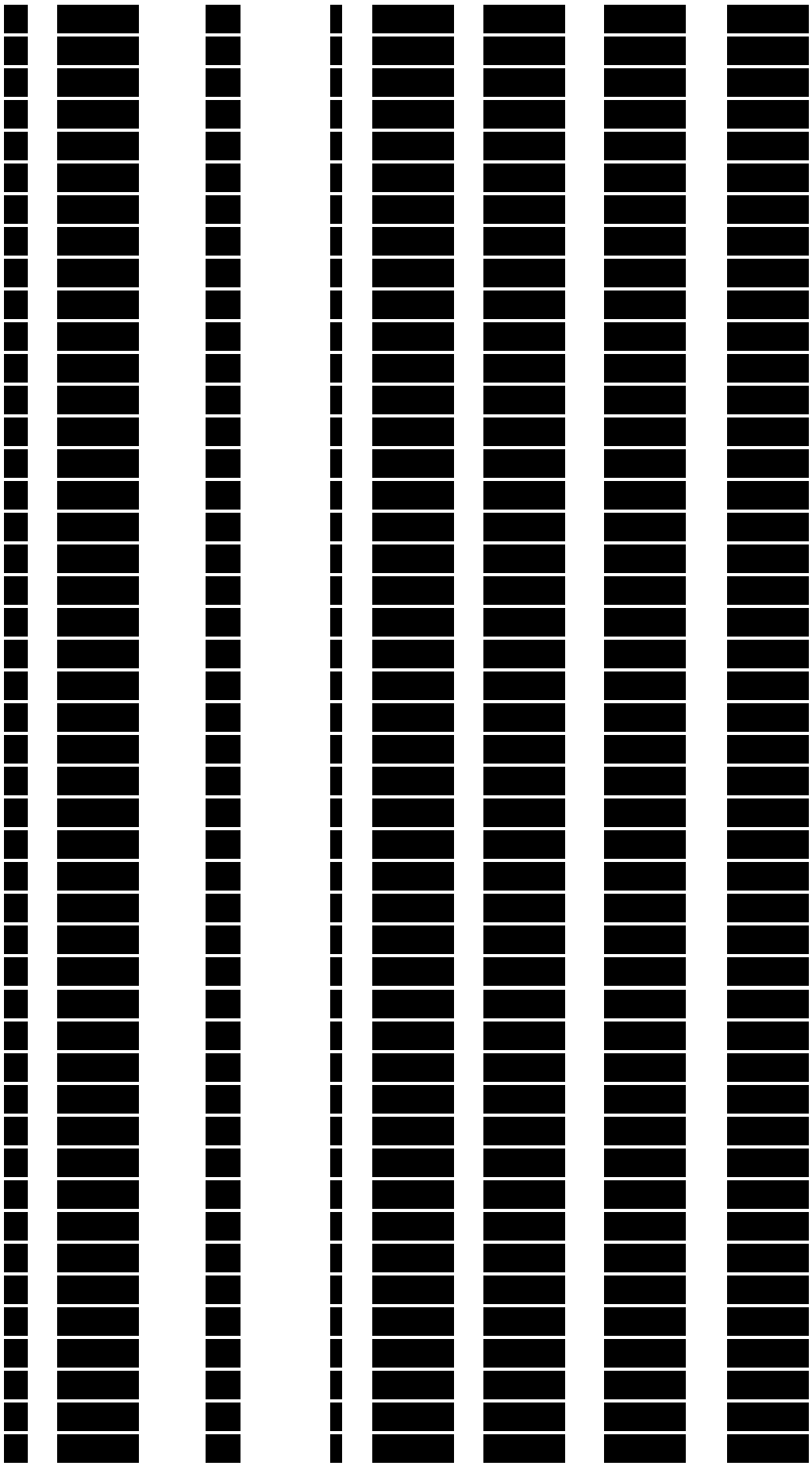
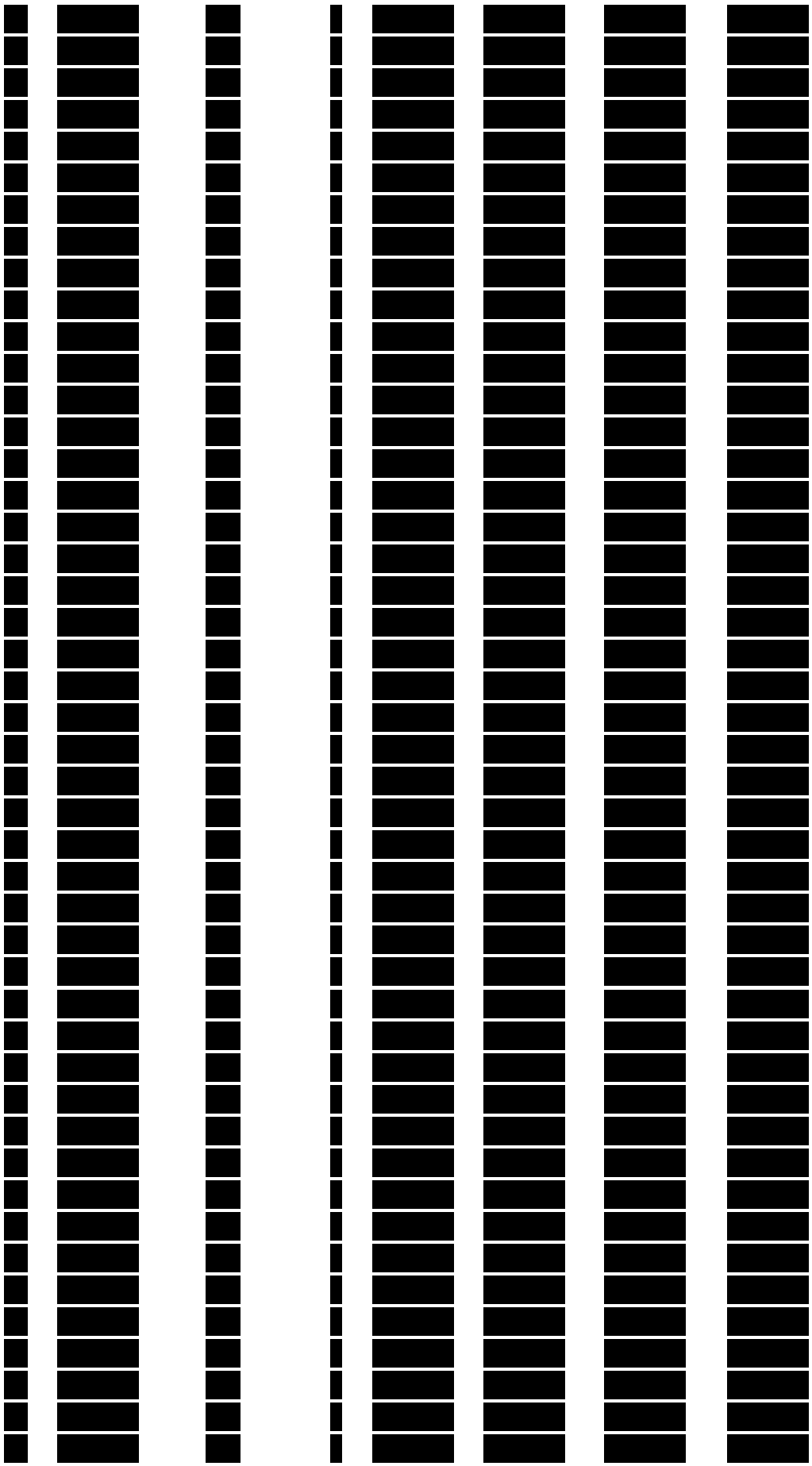
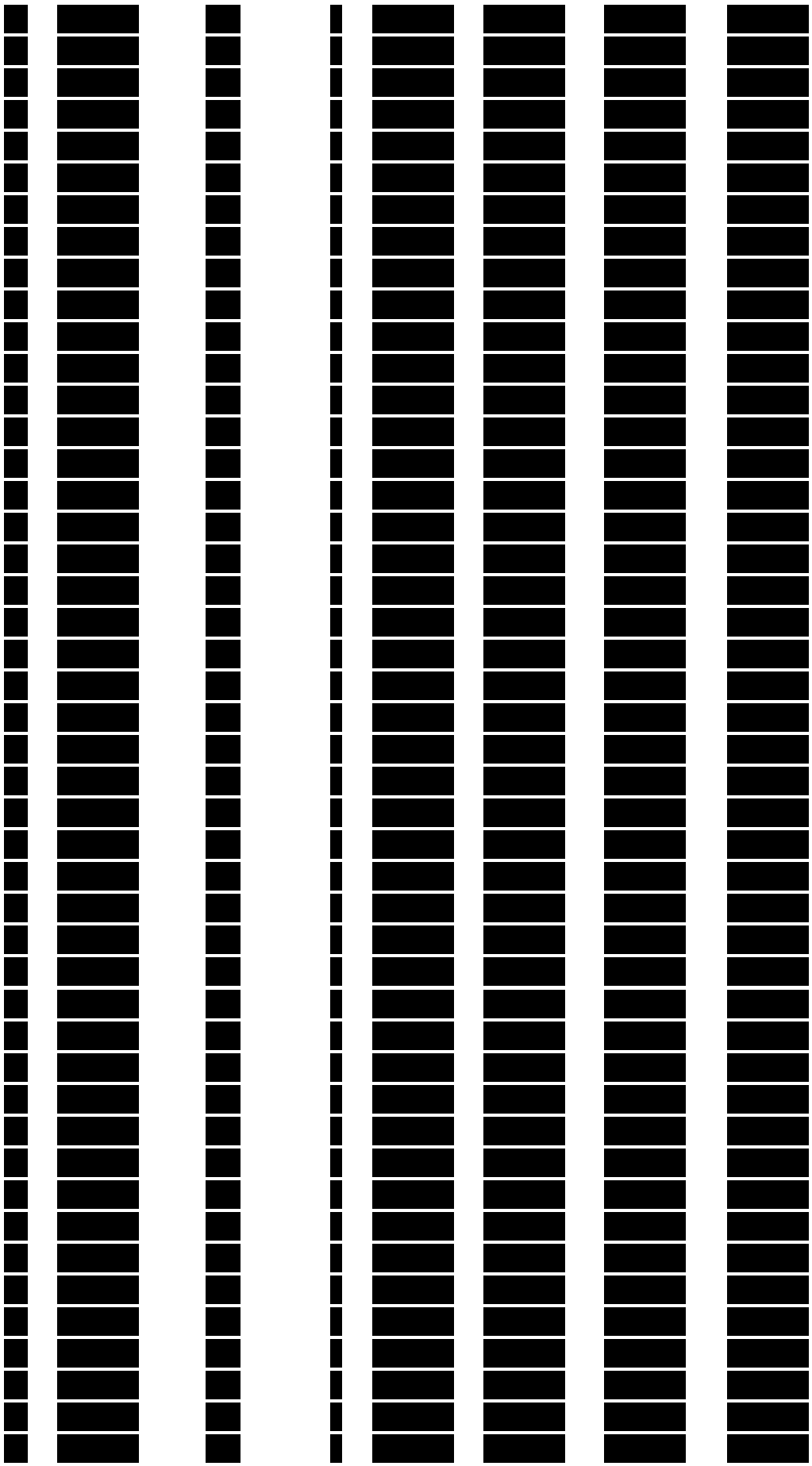


Table 4. KM Data - OS everolimus CheckMate025 study









[redacted]

Table 5. KM Data - OS everolimus RECORD-1 study

	time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]							

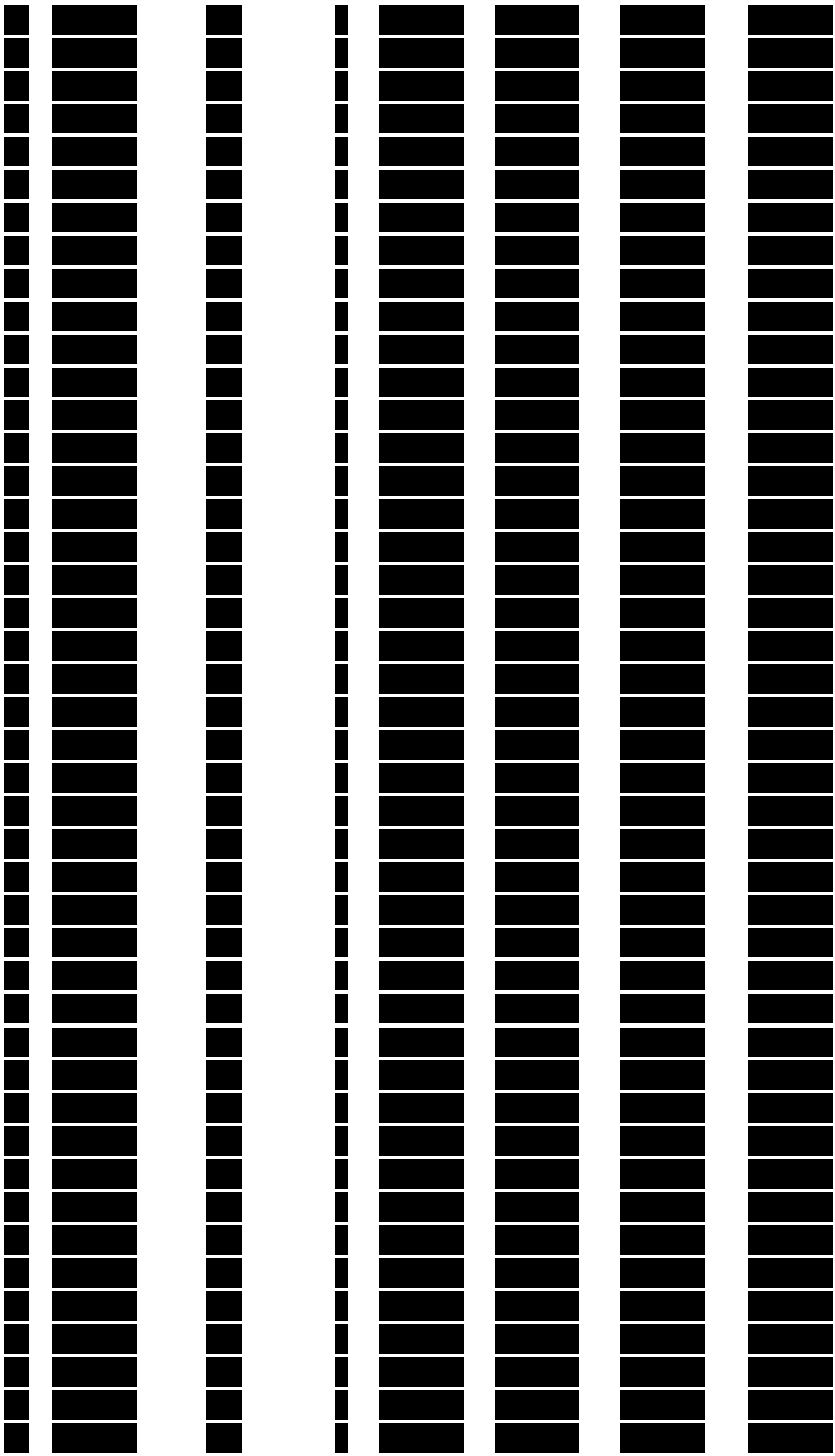
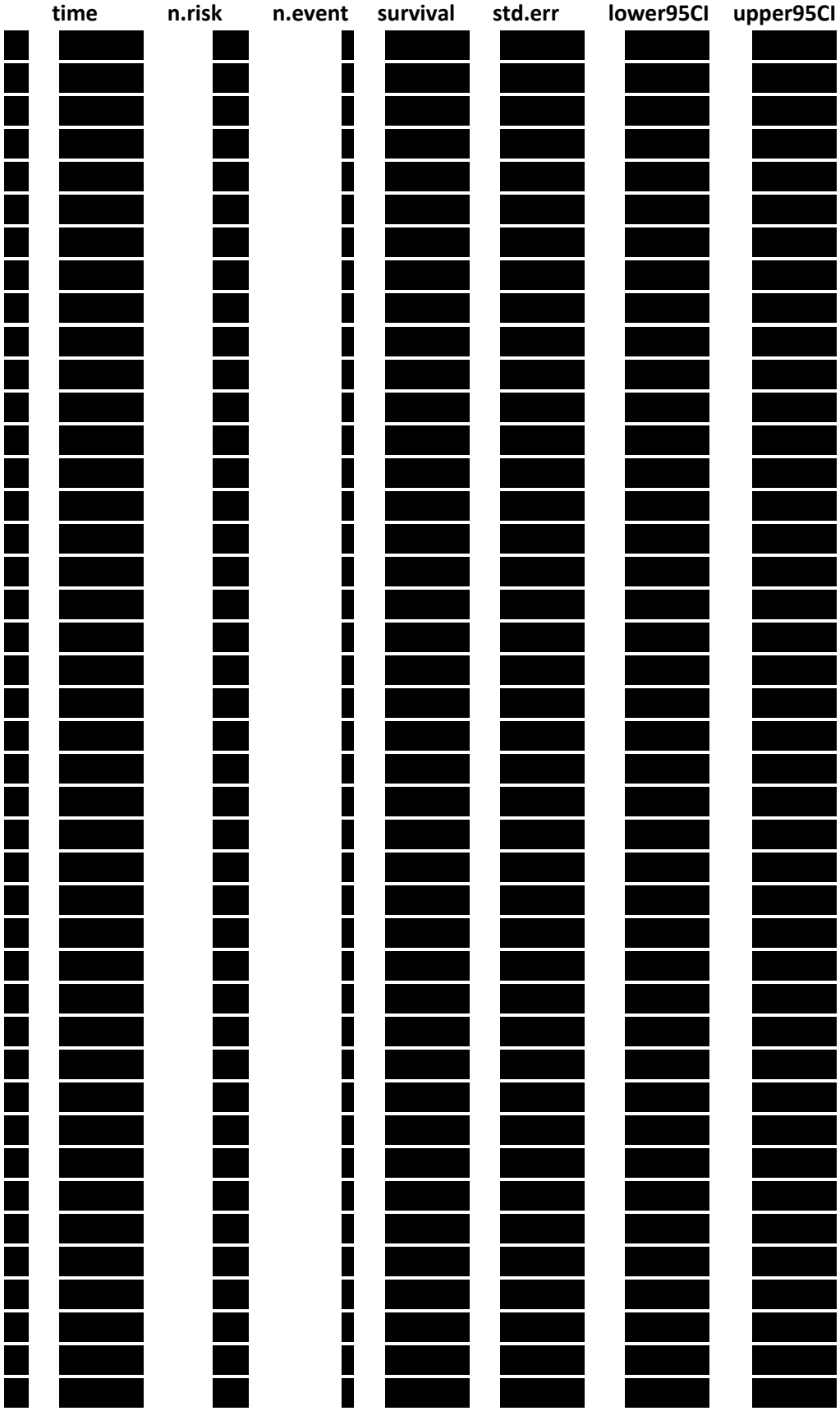
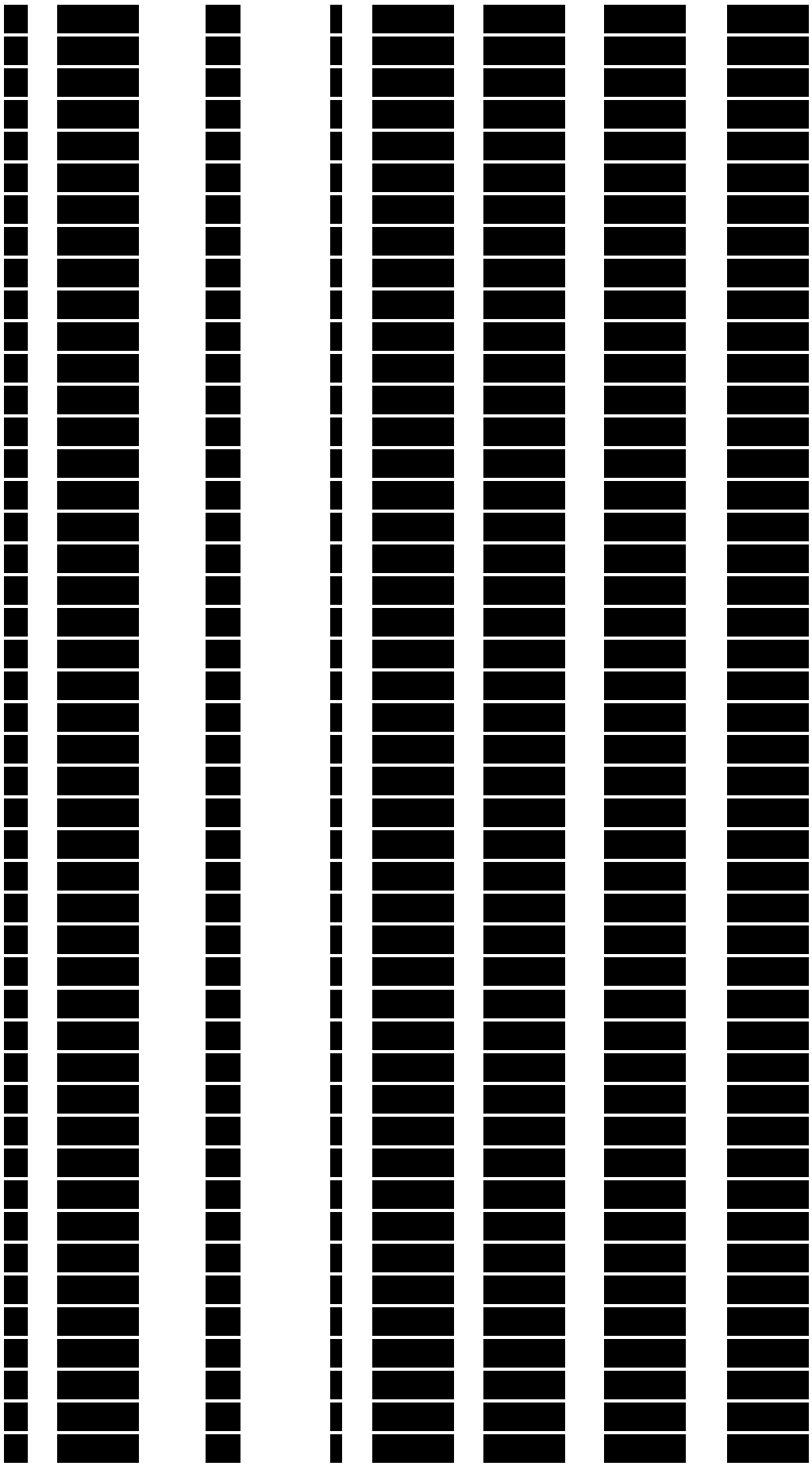


Table 6. KM Data - OS nivolumab CheckMate025 study





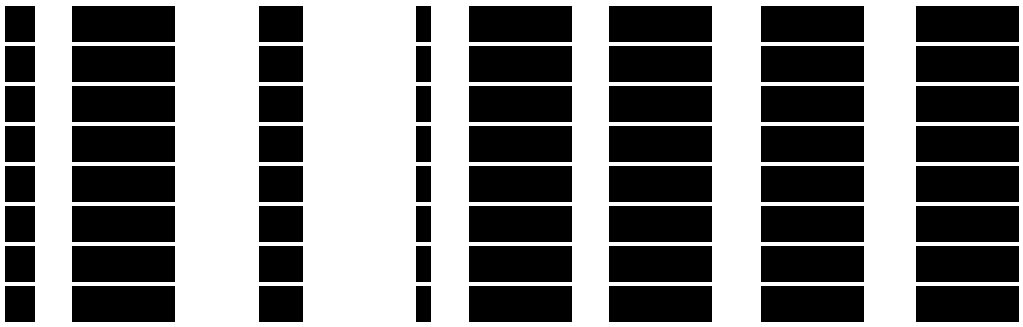
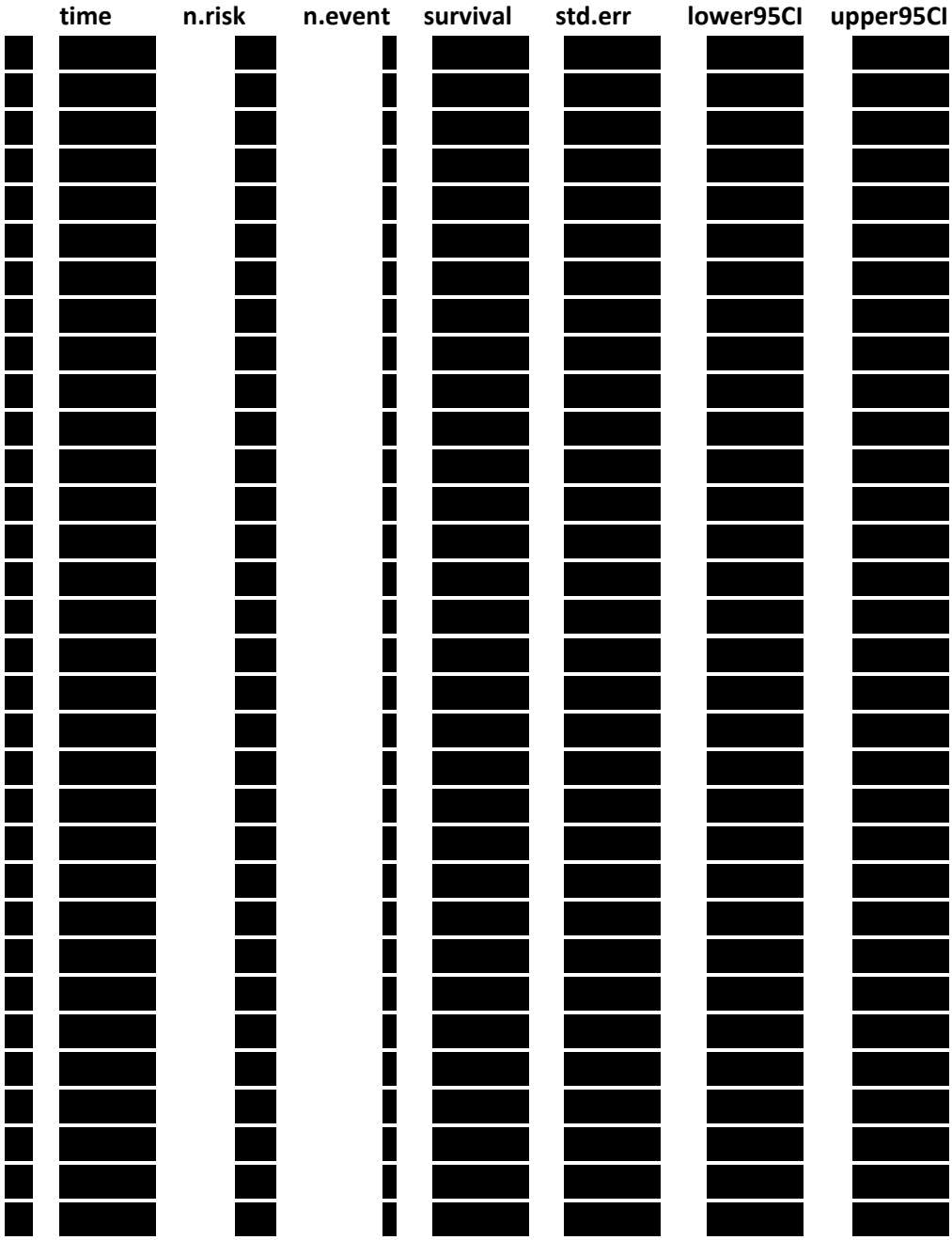


Table 7. KM Data - OS placebo RECORD-1 study



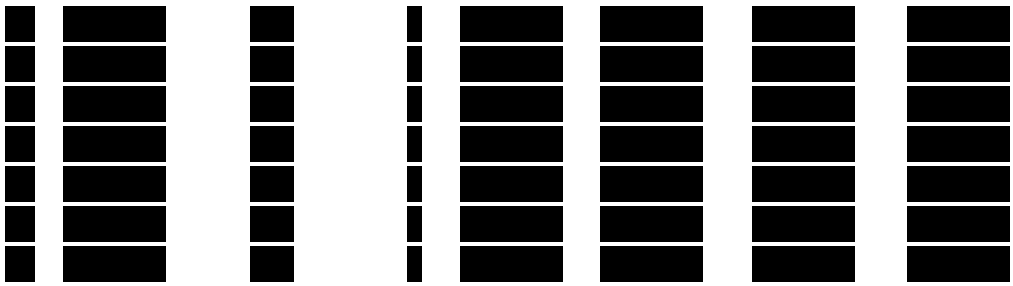
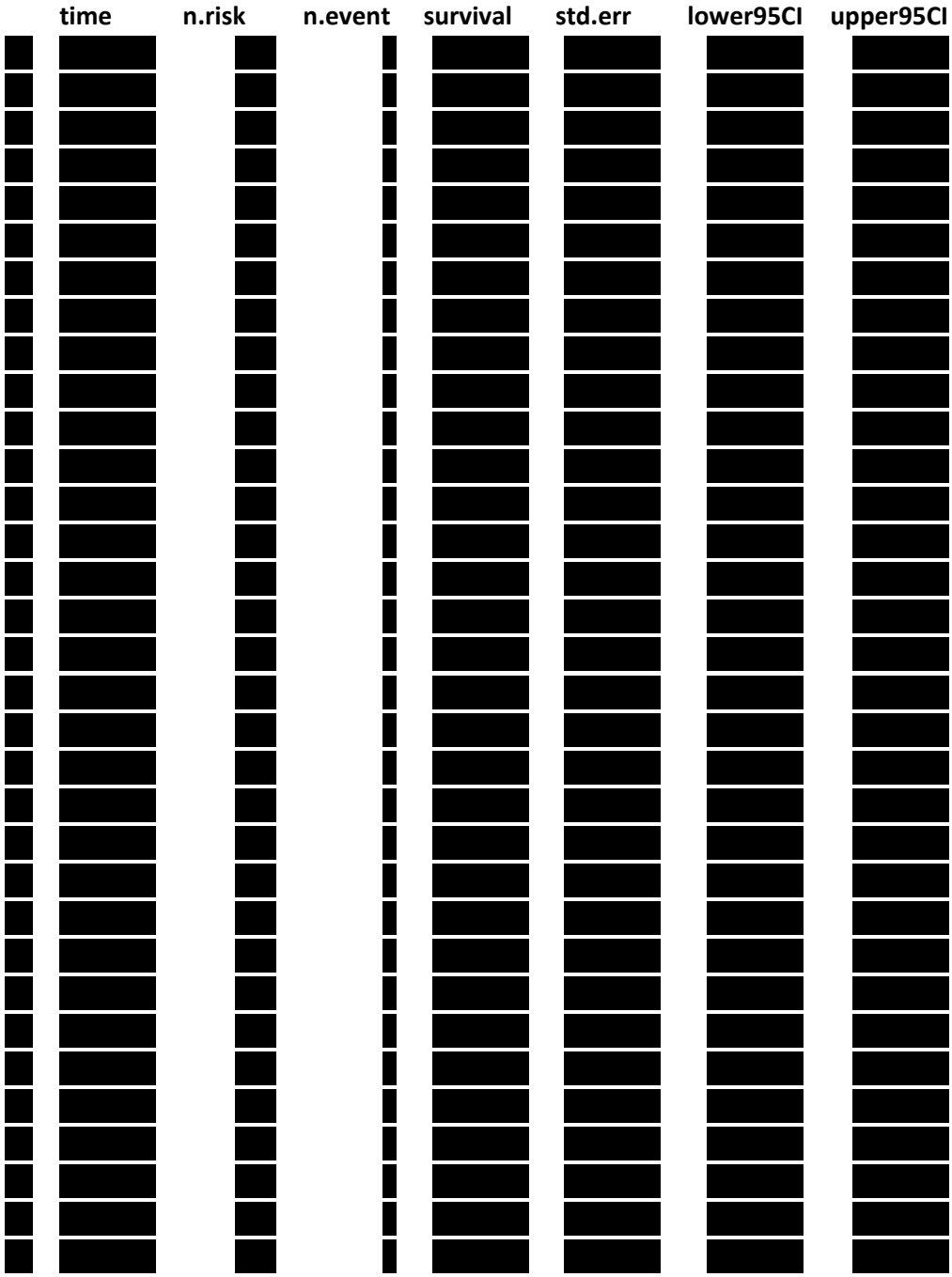


Table 8. KM Data - OS placebo TARGET study



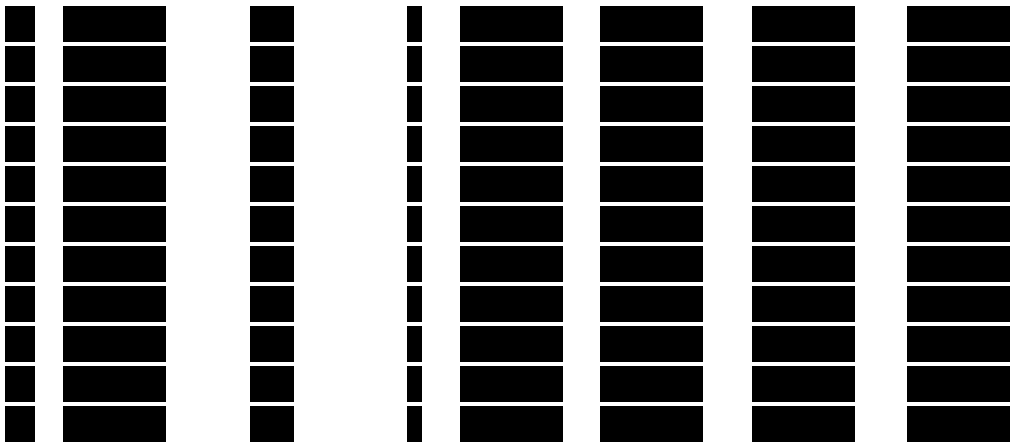
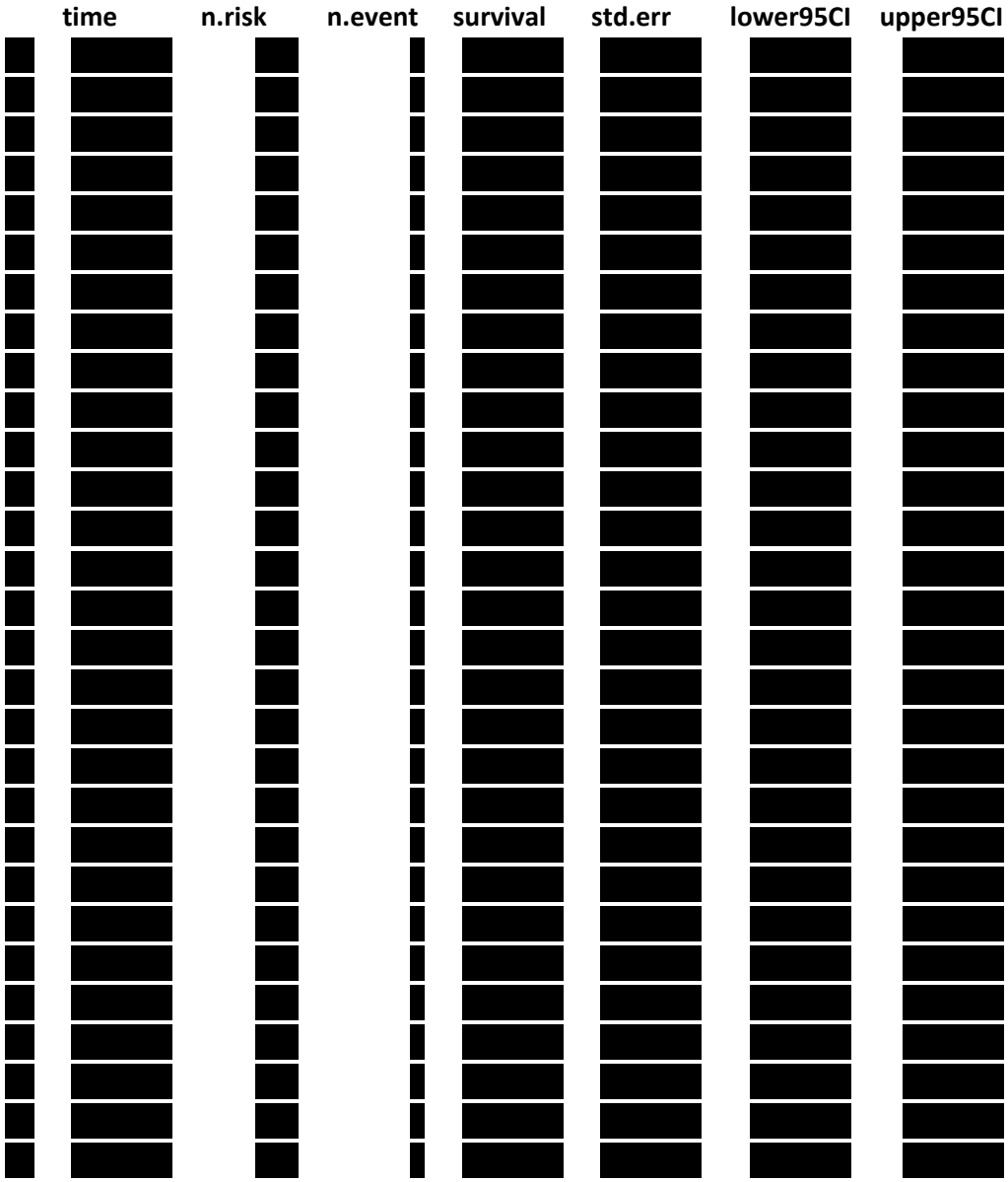
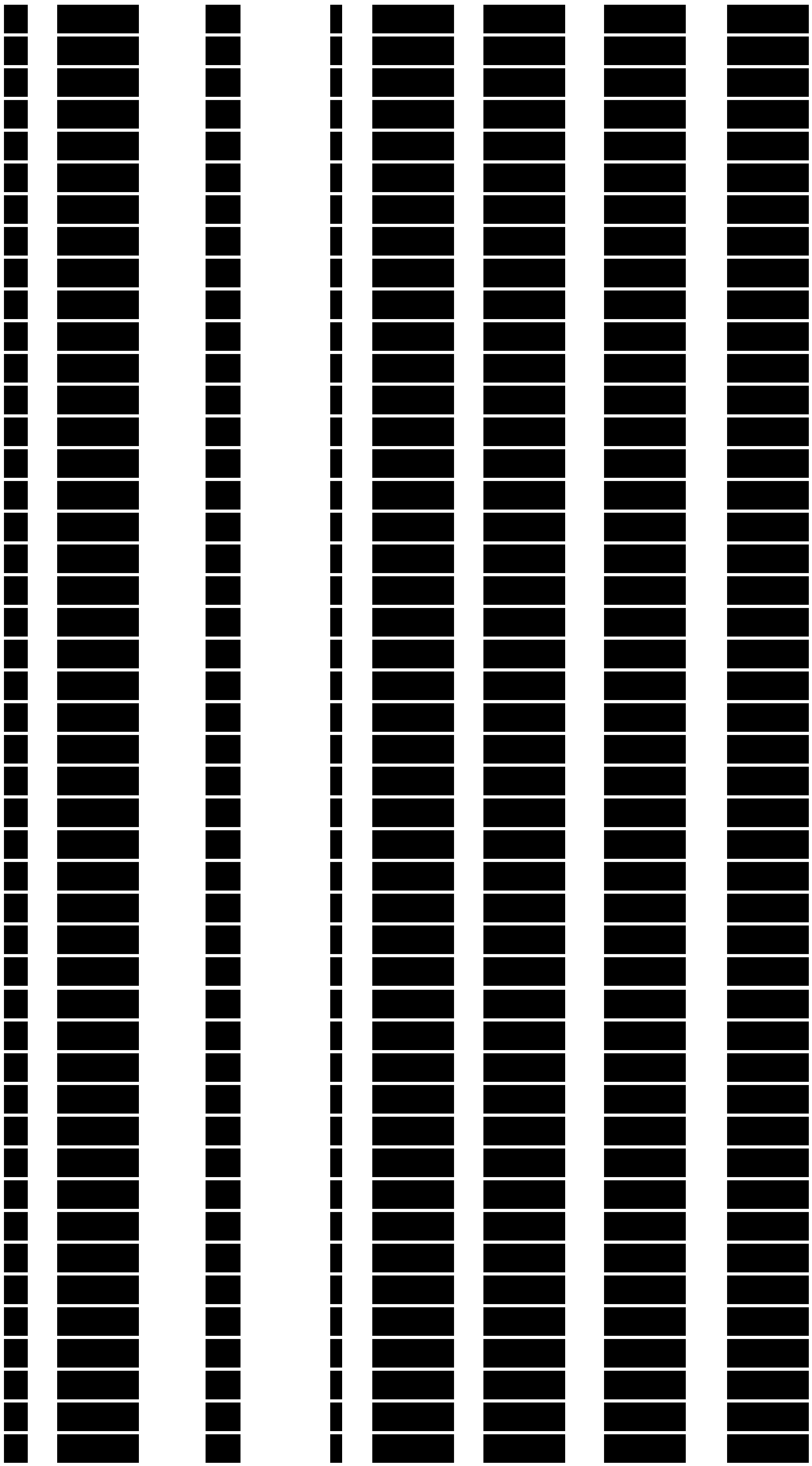


Table 9. KM Data - OS sorafenib AXIS study





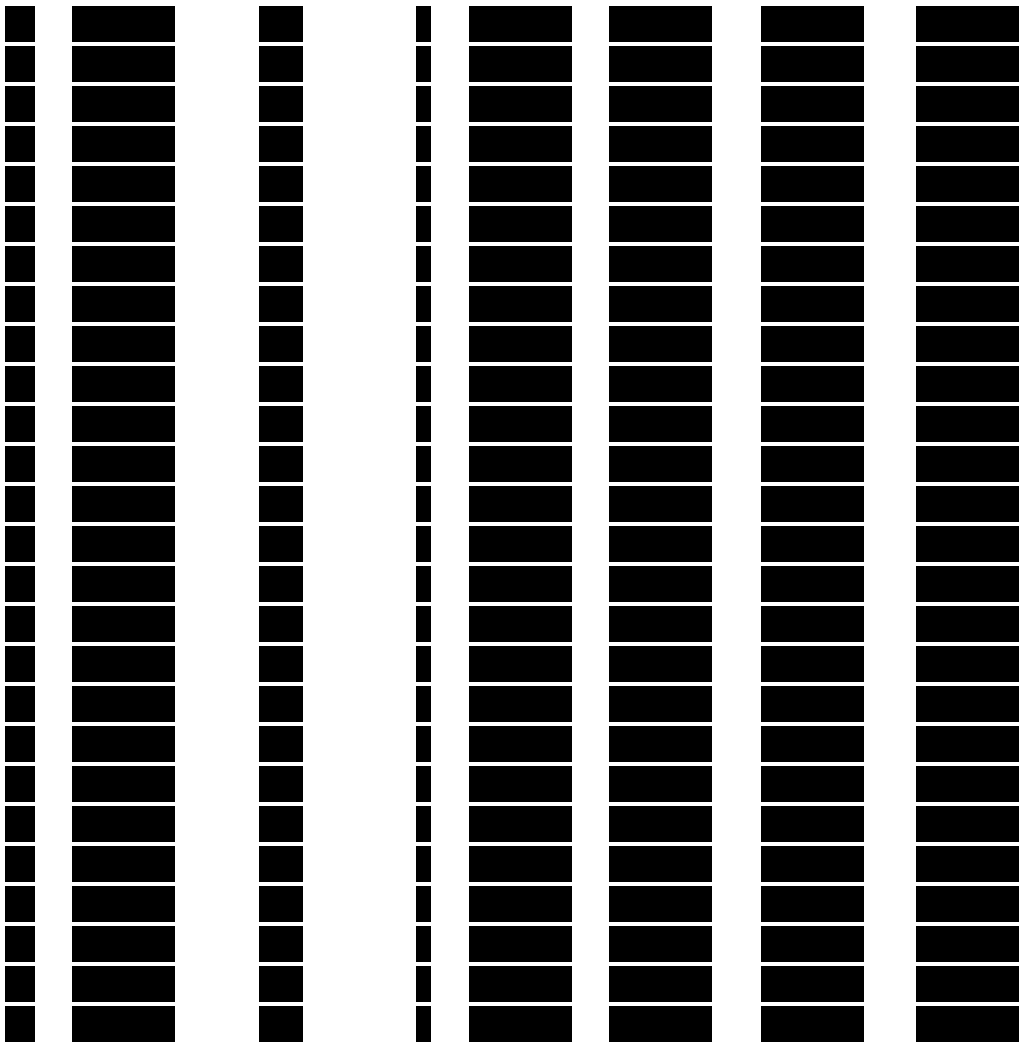
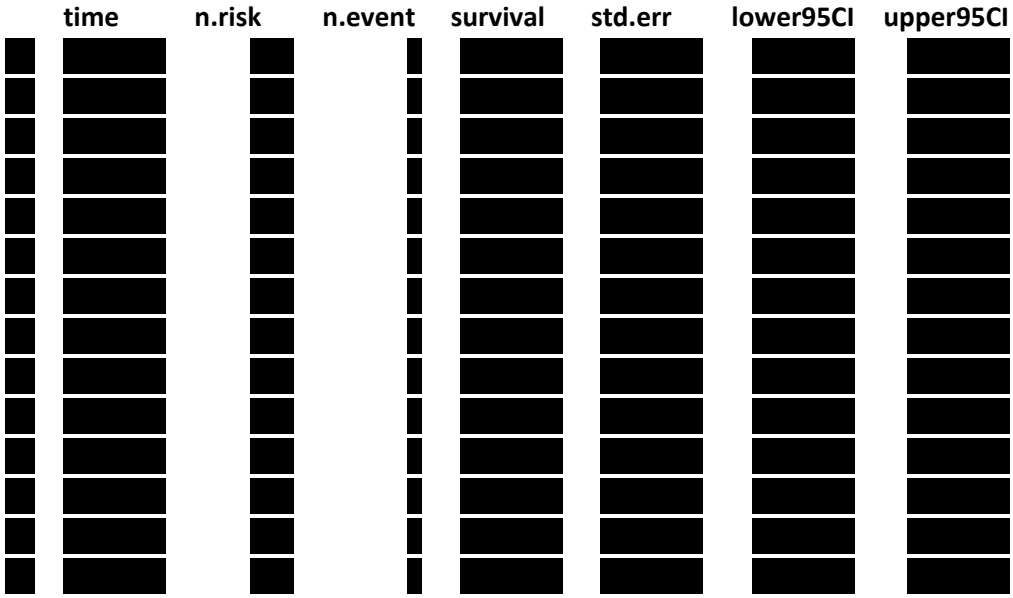
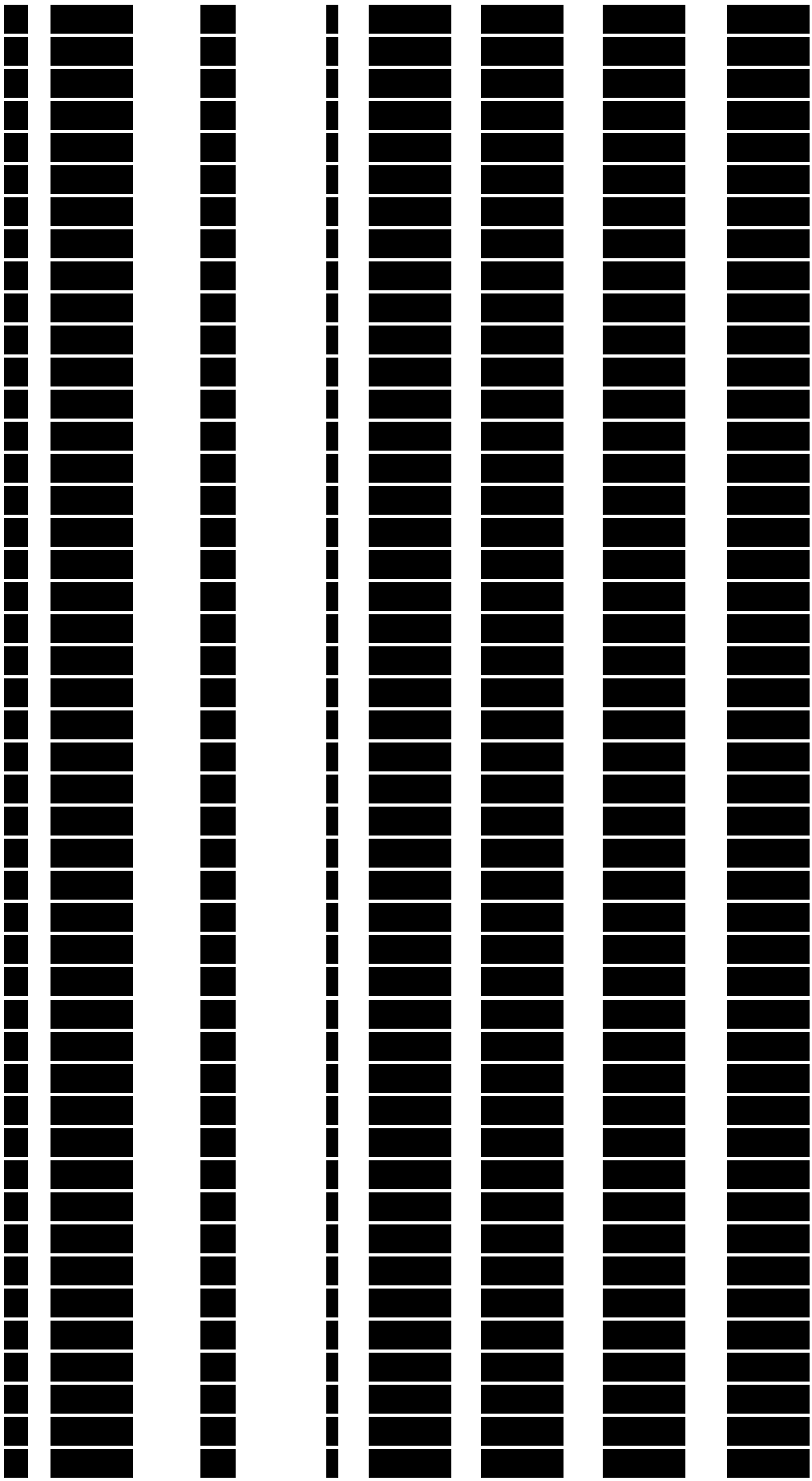


Table 10. KM Data - OS sorafenib TARGET study





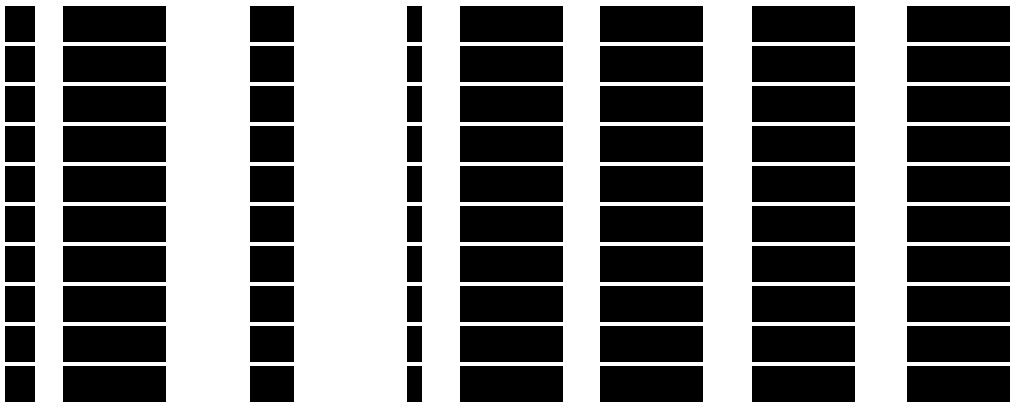
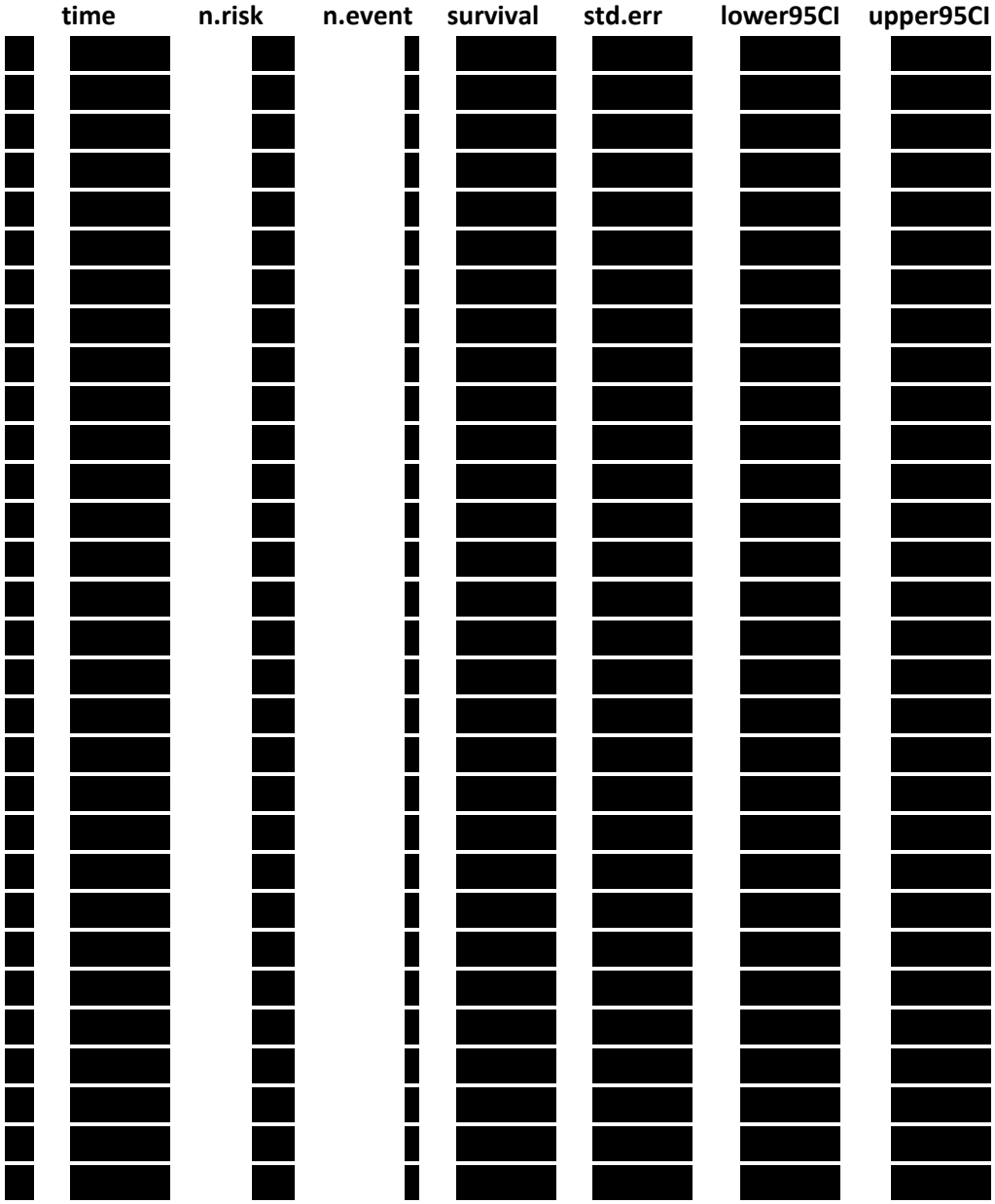


Table 11. KM Data - PFS axitinib AXIS study



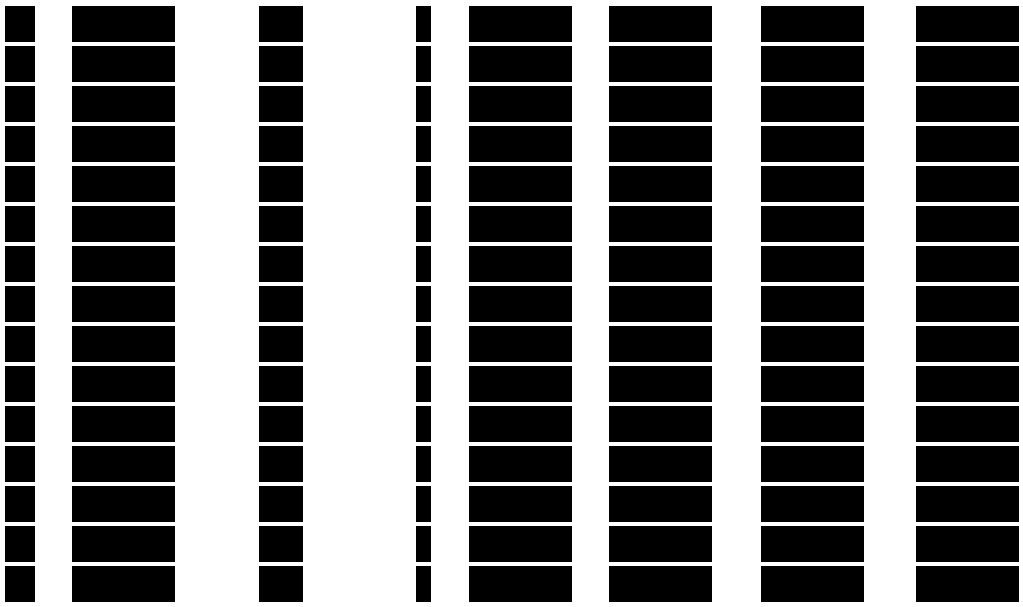
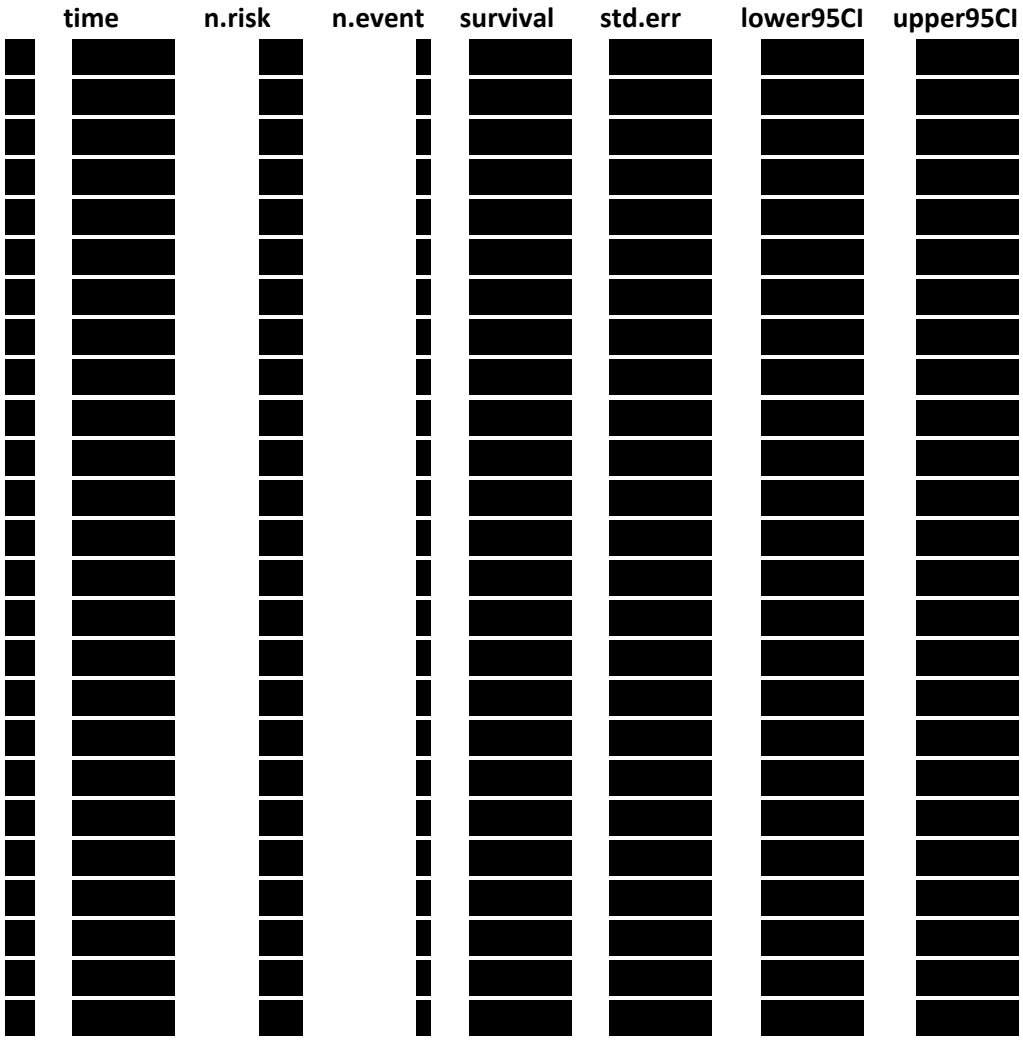
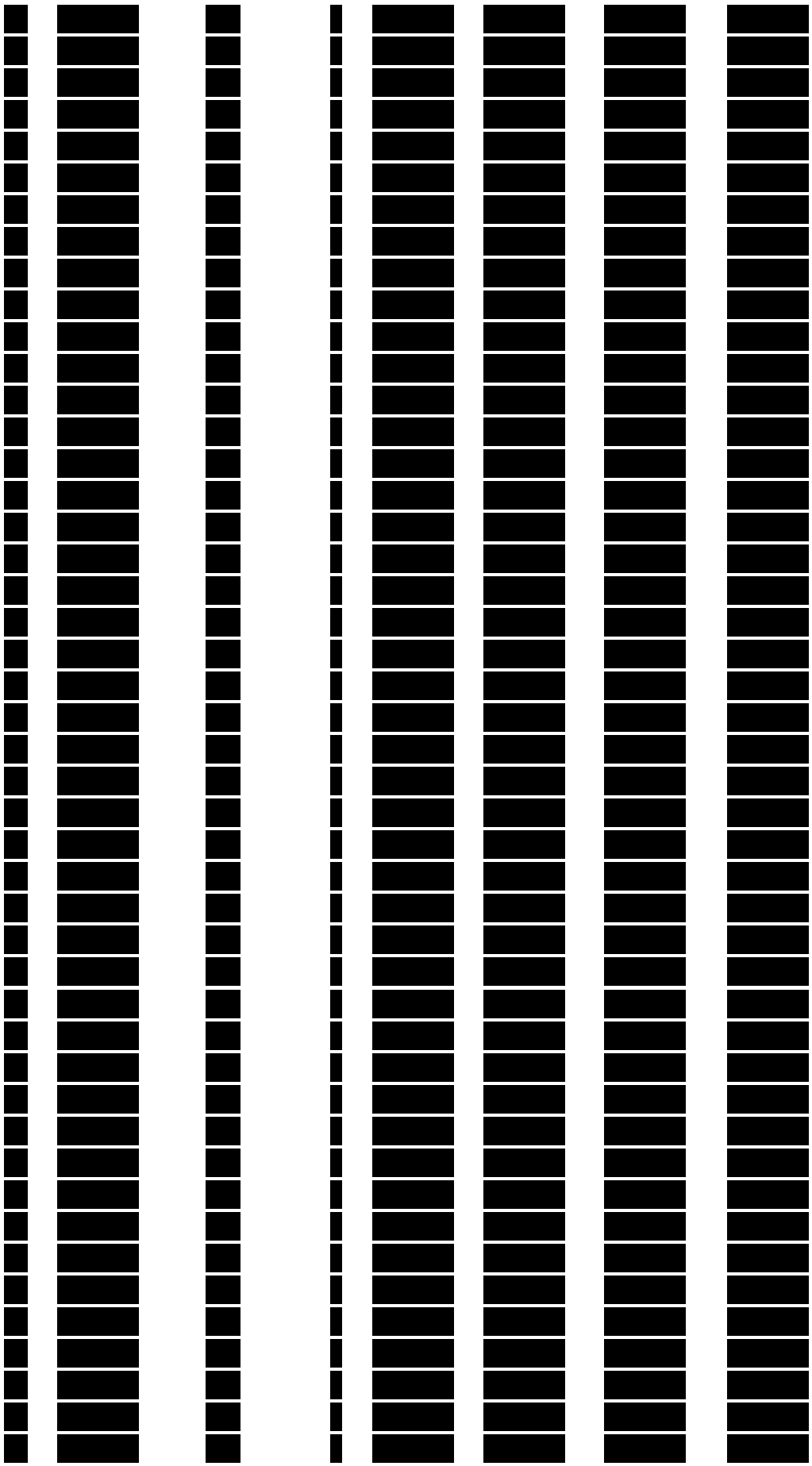
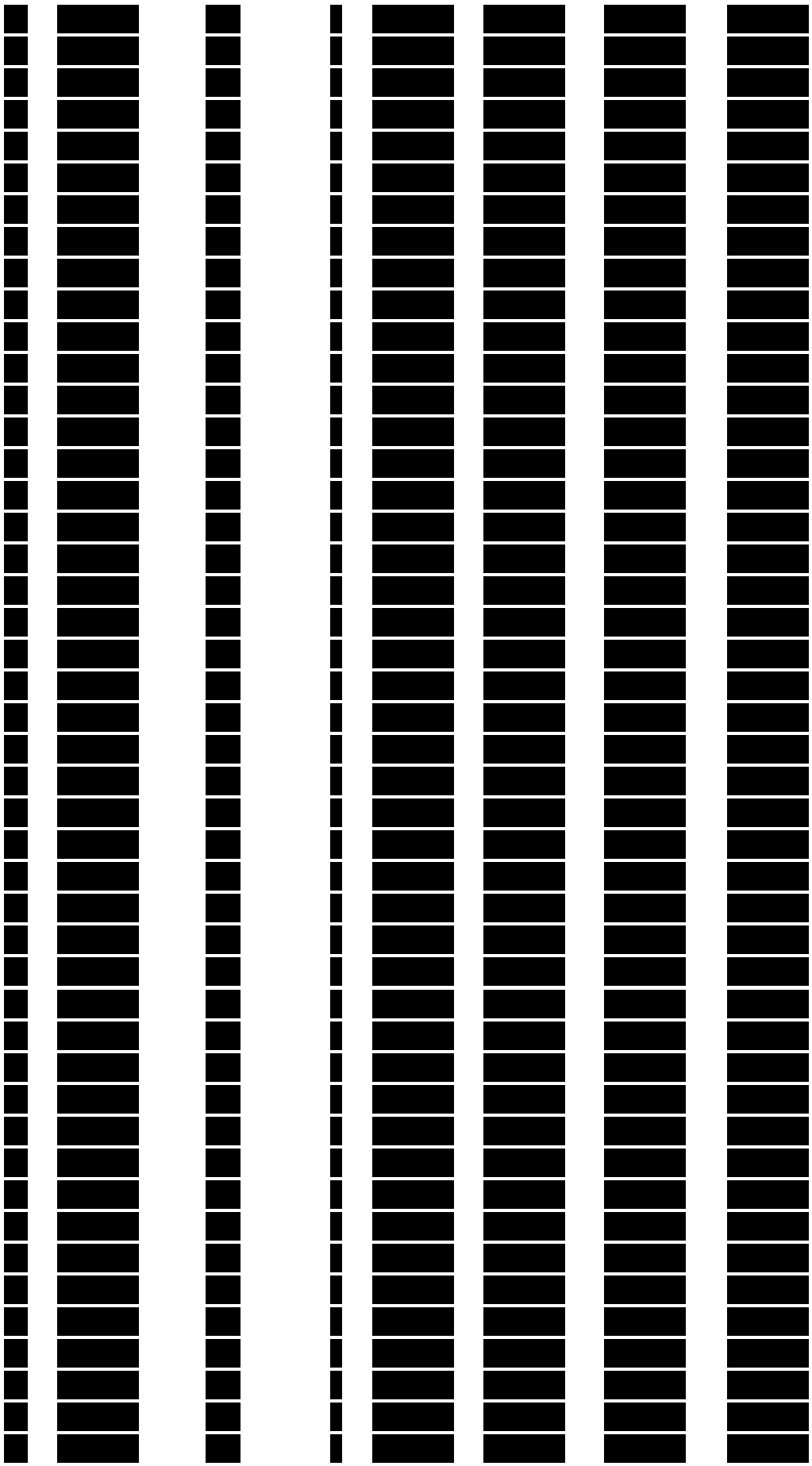


Table 12. KM Data - PFS everolimus CheckMate025 study







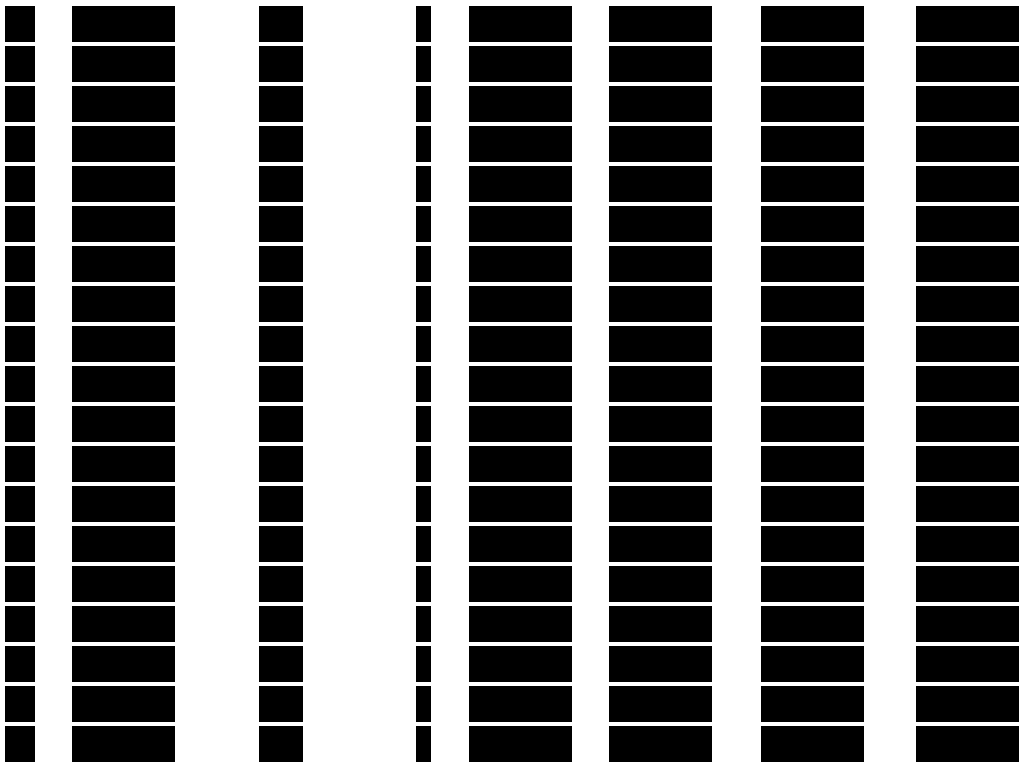


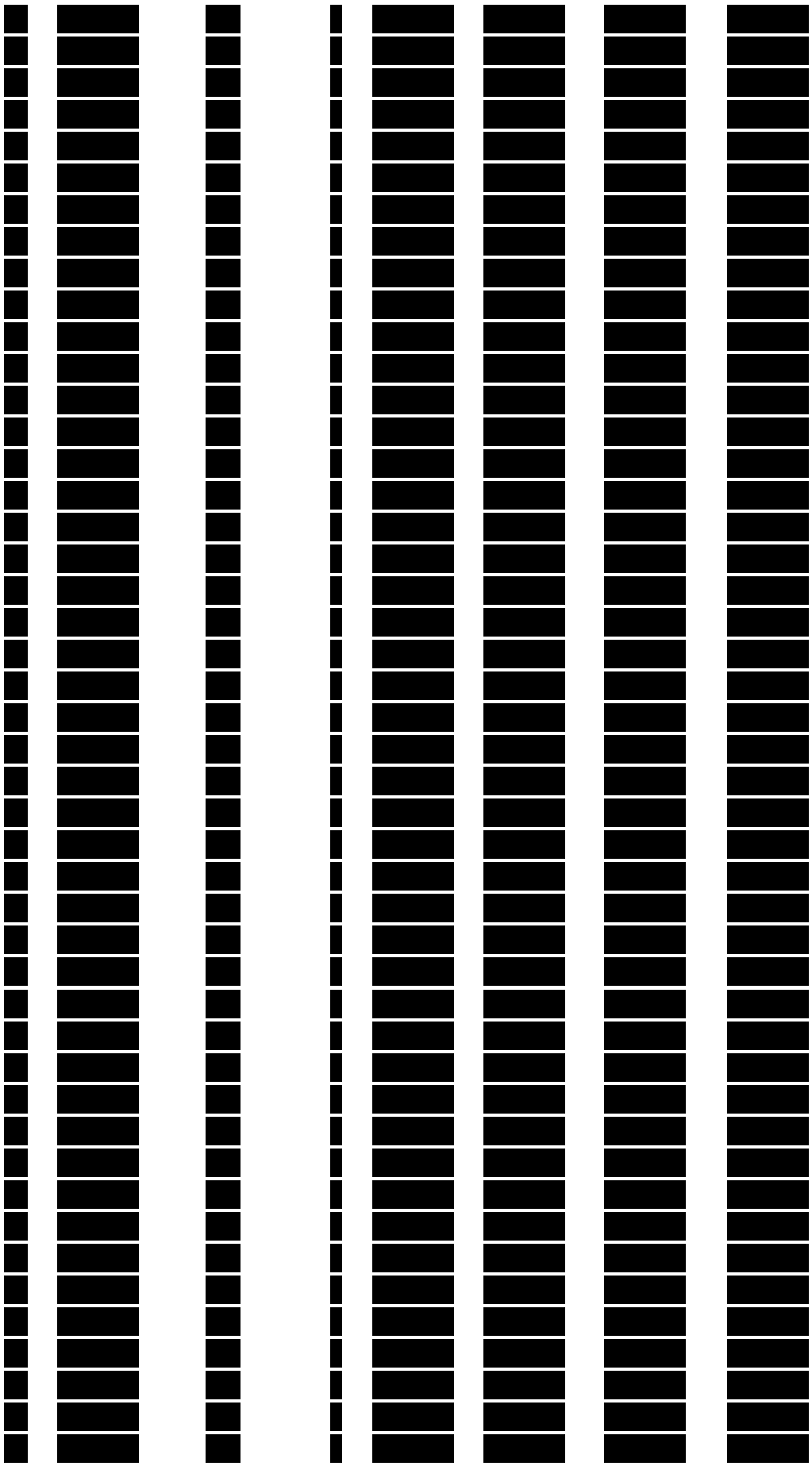
Table 13. KM Data - PFS everolimus RECORD-1 study

	time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]							

[redacted]

Table 14. KM Data - PFS nivolumab CheckMate025 study

time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]						



[redacted]

Table 15. KM Data - PFS placebo RECORD-1 study

time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]						

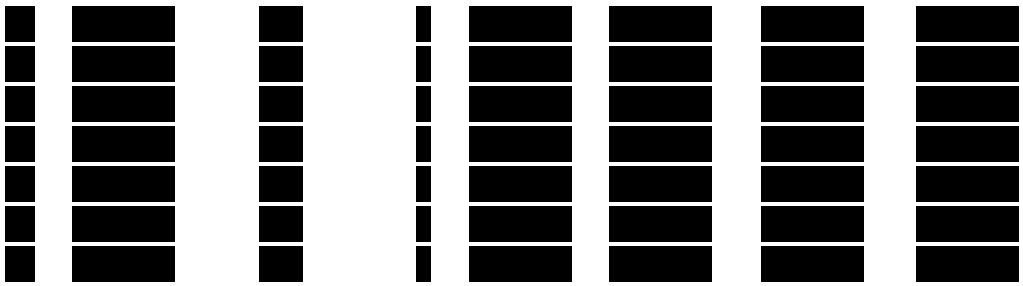
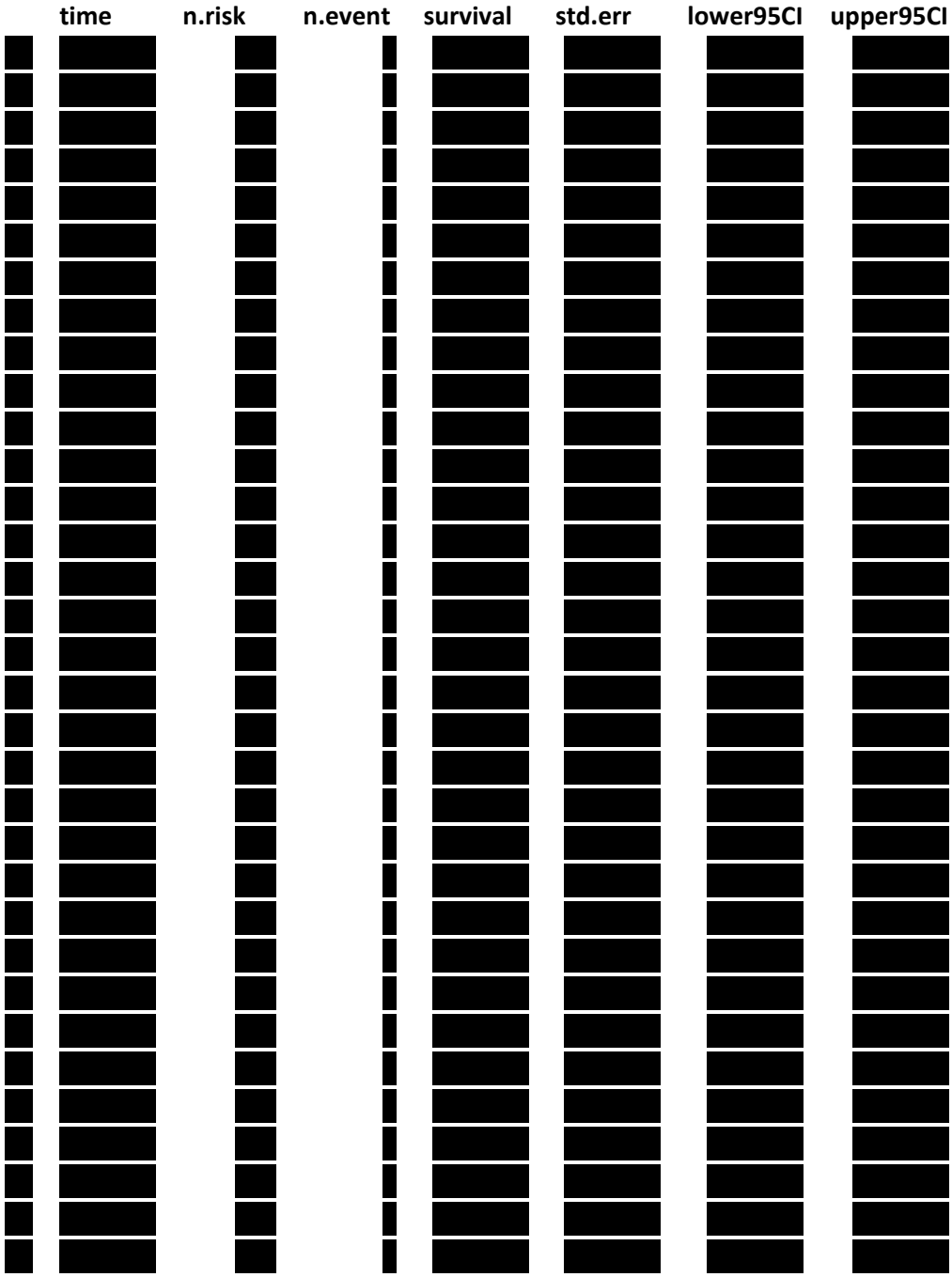


Table 16. KM Data - PFS placebo TARGET study



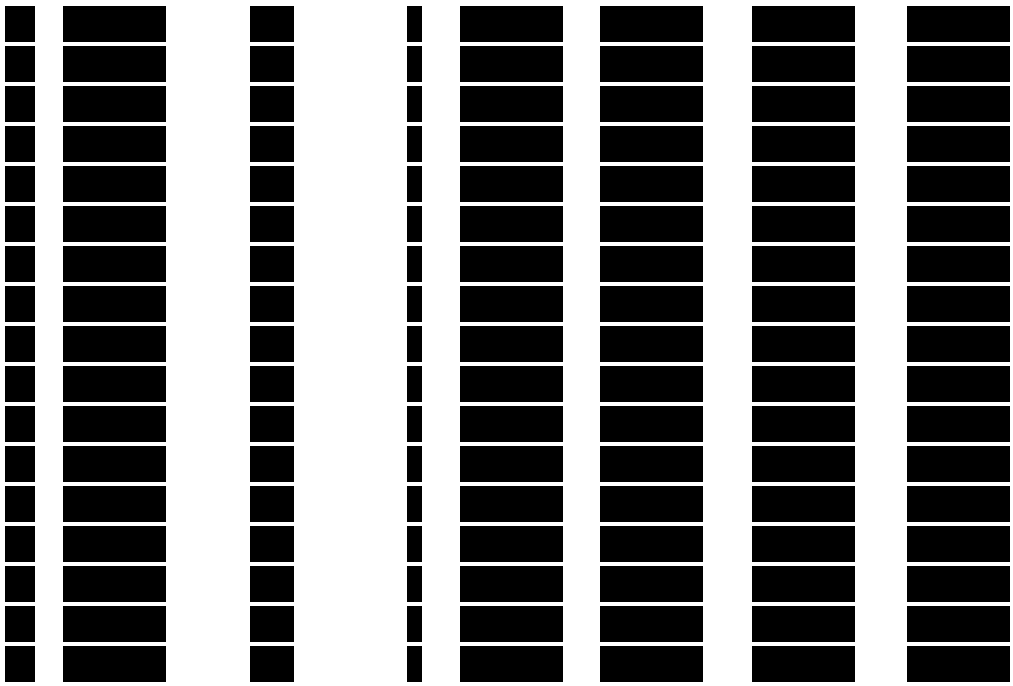
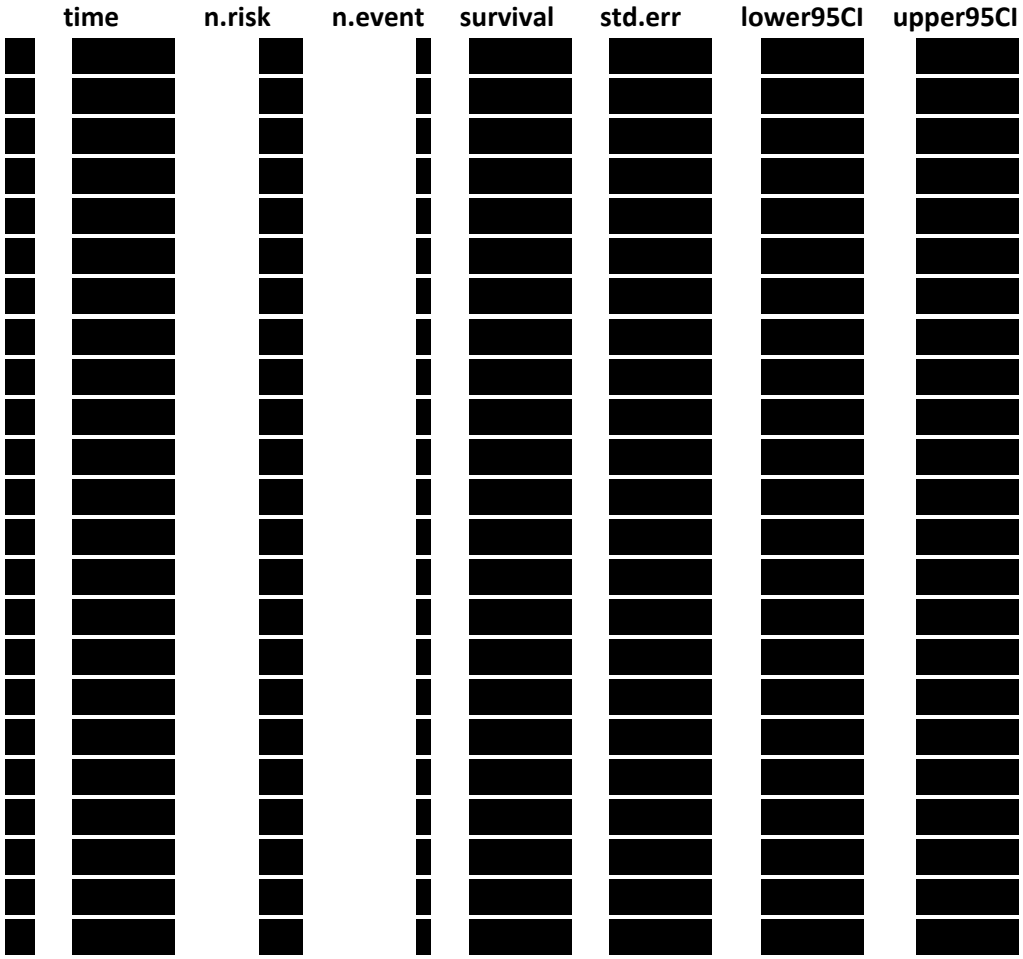


Table 17. KM Data - PFS sorafenib AXIS study



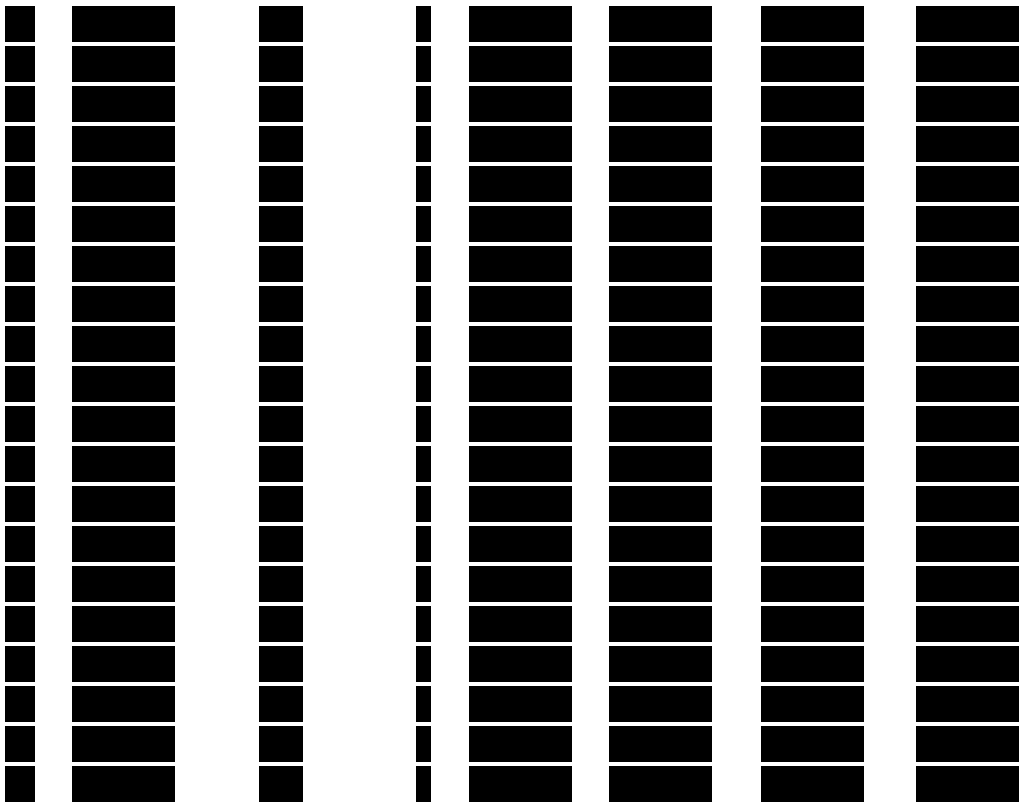
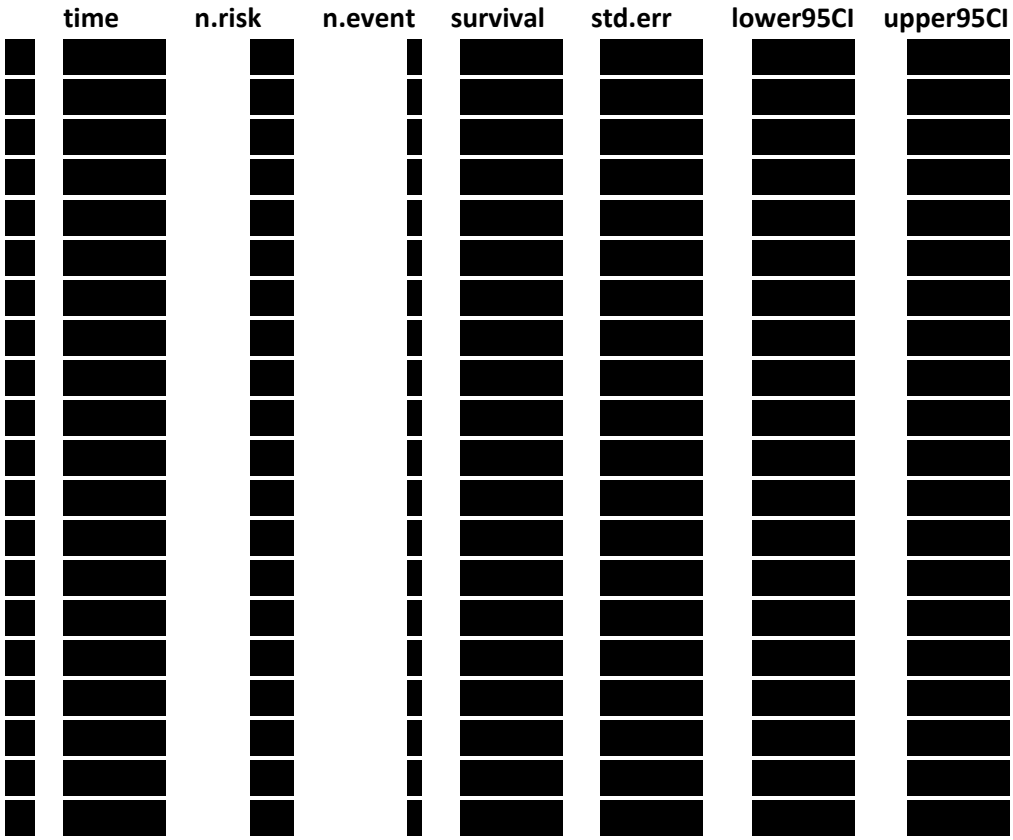


Table 18. KM Data - PFS sorafenib TARGET study



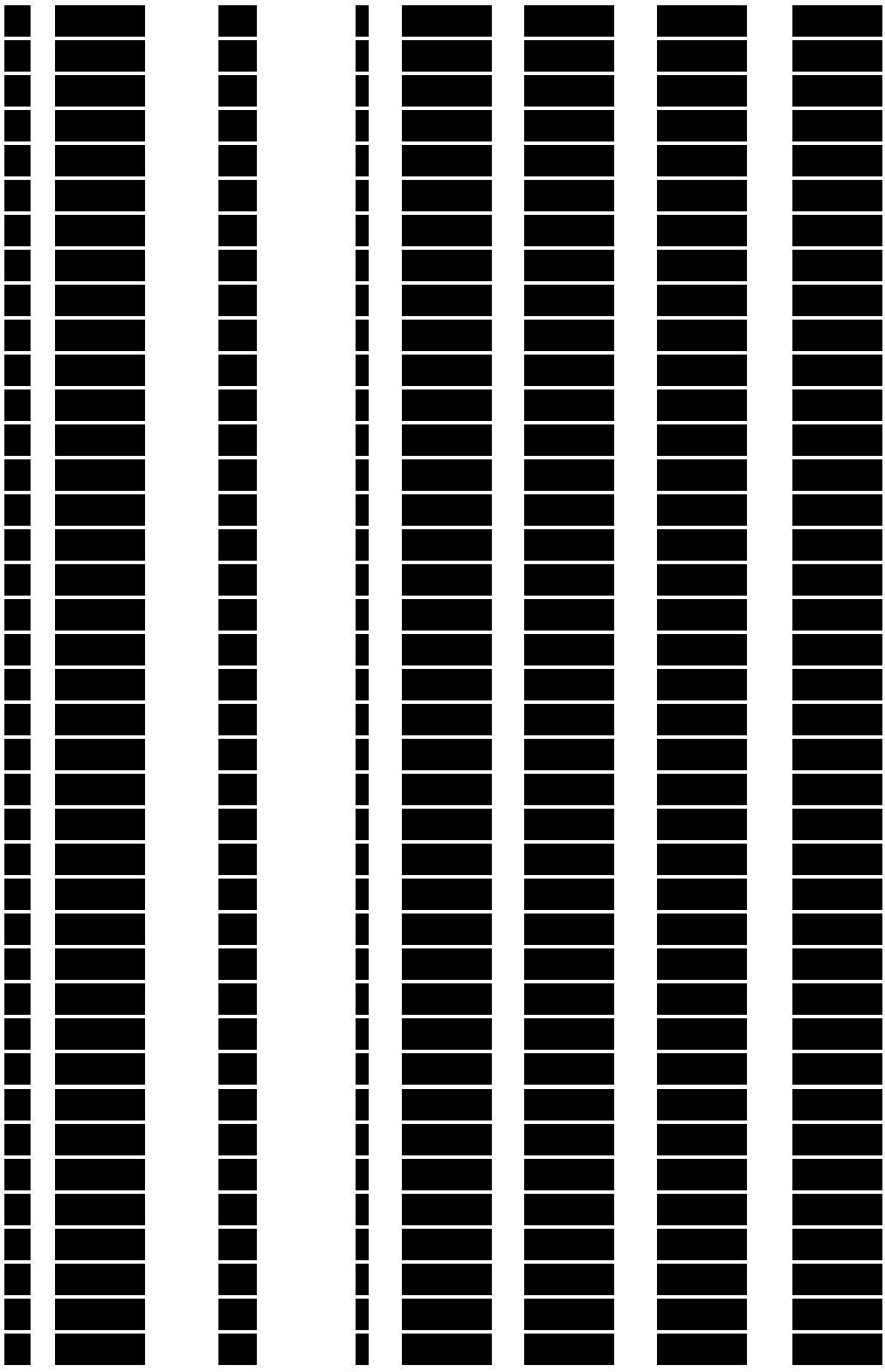


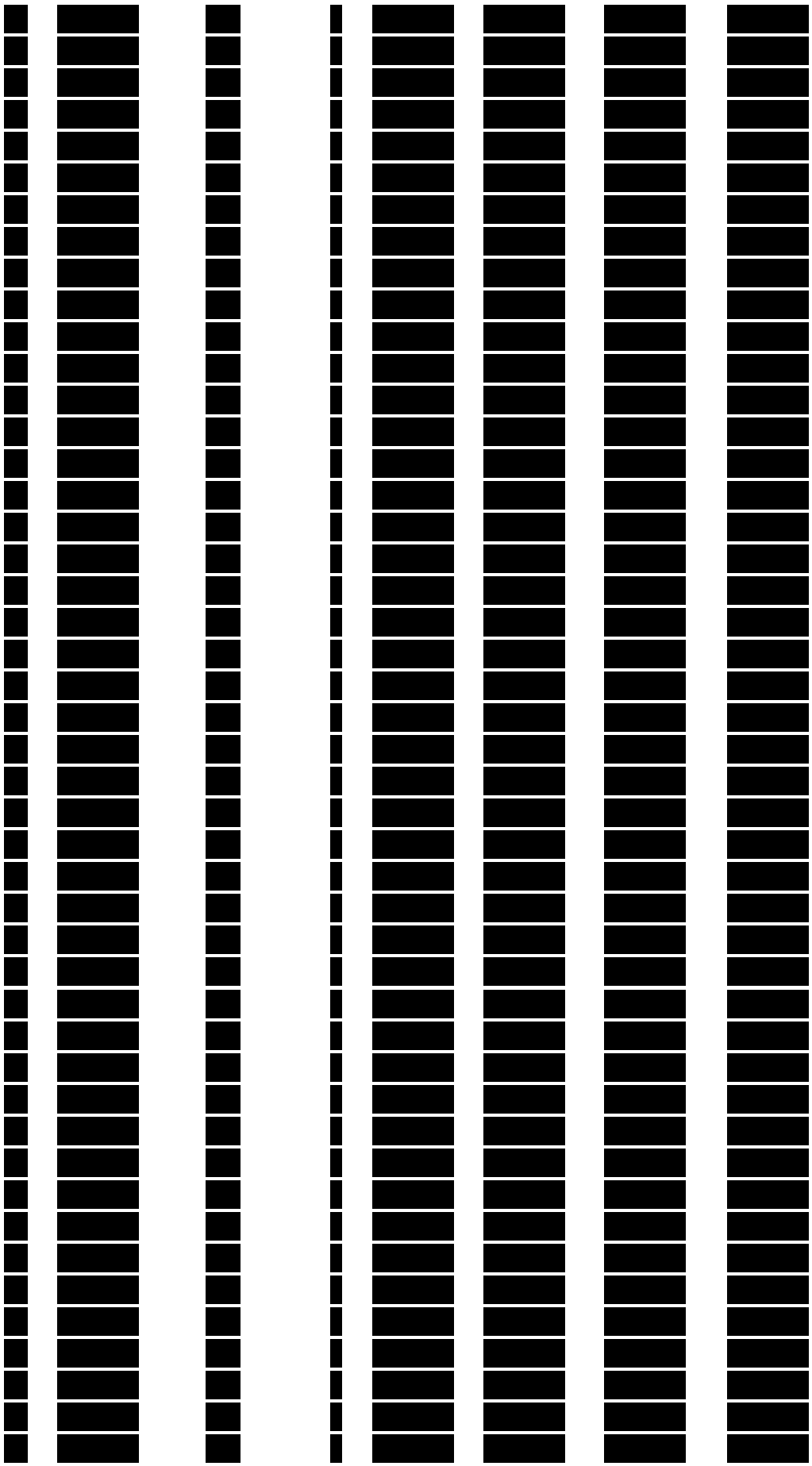
Table 19. KM Data - TTD everolimus CheckMate025 study

	time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]							

[redacted]

Table 20. KM Data - TTD nivolumab CheckMate025 study

time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]						



[redacted]

B2. **Priority question**: Please provide the KM plots for TTD in the METEOR trial and the KM data for OS, PFS and TTD from the METEOR trial.

RESPONSE: Please see KM plots from Figure 28 to Figure 69. KM data is provided in Tables 26 to 31.

Figure 28. KM Plot - OS cabozantinib METEOR study

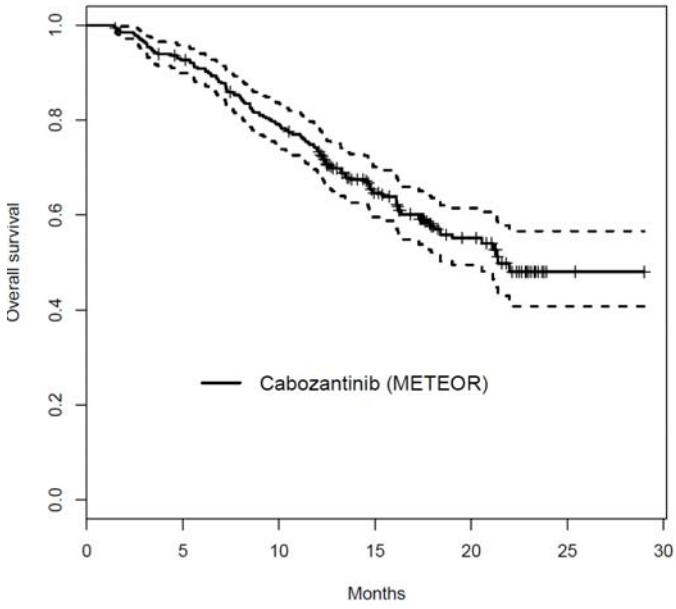


Figure 29. KM Plot - OS everolimus METEOR study

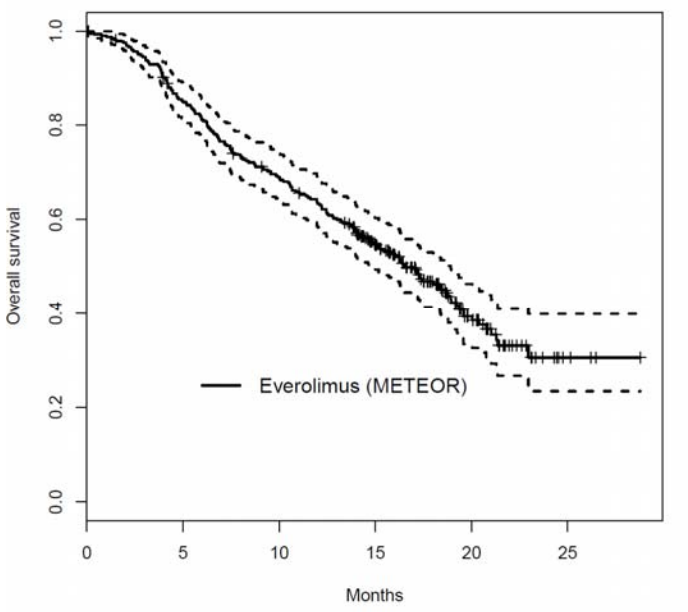


Figure 30. KM Plot - PFS cabozantinib METEOR study

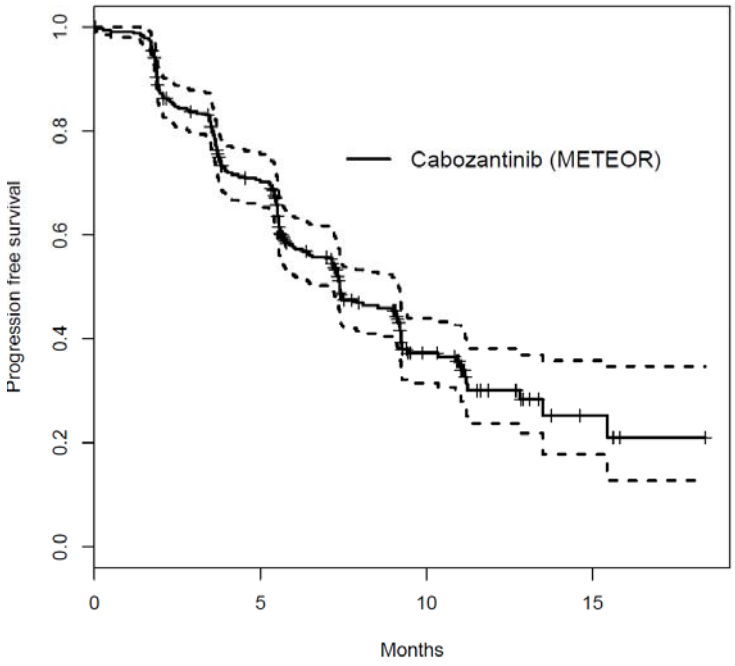


Figure 31. KM Plot - PFS everolimus METEOR study

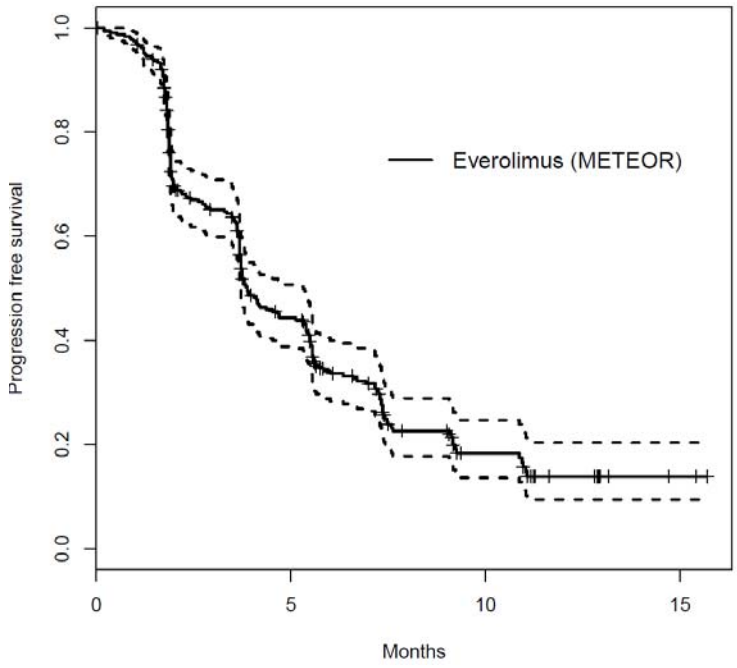


Figure 32. KM Plot - TTD cabozantinib METEOR study

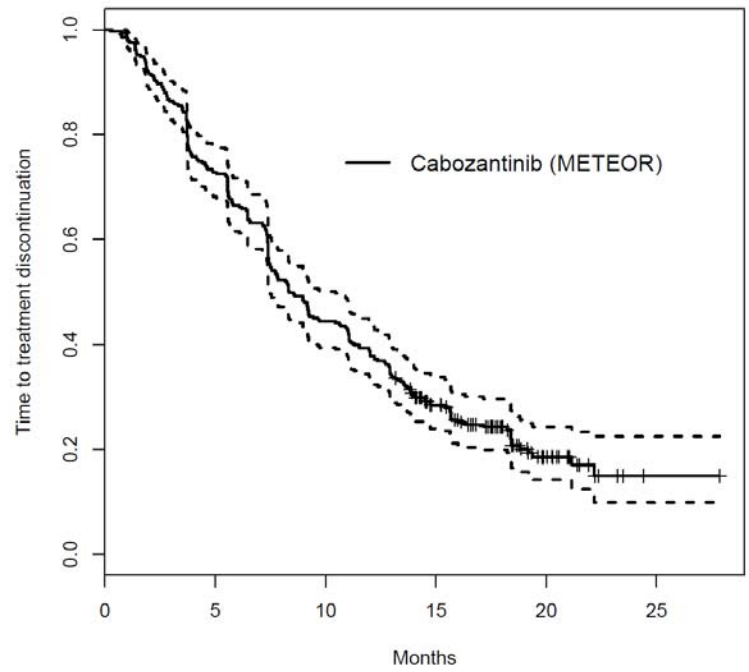


Figure 33. KM Plot - TTD everolimus METEOR study

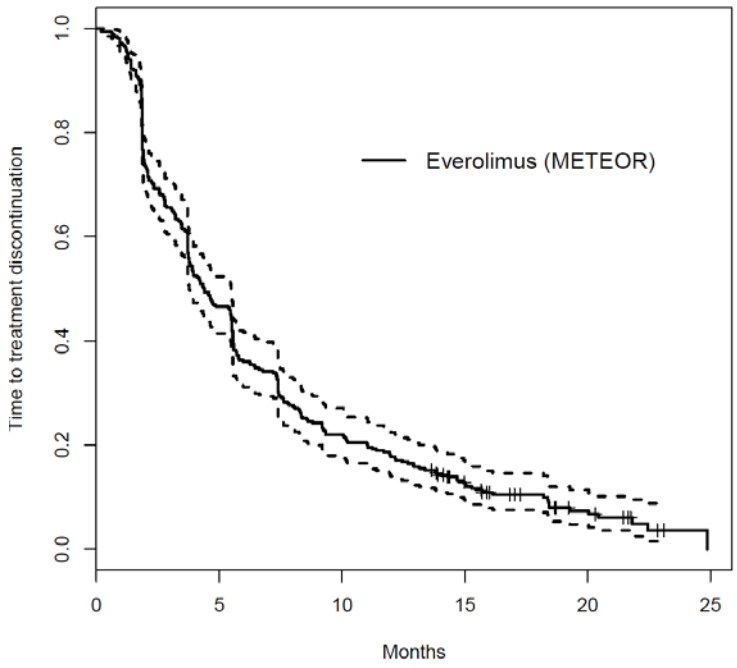
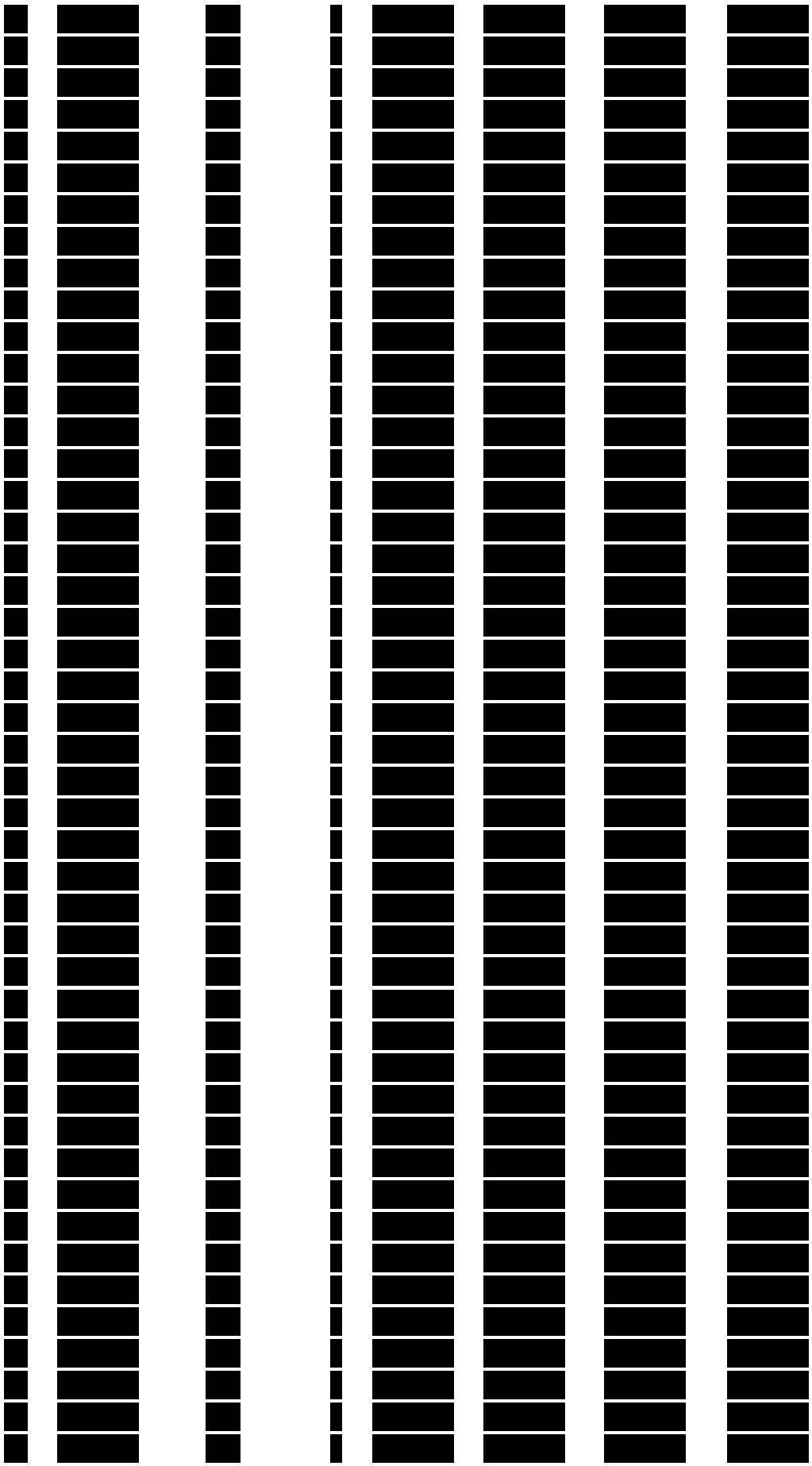
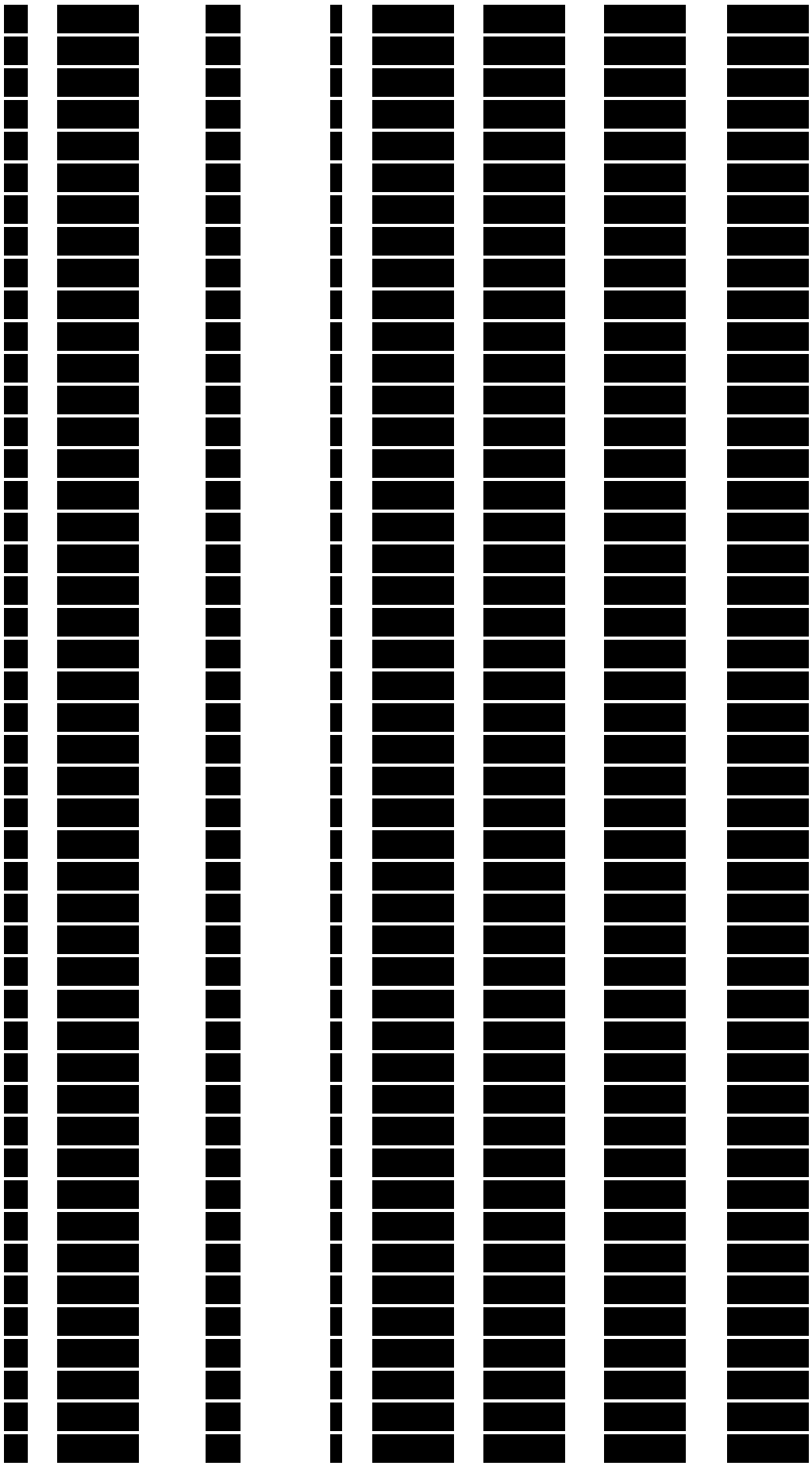


Table 21. KM Data - OS cabozantinib METEOR study

time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]						





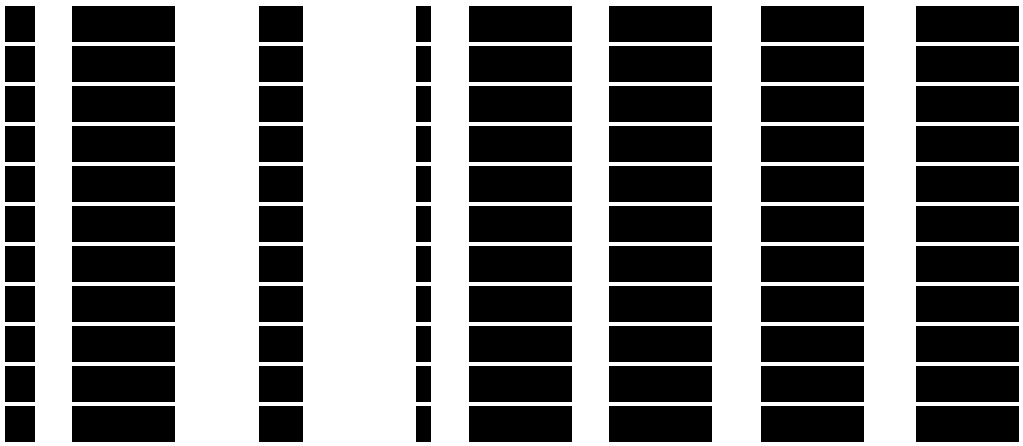
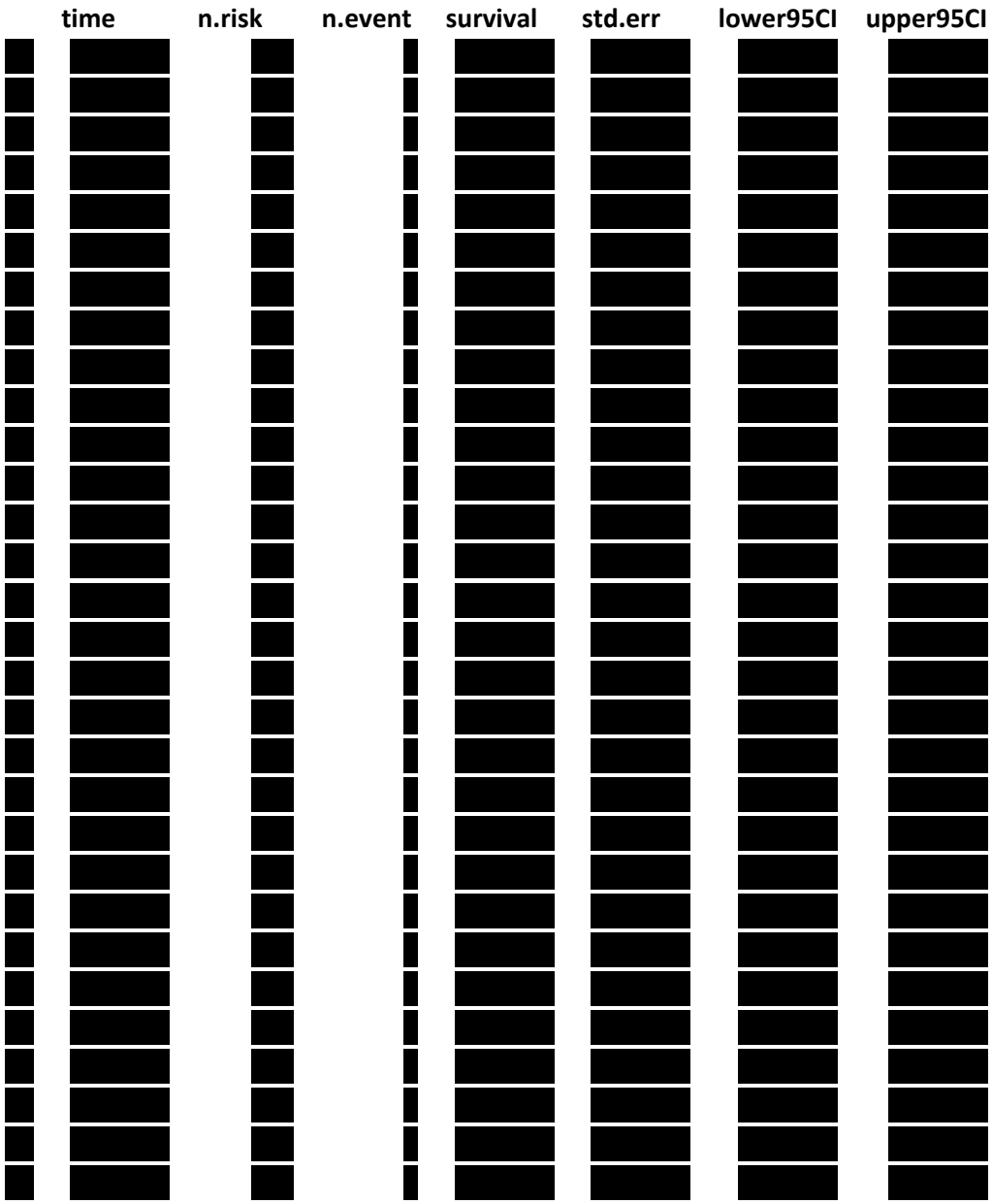
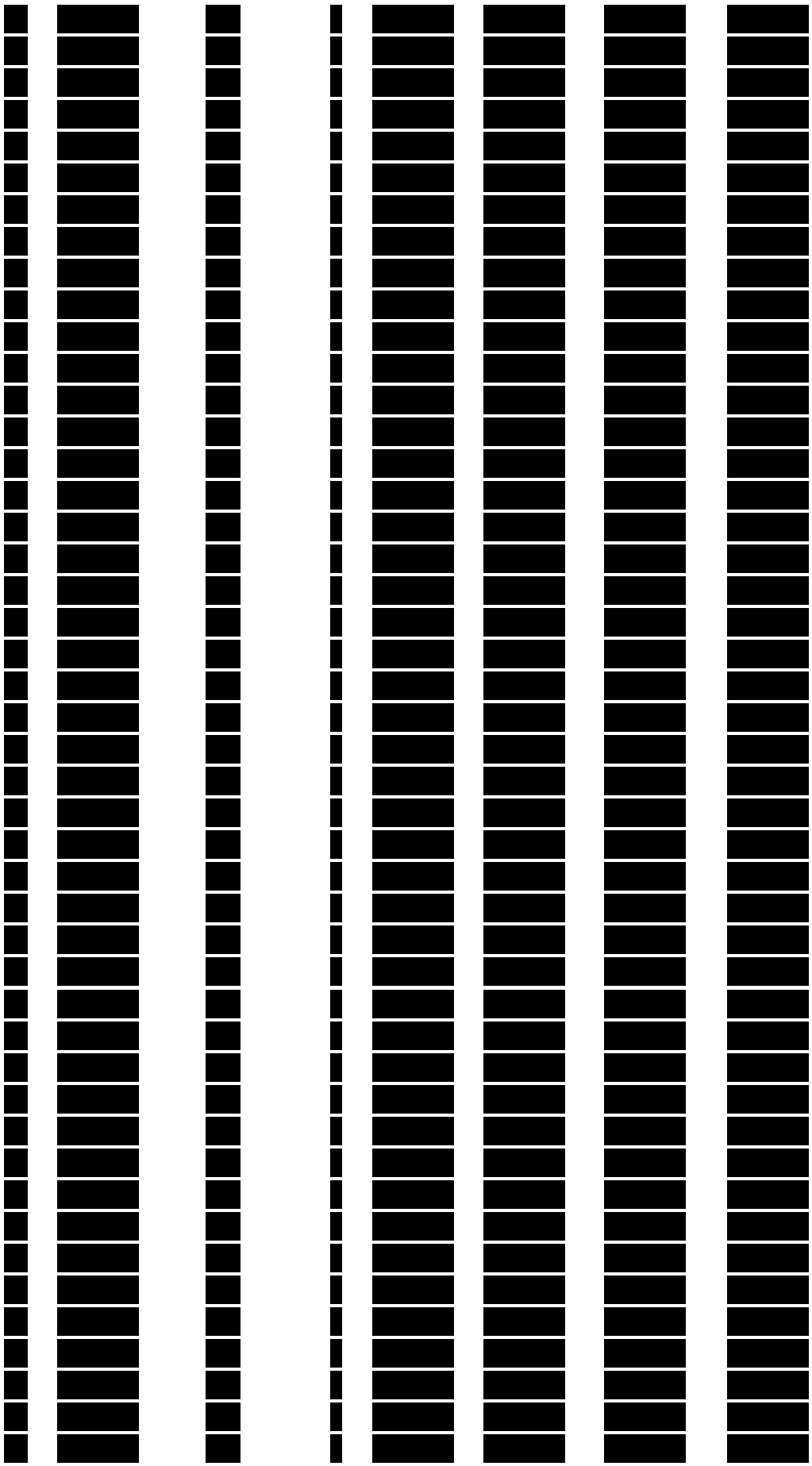
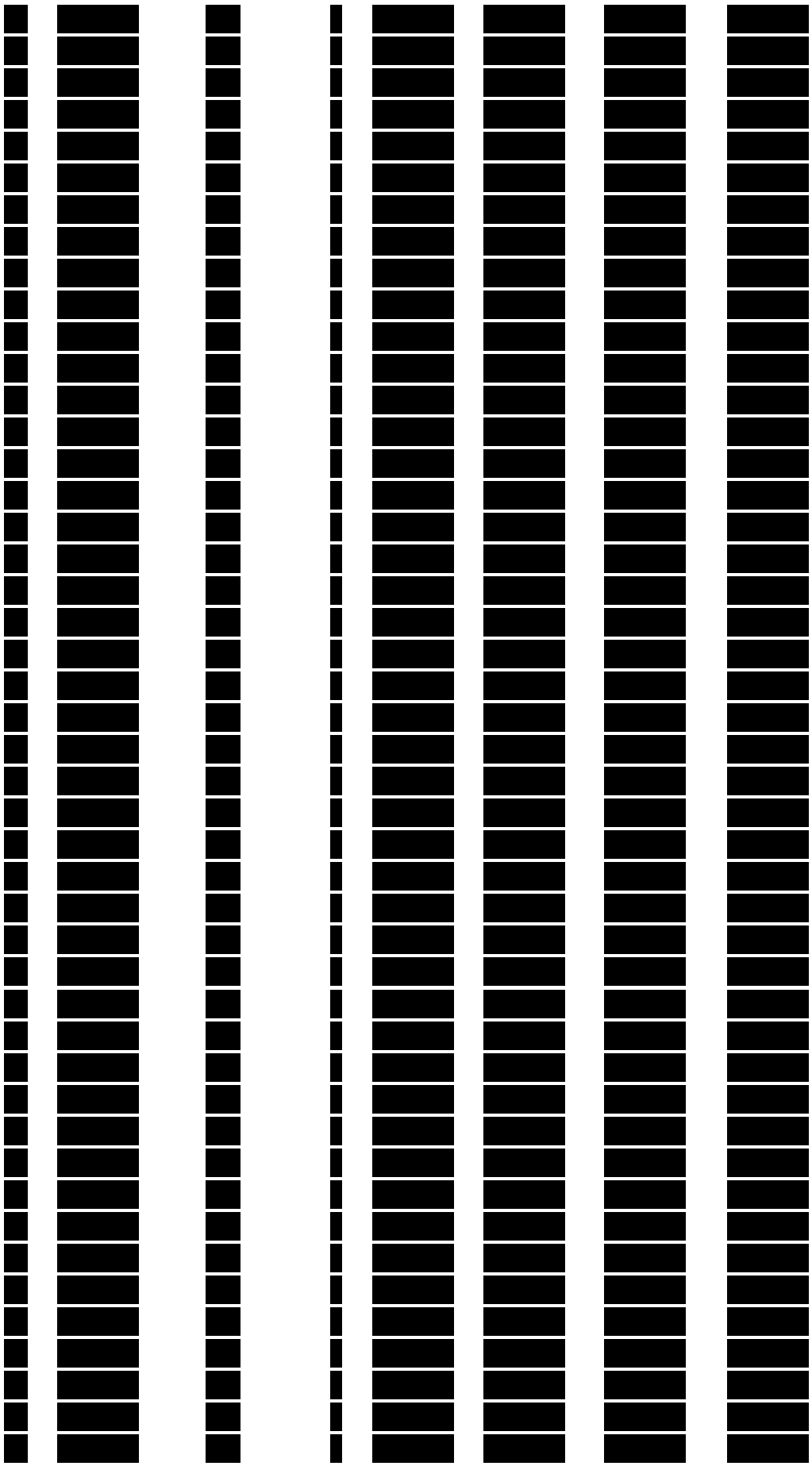


Table 22. KM Data - OS everolimus METEOR study







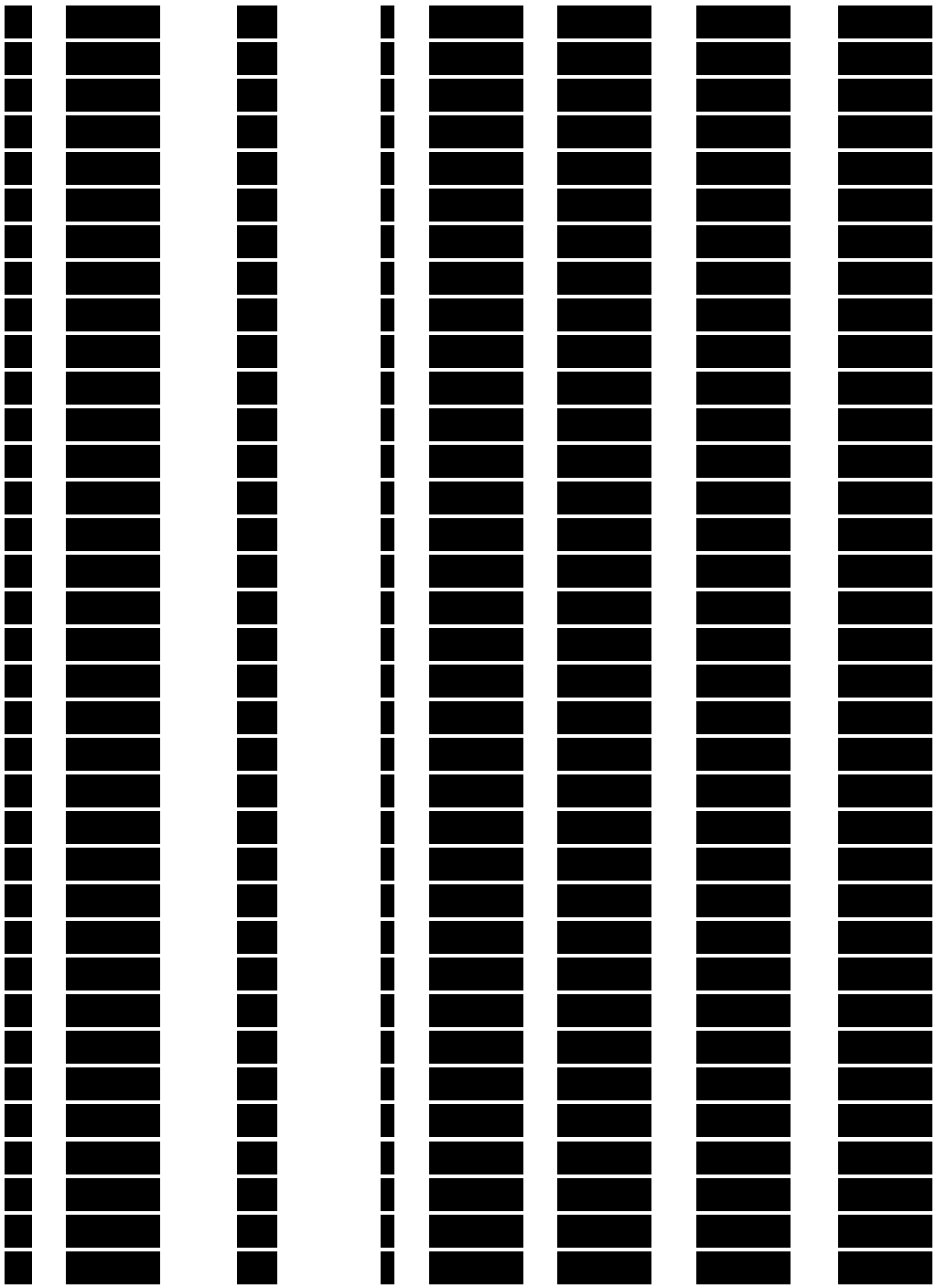
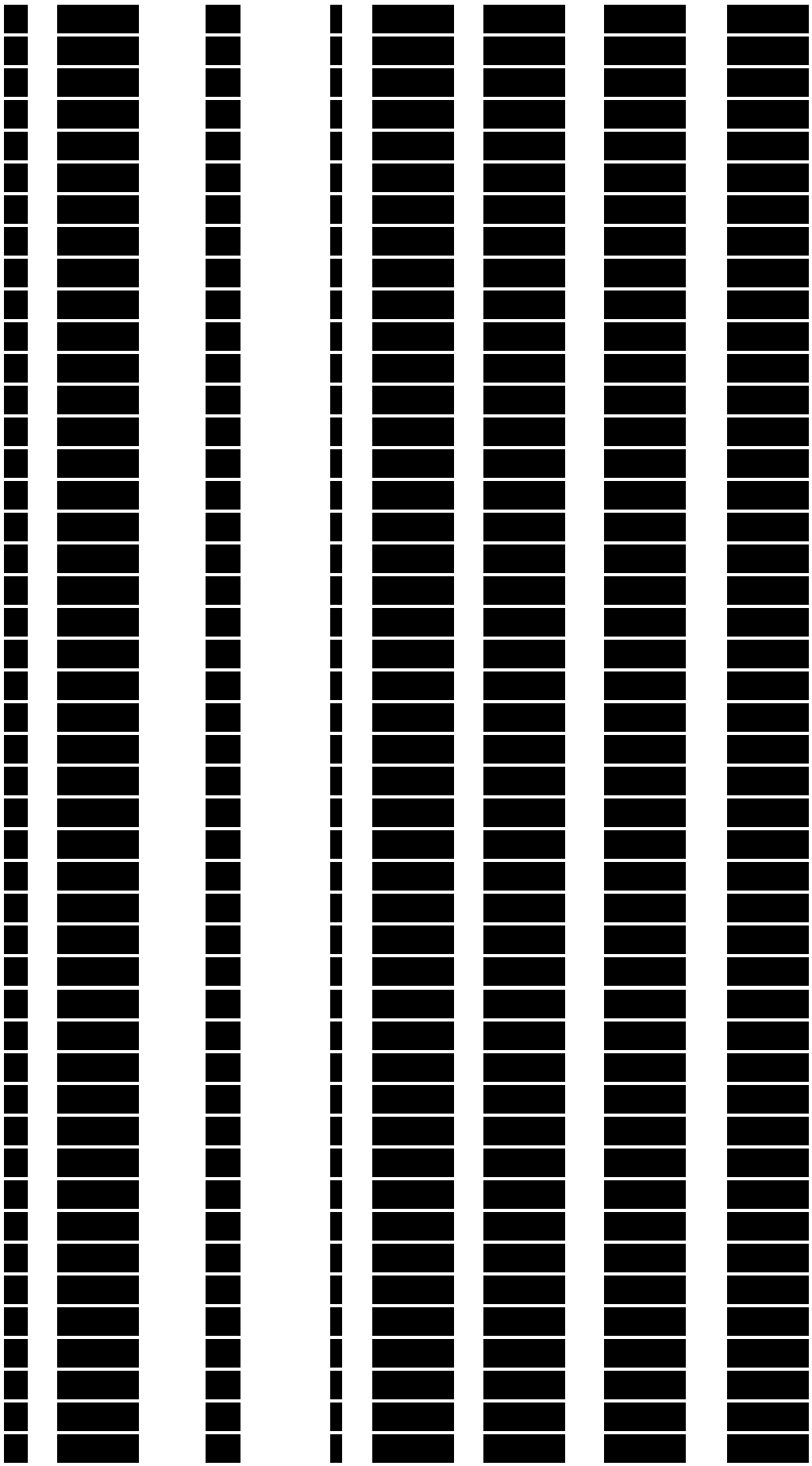
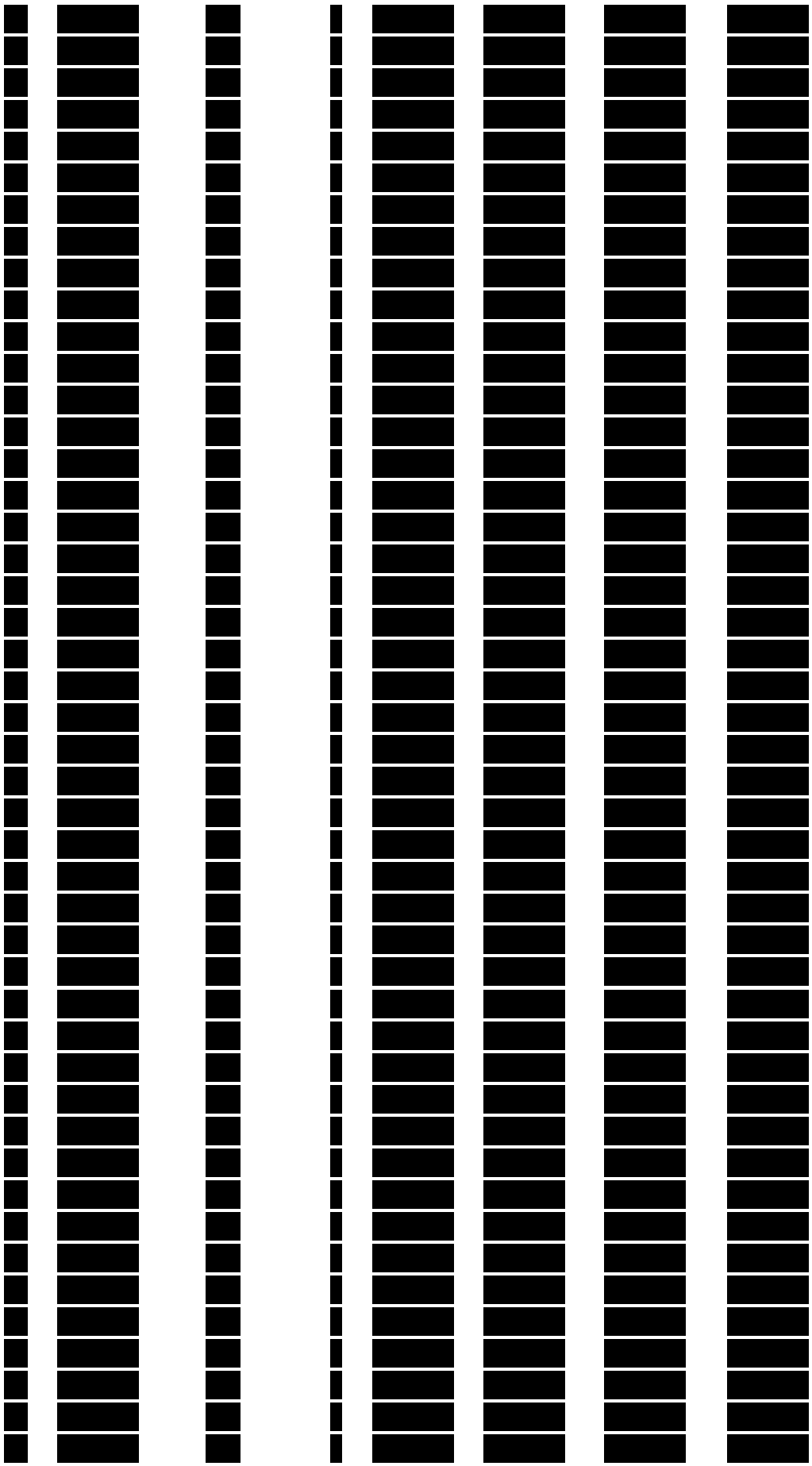


Table 23. KM Data - PFS cabozantinib METEOR study

time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]						





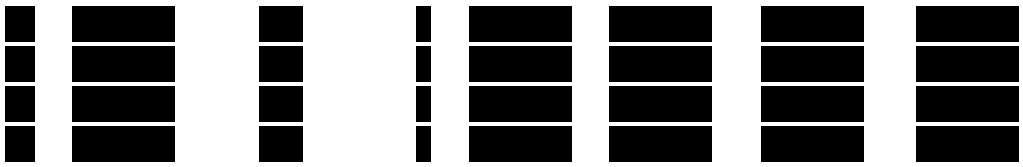
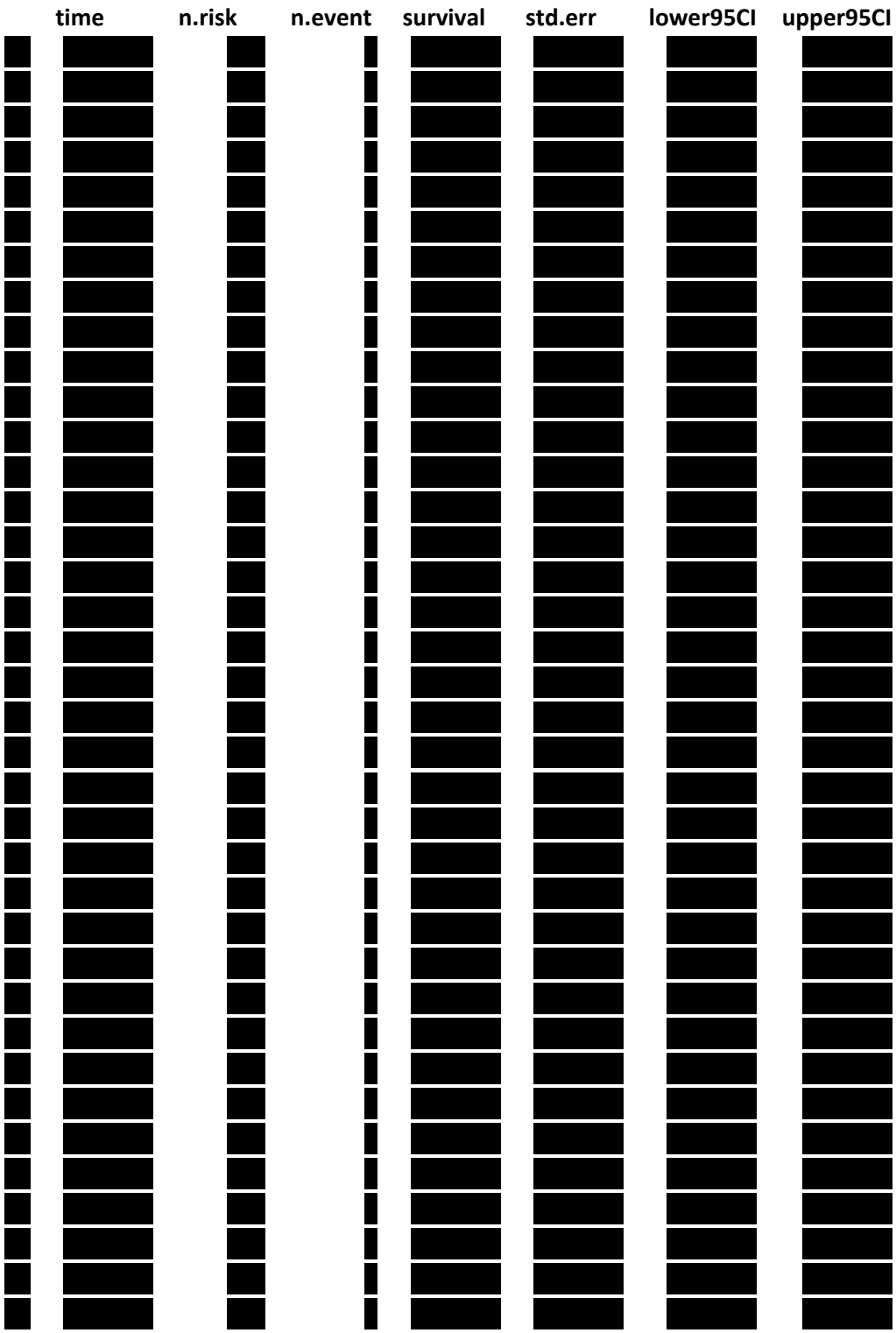
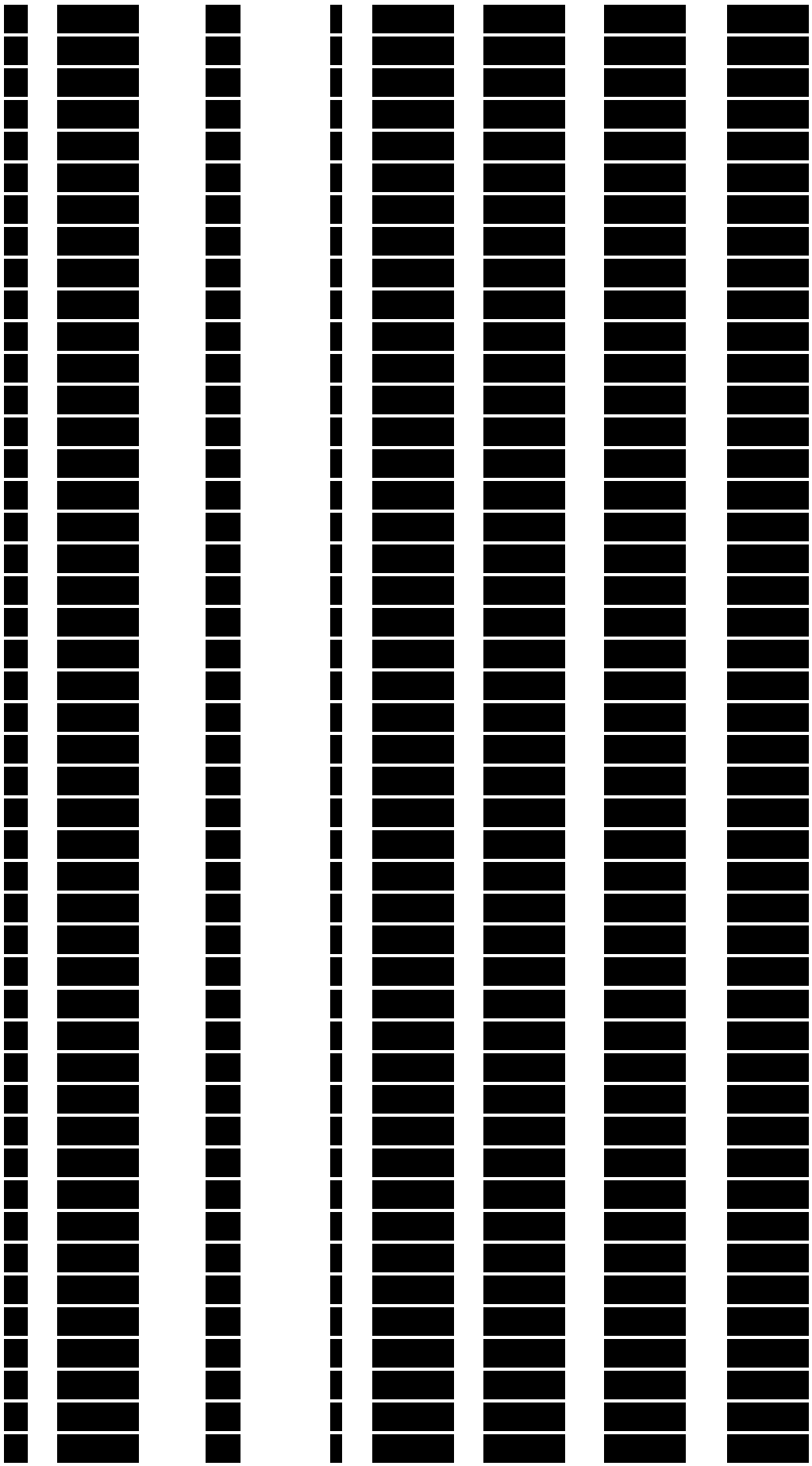


Table 24. KM Data - PFS everolimus METEOR study





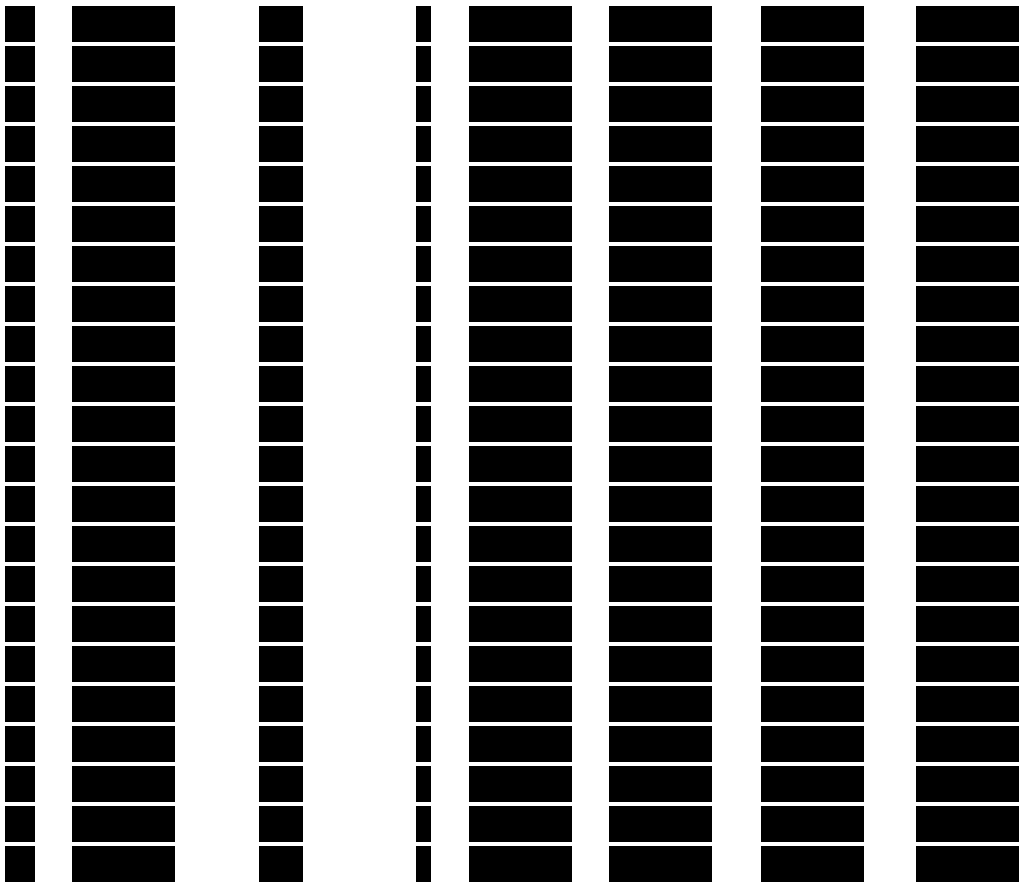
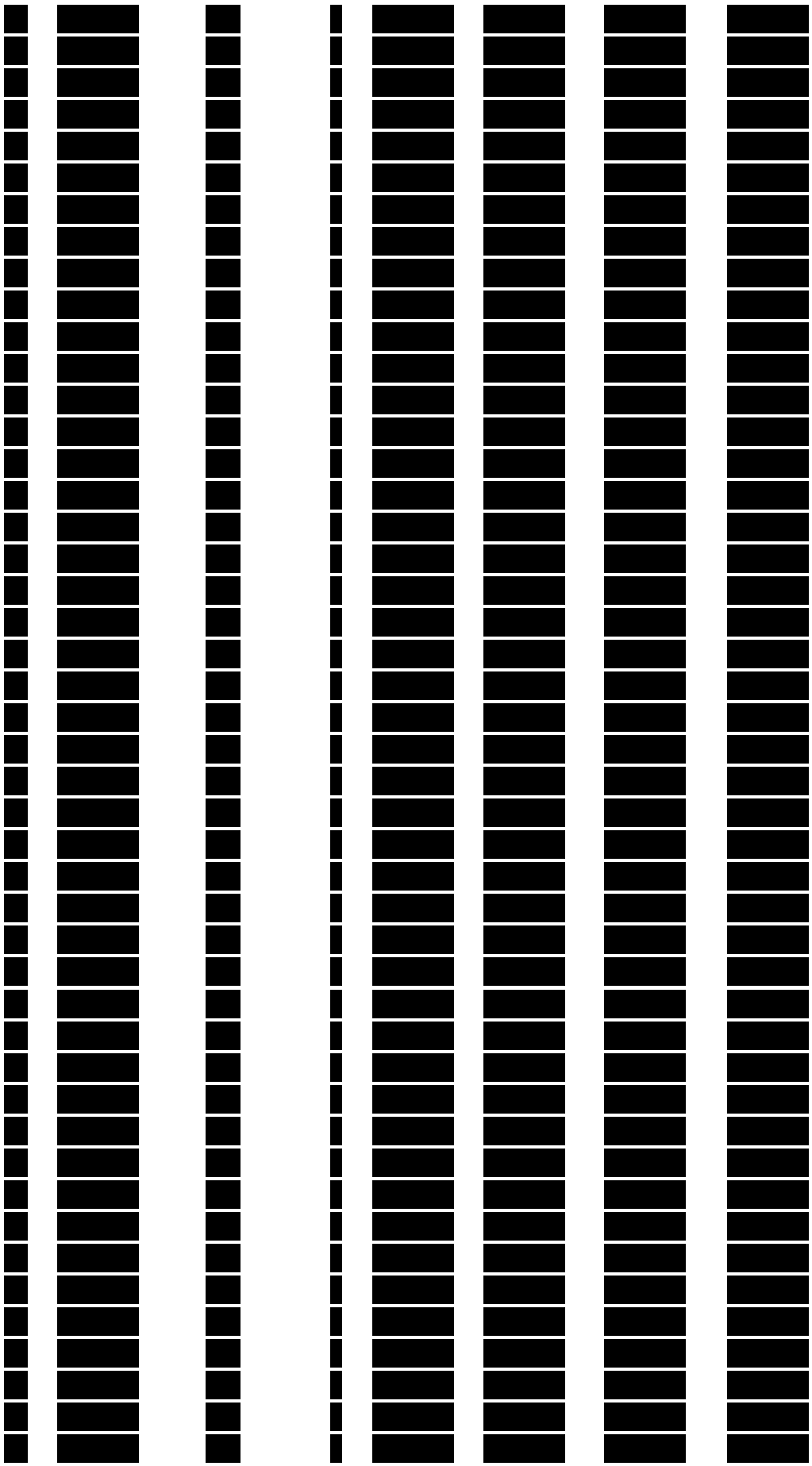
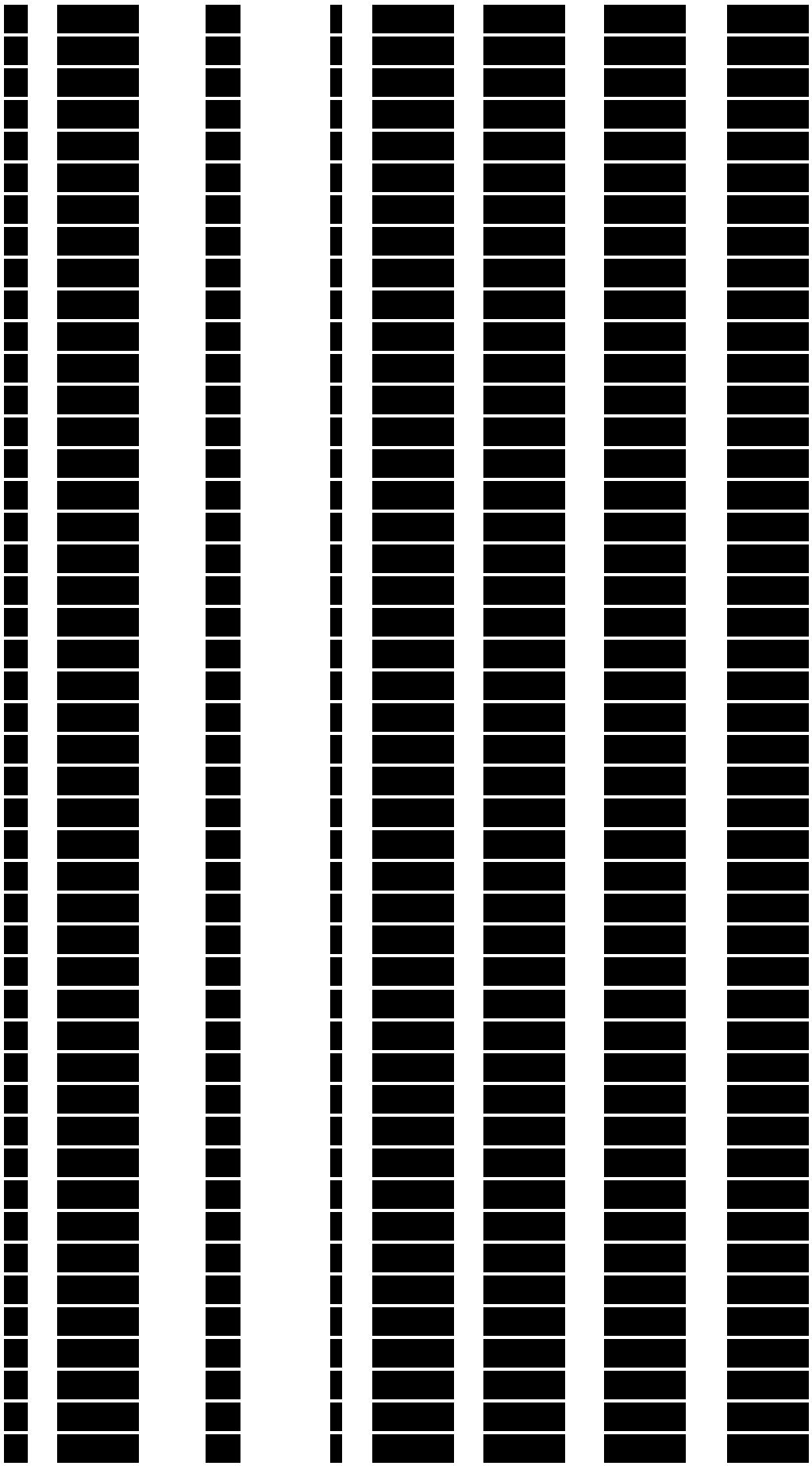


Table 25. KM Data - TTD cabozantinib METEOR study

time	n.risk	n.event	survival	std.err	lower95CI	upper95CI
[redacted]						





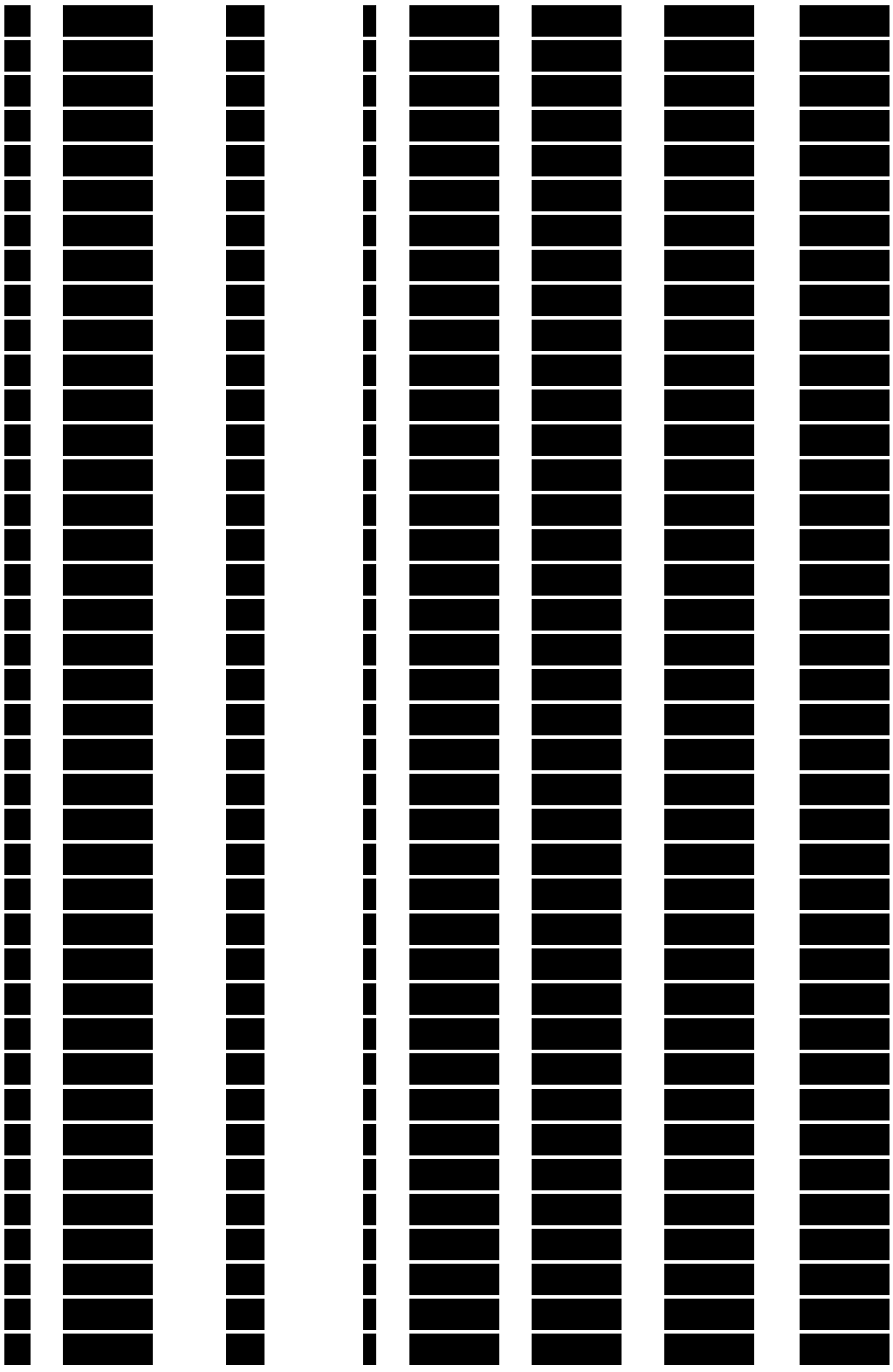
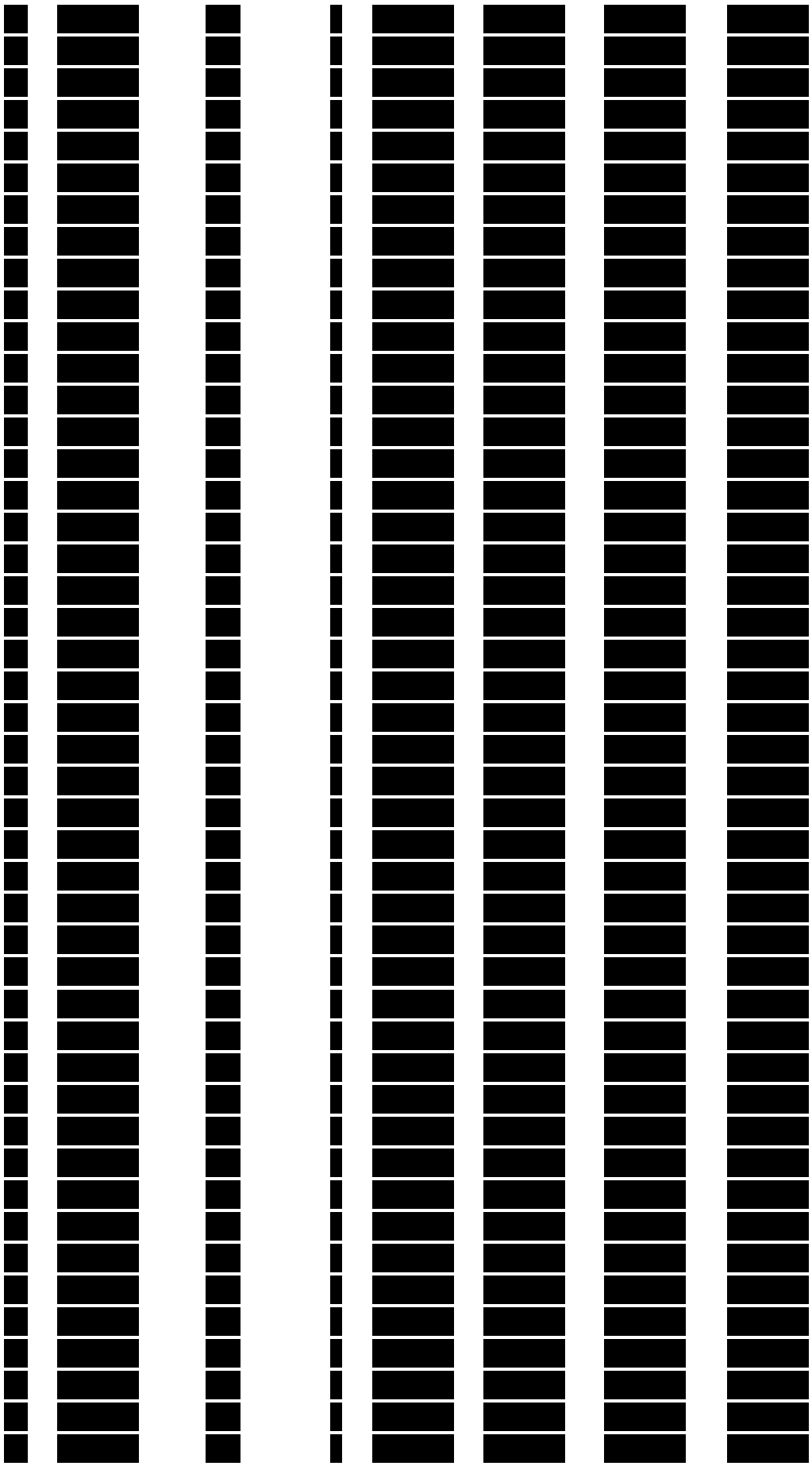
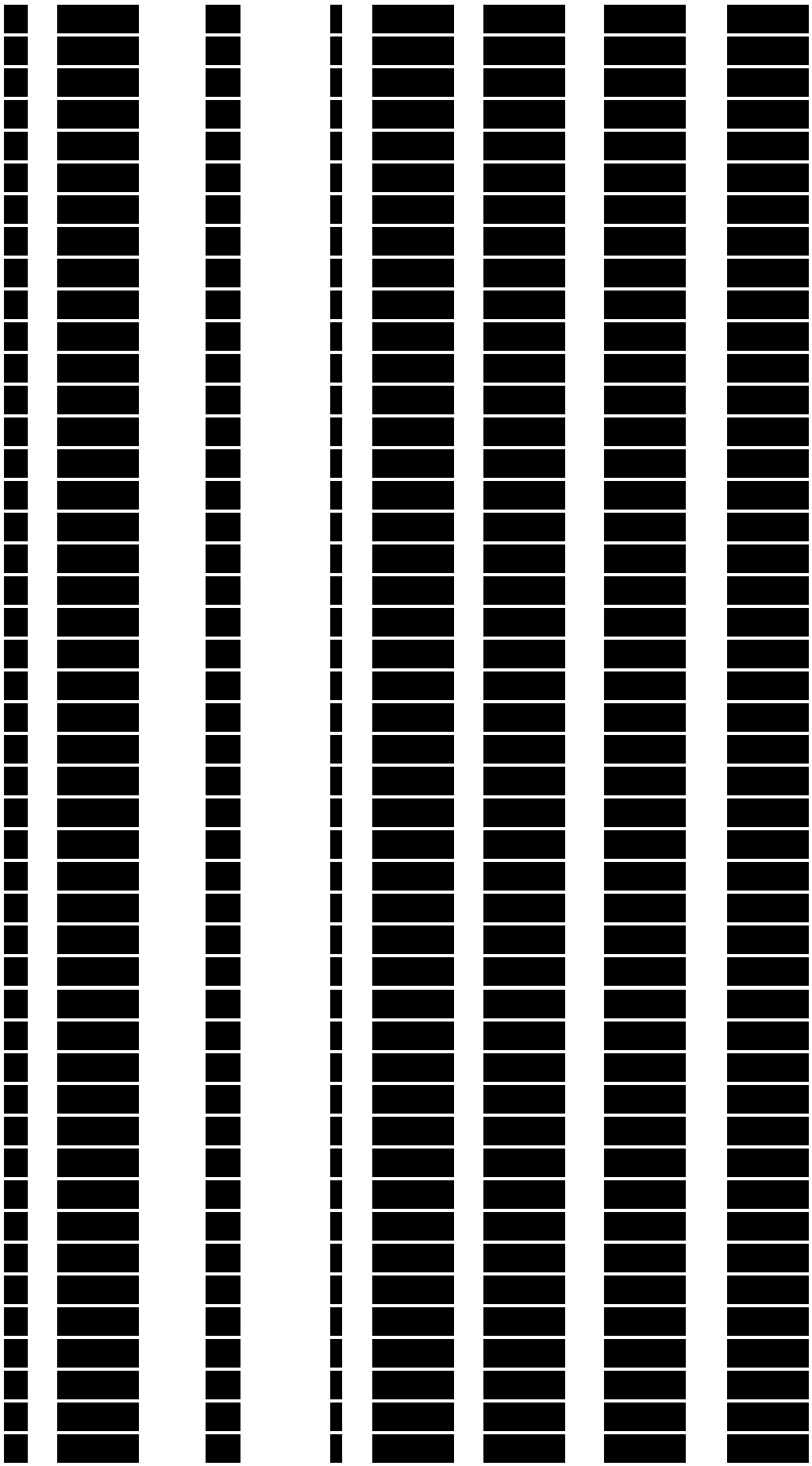
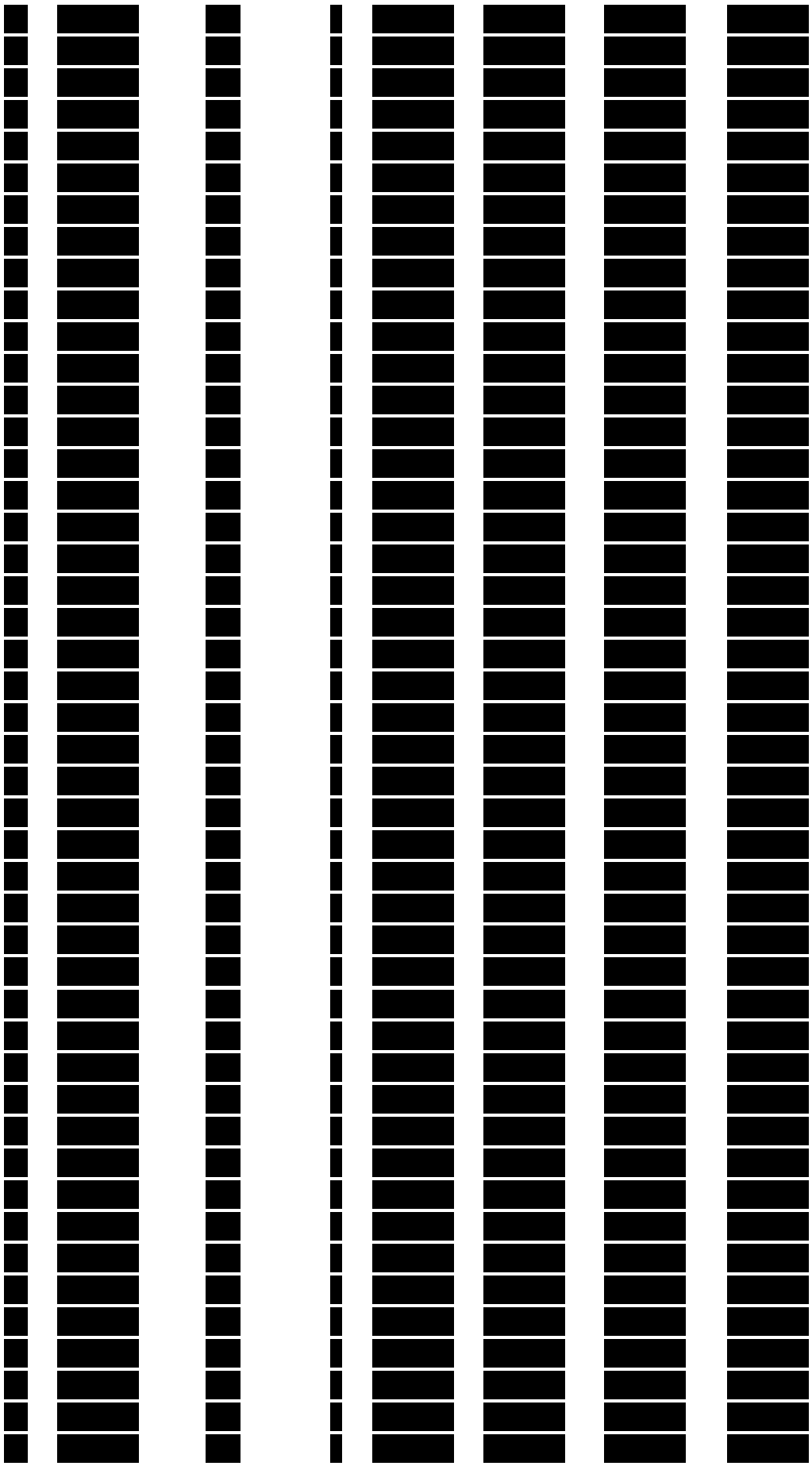


Table 26. KM Data - TTD everolimus METEOR study

	time	n.risk	n.event	survival	std.err	lower95CI	upper95CI







[redacted]

B3. **Priority question:** Please provide plots of KM data along with superimposed fitted curves for PFS, OS and TTD for both arms of the METEOR trial and the re-generated data for all treatments in the NMA. Please provide these for each of the parametric functions tested.

RESPONSE: Plots with KM data with superimposed fitted curves are provided in Figures 55 to 69.

Figure 34. Comparison of re-generated KM data and fitted curves – OS axitinib

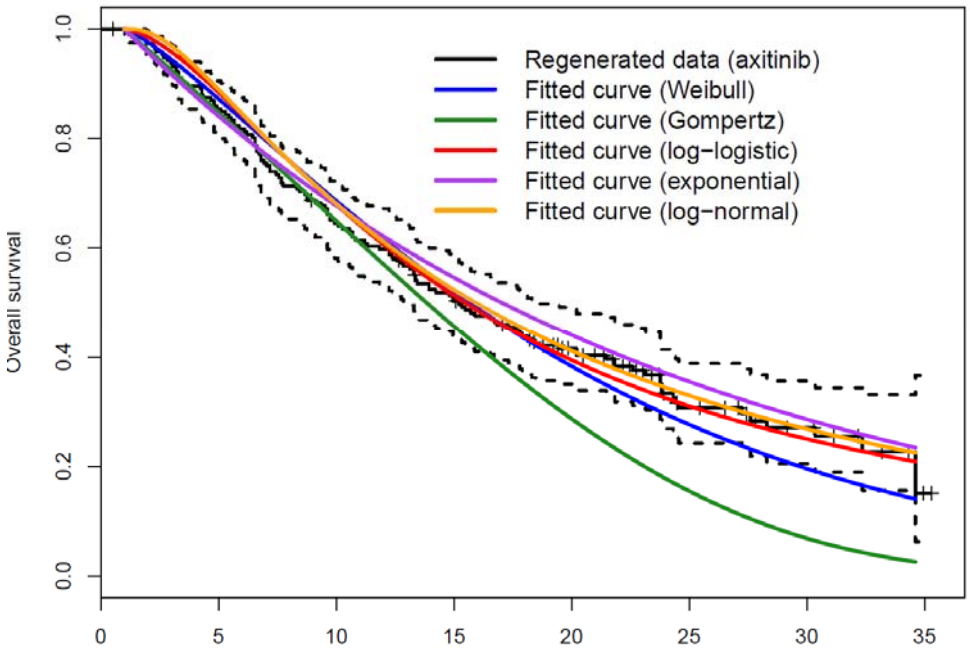


Figure 35. Comparison of re-generated KM data and fitted curves – OS cabozantinib

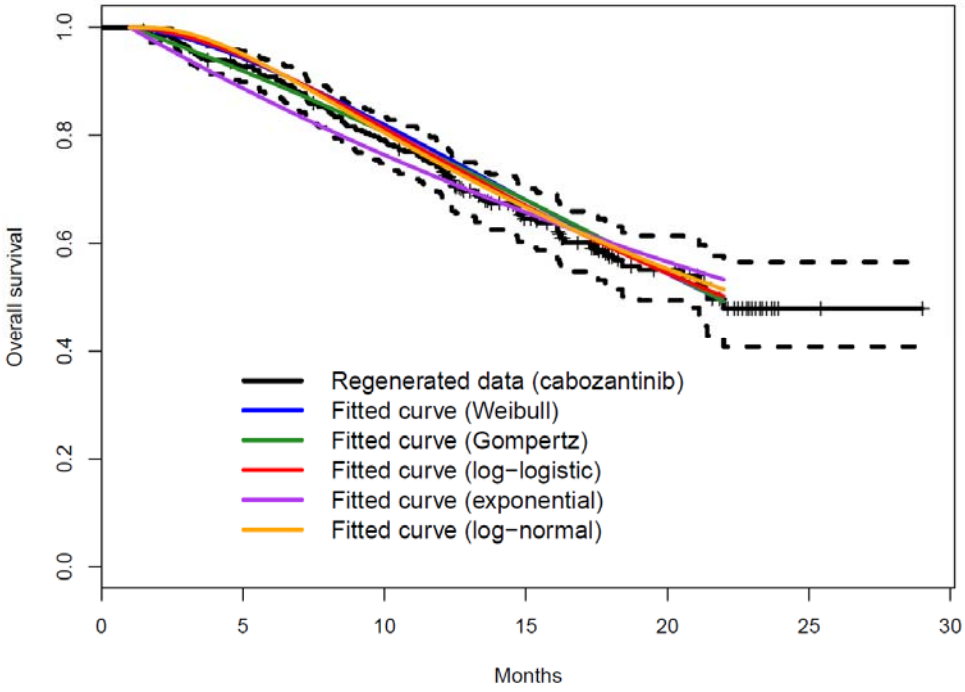


Figure 36. Comparison of re-generated KM data and fitted curves – OS everolimus

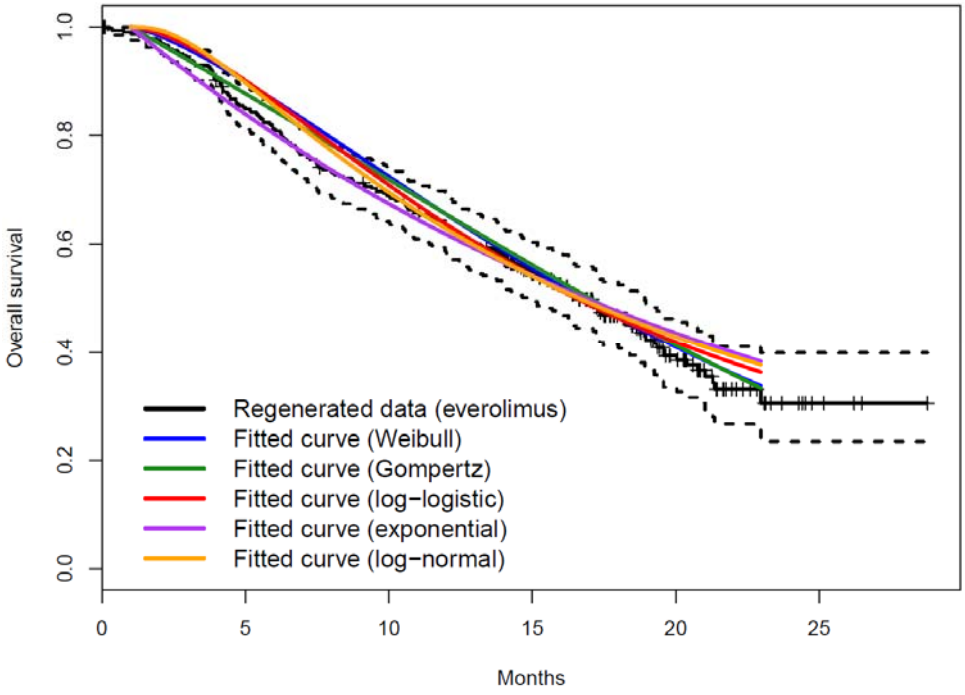


Figure 37. Comparison of re-generated KM data and fitted curves – OS nivolumab

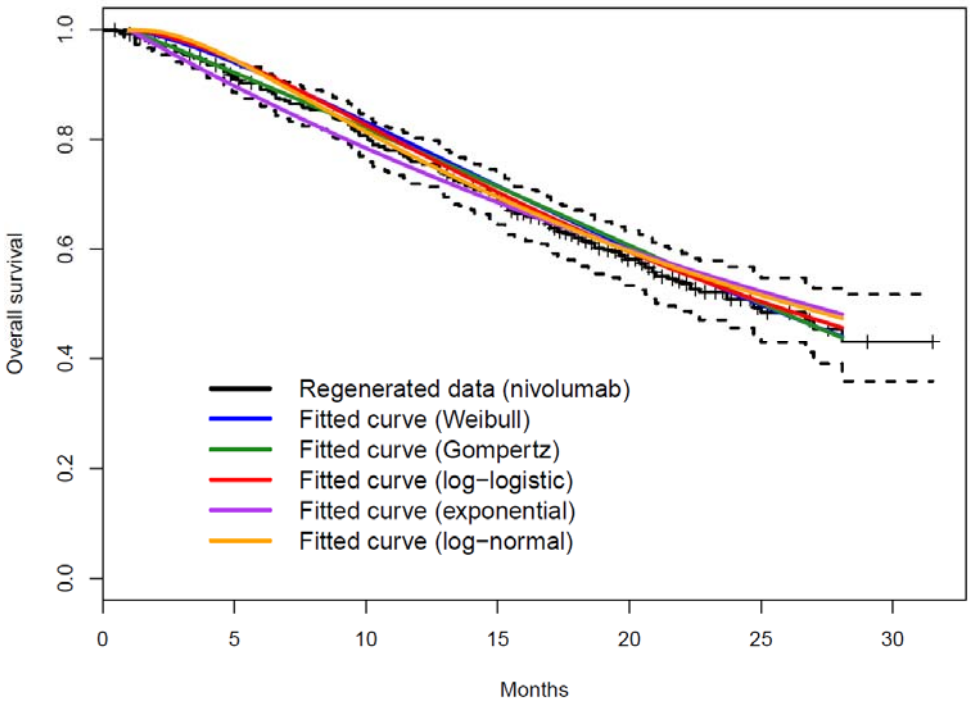


Figure 38. Comparison of re-generated KM data and fitted curves – OS placebo

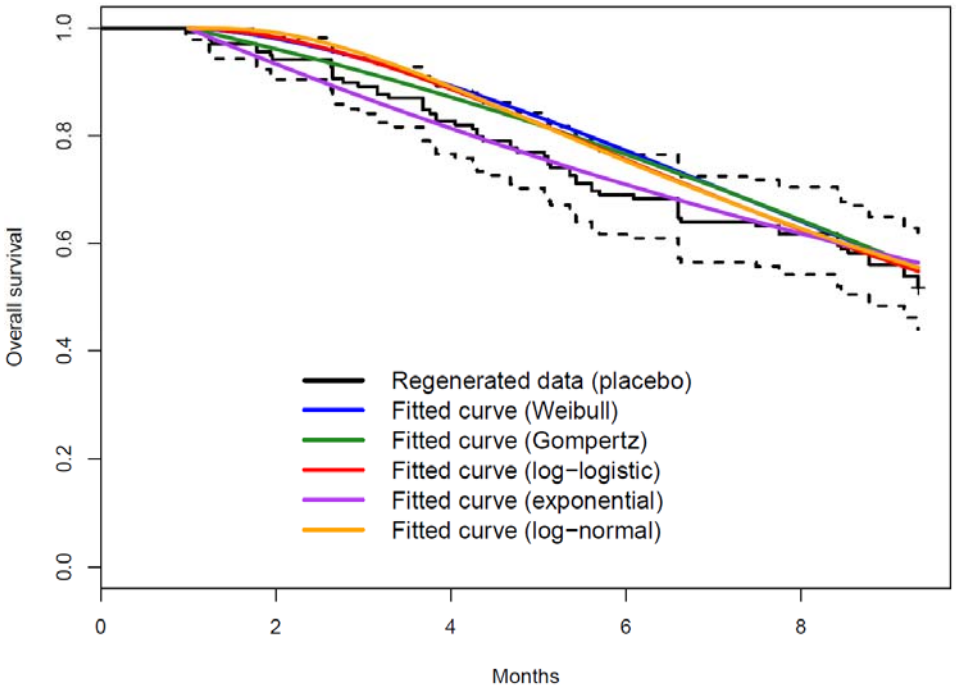


Figure 39. Comparison of re-generated KM data and fitted curves – OS sorafenib

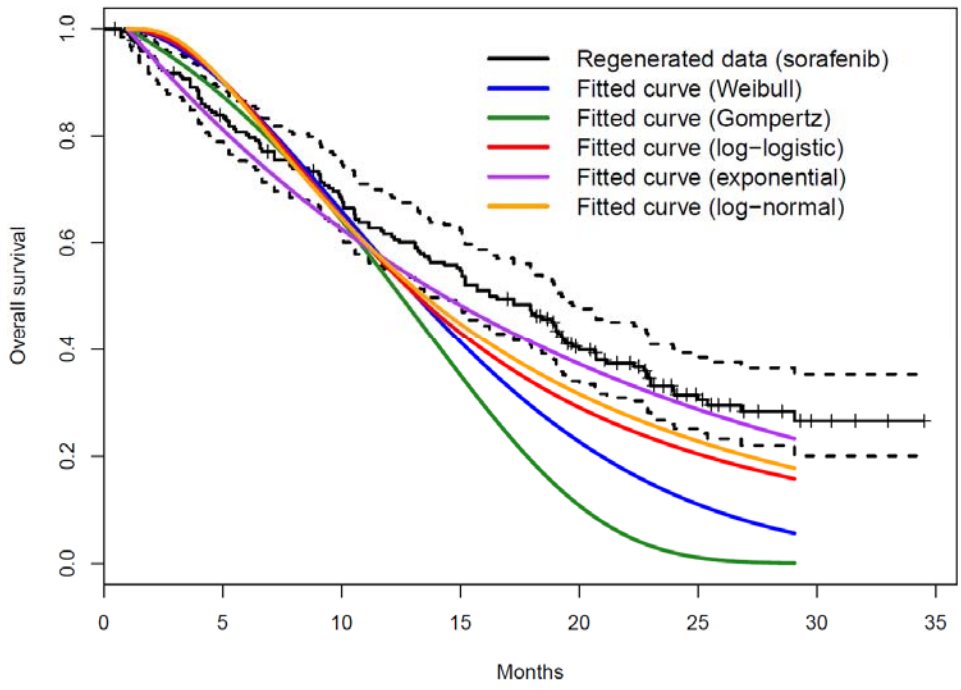


Figure 40. Comparison of re-generated KM data and fitted curves – PFS axitinib

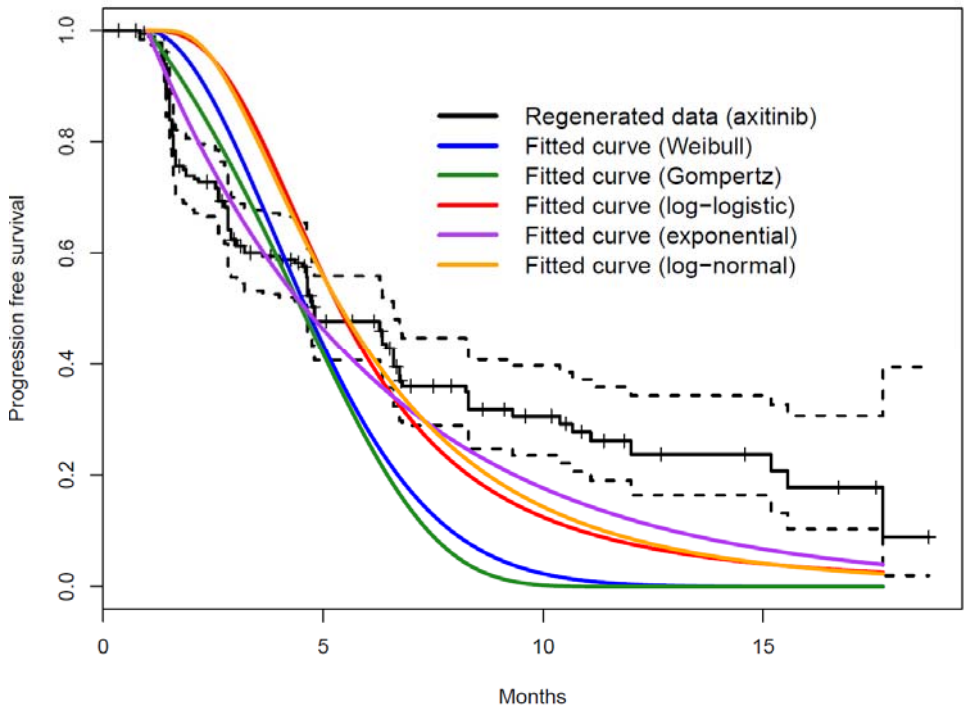


Figure 41. Comparison of re-generated KM data and fitted curves – PFS cabozantinib

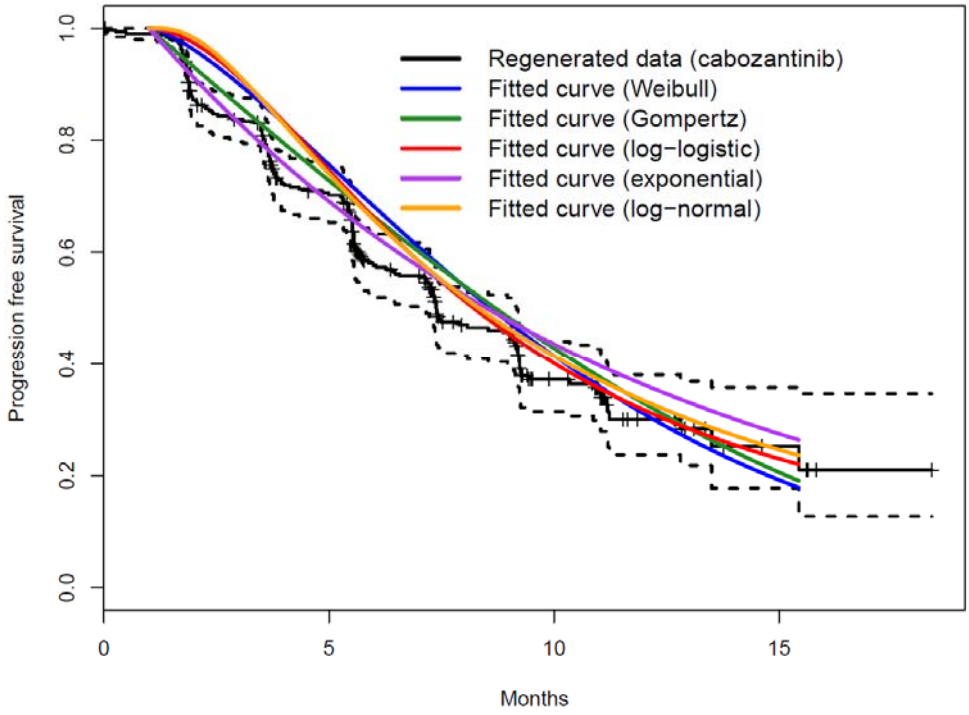


Figure 42. Comparison of re-generated KM data and fitted curves – PFS everolimus

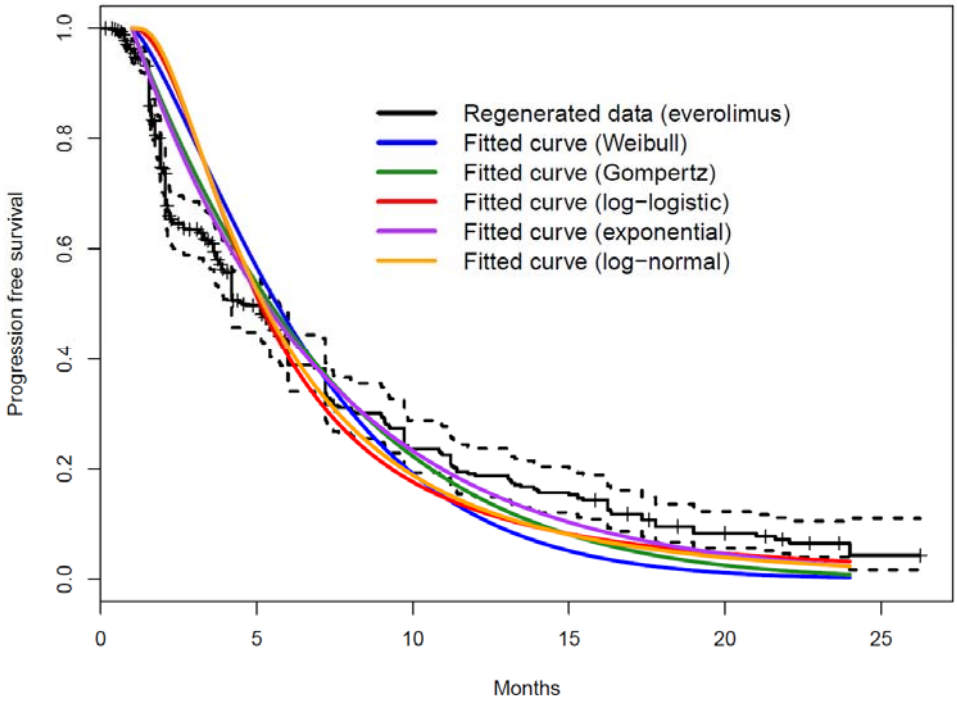


Figure 43. Comparison of re-generated KM data and fitted curves – PFS nivolumab

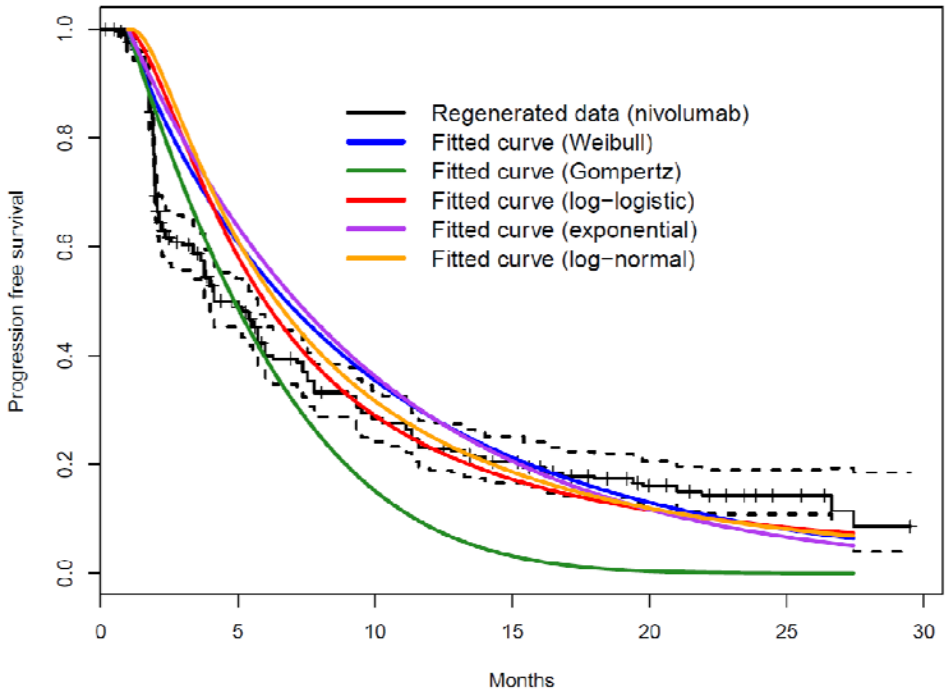


Figure 44. Comparison of re-generated KM data and fitted curves – PFS placebo

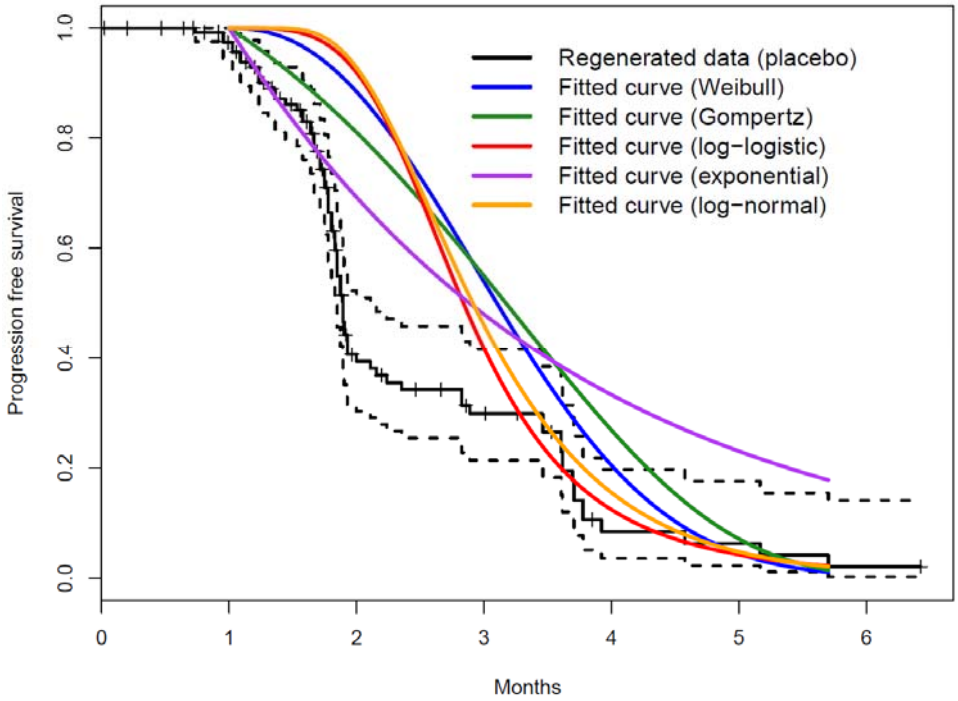


Figure 45. Comparison of re-generated KM data and fitted curves – PFS sorafenib

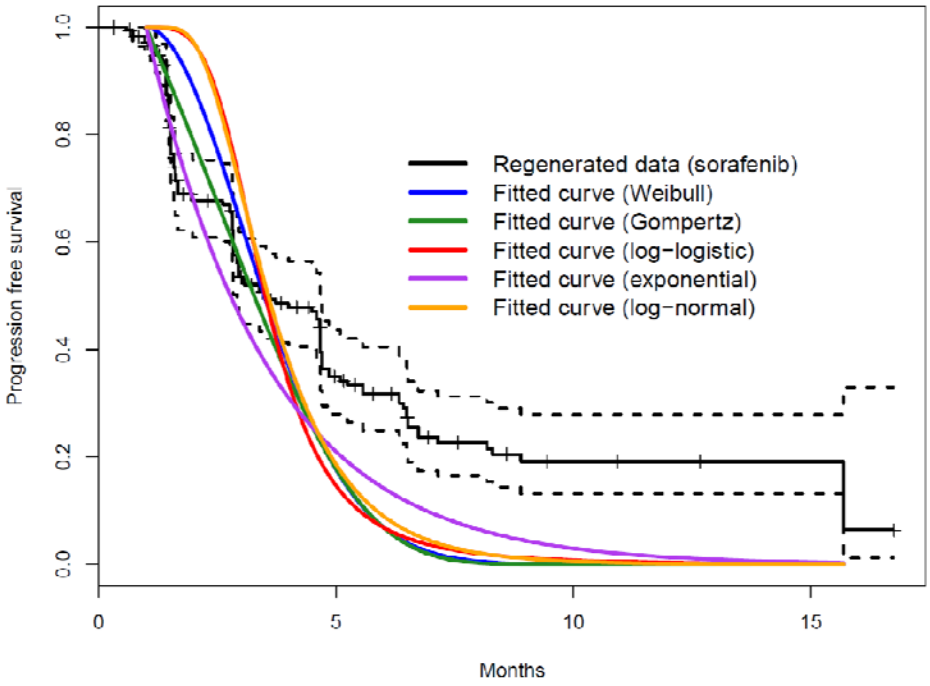


Figure 46. Comparison of re-generated KM data and fitted curves – TTD cabozanitinib

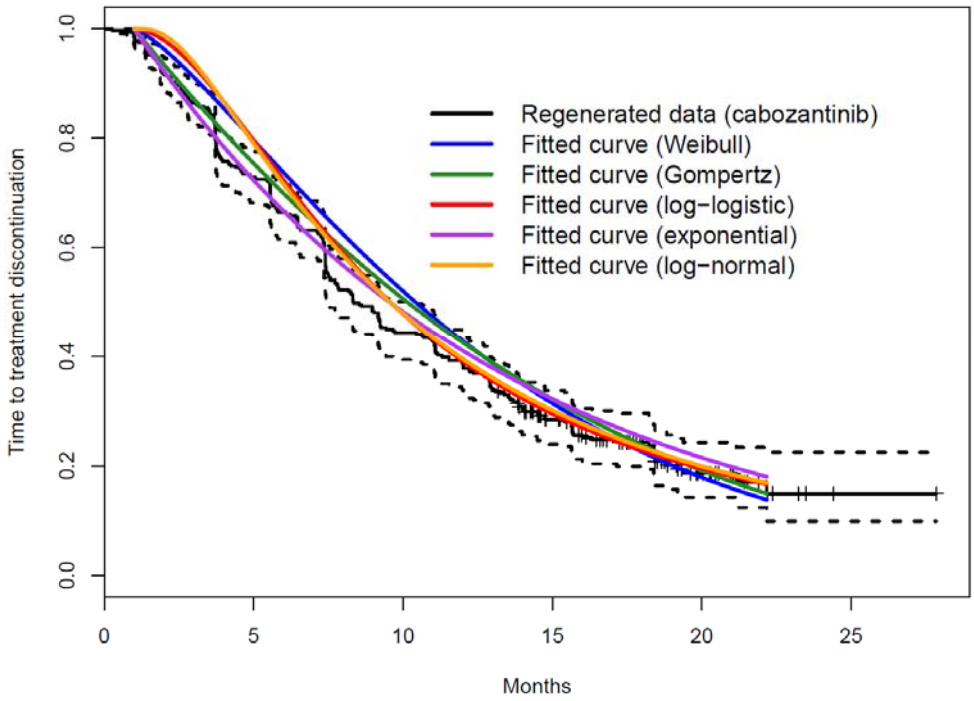


Figure 47. Comparison of re-generated KM data and fitted curves – TTD everolimus

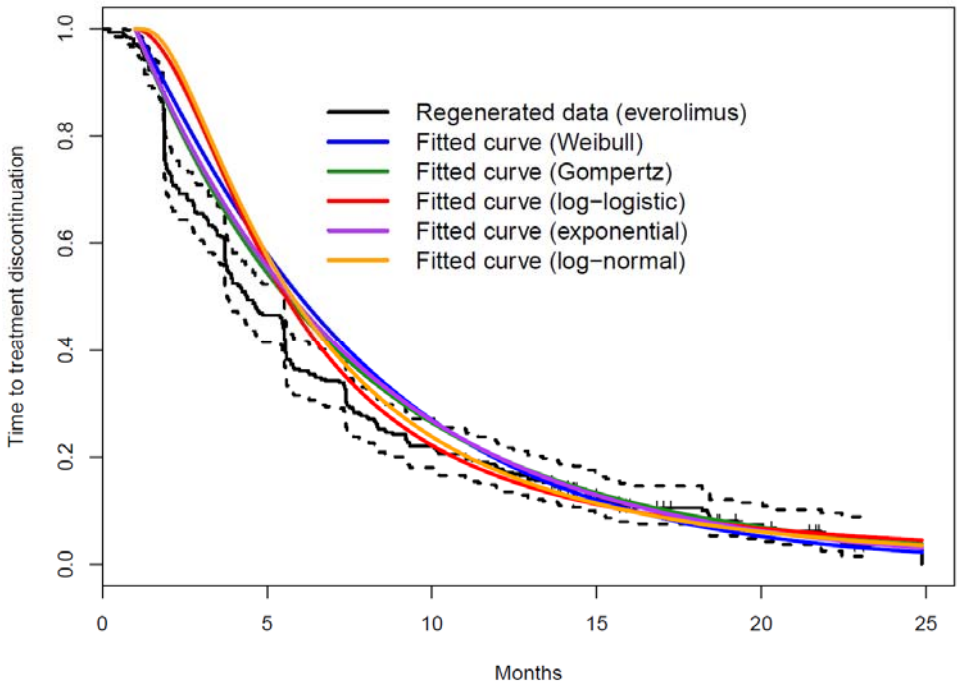
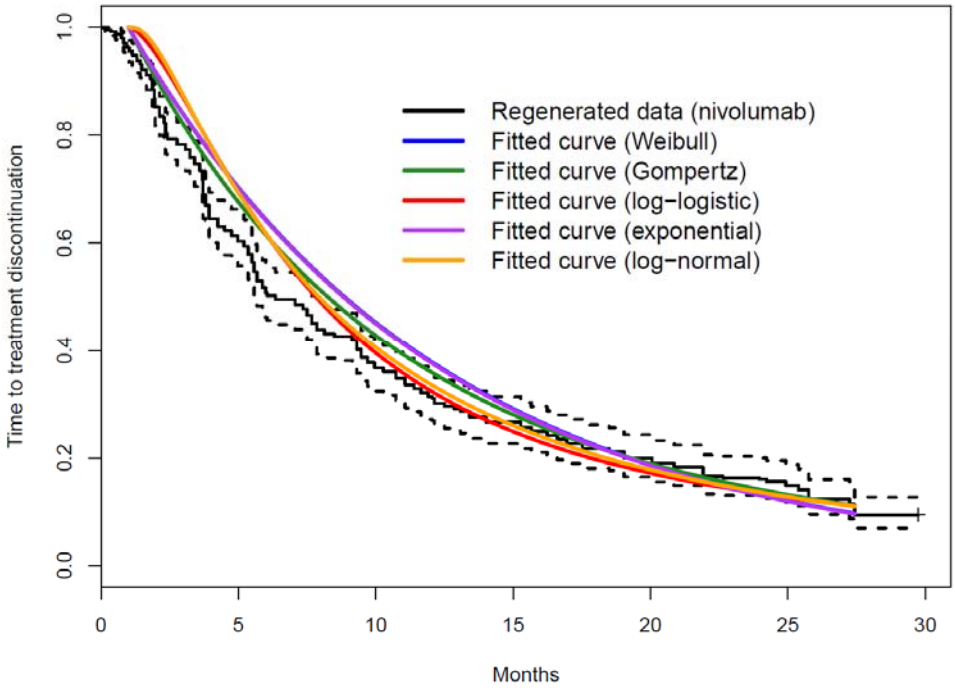


Figure 48. Comparison of re-generated KM data and fitted curves – TTD nivolumab



B4. **Priority question:** For OS, PFS and TTD in the METEOR trial data, please provide:

a) Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time)
b) Log(survival function / (1-survival function)) plots versus Log(time)

c) Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time)

RESPONSE: Please see Figure 49 to Figure 72, Figure 73 to Figure 75 and Figure 76 to Figure 78 for a,b, c respectively.

Figure 49. Log-cumulative hazard plot – OS

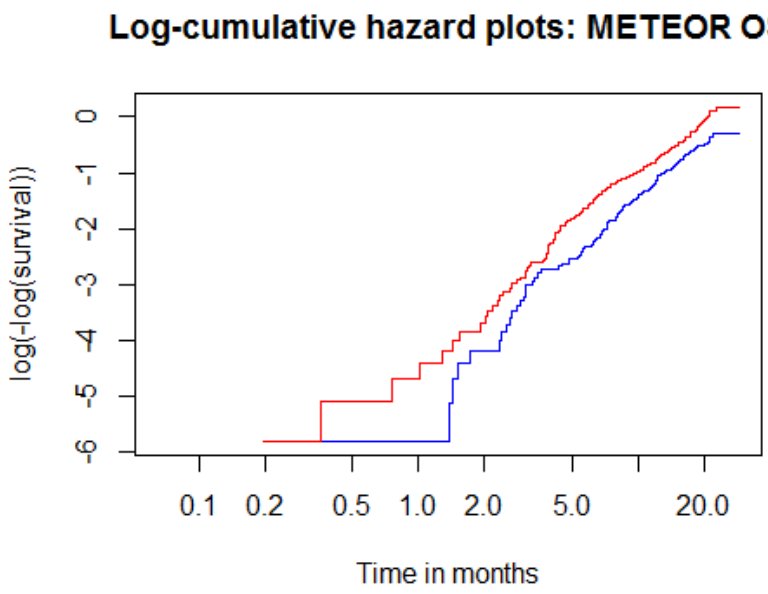


Figure 50. Log-cumulative hazard plot – PFS

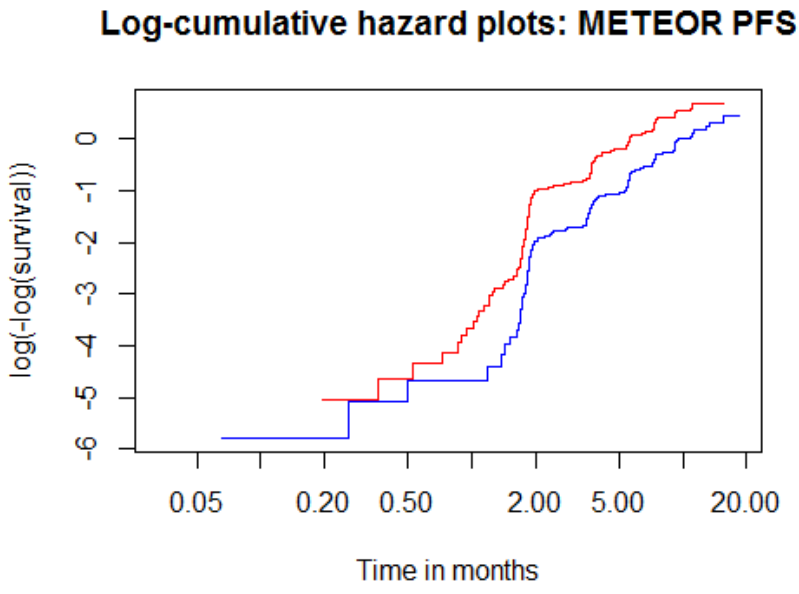


Figure 51. Log-cumulative hazard plot – TTD

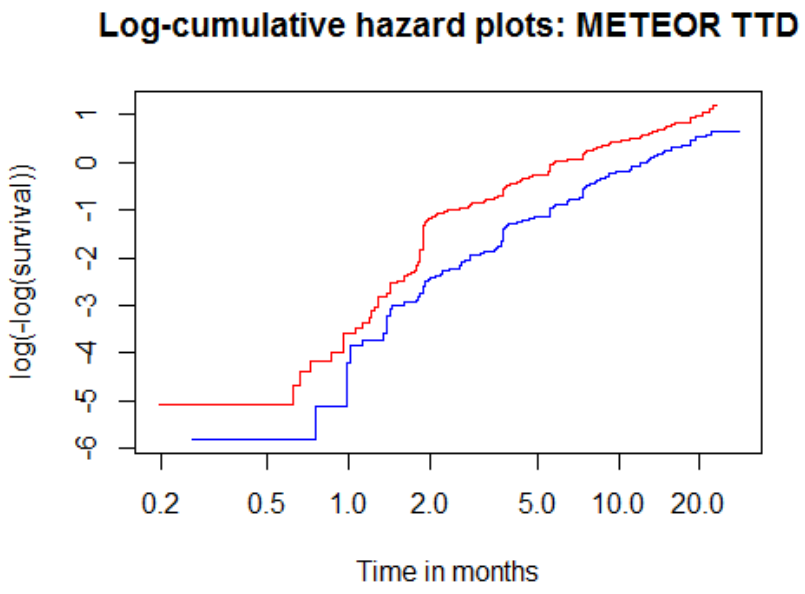


Figure 52. Log(survival function / (1-survival function)) plots versus Log(time) – OS

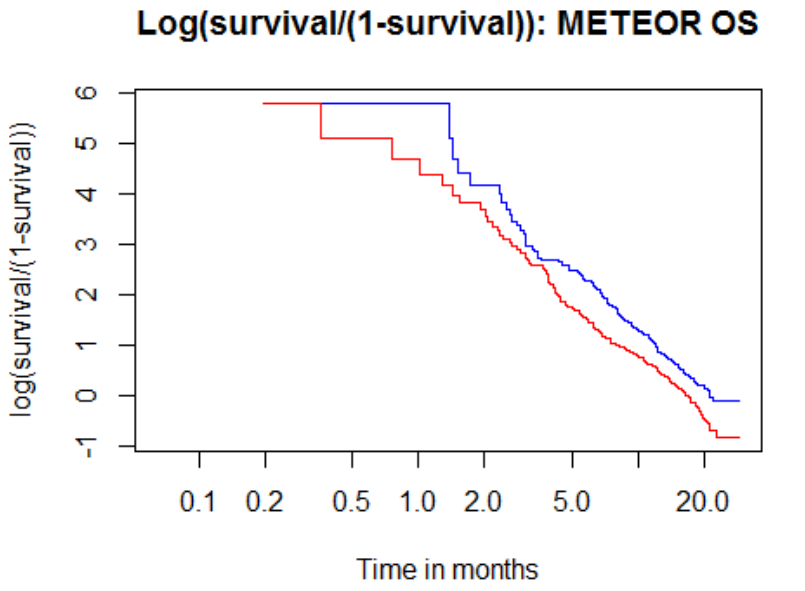


Figure 53. Log(survival function / (1-survival function)) plots versus Log(time) – PFS

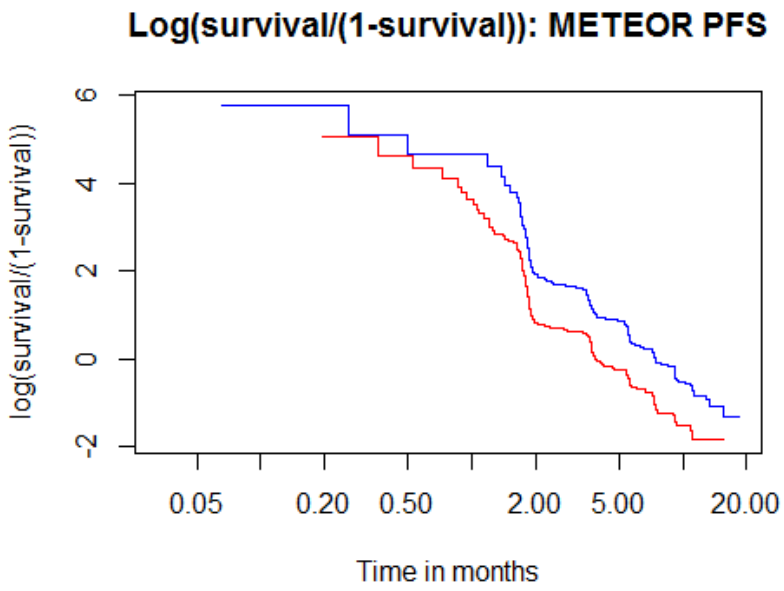


Figure 54. Log(survival function / (1-survival function)) plots versus Log(time) – TTD

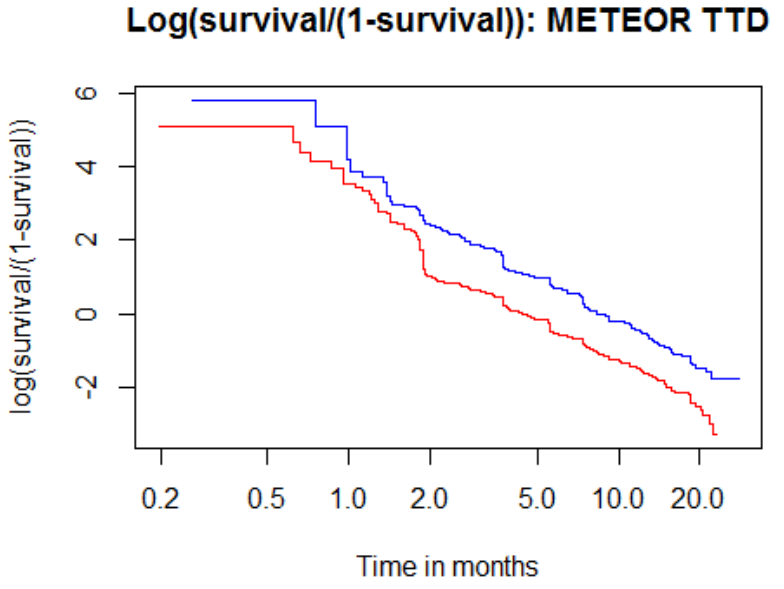


Figure 55. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – OS

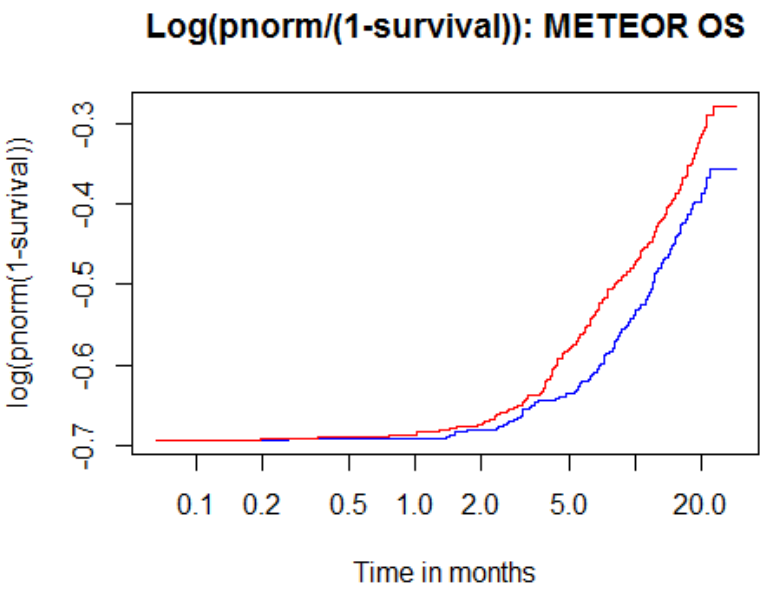


Figure 56. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – PFS

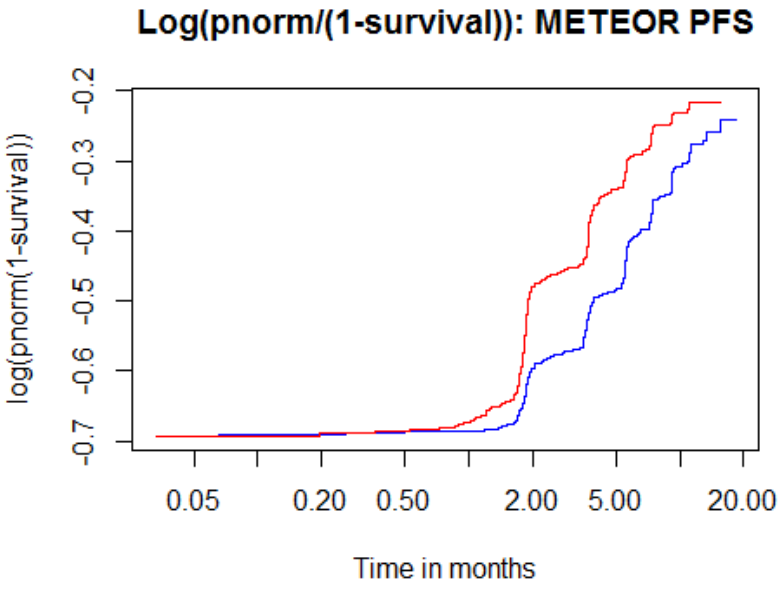
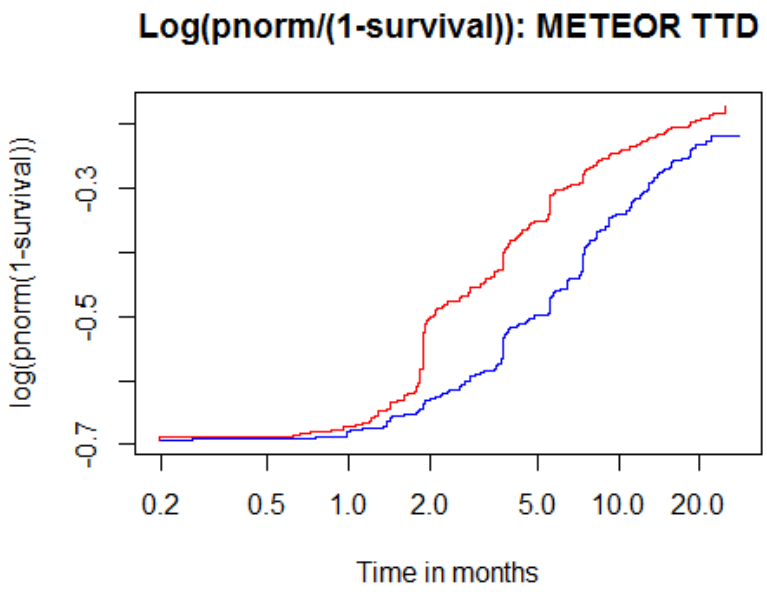


Figure 57. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – TTD



B5. **Priority question:** For OS, PFS and TTD in the re-generated data used in the NMA, please provide:

a. Log(survival function / (1-survival function)) plots versus Log(time)

b. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time)

RESPONSE: Log(survival function / (1-survival function)) plots are provided from Figure 67 to Figure 75. The Log(inverse standard normal distribution function(1-survival function)) plots are provided from Figure 97 to Figure 105. Additionally, Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) are provided from Figure 79 to Figure 87.

Figure 58. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – AXIS OS

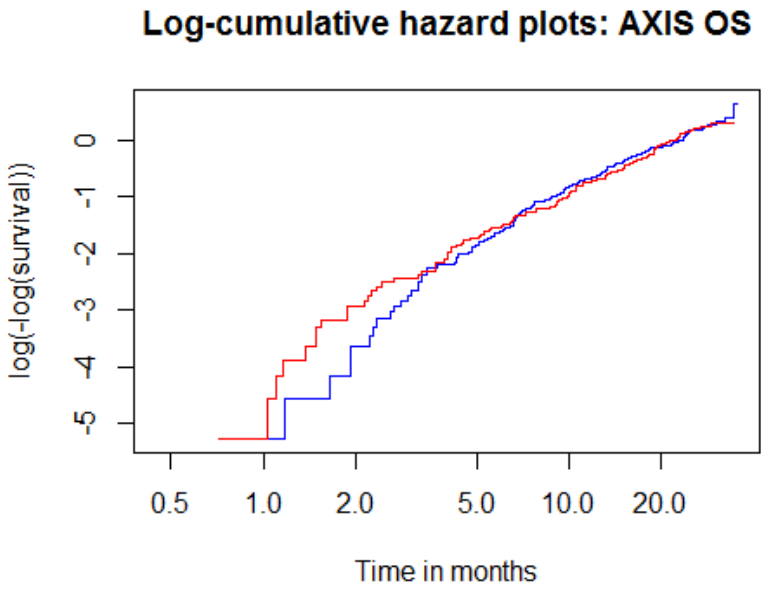


Figure 59. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – AXIS PFS

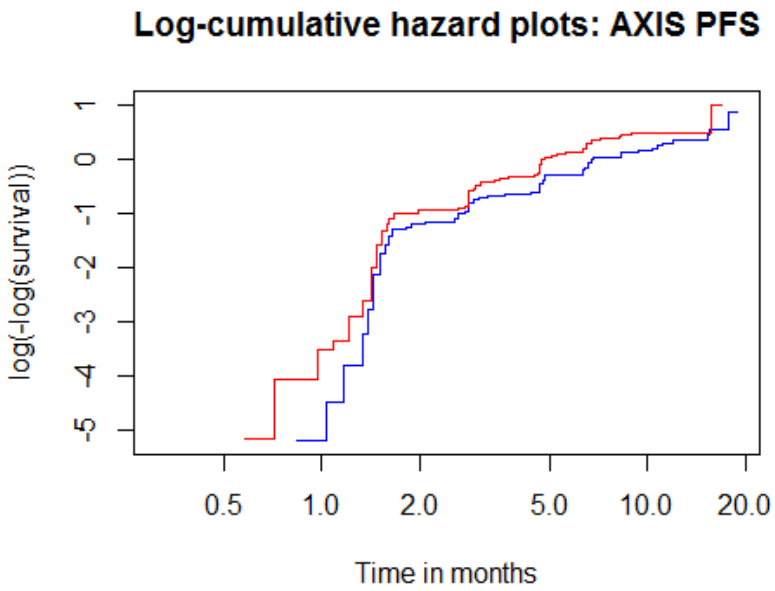


Figure 60. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – CheckMate025 OS

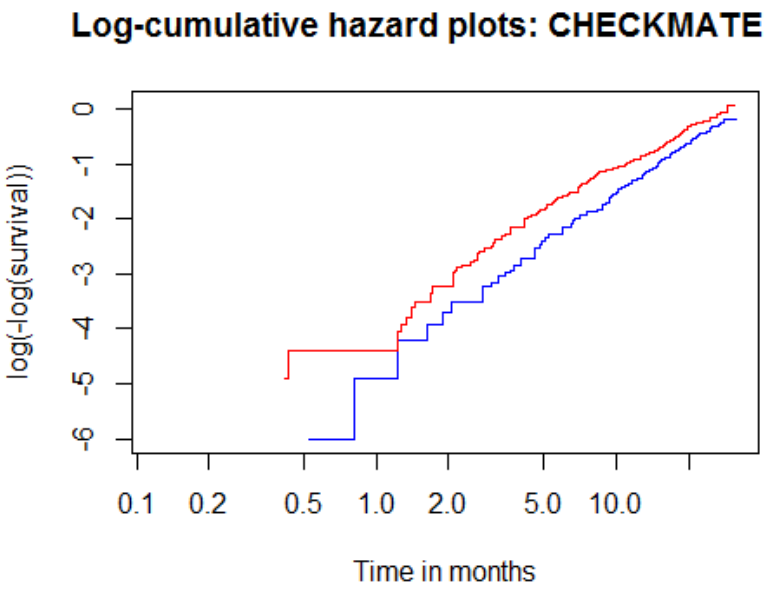


Figure 61. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – CheckMate025 PFS

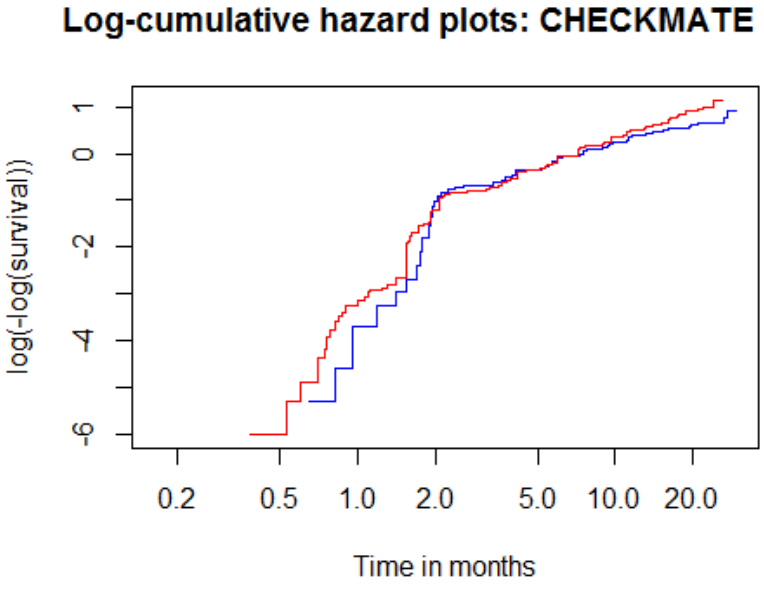


Figure 62. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – CheckMate025 TTD

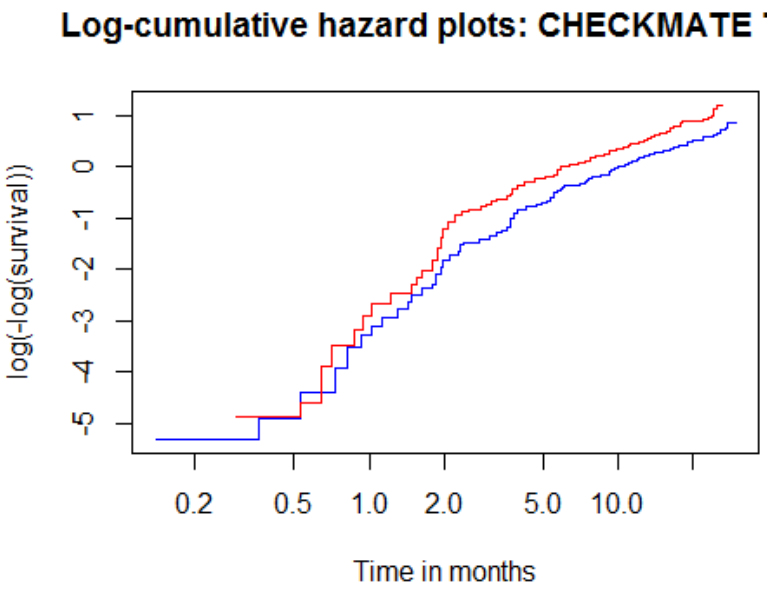


Figure 63. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – RECORD-1 OS

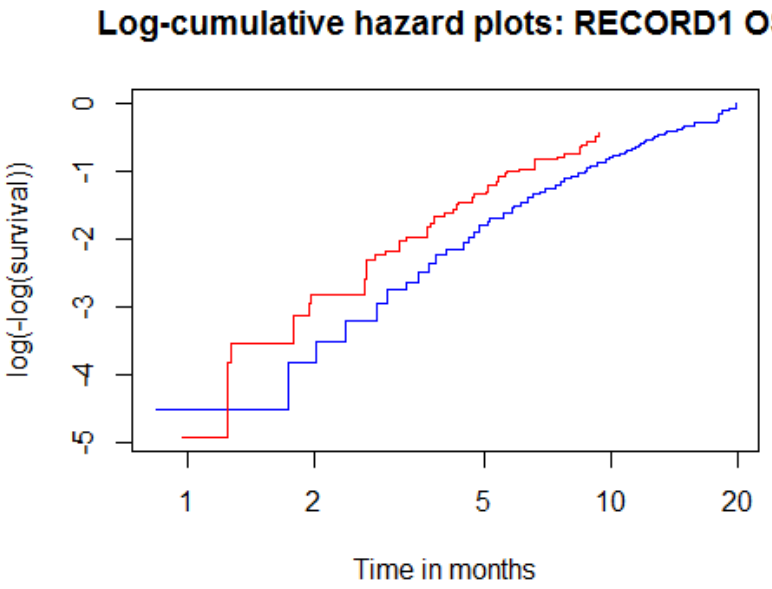


Figure 64. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – RECORD-1 PFS

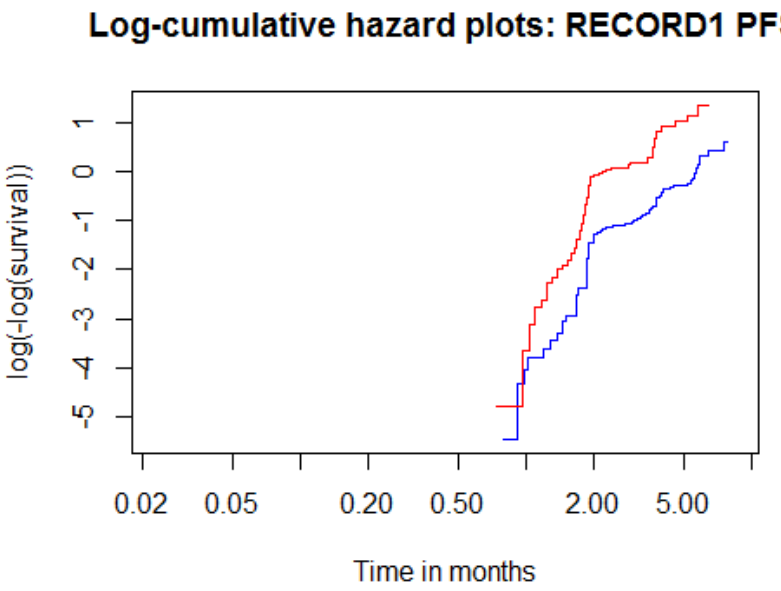


Figure 65. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – TARGET OS

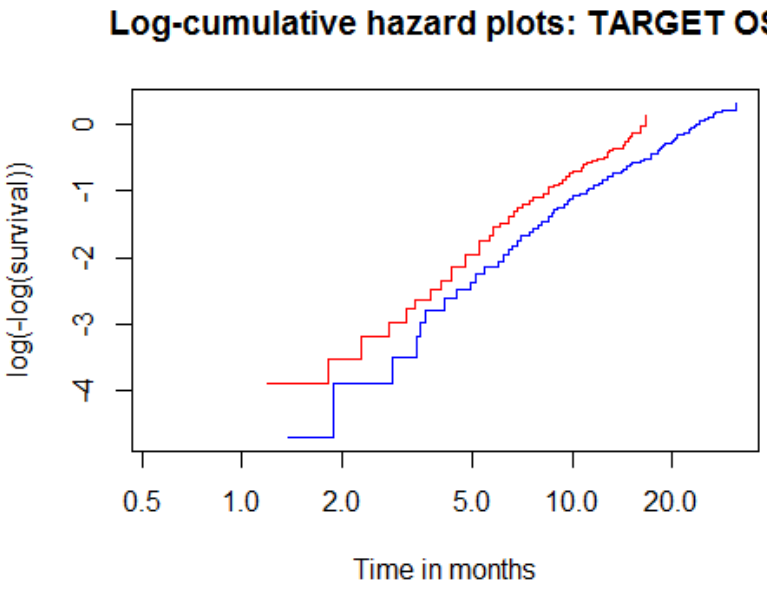


Figure 66. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – TARGET PFS

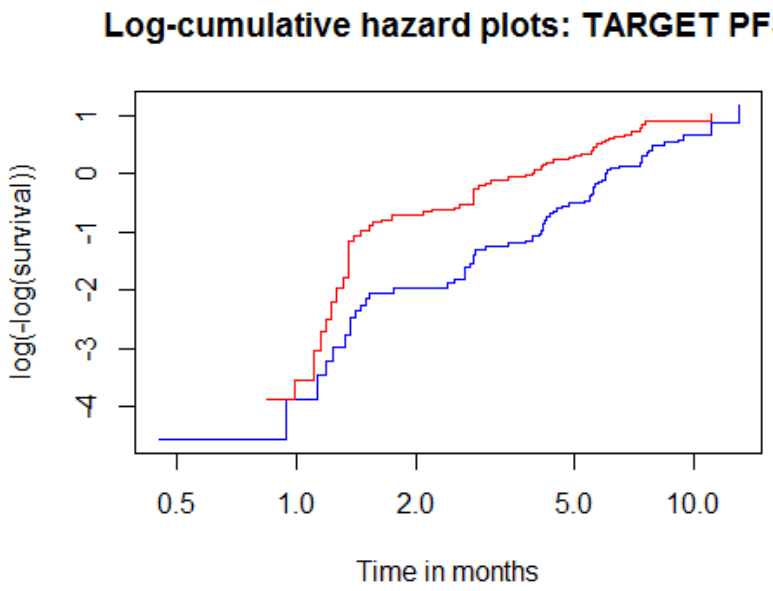


Figure 67. Log(survival function / (1-survival function)) plots versus Log(time) – AXIS OS

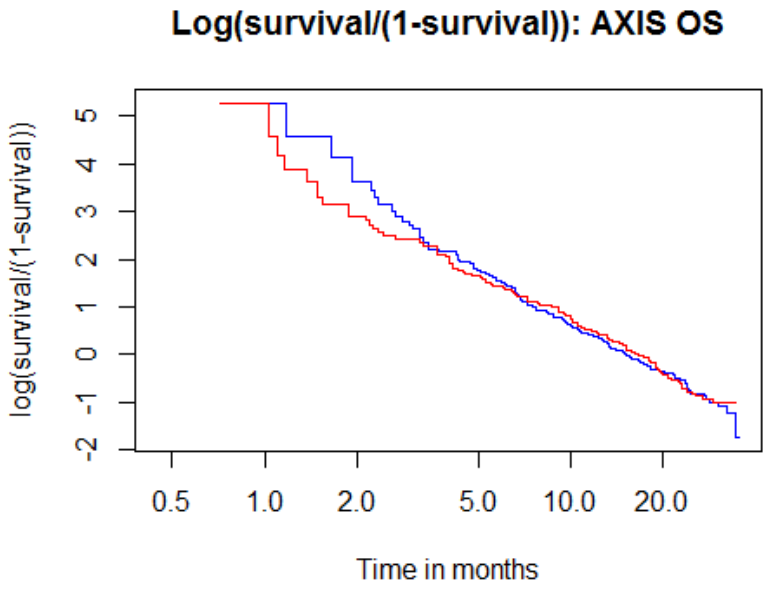


Figure 68. Log(survival function / (1-survival function)) plots versus Log(time) – AXIS PFS

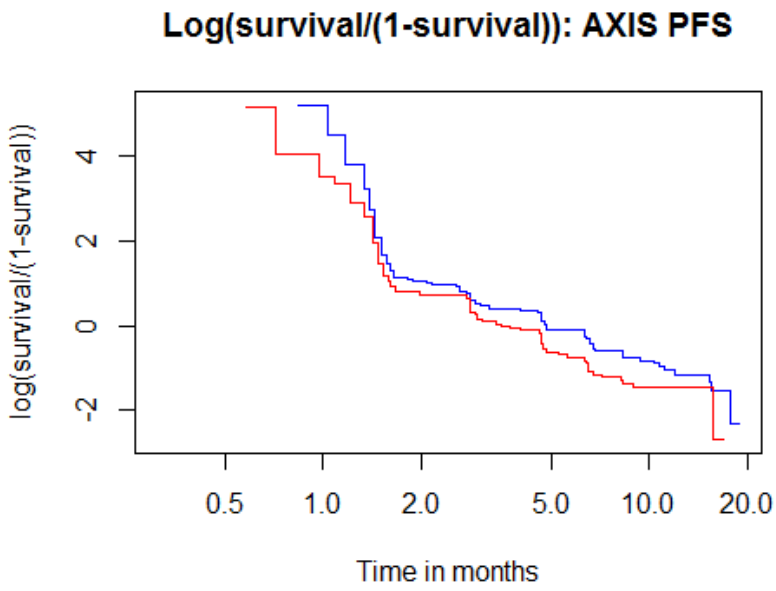


Figure 69. Log(survival function / (1-survival function)) plots versus Log(time) – CheckMate025 OS

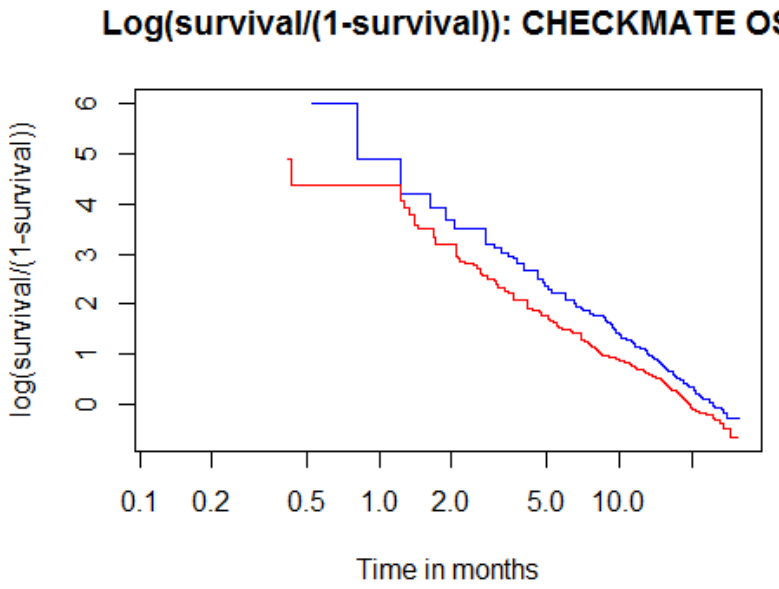


Figure 70. Log(survival function / (1-survival function)) plots versus Log(time) – CheckMate025 PFS

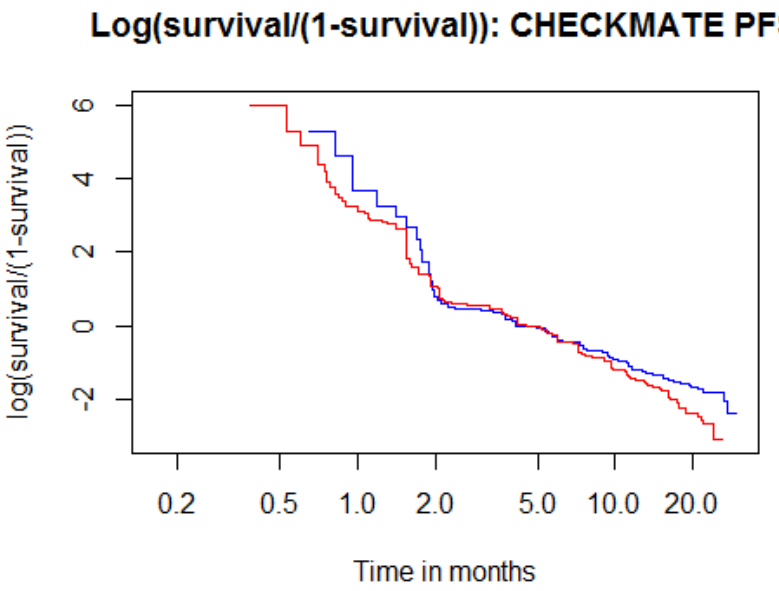


Figure 71. Log(survival function / (1-survival function)) plots versus Log(time) – CheckMate025 TTD

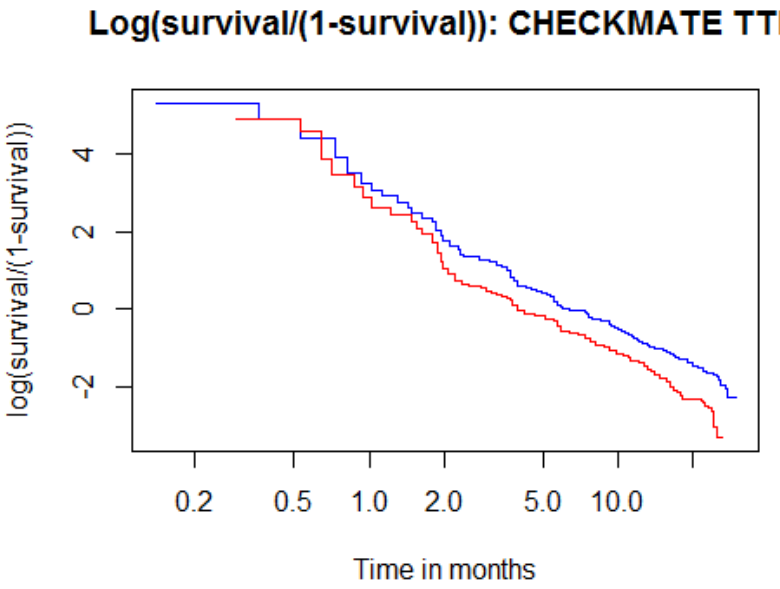


Figure 72. Log(survival function / (1-survival function)) plots versus Log(time) – RECORD-1 OS

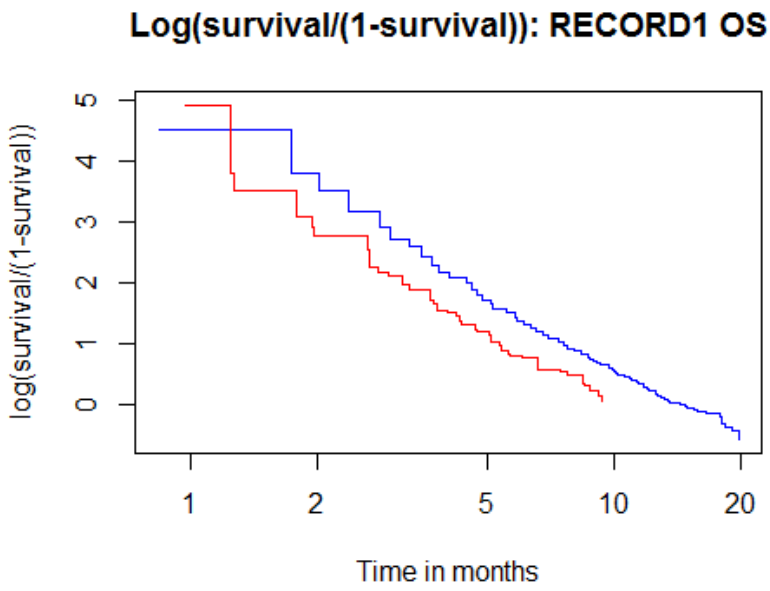


Figure 73. Log(survival function / (1-survival function)) plots versus Log(time) – RECORD-1 PFS

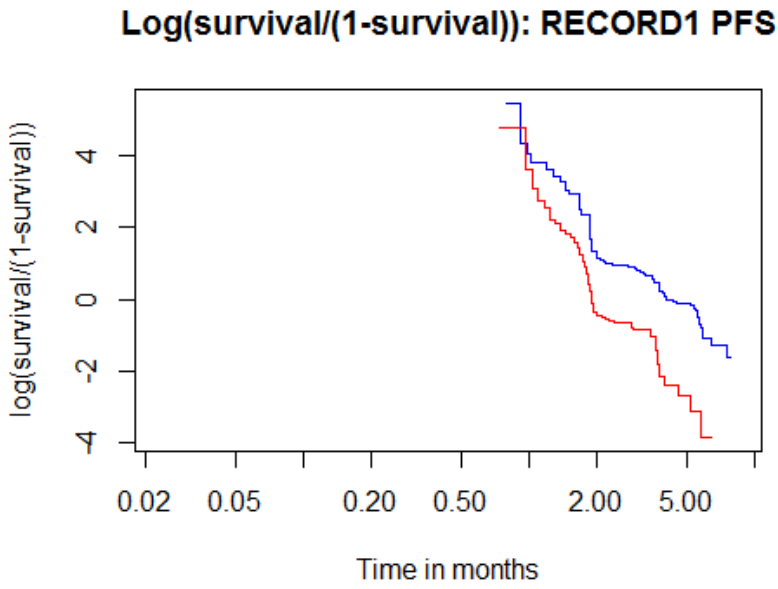


Figure 74. Log(survival function / (1-survival function)) plots versus Log(time) – TARGET OS

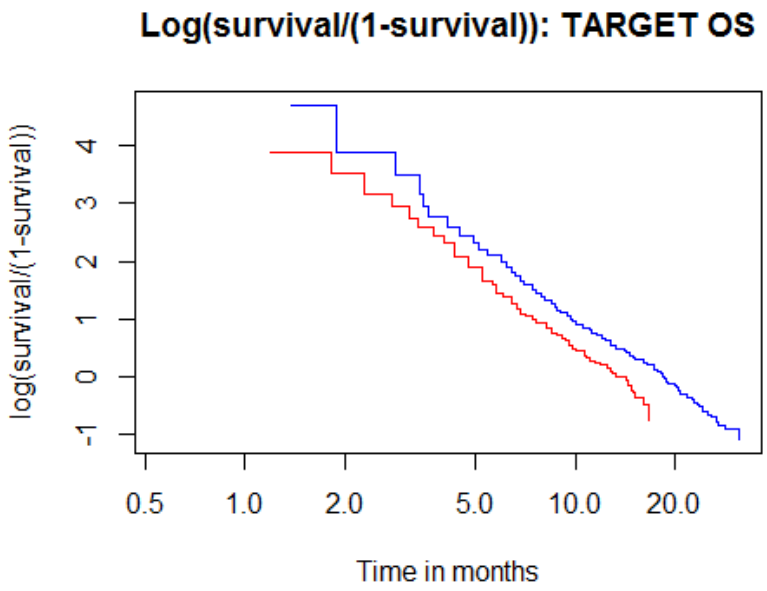


Figure 75. Log(survival function / (1-survival function)) plots versus Log(time) – TARGET PFS

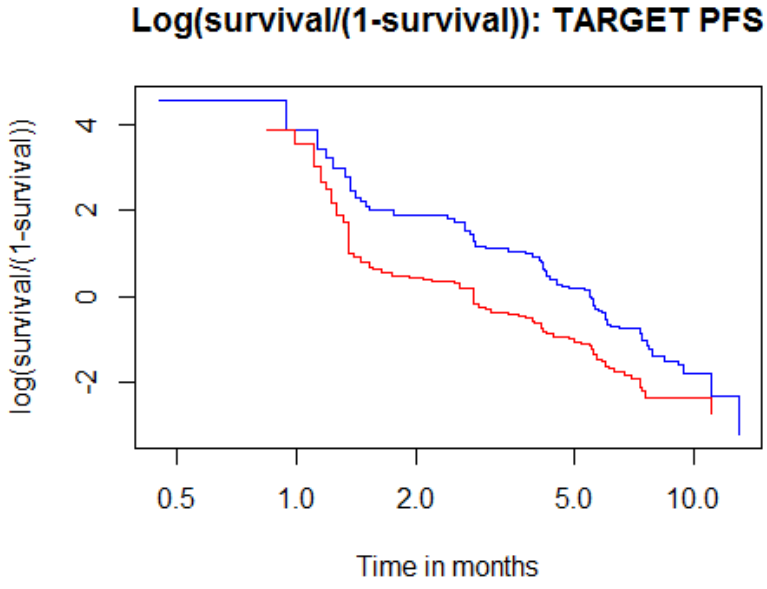


Figure 76. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – AXIS OS

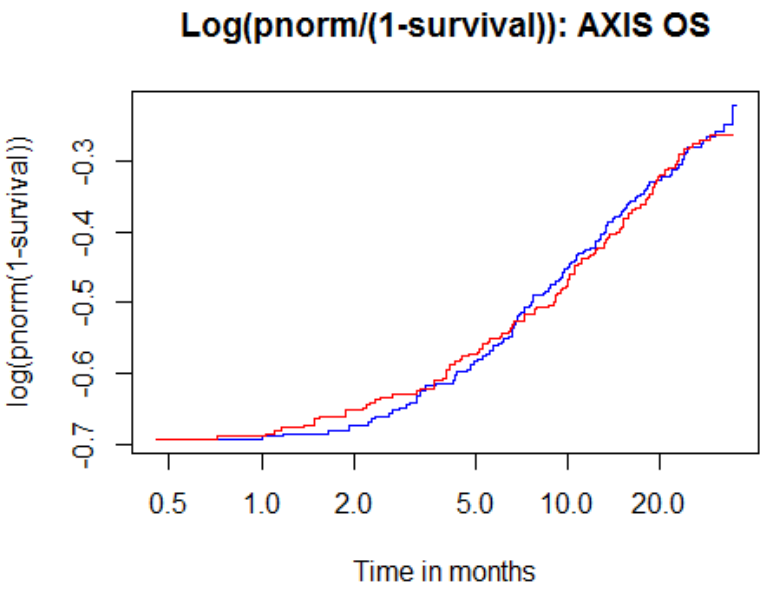


Figure 77. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – AXIS PFS

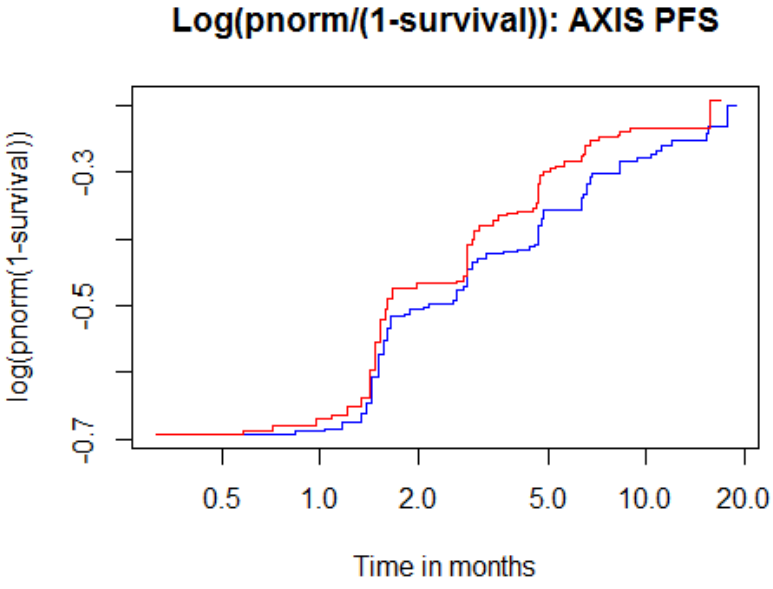


Figure 78. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – CheckMate025 OS

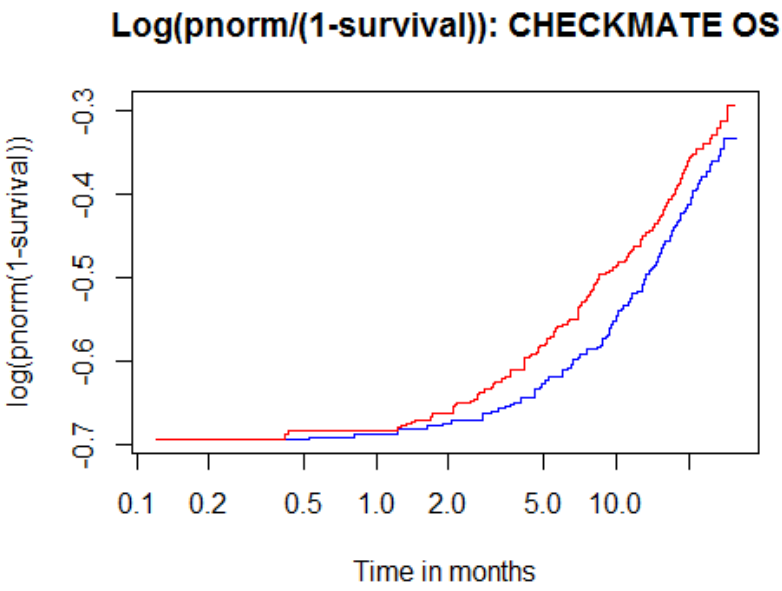


Figure 79. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – CheckMate025 PFS

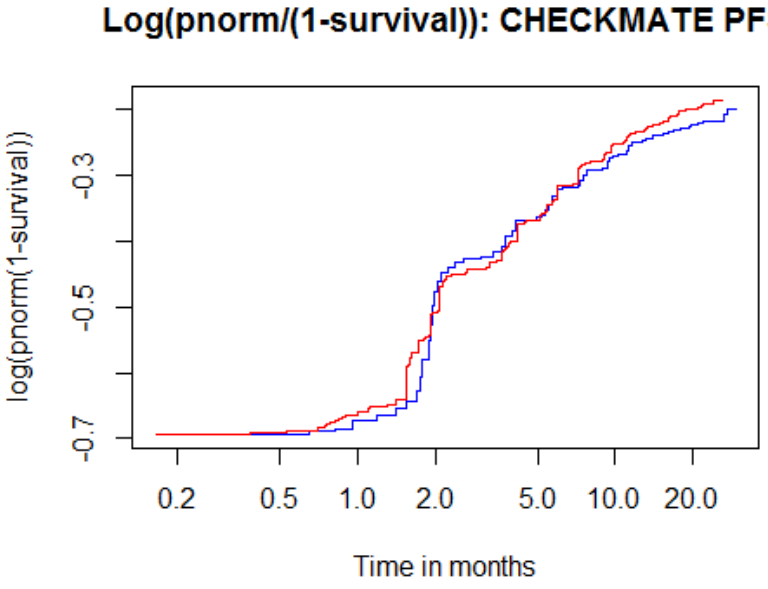


Figure 80. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – CheckMate025 TTD

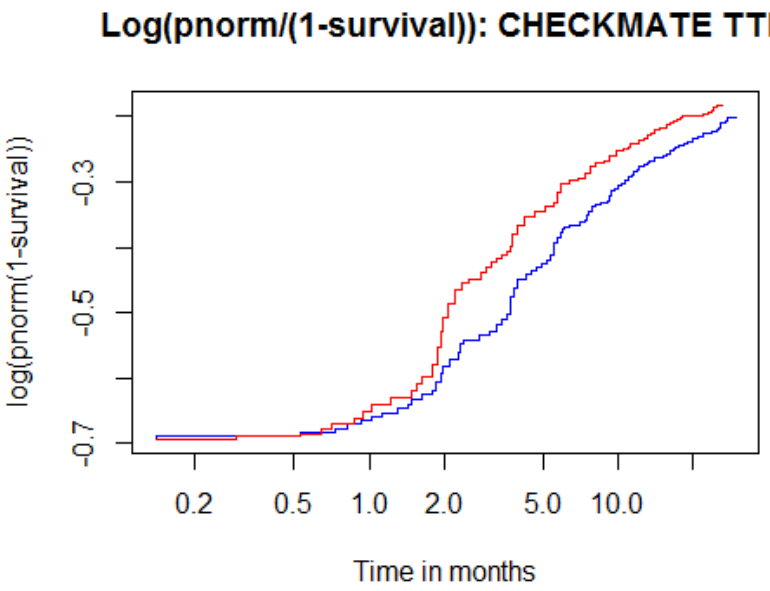


Figure 81. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – RECORD-1 OS

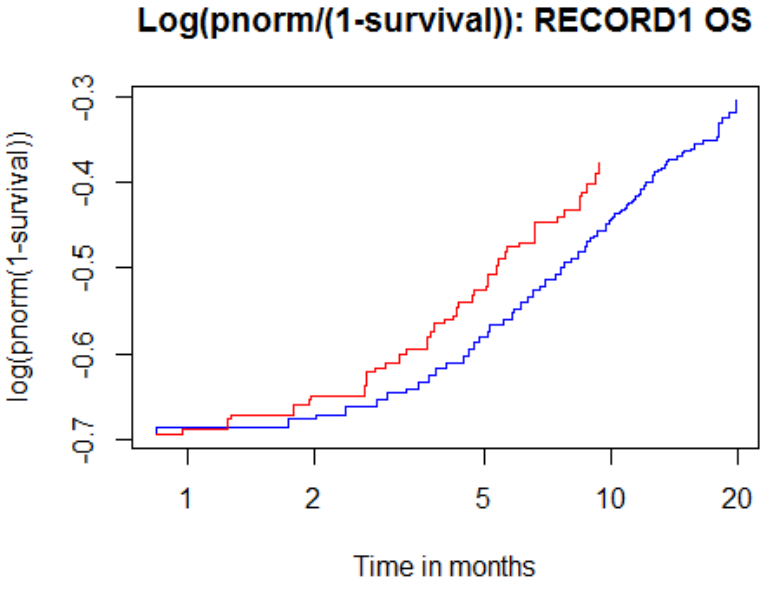


Figure 82. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – RECORD-1 PFS

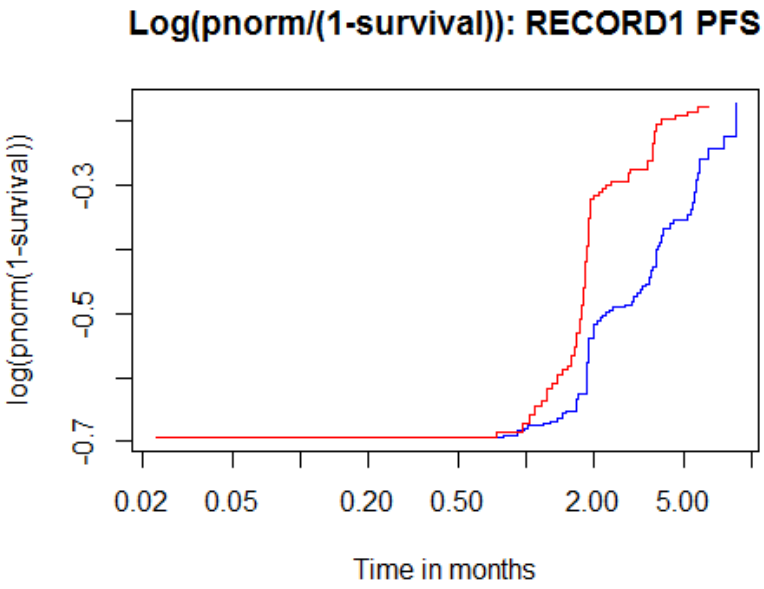


Figure 83. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – TARGET OS

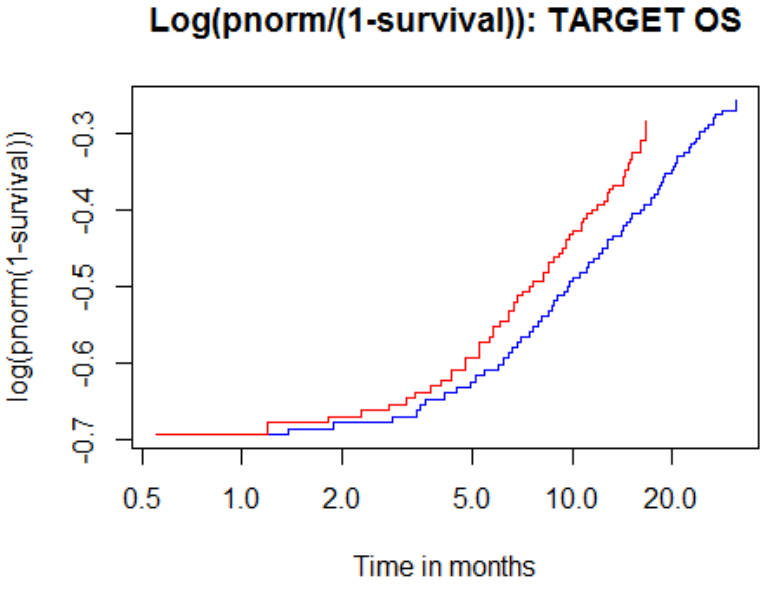
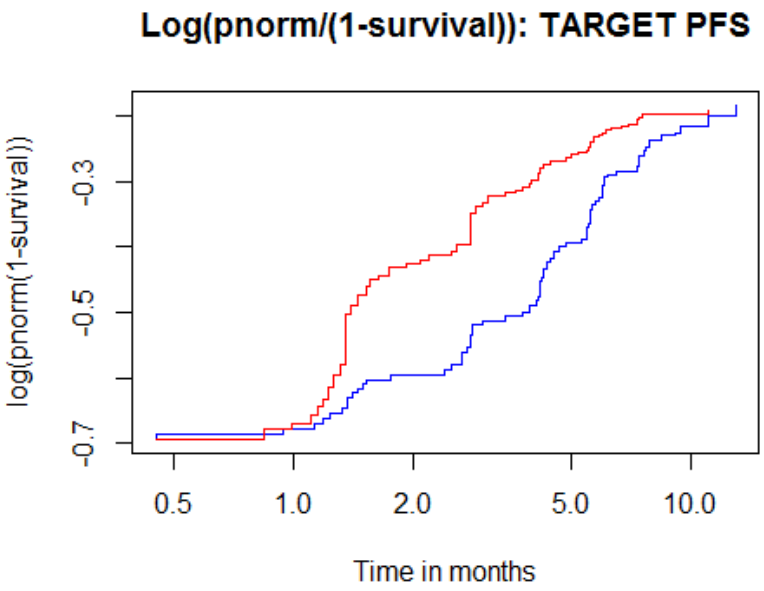


Figure 84. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – TARGET PFS



B6. **Priority question**: On page 90 of the submission, table 32 outlines the studies included for the NMA and whether the proportional hazard (PH) assumption holds. Please:

a. Give further details on the justification used to determine whether this assumption holds for both PFS and OS in each of the trials;

b. Undertake the same assessment process with regards to a proportional odds and accelerated failure time assumption based on the plots requested in B4 and B5.

RESPONSE:

a) Therneau and Grambsch test was applied to assess whether PH assumption holds at the significant level of p=0.05. Table 27 shows the p-values for score test of PH assumption for OS and PFS in the included studies. Small p-values of Therneau & Grambsch test indicate that slopes are non-zero. Non-zero slope is an indication of a violation of the PH assumption.

Table 27. Score test of proportional hazards assumption

Study Name		Rho	Chi-Square	P-value
METEOR	OS	-0.0466	0.692	0.406
	PFS	-0.0966	3.56	0.0593
AXIS	OS	-0.0217	0.121	0.728
	PFS	-0.00421	0.00405	0.949
CheckMate025	OS	0.11	4.72	0.0298
	PFS	-0.0811	4.1	0.043
RECORD-1	OS	-0.0939	1.54	0.215
	PFS	-0.04	0.39	0.532
TARGET	OS	0.102	5.8	0.016
	PFS	0.218	26.7	2.36e-07

b) Please see Table 28 below for a summary of whether proportional hazard and/or odd assumption holds and an assessment whether joint lognormal distribution fits the data. The assessment of a proportional odds and accelerated failure time assumption (lognormal) were done by subjective visual checking the plots generated for B4 and B5.

Table 28. Summary of PH assumption – OS, PFS

Study name	Proportional hazard assumption holds?		Proportional odd assumption holds?		Joint lognormal distribution fit the data?	
	PFS	OS	PFS	OS	PFS	OS
METEOR	Y	Y	Y	N	Y	N
RECORD-1	Y	Y	N	Y	N	Y
CheckMate025	N	N	N	N	N	N
TARGET	N	N	N	N	N	N
AXIS	Y	Y	N	N	N	N

B7. **Priority question:** If a proportional odds assumption holds for PFS, OS and TTD, for any of the comparisons resulting to the response to question B4 and B5, please fit a proportional odds log-logistic model where relevant and report the results of the economic model as a scenario analysis.

RESPONSE: Based on the assessment for question B6 b) it can be concluded that proportional odds assumption does not work across all the relevant studies. Therefore, it is considered that the proportional odds log-logistic model is not suitable for the NMA. In addition, based on the assessment of TTD for METEOR and

CcheckMate025 study (Table 29) it is considered to be inappropriate to apply proportional odds loglogistic model on TTD.

Table 29. Summary of PH assumption - TTD

Study name	Proportional hazard assumption holds?	Proportional odd assumption holds?	Joint lognormal distribution fit the data?
METEOR	N	N	N
CheckMate025	N	N	N

B8. **Priority question:** Given that a PH assumption holds for the METEOR trial data, please use a joint proportional hazards model to fit appropriate parametric curves for PFS, OS and TTD, and use these curves to perform a trial-based scenario analysis in the economic model.

RESPONSE: The results of Therneau and Grambsch test (see Table 27) indicate that for PFS and OS data from METEOR, a joint proportional hazards model can be used. This does not apply to TTD, where p=0.00448. Therefore, the proportional hazard model distributions (exponential, Weibull and Gompertz), were added for PFS and OS (model provided as a separate file). Please note that only exponential, Weibull and Gompertz distributions are working for PFS and OS choices when choosing METEOR as a data source in the drop-down box “efficacy data source” (Sheet “User Input”, Cell C12). If METEOR results are chosen for “efficacy data source”, choosing lognormal, loglogistic or gamma distribution will generate error in the results as these are not proportional hazard model distributions.

B9. **Priority question**: Whether the relative treatment effect for cabozantinib in 2nd and 3rd line treatment for advanced RCC is equivalent or not, the baseline inputs in the economic model are likely to differ and therefore may result in different outcomes. Please provide separate base case analyses for the 2nd and 3rd line treatment for advanced RCC of cabozantinib compared with all relevant comparators using appropriate model inputs based on the subgroup analyses requested in questions A4 to A7.

RESPONSE: Since a NMA for PFS, OS and TTD was only feasible for the subgroup of patients with only 1 prior VEGFR-TKI a new base case has been provided for the 2nd line treatment for advanced RCC of cabozantinib compared with all relevant comparators using model inputs based on the analyses presented in question A6.

B10. **RESPONSE:** Since a NMA for PFS, OS and TTD was only feasible for the subgroup of patients with only 1 prior VEGFR-TKI a new base case has been provided for the 2nd line treatment for advanced RCC of cabozantinib compared with all relevant comparators using model inputs based on the analyses presented in question A6. A flexible spline-based survival model approach was deemed appropriate in the

ongoing nivolumab technology appraisal (ID853). Please explain why spline curves were not considered for the survival analysis in this appraisal.

RESPONSE: In the on-going nivolumab single technology appraisal a 'spline odds 2-knot' model was used for modelling PFS and 'spline hazard 2-knot' to predict time to stopping treatment. The ERG considered that the company did not justify its choice of a complex spline-based model for time to stopping treatment. The ERG advised that a simpler model would also fit the data well and accordingly the ERG's exploratory analyses used a log-normal curve (base case) or a generalised gamma curve (sensitivity analyses). In this appraisal a parametric survival curve NMA was used. Analysing spline-based curves in this type of NMA was not deemed feasible.

B11. The model appears to calculate the cost of subsequent treatment for all patients whose disease progressed. However, the active treatment costs are calculated for all patients who have not yet discontinued treatment (based on the TTD data) but may have progressed. This results in a proportion of patients in the model receiving both active treatment and subsequent treatment, concurrently. Please amend this inaccuracy and provide the updated model results. Please also clarify any assumptions made following the amendments.

RESPONSE: The model engine has been modified so that the patients in the model receive either active treatment or subsequent treatment, instead of both of them.

B12. The submission states that Table 56 on page 128 shows the results of the utility regression analyses with and without the treatment effect included as a covariate. However, only the results without the treatment effect appear to be presented. Please provide the results of the analysis that includes the treatment effect as a covariate.

RESPONSE: The treatment effect as a covariate was tested and the coefficient was found not to be significant at the level of p=0.01, see Table 30 below. The covariates of treatment effect and week were then excluded, and the utility data was refitted with the covariates of baseline index value, progression and AE, see Table 31. The results in Table 31 show that the covariates of progression and AE are both significant at the level of p=0.01.

Table 30. SAS output including treatment effect as a covariate

Solution for Fixed Effects								
Effect	Planned Treatment	progress	AE	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				0.2537	0.02720	608	9.33	<.0001
Base				-0.3379	0.03039	2175	-11.12	<.0001
TRTP	CABOZANTINIB			0.000731	0.01081	2175	0.07	0.9461
TRTP	EVEROLIMUS			0	.	.	.	.
week				-0.00062	0.000285	552	-2.18	0.0293
progress		1		-0.03251	0.007391	2175	-4.40	<.0001
progress		0		0	.	.	.	.
AE			1	-0.05558	0.006808	2175	-8.16	<.0001
AE			0	0	.	.	.	.

Table 31. SAS output excluding treatment effect as a covariate

Solution for Fixed Effects							
Effect	progress	AE	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			0.2498	0.02590	609	9.64	<.0001
Base			-0.3400	0.03016	2175	-11.27	<.0001
progress	1		-0.03990	0.006597	2175	-6.05	<.0001
progress	0		0	.	.	.	.
AE		1	-0.05515	0.006813	2175	-8.09	<.0001
AE		0	0	.	.	.	.

B13. Please explain how the estimates in Table 56 on page 128 of the submission should be used to estimate the utility of a progression-free patient who has not experienced an adverse event, i.e. without applying the decrements for progression or adverse events.

RESPONSE: For a progression-free patient who has not experienced an adverse event, the average EQ-5D index score for patients without disease progression (0.817) was used in the analysis, as described in text on Page 128 of the Ipsen submission.

B14. Please give further detail and justification on how the adverse events utility decrement has been estimated and applied.

RESPONSE: METEOR patient level data was analysed to derive the average decrement to patient's utility when they experienced grade 3 or 4 AEs during the trial. The dates of AEs in the METEOR patient level data were compared with the dates when EQ-5D were collected in the trial to decide whether the patients was

experiencing an adverse event at the time of EQ-5D data collection. If the patient was experiencing a treatment-emergent grade 3/4 AE, 1 was assigned to the covariate AE. Otherwise, 0 was assigned to the covariate AE. After fitting the data with the repeated measure mixed-effect model, the impact of AE on patient's utility was obtained, which was applied to any treatment-emergent grade 3/4 AE in the model.

Before deciding to use an average AE utility decrement for cabozantinib and everolimus, the METEOR data was analysed to understand whether the AE decrement differed by treatment arm. Table 32 shows the results when fitting the EQ-5D data with baseline EQ-5D index, progression, and the interaction term between AE and treatment. The results show that when an AE occurs, both cabozantinib and everolimus have similar and significant decrements (-0.05362 and -0.05959). Also cabozantinib and everolimus have a similar decrement when an AE doesn't happen (-0.00163, not significant and 0 for cabozantinib and everolimus, respectively). Further, the covariate AE was added into the model and the EQ-5D data was fit with baseline EQ-5D index, progression, AE and the interaction between AE and treatment (see Table 33). The results show that the interaction term between AE and treatment is not significant and there is no distinction between treatment arms for AEs. As such it was decided that an average across the treatments should be used in the model (Table 34).

Table 32. SAS output of EQ-5D data with baseline EQ-5D index, progression, and the interaction term between AE and treatment

Solution for Fixed Effects								
Effect	Planned Treatment	progress	AE	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				0.2509	0.02710	608	9.26	<.0001
Base				-0.3403	0.03027	2174	-11.24	<.0001
progress		1		-0.03979	0.006613	2174	-6.02	<.0001
progress		0		0	.	.	.	.
TRTP*AE	CABOZANTINIB		1	-0.05362	0.01321	2174	-4.06	<.0001
TRTP*AE	CABOZANTINIB		0	-0.00163	0.01096	2174	-0.15	0.8815
TRTP*AE	EVEROLIMUS		1	-0.05959	0.01057	2174	-5.64	<.0001
TRTP*AE	EVEROLIMUS		0	0	.	.	.	.

Table 33. SAS output of EQ-5D data with additional covariate for interaction between AE and treatment

Solution for Fixed Effects								
Effect	Planned Treatment	progress	AE	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				0.2509	0.02710	608	9.26	<.0001
Base				-0.3403	0.03027	2174	-11.24	<.0001
progress		1		-0.03979	0.006613	2174	-6.02	<.0001
progress		0		0	.	.	.	.
AE			1	-0.05959	0.01057	2174	-5.64	<.0001
AE			0	0	.	.	.	.
TRTP*AE	CABOZANTINIB		1	0.005978	0.01585	2174	0.38	0.7061
TRTP*AE	CABOZANTINIB		0	-0.00163	0.01096	2174	-0.15	0.8815
TRTP*AE	EVEROLIMUS		1	0	.	.	.	.
TRTP*AE	EVEROLIMUS		0	0	.	.	.	.

Table 34. SAS output – AE decrement analysis

Solution for Fixed Effects							
Effect	progress	AE	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			0.2498	0.02590	609	9.64	<.0001
Base			-0.3400	0.03016	2175	-11.27	<.0001
progress	1		-0.03990	0.006597	2175	-6.05	<.0001
progress	0		0	.	.	.	.
AE		1	-0.05515	0.006813	2175	-8.09	<.0001
AE		0	0	.	.	.	.

B15. Please clarify why treatment-emergent adverse events were used in the model rather than treatment-related adverse events.

RESPONSE: Treatment-emergent adverse events (TEAEs) include any event related temporally to the administration of the drug (i.e. occurs during treatment phase), while treatment-related adverse events (TRAEs) are a subset of AEs, which include event that can be considered causally related to the treatment administered (i.e. occurs during treatment phase AND clinical judgement considers the AE to be related to treatment). Given the consideration that any Grade 3 or higher TEAEs would also have an impact on the patients' costs and HRQoL, Ipsen considered using TEAEs in the model more appropriate than TRAEs. TEAEs were used when available (patient level data or literature), and TRAEs only if no TEAE were identified. For nivolumab it was not possible to identify TEAEs, making it likely that AEs for nivolumab might have been underestimated in the model.

B16. Please clarify what the disutility value for axitinib, given in Table 63 on page 133 of the submission, relates to. It appears too high for a disutility.

RESPONSE: In TA 333 a disutility related to adverse events was not included in the analysis because the HRQoL estimates included in the AXIS trial reflected the adverse event profile associated with axitinib. Here the value should be NA.

B17. Please clarify why an adverse event related disutility is not given in Table 62 on page 132 for axitinib.

RESPONSE: In TA 333 a disutility related to adverse events was not included in the analysis because the HRQoL estimates included in the AXIS trial reflected the adverse event profile associated with axitinib. Therefore NA was indicated.

B18. Please explain why the costs of adverse events were not considered for nivolumab in Table 76 on page 148.

RESPONSE: The model only included those adverse events with >5% incidence. For nivolumab, only treatment-related AEs were available as the treatment-emergent AEs were not reported. As the treatment-related AEs are normally expected to be lower than treatment-emergent AEs, no treatment-related AEs for nivolumab were found to be higher than the 5% cut-off point and as such zero cost was applied in the analysis. See also response to priority question B14.

B19. For the comparison of cabozantinib with nivolumab, the model results reported in the submission appear to be based on the model in which wastage was excluded. However, the submission implies that the base case includes wastage for nivolumab. Please clarify this discrepancy.

RESPONSE: The cost of nivolumab excludes the wastage of nivolumab in the base case analysis. The mention of “the inclusion of wastage for nivolumab” on Page 136 should be corrected into “the exclusion of wastage for nivolumab”.

B20. Please clarify how events are defined in the TTD survival analysis, and in particular if patients who die are considered to discontinue treatment or are censored.

RESPONSE: TTD was defined as “date of last dose decision ongoing – date of first exposure to treatment +1”, which is consistent with treatment duration reported in the study publication. If the patient died or was still on treatment by the end of the study, the patient was censored.

B21. Please provide the references for the studies listed in Appendix 21.

RESPONSE: Copies are provided.

B22. The ERG found some discrepancies between the values reported in the submission and in the Excel model. Please clarify what are the correct values in Table 35 below.

RESPONSE: Please see **Table 35** below.

Table 35. Discrepancies between the economic model and the company submission

Outcomes/Analysis	Reference in the model	Company submission	Correct values
QALYs for everolimus during PFS	'engine-e'!K8	Table 82, page 158	Correct value: 0.45. Please note that the everolimus engine can be generated from METEOR data and NMA data. If comparing Table 82 in the report and the engine cell 'engine-e'!K8, please ensure that METEOR study has been chosen as the data source in sheet 'User Input'. The discrepancy is caused by the difference in the data source. When comparing cabozantinib with everolimus, the METEOR data were used instead of NMA data.
QALY increment and absolute increment for everolimus during PFS	'engine-e'!K8-'engine-c'!K8	Table 82, page 158	Correct value: 0.38. See above explanation.
QALYS for nivolumab during PFS	'engine-n!K8	Table 84, page 160	Correct value: 0.52. The data is correct in both model and report. The difference is caused by rounding: the QALYs for nivolumab during PFS is 0.5246. After rounding to two decimal for the report, it is 0.52.
-Total costs for cabozantinib, and axitinib. -Increment, absolute increment and %absolute increment of cabozantinib compared to axitinib.	-'engine-c'!K8 and 'engine-a'!K8 -'engine-c'!K8 - 'engine-a'!K8	Table 85, page 160	Correct values: - Total cost for cabozantinib 85,781 - Total cost for axitinib 38,331 - Increment 47,451 - Absolute increment 47,451 - % absolute increment of cabozantinib compared to axitinib 124% The data have shifted in the report by 1 cell.
Treatment acquisition costs for everolimus	'engine-e'!E6	Table 86, page 161	Correct value: 16,366. The first number i.e. 1 was missing in the report.
Treatment acquisition costs for cabozantinib	'engine-c'!E6	Table 86, page 161	Correct value: 71,253 Please make sure that data source in the model is changed to METEOR in the user

			input sheet.
Disease management cost for cabozantinib	'engine-c'!E6	Table 86, page 161	Correct value: 1,677 Please make sure that data source in the model is changed to METEOR in the user input sheet.
-Total costs for cabozantinib, and everolimus. -Increment, absolute increment and %absolute increment of cabozantinib compared to axitinib.	-'engine-c'!K8 and 'engine-e'!K8 -'engine-c'!K8 - 'engine-e'!K8	Table 86, page 161	Correct values: - Total costs for cabozantinib 86,081 - Total costs for everolimus 31,923 - Increment and absolute increment is 54,158 - %absolute increment of cabozantinib compared to axitinib is 170% The data have shifted in the report by 1 cell.
-Total costs for cabozantinib, and BSC. -Increment, absolute increment and %absolute increment of cabozantinib compared to BSC.	-'engine-c'!K8 and 'engine-b'!K8 -'engine-c'!K8 - 'engine-b'!K8	Table 87, page 161	Correct values: - Total cost for cabozantinib is 85,781 - Total cost for BSC is 8,155 - Increment and absolute increment are 77,626. - %absolute increment of cabozantinib compared to BSC is 952% The data have shifted in the report by 1 cell.
-Treatment acquisition costs for nivolumab -Total PFS costs for nivolumab -Total costs for cabozantinib, and nivolumab. -Increment, absolute increment and %absolute increment of cabozantinib compared to nivolumab.	-'engine-n!' AF14 -'engine-n!' E4 -'engine-c'!K8 and 'engine-b'!K8 -'engine-c'!K8 - 'engine-b'!K8	Table 88, page 162	Correct value: - Treatment acquisition cost for nivolumab is 65,700 - Total PFS cost for nivolumab is 70,708 - Total cost for cabozantinib is 85,781 - Total cost for nivolumab is 87,097 - Increment and absolute increment are -1,316. - %absolute increment of cabozantinib compared to nivolumab is -1.5%. The data have shifted in the report by 1 cell.

Kidney Cancer UK's comments on the Cabozantinib technology appraisal

Kidney Cancer UK welcome any alternative options for patients with advanced kidney cancer. Currently there is only 1 second line and no third line treatment options recommended by NICE for people with advanced kidney cancer. This differs from healthcare organisations across Europe and America where a wide variety of medicines are available. With the hope to make advanced kidney cancer a chronic condition rather than a fatal disease, we think that more options would benefit people with kidney cancer significantly.

Cabozantinib is a small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) like the other drugs which are currently recommended for advanced kidney cancer. However it does also target MET and AXL, which is an interesting development. These receptors have been implicated in the pathobiology of metastatic renal-cell carcinoma or in the development of resistance to antiangiogenic drugs, so this treatment may have add benefits for some patients.

The results of the cabozantinib phase III METEOR clinical trial look promising. Cabozantinib increased the overall survival of people with advanced kidney cancer to an average of 20.1 months compared to 12.1 months with everolimus. The period of time before the disease progressed (progression free survival) was 7.4 months with cabozantinib compared to 2.7 months with everolimus. [1] These results show cabozantinib to be effective and provide value when used as a second line treatment after prior systemic treatment has failed.

Cabozanitib has similar side effects to other tyrosine kinase inhibitors which are already approved by NICE. A once a day tablet dosing protocol is easy to fit around daily life. Adverse effects are managed by reducing the dose and 9% of patients discontinued the drug during the trial. So we feel that cabozantinib would be a useful addition to the fight against kidney cancer, providing patients with alternative options which are greatly needed.

References

1. Choueiri et al, 2015. Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015; 373:1814-1823

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

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 Research UK

Your position in the organisation: Research Communications Officer

Brief description of the organisation: Kidney Research UK is the leading charity dedicated to research into kidney disease in the UK. We rely almost wholly on the generous donations of the UK public and we believe that everybody deserves a life free of kidney disease

(For example: who funds the organisation? How many members does the organisation have?)

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 is a silent condition in which the symptoms appear at a later stage. Symptoms can include extreme tiredness, weight loss, back pain, high temperatures, night sweats, anaemia, high blood pressure. Diagnosis can be delayed or missed because some symptoms can be similar to the symptoms of other conditions, which means patients are often confused, angry and frustrated as a result. They are understandably frightened and fearful about the future for themselves and their family. Patients can feel like they are a burden on their families. Family members wish they could help but are fearful for a future without their loved one.

(www.kidneycancersupportnetwork.co.uk)

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.

Our patient expert says: "I was keen to see the best outcome in terms of life expectancy."

Renal cell carcinoma (RCC) represents 2-3% of all cancers, with the highest incidence occurring in Western countries. There has been an annual increase of about 2% in incidence both worldwide and in Europe with overall mortality rates increasing. In 2012, 8,638 new kidney cancer cases were diagnosed in England (www.cancerresearchuk.org accessed 07/10/2016).
Advanced RCC is mainly resistant to radiotherapy, hormone therapy and chemotherapy. The chance of any cure at this stage of the disease is extremely slight and survival rates beyond 5 years are low.

Patients and clinicians would like access to a drug that slows down, halts or reverses tumour growth time which offers people hope, more time with their families and time to make provisions for their loved ones.

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?

Our understanding is that treatment for kidney cancer is often a postcode lottery, and options are limited.

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.

In studies cabozantinib has been associated with significantly improved overall survival versus everolimus in patients with advanced RCC who had progressed after previous VEGFR tyrosine kinase inhibitor treatment.

Response rate and progression-free survival in the clinical trials are significantly better with cabozantinib compared to other any other currently approved treatments by NICE.

Patients with advanced renal cell carcinoma (RCC) treated with cabozantinib have improved progression-free survival (PFS) compared with those treated with the standard therapy (everolimus). This offers patients more time with the family and loved ones.

Cabozantinib has shown a marked benefit in patients with bone metastases, reducing the risk of death by 46% compared with everolimus in patients with bone metastases and by 55% in patients with bone and visceral metastases thereby offering a patient a better quality of life due to reduced pain as a result of bone metastases.

Cabozantinib is a once a day oral treatment that can be taken by the patient at home which offers an easy way of taking their medication and embraces the principles of "patient choice" and allows the patient control in the home setting.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

The advantages over current treatment is increased progression-free survival at 7.4 months compared to everolimus at 3.8 months (second line) which also delays the overall survival time which, as far as we can see from" Pub Med" searches (https://www.ncbi.nlm.nih.gov/pubmed), has not be previously demonstrated in any other studies in renal cell carcinoma.

Our patient expert says: "I feel that the main advantages of the treatment under consideration concern quality of life, in particular the ability to take the treatment at home without having to spend time in hospital (as an outpatient or inpatient) hooked on a drip; the treatment can be easily administered. There are many side effects that are similar to standard chemotherapy drugs, but they seem to be not as heavy. I notice that hair loss is not featured, I would say that this would be something a female patient in particular would appreciate."

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 that we are aware of.

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.

Slight increase in diarrhoea as reported in studies which we understand from clinician discussions is manageable in the primary care setting.

Please list any concerns patients or carers have about the treatment being appraised.

None that we have been made aware of.

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.

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.

There are about 10-20% of patients who are refractory to a VEGFR in the first line setting. This figure is similar to or possibly more in the second line setting, however there are no

biomarkers that predict who will be refractory to VEGFR TKI .Therefore those who are refractory to VEGFR appear not to benefit from this treatment in the second line setting.

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.

We don't have access to this information.

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?

We would like to see a Quality of Life study.

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?

None that we are aware of.

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.

Special consideration needs to be given to patients with an uncommon cancer, as in kidney cancer, who are disadvantaged from diagnosis. Consideration also needs to be given to the lack of second line NICE-approved treatments for these patients. It is our opinion that it is the role of NICE to look at equality for all patients including those disadvantaged with a terminal illness.

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.

We are aware that those who are refractory to VEGFR appear not to benefit from cabozantinib the second line setting. Other therapies appropriateness are dependent on a clinician's evaluation.

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.

Increased progression-free survival (7.4 months) versus everolimus at 3.8 months and a 42% reduction in the hazard for progression or death. This has not been demonstrated by any other therapy and therefore offers a significant advancement for patients and families.

Are there any other issues that you would like the Appraisal Committee to consider?

Patients with kidney cancer present with symptoms that aren't always associated with kidney cancer, and may be suspected of having kidney stones or bowel disorders, which ultimately delays the final diagnosis. Therefore life-prolonging treatment becomes even more necessary to help patients put their affairs in order.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Renal cell carcinoma (RCC) represents 2-3% of all cancers, with the highest incidence occurring in Western countries. There has been an annual increase of about 2% in incidence both worldwide and in Europe with overall mortality rates increasing. In 2012, 8,638 new kidney cancer cases were diagnosed in England.
- Patients with advanced renal cell carcinoma (RCC) treated with cabozantinib have improved progression-free survival (PFS) compared with those treated with the standard therapy (everolimus). This offers patients more time with the family and loved ones.
- Special consideration needs to be given to patients with an uncommon cancer, as in kidney cancer, who are disadvantaged from diagnosis. Consideration also needs to be given to the lack of second line NICE-approved treatments for these patients.
- Advanced RCC is mainly resistant to radiotherapy, hormone therapy and chemotherapy. The chance of any cure at this stage of the disease is extremely slight and survival rates beyond 5 years are low.
- Patients and clinicians would like access to a drug that slows down, halts or reverses tumour growth time which offers people hope, more time with their families and time to make provisions for their loved ones.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Thank you for agreeing to make a submission on your organisation's 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 submission, 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: [redacted]

Name of your organisation: NCRI-RCP-RCR-ACP

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

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?

Current treatment for VEGF refectory disease is with axitinib, which is NICE approved. Everolimus has positive data and was on the CDF. It has been recently removed although data on axitinib and everolimus is similar.

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?

The focus has been on clear cell renal cancer.

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)?

Specialist oncology clinics should be treating these patients.

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?

The drug is currently available on a named patients basis.

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.

Both the EUA ESMO and NCCN guidelines recommend caboznatinib in VEFG refectory disease.

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Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

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?

Cabozantinib has significantly outperformed an established targeted therapy with response, progression and survival advantages over everolimus. No other drug has achieved this. While there is toxicity, this is in line with expected toxicity. Impact on quality of life, presented at ESMO 2016 does not appear deleterious.

This is reflected in the ESMO and EAU guidelines which recommend cabozantinib above all other targeted therapies in VEGF resisitant clear cell cancer.

The clinical community is very familiar with giving oral VEGF targeted therapy. Cabozantinib is likely to be given instead of other oral drugs with less compelling data (as outlined in the EAU guidelines).
The drugs has a toxicity profile in line with previous VEGF targeted therapy.

European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor-Targeted Therapy.

Powles T, Staehler M, Ljungberg B, Bensalah K, Canfield SE, Dabestani S, Giles RH, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Volpe A, Bex A. Eur Urol. 2016 Jun 24.

Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial.Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, Hammers HJ, Donskov F, Roth BJ, Peltola K, Lee JL, Heng DY, Schmidinger M, Agarwal N, Sternberg CN, McDermott DF, Aftab DT, Hessel C, Scheffold C, Schwab G, Hutson TE, Pal S, Motzer RJ; METEOR investigators. Lancet Oncol. 2016 Jul;17(7):917-27

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, Hammers H, Hutson TE, Lee JL, Peltola K, Roth BJ, Bjarnason GA, Géczi L, Keam B, Maroto P, Heng DY, Schmidinger M, Kantoff PW, Borgman-Hagey A, Hessel C, Scheffold C, Schwab GM, Tannir NM, Motzer RJ; METEOR Investigators. N Engl J Med. 2015 Nov 5;373(19):1814-23.

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.

Recent data from ESMO 2016 shows that cabozantinb outperformed sunitiinb in front line metastatic renal cancer. This underpins the hypothesis that cabozantinib is the most active VEGF targeted therapy. (Choueiri et al ESMO 2016)

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Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Implementation issues

The NHS is required by the Department of Health 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 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)?

The clinical community is very familiar with giving oral VEGF targeted therapy. Cabozantinib is likely to be given instead of other oral drugs with less compelling data (as outlined in the EAU guidelines).
The drugs has a toxicity profile in line with previous VEGF targeted therapy. I don't think additional training will be required.

Equality
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.

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Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **I do not believe there to be any inequality issues.**

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Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

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: Dr Kate Fife

Name of your organisation

Cambridge University Hospitals NHS Foundation Trust

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: none

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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.

The management of metastatic renal cancer is complex. It is an unusual malignancy in that the disease course and prognosis varies widely; from death within a few months, to survival for a decade or more with metastases. For selected patients, a nephrectomy may be appropriate even in the presence of metastases; this decision is best made by experienced multidisciplinary teams. Many patients with indolent cancer can undergo surveillance rather than drug treatment as an initial treatment option. 75% of patients have clear cell renal cancer (ccRCC) and 10-15% papillary RCC; although the METEOR trial was in ccRCC, patients with papillary RCC should theoretically benefit as well in view of frequent MET overexperession or mutation in this group.
For the last decade, oral anti-angiogenic tyrosine kinase inhibitors (TKIs) have been standard of care for first line therapy. Both sunitinib and pazopanib are NICE approved agents. We also have access to a second line TKI, axitinib, NICE approved in 2015. In November 2016, nivolumab, an immunotherapy agent given intravenously, was NICE approved for use in post-first line setting.
There are several major centres for kidney cancer within the UK, although many patients are treated at smaller centres. For example, the current UK wide STAR trial of first line therapy is open at 56 sites. Cabozantinib should be prescribed by oncologists specialising in kidney cancer, in an outpatient setting, with suitable and adequately trained specialist nurse support. It is not currently available although some centres have a patient access scheme.
There are European Association of Urology guidelines which recommend cabozantinib or nivolumab as second line options for metastatic kidney cancer in

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Single Technology Appraisal (STA)

view of the overall survival benefit demonstrated (EUROPEAN UROLOGY 7 0 (2 0 1 6) 7 0 5 – 7 0 6)

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?

Until recently, the standard second line therapy for metastatic RCC has been axitinib which demonstrated a PFS benefit against another tki, sorafenib, in the phase 3 AXIS trial (Patients previously treated with sunitinib had a PFS 6.5 months and OS 15.2 months).
Nivolumab demonstrated an OS benefit over everolimus of 25 months vs 19.6 months (Checkmaate 025). Cabozantinib has also demonstrated a survival benefit over everolimus of 21.4 vs 16.5 months (METEOR).

The clinical trial setting of METEOR reflects NHS practice. Patients were in favourable, intermediate and poor prognostic categories were treated and patients had performance status 0 (705) or 1 (30%). Patients would start cabozantinib (or nivolumab) after objective progression on their CT scans after treatment on sunitinib or pazopanib.

The side effects of Cabozantinib are significant, particularly diarrhoea (74% of trial patients), hypertension (37%), fatigue (56%) and hand-foot soreness (42%). These can adversely affect quality of life although I'm not aware of this data having been published yet. These are side effects that we are used to managing, but they are difficult for patients to cope with because of their chronic nature.

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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

No issues

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.

I am not aware of any relevant UK additional sources of information such as audit, as the technology is new.

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Single Technology Appraisal (STA)

Implementation issues

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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)?

Cabozantinib is an oral drug prescribed in a specialist oncology outpatient setting. It is a similar class of drug to those currently available; as such no special provision would be required.

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Single Technology Appraisal (STA)

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

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: Robert Hawkins

Name of your organisation The Christie Hospital and University of Manchester

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:

NONE

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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.

Cabozantinib was tested in a Phase III trials compared to Everloimus after patients had failed at least one prior TKI and may have failed other therapies in addition including immunotherapy (cytokines, anti-PD1 antibodies). The trial demonstrated superior efficacy in all key endpoints..

Cabozantinib therefore has a broad application in patients who have failed TKI therapy – this is currently the major first line therapy (Sunitinib or Pazopanib) and a common second line therapy (Axitinib). Cabozantinib showed a trend to better efficacy than Everolimus in all sub groups tested and therefore it is hard to pick subgroups of patients with enhanced efficacy.

Cabozantinib would be available through specialist oncology clinics.

Cabozantinib is widely available through an access scheme at present. The practical management is very similar to that of related drugs so there are no barriers to its introduction although there may be capacity issues as it will clearly increase activity.

Its use is supported in its licenced indication by ESMO guidelines

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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?

Cabozantinib is an oral TKI and will be easy to introduce, as management is very similar to other drugs in the RCC pathway. This differs from Nivolumab that is an alternative, which can be used before or after Cabozantinib. This require frequent intravenous dosing which incurs costs and inconvenience but is nevertheless relatively easily delivered.

Similar comments apply to assessments on therapy – these would be routine with patients generally stopping treatment either because of progression or intolerance. Again the decision to stop is somewhat easier than for Nivolumab where early progression can occasionally be followed by later response. This is however impossible to judge at the time and can lead to continuation where changing therapy might be a better option (or vice versa).

The trial was well-conducted large trial that broadly reflects patients in routine practice. As with all trials it is biased towards the better performance status patients and those with relatively normal blood parameters. Nevertheless the agent seemed to perform particularly well in some poor prognosis groups such as those with liver and bone metastases.

As indicated the toxicity if this drug is well recognised and manageable by clinicians who work in this field.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Equality and Diversity

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- 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

There are no special issues here.

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.

No

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)?

There are no particular issues other than general capacity in the NHS.

Cabozantinib for previously treated advanced renal cell carcinoma

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 16/10/09

BMJ Technology Assessment Group

Cabozantinib for previously treated advanced renal cell carcinoma

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

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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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All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
AE	Adverse event
AFT	Accelerated failure time
AJCC	American Joint Cancer Committee
AIC	Akaike's Information Criteria
AICC	Corrected Akaike's Information Criteria
ASCO	American Society of Clinical Oncology
BEV	Bevacizumab
BIC	Bayesian Information Criteria
BNF	British National Formulary
BSC	Best supportive care
CDF	Cancer Drugs Fund
CEACs	Cost-effectiveness acceptability curves
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cochrane CENTRAL	Cochrane Central Register of Controlled Trials
CONSORT	Consolidated Standards of Report Trials
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse events
DIC	Deviance information criteria
DRS	Disease related symptoms
DSU	Decision Support Unit
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
ECX	Epirubucin combined with cisplatin and capecitabine
EMA	European Medicines Agency
EOL	End of life
EOX	Epirubicin combined with oxaliplatin and capecitabine

EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 dimension
ERG	Evidence review group
ES	Effect size
ESMO	European Society of Medical Oncology
EU	European Union
FDA	US Food and Drug Administration
FE	Fixed effects
FKSI	Functional Assessment of Cancer Therapy Kidney Symptom Index
GemCap	Gemcitabine and capecitabine
GP	General practitioner
HC	Health Centre
HR	Hazard ratio
HRQoL	Health related quality of life
HSUVs	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
ICUR	Incremental cost utility ratio
IFN	Interferon
IL2	Interleukin 2
IMDC	International Metastatic RCC Database Consortium
IPD	Individual patient data
IQR	Inter-quartile range
IRC	Independent radiology committee
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
kg	kilogram
KM	Kaplan-Meier
LLN	Lower limit of normal
LSMean	Least squares mean
LY	Life year
MA	Marketing authorisation
MAA	Marketing authorisation application

MCMC	Markov Chain Monte Carlo
MCBS	Magnitude of Clinical Benefit Scale
MET	Hepatocyte growth factor receptor protein
mg	Milligram
MIMS	Monthly Index of Medical Specialties
mOS	Median overall survival
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Centre
MTA	Multiple technology appraisal
mTOR	Mammalian target of rapamycin
NICE	National Institute for Health and Care Excellence
NCCN	National Comprehensive Cancer Network
NCPE	National Centre for Pharmacoeconomics
NE	Not estimable
NHS	National Health Service
NHS EED	National Health Service – Economic Evaluation Database
NMA	Network meta-analysis
NR	Not reported
ONS	Office for National statistics
ORR	Objective response rate
OS	Overall survival
OWSAs	One-way sensitivity analyses
OxMdG	Oxaliplatin, 5-Fluorouracil &. Folinic Acid
PCT	Primary care trust
PD	Progressed disease
PD-1	Programmed death 1
PenTAG	Peninsula Technology Assessment Group
PFS	Progression-free survival
PH	Proportional hazards
PITT	Primary endpoint intent-to-treat
PIM	Promising innovative medicine
PPES	Palmar-plantar erythrodysaesthesia syndrome
PPS	Post-progression survival

PR	Partial response
PSAs	Probabilistic sensitivity analyses
PSS	Personal Social Service
PSSRU	Personal and Social Services Unit
QALY	Quality adjusted life year
QoL	Quality of life
Q-Q	Quantile-quantile
RCC	Renal cell carcinoma
RDI	Reference daily intake
RCT	Randomised controlled trial
RE	Random effects
RECIST	Response Evaluation Criteria in Solid Tumours
RPSFT	Rank preserving structural failure time
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SMEEP	Survival Model Selection for Economic Evaluations Process
SOC	Standard of care
SR	Systematic review
SRE	Skeletal related events
SPC	Summary of product characteristics
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TRAE	Treatment related adverse events
TNM	Tumour, lymph node and metastases
TSE	Treatment side effects
TTD	Time to treatment discontinuation

TTP	Time to progression
TRAE	Treatment related adverse event
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGF	Vascular endothelial growth factor receptor
VEGF-TKI	Vascular endothelial growth factor tyrosine kinase inhibitor
VAS	Visual analogue scale
VHL	Von Hippel Lindau
WTP	Willingness to pay
ZOL	Zolendronic acid

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of cabozantinib, (CABOMETYX®; Ispen) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of cabozantinib in the treatment of people who have received previous vascular-endothelial growth factor (VEGF)-targeted therapy for advanced renal cell carcinoma (RCC).

In 2016, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of cabozantinib following an accelerated review as a result of it being granted Promising Innovative Medicine (PIM) status. Marketing Authorisation was granted on 9 September 2016 for the use of cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior VEGF-targeted therapy.

The clinical evidence presented in the company's submission (CS) for cabozantinib is derived from the METEOR phase III randomised controlled trial. METEOR compared cabozantinib with everolimus in patients with advanced clear-cell renal cell carcinoma, who had been previously treated with at least one VEGF-TKI (tyrosine kinase inhibitor). The final scope issued by NICE specified the population of interest to be people who have received previous VEGF-targeted therapy for advanced renal cell carcinoma. The evidence review group (ERG) notes that over 70% of patients in METEOR had only received one prior VEGF-TKI and the remaining patients had received 2 or more prior VEGF-TKIs. The ERG considers the population in METEOR to be relevant to the decision problem.

The comparator in METEOR was everolimus. In the final scope issued by NICE, the comparators of interest were identified as axitinib, everolimus, nivolumab and best supportive care (BSC). All comparators were considered in the CS and are in keeping with those currently used in UK clinical practice.

All clinically relevant outcomes were reported in the CS for the comparison of cabozantinib with everolimus. However, the ERG notes the omission of treatment related adverse events (TRAEs) reporting from METEOR in the CS and that comparison of HRQoL, response rates and adverse effects for cabozantinib and axitinib, nivolumab or best supportive care are not presented in the CS. In addition, the ERG notes that the long term safety and efficacy of cabozantinib cannot be assessed from the data that are currently available.

The company also provided subgroup data by type of prior VEGF-TKI therapy, number of prior VEGF-TKI therapies, baseline Heng score and baseline MSKCC scores from METEOR as requested in the NICE final scope albeit for limited outcomes (PFS and OS only).

1.2 Summary of clinical effectiveness evidence submitted by the company

In METEOR, 658 patients were randomised (330 to cabozantinib, 328 to everolimus), to receive open-label cabozantinib 60mg orally once daily or 10mg everolimus orally once daily. A total of 564 patients (85.7%) discontinued treatment with uneven dropout rates between the treatment groups (257 [78%] patients in cabozantinib group, 297 [91%] patients in the everolimus group). The main reason for discontinuation was disease progression (64% vs 58%; cabozantinib group and everolimus group, respectively).

The baseline characteristics appeared to be well balanced between trial groups and the trial population was considered broadly representative of patients seen in current UK clinical practice. Although METEOR contained a high proportion of patients with an ECOG performance status of 0 (67%), which would be reflective of the fitter patients found in current practice.

For the primary outcome PFS, the use of the primary end point intention to treat analysis (PITT), which comprised the first 375 patients randomised and was pre-specified (for statistical reasons), has limited use with regards to decision-making as opposed to the full ITT population. The statistical analyses carried out were appropriate for the secondary outcomes, PFS, OS and ORR using an intention to treat analysis (ITT). Due to limited head-to-head data, comparisons between key comparators were determined using indirect evidence from a survival curve-based NMA.

PFS in METEOR was statistically significantly longer with cabozantinib compared to everolimus and the median PFS was 7.4 months vs 3.8 months, respectively (HR 0.58; 95% CI: 0.45 to 0.75; p-value <0.001). A similar clinical benefit to that observed for PFS in the PITT population of METEOR was also observed in the ITT population (HR 0.51; 95% CI: 0.41 to 0.62; p<0.0001). Cabozantinib was associated with a statistically significantly longer median overall survival (OS) of 4.9 months compared to everolimus (HR 0.66; 95% CI: 0.53 to 0.83; p=0.00026). The median OS was 21.4 months (95% CI: 18.7 to not estimable) in the cabozantinib group and 16.5 months (14.7 to 18.8) in the everolimus group.

The objective response rate (ORR) was also statistically significantly higher with cabozantinib (17%; 95% CI 13 to 22) compared with everolimus (3%; 95% CI 2 to 6; (as per independent radiology review committee assessment [IRC])). In terms of HRQoL, the FKSI-19 total score estimated mean change from baseline was similar for cabozantinib compared with everolimus (-3.48 and -2.21, respectively) and no clinically significant treatment difference in EQ-5D score between cabozantinib and everolimus.

OS was consistently longer with cabozantinib compared with everolimus irrespective of the number of prior VEGF-TKIs or the duration since first treatment with a VEGF-TKI. In terms of prognostic score, the ERG considers the results to be more inconclusive because they weren't statistically significant,

although the HRs do suggest a trend favouring cabozantinib over everolimus in terms of improving OS irrespective of baseline MSKCC or Heng risk category.

The proportion of patients experiencing an adverse event (AE) was the same for both the cabozantinib and everolimus treatment groups (92%) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%). The most common TEAEs of any grade in the cabozantinib group compared with the everolimus group were diarrhoea (75% vs 28%), fatigue (59% vs 47%) and nausea (52% vs 30%). The company reported that the majority of the TEAEs were managed through study drug dose reductions. The TEAEs that were most likely to lead to permanent discontinuation of cabozantinib were reported to be decreased appetite and fatigue. The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus) and fatigue (11% vs 7%, cabozantinib vs everolimus).

The company conducted a survival curve-based network meta-analysis (NMA) due to the absence of head-to-head trials comparing cabozantinib with axitinib, nivolumab, and BSC in patients with advanced RCC who have progressed after previous VEGF-TKI treatment. There were five trials included in the NMA: METEOR, AXIS, Checkmate 025, RECORD-1 and TARGET. They were all RCTs although there were differences between the trials in terms of the presence/absence of cross-over design, number and type of prior therapies, and baseline prognostic scores.

The results of the NMA suggest that cabozantinib prolongs OS and PFS compared to axitinib, BSC (represented by placebo), everolimus and nivolumab. The ERG has concerns that the company's NMA results were unreliable as a result of the heterogeneity of the trials included in the network, the lack of cross-over free OS data for TARGET and the use of immature OS data for TARGET. The ERG is particularly concerned about the overall survival estimate for axitinib generated by the company NMA as it is only linked into the network via TARGET. TARGET was a placebo-controlled trial and if it is assumed that sorafenib is likely to be more effective than placebo; utilising immature survival data is likely to underestimate the benefit of sorafenib over placebo. The results of AXIS show similar efficacy for axitinib and sorafenib and so the potential underestimating of OS in TARGET means that the survival benefit for axitinib will similarly be underestimated in the company's NMA.

1.3 Summary of cost effectiveness evidence submitted by the company

The company submitted a *de novo* economic model developed using Microsoft Excel® that evaluated cabozantinib in two separate cost-utility analyses. The first was a trial-based analysis comparing cabozantinib with everolimus, using effectiveness data obtained solely from the METEOR trial.[1] The second analysis compared cabozantinib with everolimus, axitinib, nivolumab and best supportive care (BSC) as pairwise comparisons, and the effectiveness data was derived from a network meta-analysis

(NMA) based on trials identified in a systematic review of the literature, to estimate the parameters of independently fitted parametric survival curves.[2-5] No subgroup analyses were provided initially to estimate the cost effectiveness of cabozantinib at second-line and third-line separately. A second-line subgroup analysis was provided at the clarification stage but the subgroup data were not available for all trials in the network.

The two analyses used the same partitioned survival model structure, with three health states: progression-free; progressed disease; and death. All patients entered the model in the progression-free state and could transition to progressed disease or death at each of the four-weekly model cycles. From the progressed disease state, patients could transition to the death state at each future cycle. The model had a time horizon of 30 years, which was deemed sufficient to capture the lifetime of almost all patients in the model, and the four-week duration of the model cycles was justified as the duration of treatment follow-up. Annual discount rates of 3.5% were applied to both costs and QALYs in the model, and the National Health Service (NHS) and Personal Social Services (PSS) perspective was adopted for costs, in line with the NICE reference case.[6]

For the METEOR trial-based economic evaluation, the proportion of patients in each health state at any given model cycle was estimated by fitting and extrapolating parametric survival curves to Kaplan-Meier (KM) data for progression-free survival (PFS) and overall survival (OS) for each group in the METEOR trial. [1] These curves were fitted independently and assessed using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for goodness-of-fit. A visual inspection and clinical expert opinion were also used by the company as a validation of the curves.

For OS, the company chose to use the log-logistic distribution for each group, which provided the best fitting curve to the cabozantinib data but was only the second best fit for the everolimus data. The Weibull provided the best fit to the everolimus data but the company chose to use the same distribution for both groups, as recommend by the NICE DSU Technical Support Document 14.[7] For PFS, the log-logistic distribution was also used for each group, as it provided the best fit to the cabozantinib group, while the best fit for the everolimus group was the log-normal distribution.

Time to treatment discontinuation (TTD) data were used to estimate the acquisition costs of the active treatment as well as the time at which subsequent treatments were applied in the model. Parametric survival curves were used to estimate and extrapolate KM data for TTD in each group of the METEOR trial in the same way as for PFS and OS. The log-normal distribution was chosen as the best fitting curve.

For the NMA-based economic evaluation, the estimation and extrapolation of parametric survival curves was based on regenerated KM data from the CheckMate 025, AXIS, RECORD-1 and TARGET

trials, as well as the KM data from METEOR.[1-5] The NMA estimated the parameters of independently fitted survival curves for each group in each trial in the network, and adjusted the parameters to the everolimus group of the METEOR trial. A single family of distributions was fitted to each group in each trial and the goodness-of-fit of the parametric survival curves for both PFS and OS was assessed using the Deviance Information Criterion (DIC). This provided a global measure of fit and did not indicate the goodness-of-fit of a particular curve to the KM data of a particular trial group. Visual inspection and clinical expert opinion were also used to determine the most appropriate parametric curves to use. The company deduced that the log-normal provided the best fit for both OS and PFS, and this was used in the company's base case for the curves of each comparator.

The TTD data for the trials in the network were also included in the NMA to estimate and extrapolate using fitted parametric survival curves. The regenerated KM data from the trials was used in the same way as for PFS and OS, to estimate the parameters of the best fitting curve and adjust them to the everolimus group of METEOR. KM data for axitinib were not available so PFS data were used as a proxy for TTD.

Across the two analyses, the acquisition cost of each treatment was based on its marketing authorisation. Relative dose intensities were applied to estimate the true cost of the treatments compared, and were taken from the respective trial data. Management costs were estimated by health state and were based on the expert clinician opinion of oncologists practising in the UK. Nivolumab is the only treatment that is administered intravenously, with all other comparators being oral, therefore, it incurred additional costs of equipment and staff costs for monitoring. Wastage of nivolumab was not assumed in the model but was incorporated into the model design as an option. Costs related to adverse events were limited to those events that occurred in 5% of patients in each group of the relevant trials. Treatment-emergent adverse events (TEAEs) were used, with the exception of nivolumab, which used treatment-related adverse events due to a lack of data.

Health state utility values were estimated using EQ-5D-5L data from the METEOR trial in a regression analysis, including the effect of adverse events (AEs) as a variable to derive an AE related disutility. These utilities were estimated and applied across both the trial-based and NMA-based economic analyses.

A range of one-way sensitivity analyses and scenario analyses were performed as well as a probabilistic sensitivity analysis to test the impact of uncertainty of all relevant parameters on the model results.

The results of the company's corrected base case in the trial-based model showed that the incremental cost of using cabozantinib compared to everolimus was [redacted] with an incremental QALY gain of [redacted] This resulted in an incremental cost effectiveness ratio (ICER) of [redacted].

For the NMA-based model, the company's corrected base case showed increased incremental costs of [redacted]; and £[redacted], for cabozantinib compared to axitinib, everolimus and best supportive care (BSC), respectively. For the comparison with nivolumab, cabozantinib showed an overall cost saving of £[redacted]. The incremental QALY gain for cabozantinib was [redacted], [redacted], [redacted] and [redacted] QALYs compared to axitinib, everolimus, BSC and nivolumab respectively, resulting in ICERs of £[redacted]; £[redacted]; and £[redacted] compared to axitinib, everolimus and BSC respectively. Nivolumab was dominated by cabozantinib due to the lower cost and positive QALY gain.

The ERG provided some additional analyses around the company's model and produced their own preferred base case analysis. The results of the trial-based and NMA-based ERG preferred base case are summarised in Table 1 and Table 2, respectively.

Table 1: ERG's base case ICER – trial based analysis

Results per patient	Cabozantinib	Everolimus	Incremental value
Company (corrected) base case			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
Weibull distribution for OS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER (with all changes incorporated)			[redacted]
HSUV's from AXIS trial			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER (with all changes incorporated)			[redacted]
GP costs excluded			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER (with all changes incorporated)			[redacted]
ERG preferred base case ICER			[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PH, proportional hazards; HSUV, health state utility value; GP, general practitioner; ERG, evidence research group.

Table 2: ERG's base case ICER – NMA based analysis

Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Nivolumab (5)	Incremental value (1-2)	(1-3)	(1-4)	(1-5)
Company (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						[redacted]	[redacted]	[redacted]	[redacted]
PH assumption for OS									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
HSUV's from AXIS trial									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab wastage included									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
GP costs excluded									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred base case ICER						[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PH, proportional hazards; HSUV, health state utility value; GP, general practitioner; ERG, evidence research group.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

- The ERG considers METEOR to be a well-designed and conducted trial, and is of the view that the trial is reflective of English clinical practice, although METEOR contained a high proportion of patients with an ECOG performance status of 0 (67%) which would be reflective of the fitter patients found in current practice.

- Safety and clinical efficacy results of METEOR are relevant to the decision problem as outlined in the NICE final scope for this STA and those considered by the ERG's clinical experts to be the key ones for patients with advanced RCC.

- All relevant comparators as specified in the NICE final scope for this STA were considered within the CS.

- Cross-over is always a problem in assessing OS in clinical trials and is a problem in RECORD-1 and TARGET included in the company's NMA. However, for one of the studies, RECORD-1 cross-over adjusted OS data using the rank-preserving structural failure time (RPSFT) model published by Korhonen *et al.* 2012 were used in the NMA to minimise bias introduced by the cross-over effect.

Economic

- The economic evaluation was well presented, with the inputs and assumptions reported clearly in the CS. The electronic model design was sound, and the ERG did not encounter any major difficulty to check and confirm that the methodologies were applied as stated in the CS and correctly implemented in the model. The company conducted an appropriate range of scenario analyses.

1.4.2 Weaknesses and areas of uncertainty

Clinical

- The open label design of METEOR maybe a potential source of bias particularly, for subjective outcomes including HRQoL (where patients in the cabozantinib group may have overestimated

their HRQoL). The company states that it was open label to, "allow appropriate management of adverse events". The ERG considers that management of adverse events through dose reductions is common practice in clinical trials and that this could have been done while maintaining blinding to the treatments in METEOR.

- There was an omission of TRAEs reporting from METEOR in the CS. In addition, comparison of HRQoL, response rates and adverse effects for cabozantinib and axitinib, nivolumab or best supportive care were not presented in the CS.

- The ERG does not consider the METEOR trial level data for the subgroup of people with two or more prior VEGF-TKIs to address the NICE decision problem for the potential third line positioning of cabozantinib in the advanced RCC treatment pathway. This is because the comparator in METEOR is everolimus and the ERG's clinical experts report it is mainly used at second line and infrequently, if at all at third line. The ERG therefore consider the key comparator's for cabozantinib at third line to be BSC and nivolumab.

- The ERG does not consider the company to have provided suitable subgroup data by line of therapy for the comparison of cabozantinib with the axitinib, nivolumab and BSC in the NICE final scope for the potential second or third line positioning of cabozantinib. This is because the comparator trials used in the NMA for second line cabozantinib contained patients with varying numbers of prior VEGF therapies and so were not the same population as the METEOR subgroup (i.e. second line patients). The company provided no analysis for the third line position.

- The ERG has concerns that the company's NMA results may be unreliable as a result of the heterogeneity of the trials included in the network, the lack of cross-over free OS data for TARGET and the use of immature OS data for TARGET. The ERG is particularly concerned about the overall survival estimate for axitinib generated by the company NMA as it is only linked into the network via TARGET and thus it is likely to be underestimated. In addition, the ERG considers that the impact of subsequent active treatments in AXIS is highly likely to bias the estimated treatment effect for OS, with differences between treatment groups in OS likely to be minimised as a result.

Economic

- For the trial-based economic evaluation, the company did not consider the Weibull as an alternative distribution for OS in each group. Applying the Weibull distribution would avoid the extended and potentially unrealistic tail in the resulting survival curve when using a log-logistic distribution, and would also be in line with the log-cumulative hazard plots that the

company provided, showing linearity between log-cumulative hazard and log time for each group in the METEOR trial. The lack of consideration of the Weibull was found to be a key source of uncertainty by the ERG. A similar issue was seen in the estimation and extrapolation for PFS curves; however, the impact on the results was considered by the ERG to be less of a concern.

- For the NMA-based model, the key weakness was the poor fit of the estimated survival curves for PFS and OS because of the limitations of the NMA methods adopted. As only a single family of parametric curves was used for all comparators, and the goodness-of-fit being assessed to the model globally, the estimation and extrapolation of PFS and OS in the NMA-based model are potentially unreliable and could cause unrealistic differences in the inherent treatment effect as determined by the resultant independent curves. This unreliability is propagated through the network when adjusted to the everolimus group of the METEOR trial and so the unreliability is potentially compounded for axitinib, which is dependent on the fitted curves for AXIS, TARGET and RECORD-1.[2, 4, 5]

- For both models, the resource costs were considered to be unrealistic of UK clinical practice by the ERG based on clinical expert opinion. In particular, the GP visit was not considered to be incurred for these patients, as they would be managed by the consultant oncologist. The costs of nivolumab in the NMA-based model were also considered to be unreflective of practice as wastage of vials was not included in the model.

- The ERG's clinical experts also believed that the utility values used were unrealistic and did not reflect the health states of patients in a real-world setting. When presented with alternative values from current NICE appraisals in renal cell carcinoma, the values used in TA333 were considered a better reflection.

- The acquisition cost of the comparators does not reflect the actual cost to the NHS as these do not incorporate the patient access schemes under which the drugs are approved on the NHS. This means that the ICERs are likely to be considerably underestimated.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

Clinical

The ERG consider that the impact of not using mature and crossover-free OS data for TARGET and not adjusting for subsequent active treatments in AXIS is likely to minimise the OS estimate for axitinib in the network. The ERG's clinical experts reported that they would expect similar if not slightly better

efficacy with axitinib when compared to everolimus and so the ERG conducted a conservative exploratory analysis to explore the impact of assuming axitinib and everolimus have equal efficacy. This analysis enables the exclusion of TARGET from the NMA as it is no longer required to provide a link between axitinib and the other comparators. However, based on clinical advice, the assumption of equal efficacy to everolimus could potentially under-estimating the efficacy of axitinib. The remaining comparators in the ERG's NMA were: cabozantinib, nivolumab, placebo and everolimus.

The results of the ERG's NMA show a similar treatment ranking to that seen in the company's NMA with cabozantinib having the lowest HR for OS and cabozantinib is associated with a statistically significant increase in OS (HR 0.65; 95% Credible Interval [CrI] 0.527 to 0.825). The estimated median PFS and OS based on the ERG's NMA are generally in keeping with those estimated from the company's NMA.

Economic

The ERG performed a limited number of scenario analyses around the company's corrected base case for both the trial-based model and the NMA-based model. These were around the estimate and extrapolation of survival cures for PFS and OS; health state utility values used in the model; and resource use included in the overall costs.

The following changes were made to both models, after consulting with clinical experts in renal cell carcinoma:

- Changing health state utility values to those from TA333;
- Removing the GP cost applied to the management of patients.

For the trial-based model, the OS survival curves were changed to the Weibull distribution as this was the best fitting curve to the everolimus group, and log-cumulative hazard plots indicated linearity between log-cumulative hazard and log time; a characteristic of the Weibull distribution.

For the NMA-based model, the OS curves were regenerated based on a hazard ratio (HR) based NMA performed by the ERG to estimate the HR for OS, for cabozantinib, nivolumab and BSC compared to everolimus. The HR for axitinib compared to everolimus was assumed to be equal to one due to concerns the ERG have about the company's NMA potentially underestimating survival with axitinib. The company's NMA included the TARGET trial (sorafenib vs placebo) as a link to the AXIS trial (axitinib vs sorafenib) but the OS results from TARGET are potentially confounded by patient cross-over. The TARGET trial also showed that the hazards between the two groups were not proportional, but this may have been a result of the confounding. The ERG's clinical experts consider that assuming

the same OS for axitinib as that for everolimus would result in a conservative estimate of the ICER, as axitinib is deemed to be more effective than everolimus in clinical practice. These HRs were applied to the independently fitted Weibull curve that the company derived for the everolimus group of the METEOR trial. The NMA-based model also included wastage for nivolumab, which was excluded in the company's base case.

All these changes were incorporated into the ERG's preferred base case for each of the two analyses presented by the company. For the trial-based model, the ERG's preferred base case resulted in an increased ICER of £[redacted] per QALY compared to the company's corrected base case ICER of £[redacted]. For the NMA-based model, the ERG's base case resulted in ICERs of £[redacted]; £[redacted]; and £[redacted] for cabozantinib compared to axitinib, everolimus and BSC, respectively. These results show increased ICERs compared to the company's corrected base case ICERs of £[redacted]; £[redacted]; and £[redacted], respectively. Cabozantinib remained dominant compared to nivolumab in the ERG's preferred base case.

The ERG also performed a number of scenario analyses around the ERG's preferred base cases. For the trial based model, the OS curves were changed to the log-logistic curves derived by the company and this reduced the ICER to £[redacted] compared to the ERG's preferred base case ICER of £[redacted].

The ERG also changed the OS curves to the curves used in the NMA-based ERG base case using the company's Weibull curve for the everolimus group of METEOR and applying the ERG's HR for cabozantinib. This resulted in an ICER of £[redacted]. An additional result was estimated using this change and the same change for the PFS curves. This resulted in an ICER of £[redacted].

For the NMA-based model, the only scenario tested on the ERG's preferred base case was the use of the proportional hazard curves for PFS, applied in the same way as the OS curves in the base case. This change resulted in ICERs of £[redacted]; £[redacted]; and £[redacted], compared to axitinib, everolimus and BSC respectively, compared to the ERG's preferred base case ICERs of £[redacted]; £[redacted]; and £[redacted]. Cabozantinib remained dominant compared to nivolumab as per the ERG's preferred base case.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 3 of the company submission (CS) provides an overview of the key aspects of renal cell carcinoma (RCC). The Evidence Review Group (ERG) notes the population outlined in the National Institute for Health and Care Excellence (NICE) Final Scope[8] is people who have received previous VEGF-targeted therapy for advanced RCC. The ERG notes that the definition of advanced RCC also often includes metastatic RCC. The ERG will thus use the term advanced RCC to refer to both advanced and metastatic RCC in this report.

The ERG considers the information presented in Section 3 of the CS to be relevant to the NICE Final Scope[8] and generally comprehensive and well written.

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.

The company's overview of RCC is presented in Box 1. The ERG notes that RCC is the most common type of kidney cancer in adults in the UK.[9]

Box 1. Overview of RCC (Adapted from CS, page 25, Section 3.1)

Renal cell carcinoma (RCC) is the collective name for a group of cancers that originate in the kidney within the epithelium of the proximal renal tubules. It accounts for approximately 80% of kidney cancer cases.[10]
There are several distinct histological subtypes of RCC, with clear cell RCC the most common subtype accounting for 75% of cases.[9, 11]
Abbreviations: RCC, renal cell carcinoma.

There are numerous risk factors thought to be associated with kidney cancer as well as known hereditary syndromes. According to cancer statistics reported by Cancer Research UK, kidney cancer is more common in older people and men.[12] An overview of the aetiology and other key risk factors associated with kidney cancers is presented in Box 2.

Box 2. Aetiology of RCC (Adapted from CS, page 25, Section 3.1)

RCC exists in both sporadic and hereditary forms. Approximately 2% to 3% of RCC are hereditary and several autosomal dominant syndromes are described, each with a distinct genetic basis and phenotype, the most common one being Von Hippel Lindau (VHL) disease.[10]
Although the aetiology and risk factors for sporadic RCC are not completely understood, several risk factors have been identified. Of these, smoking, obesity and hypertension are the most well-established risk factors.[10, 12] In the UK, an estimated 42% of kidney cancers are linked to lifestyle factors including smoking (24%) and overweight and obesity (24%).[12]

Additional risk factors include end-stage renal disease, acquired cystic kidney disease, tuberous sclerosis and viral hepatitis, as well as environmental and occupational factors, such as use of analgesics, paracetamol and non-aspirin non-steroidal anti-inflammatory drugs, and exposure to asbestos.[13, 14]

Abbreviations: RCC, renal cell carcinoma; UK, United Kingdom; VHL, Von Hippel Lindau.

There are several different disease staging classification tools for RCC although the ERG's clinical experts agree with the company that the Tumour, Lymph Node and Metastases (TNM) staging is one of the most commonly used ones in England. In addition, kidney cancer maybe classified by stage using a number grading system from I to IV, with stage IV being the most advanced disease with spread outside of the kidney.[15] In addition, kidney cancer maybe classified by grading using the Fuhrman system (1 = well-differentiated; 2 = moderately-differentiated; 3 and 4 = poorly-differentiated) based on nuclear size, outline and nucleoli.[16] The ERG's clinical experts report that staging is an important prognostic indicator for RCC. In 2014, 35.9% of all cases of kidney cancer in England were stage III or IV at diagnosis and 18.3% were recorded as stage unknown at diagnosis.[17] The symptoms of RCC vary as expected according to the disease stage. Symptoms of advanced RCC may be related to the metastatic spread of the disease rather than the primary tumour. Box 3 provides an overview of the TNM disease staging tool and the symptoms associated with RCC.

Box 3. Disease staging and symptoms (Adapted from CS, page 26, Section 3.1)

Disease staging

RCC is divided into stages that describe how widespread the disease has become. Within the UK, the most commonly used staging system is the American Joint Cancer Committee (AJCC) Tumour Node Metastasis (TNM) system which classifies the size of the tumour (T), the involvement of regional lymph nodes (N) and the presence of distant metastases (M).

Symptoms

RCC is divided into stages that describe how widespread the disease has become. In the early stages of the disease RCC is relatively asymptomatic and often detected incidentally during medical investigation for other conditions.[10] Advanced RCC includes both locally advanced RCC that cannot be removed by surgery and metastatic RCC.

Due to the often indolent course of RCC, patients typically present with advanced disease. Approximately 35% of patients present with metastatic disease at initial diagnosis[18] and up to 40% of patients develop metastasis after surgery for initially localised disease.[19]

Metastatic symptoms frequently include airway obstruction, venous thromboembolism, bone pain, skeletal-related events (SREs) and hypercalcaemia[19] imposing significant morbidity and poor prognosis.

The symptoms of advanced disease and the generally poor prognosis for patients with advanced RCC can also significantly impact on all domains of patient health-related quality of life (HRQoL) including physical and psychosocial function.[20]

Abbreviations: AJCC, American Joint Cancer Committee; HRQoL, health-related quality of life; RCC, renal cell carcinoma; SRE's, skeletal-related events; TNM, Tumour Node Metastasis.

Box 4 provides an overview of the goals of treatment in advanced RCC and some of the treatment options currently available to patients. These will be discussed in more detail in relation to the NICE final scope in Section 3.

Box 4. Treatment for advanced RCC (Adapted from CS, page 28, Section 3.3)

There is no cure for advanced RCC and the goals of treatment are to extend life and delay disease progression while relieving physical symptoms and maintaining function.[21]

Advanced RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. The elucidation of the pathogenesis of RCC has played a key role in the development of targeted therapies focused on two pathways that are commonly de-regulated in RCC: the VEGF pathway which is targeted by tyrosine kinase inhibitors (TKIs) such as axitinib, sunitinib and pazopanib, and the mammalian target of rapamycin (mTOR) pathway which is targeted by mTOR inhibitors such as everolimus. More recently, nivolumab a programmed death 1 (PD-1) immune checkpoint inhibitor has become available for the treatment of RCC after prior therapy.

Abbreviations: mTOR, mammalian target of rapamycin; PD-1, programmed death 1; RCC, renal cell carcinoma; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

Prognosis of advanced RCC can be estimated using various scoring systems. A summary of the commonly used tools is provided in Box 5. The ERG notes that "survival for kidney cancer is related to stage of the disease at diagnosis"[22] but considers the company's report that median survival based on the Heng criteria varies from 5 months to 3 years, is an underestimate. The ERG are unable to validate the data in the citation used by the company in support of this. Cancer research UK[22] report 2014 data from the Office for National statistics (ONS)[23] that shows that 95% of kidney cancer patients diagnosed at stage I survived their disease for at least one year, versus 37% patients diagnosed at stage IV. The ERG notes that Heng *et al* 2009[24] reported median overall survival (mOS) was not reached in the favourable-risk group, but was 27.0 and 8.8 months in the intermediate-risk and poor-risk groups, respectively. Procopio *et* al[25] also reported similar data in 2012 although they used the Motzer staging classification for high, intermediate and poor risk (mOS was 43, 21 and 8 months for favourable-, intermediate- and poor-risk groups, respectively). The ERG acknowledges the limitation of comparing the Procopio *et al*[25] and Heng *et al*[24] data and considers it important to highlight that the data should be interpreted with caution as different risk classification systems were used, so patients in each group may differ slightly. However, they both suggest that the poor risk group have a mOS of around 8 months rather than 5 months.

Box 5. Prognosis of RCC (Adapted from CS, page 27, Section 3.2)

There are two main scoring systems used to specifically assess prognosis in individual patients with advanced RCC: the Memorial Sloane Kettering Cancer Centre (MSKCC) score and a slightly

modified version, known as the International Metastatic RCC Database Consortium (IMDC) or Heng criteria.[10]

Survival is dependent on the stage of the disease and the relative 5-year survival rate for advanced RCC is approximately one in ten.[8, 26] Using the Heng criteria to assess patient risk the median OS for patients with advanced RCC ranges from approximately 5 months (high risk patients) to 3 years (favourable risk patients).[18]

Abbreviations: IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloane Kettering Cancer Centre; OS, overall survival; RCC, renal cell carcinoma.

2.1.1 Epidemiology

The company provided an overview of the incidence of kidney cancer in the UK (Box 6) but the ERG notes that this is not specific to RCC. However, as reported above, RCC is the most common type of kidney cancer in adults in the UK.[9] The ERG also notes that published UK data for the incidence of advanced RCC are limited. The ERG considers that Ko *et al*.[27] have been incorrectly cited as the source of the statement, "In the UK, kidney cancer incidence rates have increased by 38% over the last decade, with a greater increase evident in females (40%) than in males (35%)" (Box 6). However, the ERG notes that these data are reported on the cancer research UK website.[18]

Box 6. Company's overview of the incidence and prevalence of kidney cancer in the UK (Adapted from CS, page 27, Section 3.2)

In the United Kingdom (UK) in 2013, there were 11,873 new cases of kidney cancer, making kidney cancer the seventh most common cancer in the UK and accounting for 3% of all new cancer cases. Overall in the UK in 2014, there were 4,421 deaths due to kidney cancer, the thirteenth most common cause of cancer-related deaths in the UK.[12]

In the UK, kidney cancer incidence rates have increased by 38% over the last decade, with a greater increase evident in females (40%) than in males (35%).[27] There is a higher incidence in men than in women (1.5:1), with a peak in incidence rates between the ages of 60 and 70 years.[14]

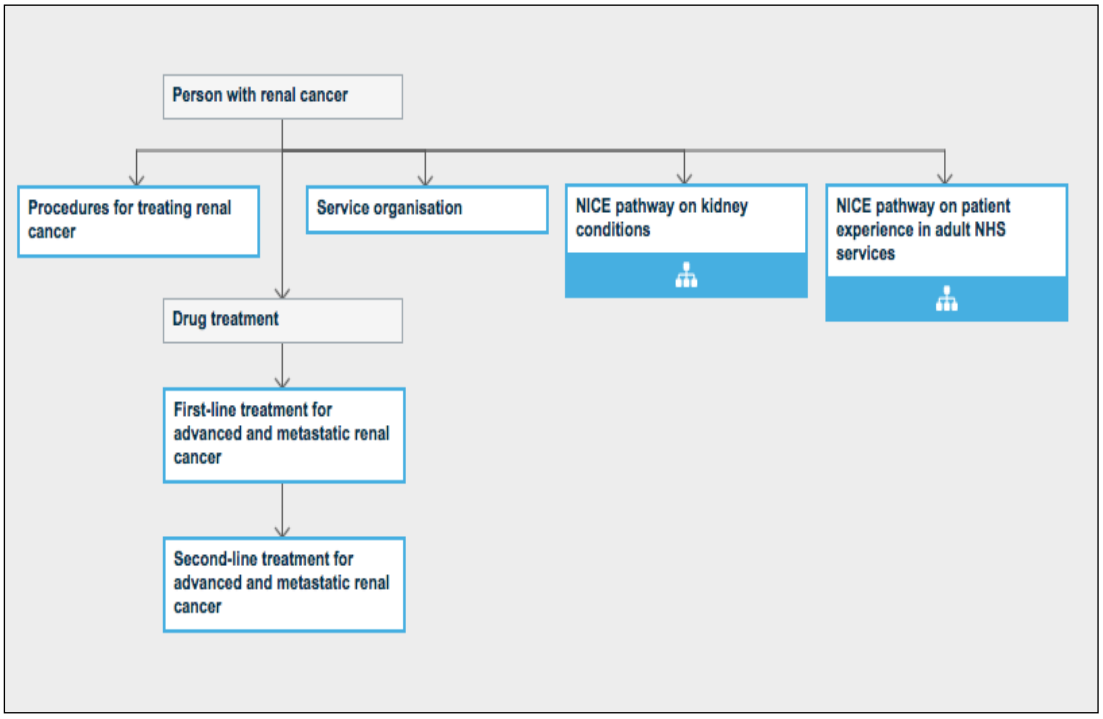
With an ageing population and increasing prevalence of risk factors such as obesity, the burden of advanced RCC is predicted to increase.[20]

Abbreviations: RCC, renal cell carcinoma; UK, united kingdom.

2.2 Critique of company's overview of current service provision

The ERG and its clinical advisors agree with the company's report that there are no current up-to-date UK specific treatment guidelines for advanced RCC and the UK treatment pathway is thus based on a combination of international guidelines, NICE recommendations and the availability of medicines via the Cancer Drugs Fund (CDF). There is a NICE pathway for renal cancer although it only covers first and second line treatment options (Figure 1).

Figure 1. NICE pathway for renal cancer[28]



Abbreviations: NHS, national health service; NICE, National Institute for Health and Care Excellence.

The recommended first and second line drug treatment options in the NICE treatment pathway for renal cancer are summarised in Box 7. The available first line options considered by NICE are pazopanib, sunitinib, bevacizumab, sorafenib and temsirolimus, of which the latter 3 drugs are not recommended by NICE. Axitinib, everolimus, sorafenib and sunitinib are the available treatment options considered for second line and the latter 2 drugs are not recommended for use by NICE. However, the ERG notes that everolimus is currently undergoing review by NICE in the cancer drugs fund (CDF) rapid reconsideration process (GID-TA10057), with guidance expected to be published in March 2017.[29]

Box 7. Company's summary of the NICE recommendations for first and second line therapy of advanced and metastatic RCC (Adapted from CS, pages 29–30, Section 3.3.1)

In summary NICE recommends:

- Sunitinib or pazopanib for the first-line treatment of patients with advanced and /or metastatic RCC with an ECOG performance status of 0 or 1 (TA169[30] and TA215[31])
- Axitinib for use in patients with advanced RCC after failure of treatment with a first-line TKI or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme (TA333[32]).

While everolimus is not recommended by NICE (TA219[33]), it is available via the Cancer Drugs Fund (CDF) for:

- People with RCC who have had prior treatment with only one previous TKI, and

• Patients contraindicated to second line axitinib or excessive toxicity to axitinib necessitating discontinuation of axitinib within three months of starting therapy and at which time there is no evidence of disease progression. Everolimus is subject to ongoing NICE CDF transition review [ID1015]. A NICE single technology appraisal (STA) of nivolumab for previously treated advanced RCC is ongoing (as of 11 October 2016) [NICE GID-TA10037] with guidance anticipated November 2016.[34]
Abbreviations:CDF, cancer drugs fund; ECOG, Eastern Cooperative Oncology Group; NICE, National Institute for Health and Care Excellence; RCC, renal cell carcinoma; STA, single technology appraisal; TKI, tyrosine kinase inhibitor.

At the time the company submitted for this STA, the STA of nivolumab for previously treated advanced RCC was still ongoing (GID-TA10037). However, on 21st October 2016 NICE released the final appraisal determination (FAD) for nivolumab[35] and the technology appraisal guidance (TA417)[36] was published on 23rd November 2016. The NICE technology appraisal guidance reports that nivolumab is recommended by NICE, 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. This means that nivolumab is a NICE recommended second and third line treatment option for advanced RCC.

Table 3 provides a summary of the published NICE technology appraisal guidance for both first and second line treatment of advanced RCC. Table 3 does not include nivolumab as the final guidance hadn't been published at the time of the CS for this STA. However, as described above, NICE has since approved Nivolumab for use in RCC (TA417).[36] In addition, everolimus is currently undergoing further review by NICE in the cancer drugs fund (CDF) rapid reconsideration process (GID-TA10057), with guidance expected to be published in March 2017.[29]

Table 3. Company's summary of related NICE technology appraisal guidance (Adapted from CS, page 30)

Date guidance issued	TA no.	Technology	Recommendation
February 2015	TA333[32]	Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment	Axitinib is recommended for use after failure of treatment with a first-line TKI or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme.
April 2011	TA219[33]	Everolimus for the second-line treatment of advanced renal cell carcinoma	Everolimus is not recommended for the second-line treatment of patients with advanced RCC
February 2011	TA215[31]	Pazopanib for the first-line treatment of advanced renal cell carcinoma	Pazopanib is recommended as a first-line treatment option for patients with advanced RCC who had not received prior cytokine therapy and with an ECOG performance status of 0 or 1 if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the patient access scheme

August 2009	TA178[37]	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	Bevacizumab, sorafenib or temsirolimus are not recommended for first line treatment Sorafenib or sunitinib are not recommended for the second-line treatment of advanced and/or metastatic RCC
March 2009	TA169[30]	Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma	Sunitinib is recommended for the first-line treatment of advanced and/or metastatic RCC in patients who are suitable for immunotherapy and with an ECOG performance status of 0 or 1
Abbreviations: ECOG, Eastern Cooperative Oncology Group; RCC, renal cell carcinoma; TA, technology appraisal; TKI, tyrosine kinase inhibitor.			

The guidelines that are frequently used to inform the treatment pathway for advanced RCC in England include:

- European Society of Medical Oncology (ESMO) Renal Cell Carcinoma: Clinical Practice Guidelines for diagnosis, treatment and follow-up (2016);[10]
- European Association of Urology (EAU) Renal Cell Carcinoma Guidelines (2016);[38]
- National Comprehensive Cancer Network (NCCN; USA) clinical practice guidelines in oncology, kidney cancer 2017.[39]

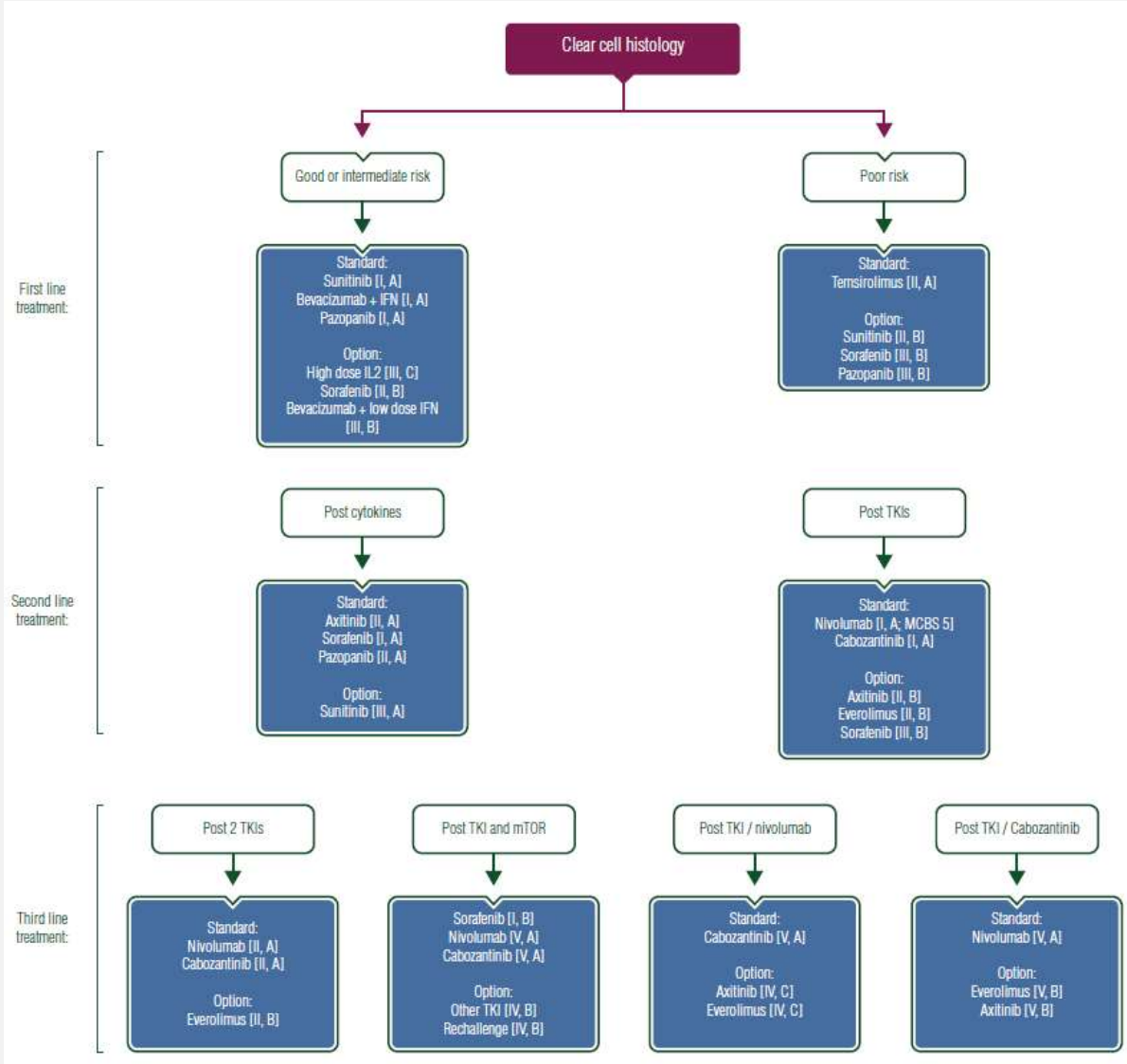
These guidelines all incorporate recommendations for cabozantinib as a treatment option at second line and the ESMO guidelines also recommend it as a third line option. A summary of the placement of cabozantinib in the treatment pathway in these guidelines is presented in Box 8. The ERG notes that nivolumab is also a treatment option where cabozantinib is positioned and none of the guidelines recommend one of the treatments over the other.

Box 8. Summary of the ESMO, EAU and NCCN RCC/kidney cancer guidelines (Adapted from CS, pages 31–33, Section 3.3.1)

The ESMO clinical practice guidelines recommend cabozantinib and nivolumab as preferred second-line treatments. Axitinib, everolimus and sorafenib are recommended as options but are not categorised as 'preferred' (Figure a).[10]

Cabozantinib is also recommended in the third-line setting (Figure 3).

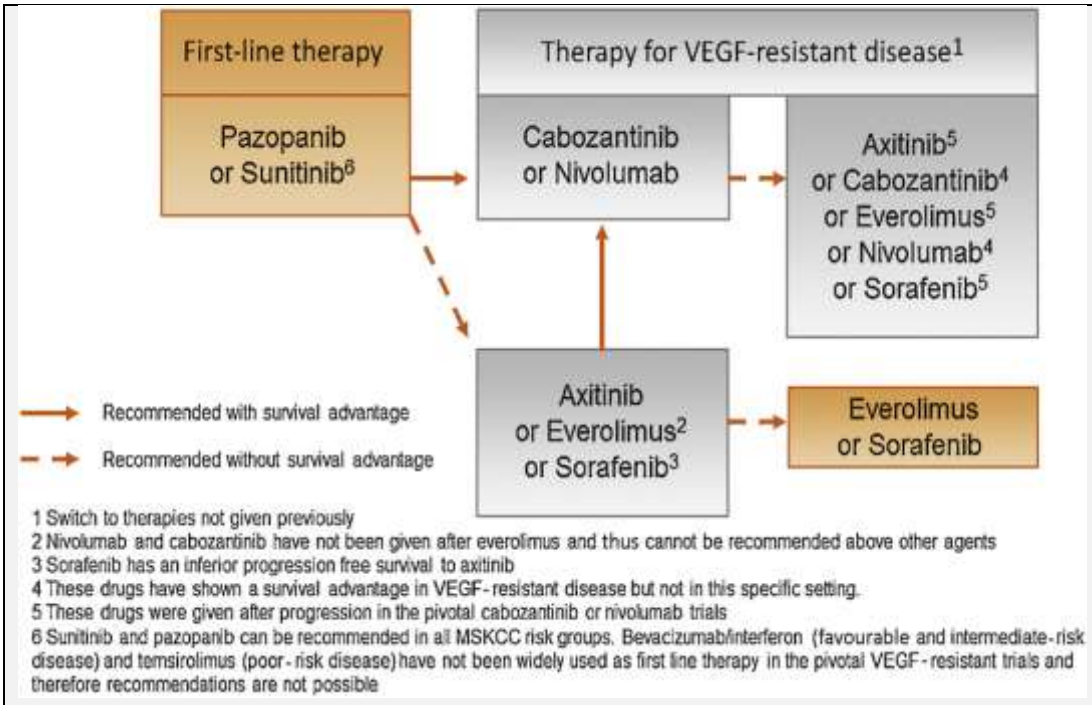
Figure a. ESMO algorithm for systemic treatment in clear cell metastatic RCC*



Source: Escudier et al 2016[10]

The EAU updated their guidelines in 2016, in response to the results of the METEOR study, to include cabozantinib as second-line therapy for metastatic RCC in patients who have failed one or more lines of VEGF targeted therapy (Figure b).[38]

Figure b: EAU evidence based recommendations for systemic therapy in patients with metastatic RCC



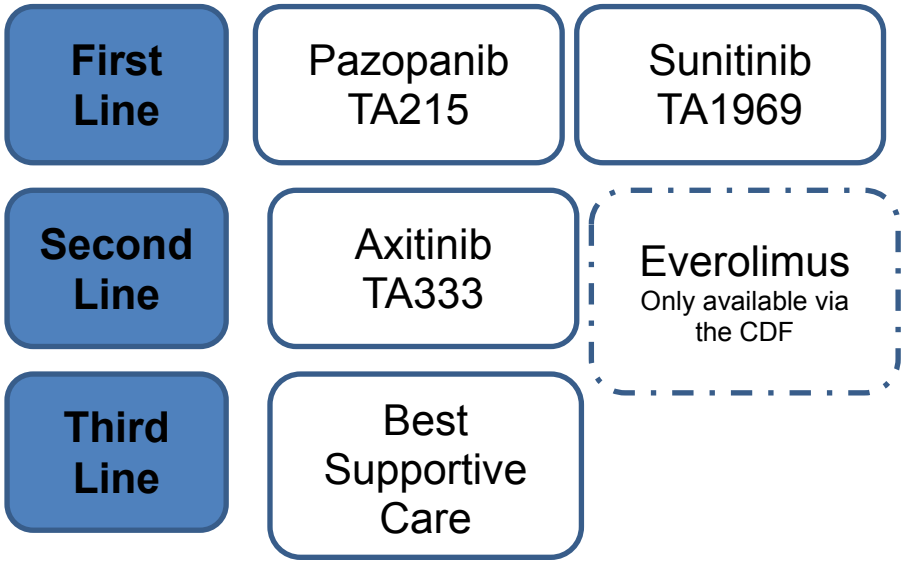
Source: Powles et al 2016[38]

In the most recent update to the NCCN guidelines 2017, and again in response to the results of the METEOR study, cabozantinib is recommended as a preferred second-line treatment after angiogenic therapy to treat advanced RCC patients.[39]

*Note: figure a in the CS also included non-clear clear cell RCC but there were no specific second line or third line therapies and no mention of cabozantanib in this pathway and so it has been omitted from this Box.
Abbreviations: EAU, European Association of Urology; ESMO, European Society of Medical Oncology; IFN, interferon; IL2, interleukin 2; MCBS, ESMO Magnitude of Clinical Benefit Scale v1.0; mRCC, metastatic renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Centre; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor receptor.

Clinical practice in England reflects the above European and US guidelines and the availability of the drugs in the NHS. Cabozantinib is not currently used in the UK NHS as it is not currently approved by NICE. Patients with advanced RCC suitable for treatment will typically have a maximum of three lines of treatment according to their disease status. Best supportive care (BSC) is the current standard of care for third line treatment although with the recent NICE approval of nivolumab this could change. Nivolumab is now NICE approved as a second and third line treatment. The company's depiction of the current treatment pathway in England is presented in Figure 2; it was reported that it was validated with clinical experts during a roundtable meeting.[40]

Figure 2. Current clinical pathway of care for advanced RCC in England (Adapted from CS, page 34, Figure 5)

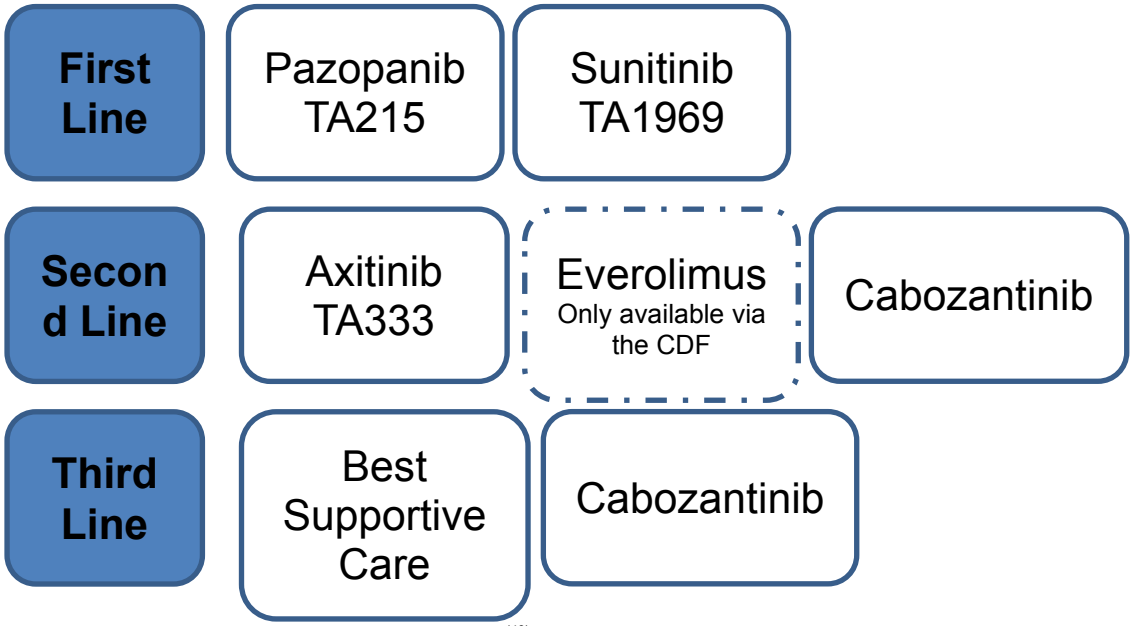


Abbreviations: CDF, cancer drugs fund; TA, technology appraisal.

The ERG's clinical advisors agree with the treatments and their sequencing presented in Figure 2. Everolimus for metastatic RCC is only available via the CDF in England for second line treatment in selected patients although the company reported that their experts consider it to be typically used as a third-line treatment. The ERG's advisors report that it is not used often due to the funding restrictions although it is considered a second line treatment option. The ERG notes that everolimus is currently undergoing review by NICE in the cancer drugs fund (CDF) rapid reconsideration process (GID-TA10057), with guidance expected to be published in March 2017.[29] The outcome of this NICE evaluation may lead to either an increase or decrease in the use of everolimus depending on whether it is approved by NICE

The company's proposed positioning of cabozantinib in the advanced RCC treatment pathway in England is presented in Figure 3. The company propose that cabozantinib will displace axitinib in the second line setting, post-tyrosine kinase inhibitor (TKI; pazopanib or sunitinib) and offer an oral alternative treatment option to IV nivolumab. The ERG notes that it will also provide a further active treatment option for all patients at third line, alongside the newly approved drug nivolumab.

Figure 3. Position of cabozantinib in the current treatment pathway (Adapted from CS, page 6, Figure 6)



Source: Ipsen Roundtable meeting. September 2016[40]
Abbreviations: CDF, cancer drugs fund; TA, technology appraisal.

The ERG and its clinical advisors note that nivolumab has been omitted from both Figure 2 and Figure 3 as at the time of submission for this STA the outcome of the nivolumab STA was still awaited. Nivolumab is now approved by NICE for use at second and third line in advanced RCC following any prior therapy. The ERG and its clinical advisors otherwise agree with the treatment pathways presented by the company.

The ERG agrees with the company's report that no change in service provision or infrastructure would be required with the introduction of cabozantinib. Cabozantinib is an oral, once-daily treatment that can be taken at home and patients would be expected to be followed up in a similar manner to those that currently receive axitinib. Further details on the company's proposed impact of cabozantinib on current service provision are presented in Box 9. The ERG's clinical advisors report that it is unlikely that dose reductions would be managed remotely but that they would most likely be done in outpatient clinics, in keeping with that of the existing oral advanced RCC treatments. The ERG's clinical advisors also reported that due to the nature of the side effect profile seen in the clinical trials for cabozantinib it is likely that it will require more outpatient clinic visits in the initial few months of treatment to enable close monitoring and prompt dose adjustments to be made. This is partly because it is a new drug and thus associated with uncertainty of how well it will be tolerated by patients, but also because it is known to be associated with adverse effects such as diarrhoea that if not managed promptly could become more serious. In addition, having active treatment options at third line as opposed to BSC will increase the burden on hospital clinics although no specific changes will be required to the service provision.

Box 9. Company's proposed resource use for cabozantinib (Adapted from CS, page 24, Section 2.4)

It is anticipated that administration of cabozantinib will utilise existing NHS infrastructure and resources with no additional requirements. There are no additional tests or investigations required for the selection of patients for cabozantinib treatment. Cabozantinib treatment should be initiated by a physician experienced in the administration of anticancer medicinal products and patients should be monitored closely during the first eight weeks of treatment for suspected adverse drug reactions which may require temporary dose interruption or reduction of cabozantinib therapy. In clinical practice the monitoring of adverse events is routine and no additional resources above those already in place will be required. Treatment emergent adverse events with cabozantinib can be managed with dose reductions, treatment interruptions and/ or supportive care. No specific concomitant therapies are required. Cabozantinib is an oral therapy and dose reductions and treatment interruptions can be managed remotely via the telephone.
Abbreviations: NHS, national health service.

The ERG notes that the company has undertaken calculations to estimate the incidence of advanced RCC in England (Box 10). The ERG is unsure why the company's translation of the 38% increase in incidence of RCC over 10 years resulted in an annual rate of 5.17%. The ERG considers a direct translation of this 38% to result in an annual rate of 3.27%. Applying this lower annual rate to the 2014 incidence rate of RCC thus results in a lower number of patients eligible for cabozantinib.

Box 10. Company's estimate of the number of patients eligible for cabozantinib in England (Adapted from CS, pages 27–28, Section 3.3)

The incidence of kidney cancer in England in 2014 was 9,123.[41] The increased UK incidence rate of 38% translates into an annualised rate of 5.17%. Applying this rate to the 2014 incidence figure of 9,123 the total number of new kidney cancer cases in 2017 is predicted to be 10,613 patients. Assuming that 80% of all cases of kidney cancer are RCC and that 35.9% of all cases of RCC present at advanced stages[18] the incidence of advanced RCC is estimated at 3,048 patients. Of these patients it is estimated that 68% would be eligible for first line systemic therapy[42] and upon failure of first line approximately 50% would go on to receive second-line treatment[43] resulting in a total number of eligible patients for second line advanced RCC of 1,037 patients.
Abbreviations: RCC, renal cell carcinoma; UK, United Kingdom.

The ERG notes that the company's estimation only accounts for second line use of cabozantinib and not third line use. The ERG's estimation of the number of patients eligible for second line treatment with cabozantinib using the revised annual incidence rate of 3.27% is 920. The ERG considers that the total number of patients potentially eligible for cabozantinib in the NHS in England will be higher than 920 as a number of patients will also be eligible for third line treatment. The ERG was unable to estimate the number eligible at third line due to time restraints and limited availability of suitable data. The ERG

also notes that the CS for the recent STA of nivolumab for RCC (TA417)[43] did not include an estimate for the number of patients eligible for nivolumab at third line. However, the ERG considers that at third line it is likely to be substantially lower than the 920 potentially eligible at second line.

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)[8], and the decision problem addressed in their submission (CS, pages 12-13), which is reported to be identical (Table 4). The company also provided additional details on their view of the comparators, reporting that they considered axitinib to be the most relevant comparator (Table 4). The ERG's opinion on the comparators is discussed in Section 3.3.

Table 4. Summary of decision problem as outlined in the company's submission.

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
Population	People who have received previous VEGF-targeted therapy for advanced renal cell carcinoma	As per scope	
Intervention	Cabozantinib	As per scope	
Comparator (s)	Axitinib Everolimus (not recommended by NICE but currently funded via the Cancer Drugs Fund) Nivolumab (subject to ongoing NICE appraisal [ID 853]) Best supportive care	As per scope	Axitinib is the only medicine currently recommended by NICE (TA333)[32] for use after failure of treatment with a first–line tyrosine kinase inhibitor or cytokine and is the most relevant comparator. At the decision problem meeting Ipsen were advised that, as the single technology appraisal of nivolumab is currently ongoing and nivolumab is not established standard of care, it is not a relevant comparator. Nivolumab has been retained in the decision problem with the view that, if recommended, nivolumab will be available and being used in clinical practice at the time cabozantinib is considered by the Appraisal Committee.
Outcomes	The outcome measures to be considered include: Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	As per scope	

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.	As per scope	
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: previous lines of treatment prognostic score 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.	As per scope	
Special considerations including issues related to equity or equality	N/A	N/A	
Abbreviations used in table: N/A, not applicable; NICE, National Institute for Health and Care Excellence; NHS, national health service; TA, technology appraisal; VEGF, vascular endothelial growth factor.			

3.1 Population

Clinical effectiveness data in the submission are derived from the METEOR trial[(1)] which was designed to evaluate the efficacy and safety of cabozantinib compared to everolimus. Patients eligible for inclusion were adults with advanced RCC who had received at least one previous VEGF-targeted therapy. There was no further restrictions on the number of previous anticancer therapies or type, other than the exclusion of patients with prior mTOR inhibitor therapy or cabozantinib therapy. Over 70% of patients had only received one prior VEGF-TKI and over [redacted] had only received the one prior systemic anticancer therapy. The most frequent prior VEGF-TKIs patients had received were sunitinib (over 60% of patients had received prior sunitinib) and pazopanib (over 40% of patients had received prior pazopanib). These are the two treatment most likely to be given at first-line in the UK and thus the

population of METEOR reflects the second-line positioning of cabozantinib in the UK based on the prior therapies received.

Patients in METEOR were also required to have a Karnofsky performance-status score of at least 70% at baseline. The ERG and its experts consider this to be a reasonable requirement and in keeping with other similar clinical trials in advanced RCC.

Baseline characteristics of the patients in METEOR are generally in keeping with those expected in the equivalent population in UK clinical practice. Patients in METEOR had a median age of around 62 years, over 70% of them were male, over 80% were from Europe or North America and over 60% had an ECOG performance status score of 0. However, the ERG notes that the actual number of UK patients enrolled in METEOR was not reported in the CS and that METEOR contained a high proportion of patients with an ECOG performance status of 0 (67%) which would be reflective of the fitter patients found in current practice.

The final scope issued by NICE specified the population of interest to be people who have received previous VEGF-targeted therapy for advanced renal cell carcinoma.

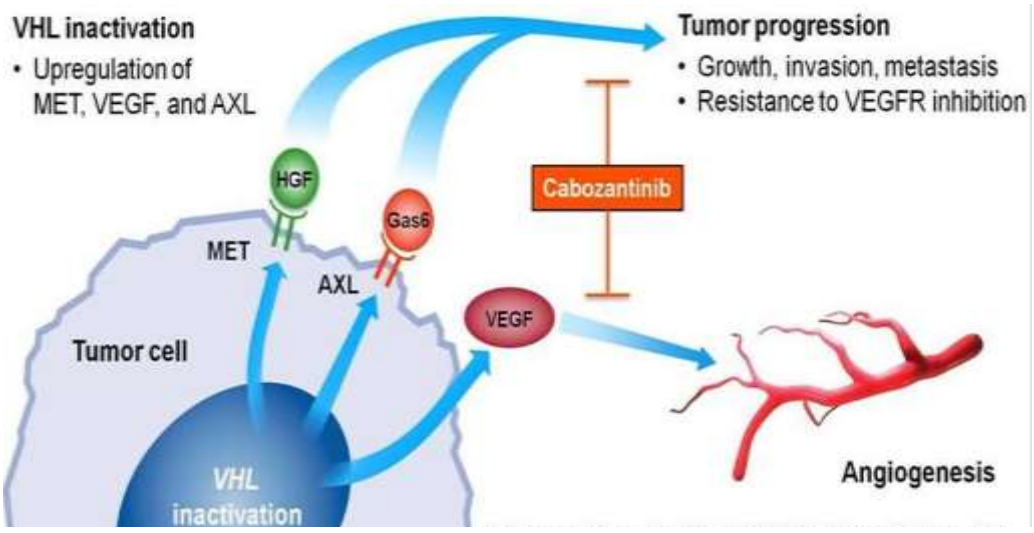
In summary, the ERG considers the data presented within the submission to be representative of patients with advanced RCC in England and Wales, and to be relevant to the decision problem that is the focus of this STA.

The ERG notes that the full trial population of METEOR provides suitable data for addressing the decision problem although it combines patients on different lines of therapy which is a potential confounder. However, the ERG also notes that the decision problem issued by NICE specified subgroup analyses by line of therapy; the company provided subgroup data for these populations for the METEOR trial data to enable a comparison of cabozantinib versus everolimus in patients with one prior VEGF-TKI and in patients with two or more prior VEGF-TKIs. The ERG notes that the clinical pathway and the ERG's clinical experts suggest that everolimus is mainly used at second line and infrequently, if at all at third line. The ERG thus does not consider the METEOR trial level data for the subgroup of people with two or more prior VEGF-TKIs to be particularly useful in addressing the NICE decision problem for the potential third line positioning of cabozantinib. The ERG instead consider the key comparator's for cabozantinib at third line to be BSC and nivolumab. In response to clarification the company provided further data for the subgroup with 1 prior VEGF-TKI using their NMA although the ERG does not consider these data to be suitable. The ERG therefore does not consider the company to have provided suitable subgroup data by line of therapy for the comparison of cabozantinib with the remaining comparators (i.e. axitinib, nivolumab and BSC) in the NICE final scope. The data provided are discussed further in Section 4.4.

3.2 Intervention

Cabozantinib, brand name CABOMETYX®, is a protein kinase inhibitor taken as an oral once-a-day tablet. Cabozantinib works by inhibiting multiple receptor tyrosine kinases (RTKs), which are thought to be involved in the suppression of tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib is reported in the CS to particularly target and inhibit the MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors (Figure 4). However, it also targets several other RTKs as well and so it has a multi-targeted mechanism of action in the treatment of RCC.

Figure 4.Cabozantinib mode of action (Reproduced from the CS, page 21, Figure 1)



Sources: Shen et al 2013[44]; Zhou et al 2015[45]

The company reported that a marketing authorisation application (MAA) was submitted to the European Medicines Agency (EMA) in January 2016 for cabozantinib use in advanced RCC. It was assigned Promising Innovative Medicine (PIM) designation in July 2016 after meeting the PIM criteria which include treatment of a life-threatening or seriously debilitating condition with high unmet need; likelihood of major advantage over current treatments; and reasonable expectation of a positive benefit risk profile. The CHMP positive opinion was issued on 21 July 2016, following an accelerated review as a result of it being granted PIM status, and Marketing Authorisation granted on 9 September 2016.

Cabozantinib is licensed for the treatment of advanced renal cell carcinoma (RCC) in adults following prior VEGF-targeted therapy. The clinical data used in support of the EMA MAA were from METEOR as all patients in the trial had previously received at least one VEGF receptor tyrosine kinase inhibitor (VEGF-TKI). This criterion was noted as a limitation of the trial and as a result the European MA has been restricted to use following at least one prior VEGF-TKI.

The ERG notes that cabozantinib also has a similar FDA approval for the treatment of advanced RCC that was granted on 25 April 2016. The FDA approval is wider as it allows cabozantinib use in patients who have received prior antiangiogenic therapy and doesn't specify that this must be a VEGF-TKI.

The company reported in the CS that they are also planning to make submissions to the Scottish Medicines Consortium (SMC) in Q4 of 2016 and the National Centre for Pharmacoeconomics (NCPE) in the Republic of Ireland in early 2017 for further approvals for the use of cabozantinib in RCC.

Cabozantinib is an oral once daily treatment and the recommended dose is 60mg with treatment continuing until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Temporary interruptions or dose reductions may be made to manage adverse events. As discussed in Section 2.2, the company report that the introduction of cabozantinib will not require any changes to the existing NHS infrastructure and resources. The company also reported that any required dose reductions and treatment interruptions could be managed remotely via the telephone. The ERG's clinical advisors report that it is unlikely these would be managed remotely but that they would most likely be done in outpatient clinics, in keeping with that of the existing oral advanced RCC treatments. Further details on the administration of cabozantinib are reported in Table 5.

Table 5. Summary of prescribing information for cabozantinib and unit cost (Adapted from the CS, page 23, Table 4)

	Cost	**Source**
Pharmaceutical formulation	Film coated tablet	SmPC[46]
Acquisition cost (excluding VAT)	£5,143.00 for a 30 tablet pack	List price
Method of administration	Oral	SmPC[46]
Doses	20 mg, 40 mg and 60 mg	SmPC[46]
Dosing frequency	Once daily	SmPC[46]
Average length of a course of treatment	Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Median duration of treatment with cabozantinib in the phase III pivotal trial (the METEOR study) was 8.3 months as of 31 December 2015.	SmPC[46] METEOR study[1]
Average cost of a course of treatment	£[redacted]	Economic model
Anticipated average interval between courses of treatments	Not applicable – retreatment is not anticipated	
Anticipated number of repeat courses of treatments	Not applicable – retreatment is not anticipated	
Dose adjustments	Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of cabozantinib therapy. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.	SmPC[46] (Table 1)
Anticipated care setting	Therapy with cabozantinib should be initiated by a physician experienced in the administration of anticancer medicinal	SmPC[46]

	products. Once initiated patients can be managed remotely with dose interruptions/reductions managed by phone.	
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; SmPC, Summary of Product Characteristics.		

The ERG notes that the dosing of cabozantinib in METEOR was in keeping with the European MA and how it would be anticipated to be used in UK clinical practice. However, the ERG also notes that the median daily dose of cabozantinib in METEOR was 43mg although the standard recommended dose is 60mg. However, the lower dose is most likely a reflection of the treatment interruptions required for the management of AEs that occurred and thus may be what would be seen in clinical practice.

3.3 Comparators

The comparators specified in the NICE final scope were axitinib, everolimus, nivolumab and best supportive care (BSC).[8] The ERG notes that nivolumab was subject to ongoing NICE appraisal at the time the company submitted for this STA but it was still included in the NICE final scope and the company included it as a comparator within their submission. The ERG also note that it has since been approved by NICE for use in advanced RCC (TA417)[36] and thus it is an important comparator in this submission as its use in clinical practice is now likely to increase. As noted in the NICE final scope,[8] everolimus is only funded in the NHS via the Cancer Drugs Fund and clinical experts report that it is not frequently used in the treatment pathway for advanced RCC. However, the ERG notes that everolimus is currently undergoing review by NICE in the cancer drugs fund (CDF) rapid reconsideration process (GID-TA10057), with guidance expected to be published in March 2017.[29] The outcome of this appraisal by NICE may lead to increased usage of everolimus should it receive NICE approval.

BSC is also a comparator in the NICE final scope but the ERG's clinical experts report that it is mainly used at third line when there are no other suitable treatment options for a patient. The ERG's clinical experts report that the recent NICE approval of nivolumab as a second and third line treatment option in RCC is likely to mean that the use of BSC at third line will reduce. However, the ERG still consider it to be a potential comparator as nivolumab is not yet an established treatment in routine clinical practice. The ERG also notes that the NICE final scope did not define BSC. According to the ERG's clinical experts BSC can include various treatments such as palliative radiotherapy, steroids (for bone pain and improve well-being), opioids (for pain control), antibiotics (for chest infection), bisphosphonates (for hypercalcaemia and bone progression) and that it is tailored to the individual patient and their symptoms. However, the ERG notes that the company included placebo data to inform the comparison of cabozantinib with BSC in the CS. The ERG considers this to be a reasonable approach given the lack of standardisation for BSC in clinical practice and acknowledges that it is standard practice in clinical trials to use placebo as a surrogate for BSC.

The ERG agrees with the CS that the most commonly used second line treatment at present is axitinib. However, with the recent NICE approval of nivolumab (TA417)[36] the ERG considers that uptake and use of nivolumab will now increase in the UK and so it is also an important comparator at both second and third line.

Everolimus was the only comparator in the NICE final scope for which there was direct head-to-head randomised controlled trial data compared to cabozantinib available; this was from the METEOR trial. The comparison of cabozantinib with the other comparators specified in the NICE decision problem was done using a network meta-analysis (NMA). However, due to differences in the baseline and study characteristics of the trials in the NMA, the company believes there is clinical heterogeneity and so they adjusted for this in the NMA. The adjustments and sources of heterogeneity will be discussed further in Section 4.4. The trials used to provide data in the NMA for axitinib, nivolumab and BSC were AXIS, Checkmate 025 and RECORD-1. In addition, TARGET was included to provide a link via sorafenib and placebo to AXIS, the axitinib RCT to be linked into the network of studies for the NMA. Placebo was used in the NMA in the CS as a surrogate for BSC, which the ERG considers to be acceptable and in keeping with previous similar STAs such as that for nivolumab.[34] The ERG's critique on the appropriateness of the trials included in the NMA and the methods used by the company is presented in Section 4.4.

3.4 Outcomes

The outcomes listed in the NICE final scope[8] were:

- Overall survival;
- Progression-free survival;
- Response rates;
- Adverse effects of treatment; and
- Health-related quality of life (HRQoL).

The ERG notes that all of these outcomes were captured in the METEOR trial and so data comparing cabozantinib with everolimus are available for all the outcomes specified in the NICE final scope. However, there is no data presented in the CS comparing response rates, adverse effects of treatment or HRQoL for cabozantinib with axitinib, nivolumab or BSC (placebo).

The ERG notes that PFS is reported for two different analysis populations in METEOR, the primary intention to treat (PITT) and the intention to treat population (ITT); these populations are discussed

further in Section 4.2. The PITT comprised of the first 375 patients randomised and was prespecifed (for statistical reasons) as the primary analysis for PFS. The ITT population was all patients randomised and an analysis for PFS using this population was also presented in the CS. All other efficacy outcomes in METEOR were reported solely for the ITT population whilst the adverse effects data were reported for the safety population, defined as patients who received at least one dose of study medication.

Response rate data presented in the CS comprised of objective response rate (ORR) assessed by an independent radiological review panel and number of patients with classification of response as complete response, partial response, stable disease or progressive disease. HRQoL was assessed in METEOR using both the EuroQol-5 dimension (EQ-5D) and the functional assessment of cancer therapy kidney symptom index (FKSI-19). The ERG considers this to be a comprehensive approach as it entails both a generic HRQoL tool and a disease specific QoL tool.

The reporting of adverse event data in the CS was limited to treatment emergent adverse effects data occurring in ≥10% of patients in either treatment group. The data was broken down by grade and presented in the CS as grade 1-2, 3 or 4 events. In addition, a breakdown of the most common grade ≥3 serious adverse effects was presented in the CS. The ERG notes that the reporting of adverse events deemed to be treatment-related (TRAEs) was omitted from the CS for all AEs except deaths. The company's rationale for the omission of TRAEs from the economic model was requested during the clarification stage. The company's response is presented in Box 11.

Box 11. Company's response to clarification question on the omission of TRAE data from the economic model (CQ response, page 119, Question B15)

Treatment-emergent adverse events (TEAEs) include any event related temporally to the administration of the drug (i.e. occurs during treatment phase), while treatment-related adverse events (TRAEs) are a subset of AEs, which include event that can be considered causally related to the treatment administered (i.e. occurs during treatment phase AND clinical judgement considers the AE to be related to treatment). Given the consideration that any Grade 3 or higher TEAEs would also have an impact on the patients' costs and HRQoL, Ipsen considered using TEAEs in the model more appropriate than TRAEs.
Abbreviations: HRQoL, health-related quality of life; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

The ERG considers that both TEAEs and TRAEs data should however, have been presented within the clinical effectiveness section of the CS.

The ERG and its clinical advisors consider the outcomes specified in the NICE final scope and reported in the CS to be appropriate and the most clinically relevant ones for patients with advanced RCC. However, the ERG notes the omission of TRAEs reporting from METEOR in the CS and that

comparison of HRQoL, response rates and adverse effects for cabozantinib and axitinib, nivolumab or best supportive care are not presented in the CS.

3.5 Timeframe

The median length of follow-up for OS and the safety outcomes in METEOR was 18.7 months (IQR 16.1 to 21.1) in the cabozantinib group and 18.8 months (16.0 to 21.2) in the everolimus group. The ERG notes that trial recruitment started on 8 August 2013 and the data cut off for the final analyses was 31 December 2015. The maximum duration of follow-up was thus restricted to 29 months in METEOR. The ERG considers the duration of follow-up in METEOR to be suitable for assessing the short-term safety and efficacy outcomes of treatment with cabozantinib. However, the ERG notes that safety and efficacy data for cabozantinib beyond 19 months are subject to uncertainty and thus long term safety and efficacy of cabozantinib cannot be assessed from the data that are currently available.

3.6 Other relevant factors

The ERG notes that the final scope issued by NICE[8] specified that evidence permitting, consideration should be given to the following subgroups:

- previous lines of treatment; and
- prognostic score.

As discussed in Section 3.1, the ERG notes that the company provided data by type of prior VEGF-TKI therapy and by number of prior VEGF-TKI therapies for METEOR. In addition, the ERG notes that subgroup data by baseline Heng and MSKCC scores from METEOR were also provided in the CS for OS. These subgroup data and their results are discussed further in Section 4.3.5.

There are no known issues relating to equality in this technology appraisal according to the CS 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 two separate search strategies to review clinical effectiveness; one to search for direct evidence relating to the effectiveness of cabozantinib and its relevant comparators in the management of previously treated advanced RCC, the other to search for trials to inform the network meta-analysis (NMA) used for indirect treatment comparison.

For the direct evidence search electronic databases (Embase, MEDLINE, Cochrane CENTRAL, Cochrane CDSR, DARE, HTA database, NHS EED) were searched in August 2016. All databases were searched from inception without date restrictions. The search was restricted to English language papers only and randomised controlled trials (RCT), non-RCT and systematic review (SR) study design were eligible for inclusion. Alongside these databases the FDA website was also searched. Proceedings of key conferences from the last three years (2013 to 2016) were also part of the direct evidence search. Relevant conferences identified by the company included: American Society of Clinical Oncology [ASCO] (searched from 2013 to 2015); ASCO Genito-Urinary Symposium (searched from 2013 to 2016); ESMO Congress (searched from 2013 to 2015); ESMO Multidisciplinary Meeting on Urological cancers (searched from 2013 to 2014); European Cancer Organisation- European Cancer Congress (searched from 2013 to 2015).

The direct evidence search strategy included terms related to the intervention of interest, cabozantinib. Terms to exclude animal studies and particular study designs were also used for the MEDLINE and Embase database searches.

For the evidence to populate the NMA search, electronic databases (Embase, MEDLINE, Cochrane CENTRAL, Cochrane CDSR, DARE, HTA database, NHS EED) were searched in June 2016. All databases were searched from inception without date restrictions. Language restrictions for NMA evidence search included eligible records to be in one of the following languages: English, French, German, Italian or Spanish. Study design was restricted to RCTs and SRs of RCTs for bibliography screening only. The FDA website and conference proceedings were not searched by the company for the indirect search as was carried out for the direct evidence search.

The NMA evidence search strategy included search terms relating to RCC and the key interventions identified by the company including: cabozantinib, everolimus, axitinib, nivolumab, sorafenib, sunitinib and lenvatinib. These comparators were part of a global search to identify all relevant evidence for the NMA, therefore some were outside the remit of the NICE final scope. The ERG notes that despite the diverse inclusion of comparators the company overlooked best supportive care and placebo in their

search strategy, which could have potentially limited the connections in the network populating the NMA. However, relevant placebo controlled RCTs were included as discussed in Section 4.1.2.2.

The Cochrane RCT search filter [47] was used for identifying RCTs in the MEDLINE and Embase databases and the Scottish Intercollegiate Guidelines Network (SIGN) systematic review filter [48] was used to identify systematic reviews in the MEDLINE and Embase database. The ERG notes that electronic database searches for evidence populating the NMA were conducted at 3rd June 2016, which was prior to the most recent METEOR trial publication.[1] This resulted in the company manually adding the trial to the list of retrieved evidence.

For both the direct and NMA evidence searches the company makes no reference in the CS as to whether the clinical trial registries (clinicaltrials.gov, clinicaltrialsregister.eu) were searched. This is an important resource to identify relevant completed and ongoing clinical trials and therefore potentially relevant evidence could have been overlooked.

The ERG considers the direct evidence and evidence to populate the NMA to be comprehensive and appropriate. The company is likely to have identified all relevant evidence to assess the direct evidence for clinical effectiveness of cabozantinib. With regards to the NMA evidence search, due to an earlier search date the company were required to manually include relevant trials of interest which may have resulted in some bias in the evidence included.

4.1.2 Inclusion criteria

4.1.2.1 Inclusion criteria for the direct evidence review

The eligibility criteria for the systematic review of direct evidence of clinical effectiveness are summarised in Table 6.

Table 6: Summary of review eligibility criteria (Adapted from CS, page 39)

	Inclusion criteria	Exclusion criteria
Population	80% or more of the study population must be adults (≥18 years of age) Previously treated metastatic renal cell carcinoma (patients who had received prior systemic therapy)	Non-human subjects; Patients aged under 18 years of age Patients with non-metastatic RCC Patients with early stage RCC If a study included groups of eligible and ineligible patients, the study was included if data for the eligible patient group were presented separately
Intervention	Cabozantinib	
Comparators	For comparative studies: Axitinib Everolimus Nivolumab Best supportive care Single-arm prospective studies were also eligible	For comparative studies: Radiotherapy, surgery and other non-relevant comparators
Outcomes	Efficacy OS PFS TTP ORR (complete or partial response) Proportion of patients with stable disease Duration of response Time to response Symptom assessments Time to deterioration (composite/individual endpoint) Safety Incidence and severity (grade) of all reported AEs Withdrawals due to AEs Incidence of serious AEs Quality of life or any other global patient-reported outcomes	Studies not investigating efficacy, safety or quality of life Studies not providing sufficient data on outcomes
Study design	Prospective randomised controlled trials Cross-over RCTs Non-RCT studies; Systematic reviews	Duplicate publications of the same trial Case reports Commentaries and letters Recommendations/ guidelines Non-systematic reviews
Language restrictions	English language only	Non-English language

Abbreviations: AE, adverse event; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell cancer; RCT, randomised controlled trial; TTP, time to progression

The ERG notes that the eligibility criteria: "80% or more of the study population must be adults (≥18 years of age)", may influence the representability of the trial population compared to the population seen in UK clinical practice. Although the ERG acknowledges that patients under the age of 18 years old are uncommon and therefore this eligibility criteria poses limited impact. A further point is the inconsistent definition of the disease state of the population. The company identify the population as

"metastatic RCC" however the population of interest specified by the NICE final scope are patients with advanced RCC. The ERG notes that within the METEOR trial the population are described as "advanced or metastatic renal cell carcinoma."[49] As discussed in Section 2, advanced RCC is inclusive of metastatic RCC, however there should be some caution when using these terms interchangeably as not all advanced stage RCC patients may have metastatic sites and this may implications in how patients respond to treatment.

4.1.2.2 Inclusion criteria for the NMA evidence review

The eligibility criteria used to identify relevant indirect evidence (Table 7) were broader than the NICE final scope [8] due to the inclusion of additional comparators (sorafenib, sunitinib and lenvatinib) as part of a global search of evidence. Studies that included comparators outside of the NICE scope but met all other eligibility criteria were included by the company but later removed from the NMA when it was refined for relevance to the NICE scope (discussed further in Section 4.1.3).

Table 7. Summary of the NMA review eligibility criteria (Adapted from CS, pg 72, Table 19)

Category	Details
Population	Patients with renal cell cancer (advanced / metastatic, previously treated)
Intervention	Cabozantinib
Comparators	Everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib
Outcomes	PFS OS Response rates Drug discontinuation Any other efficacy outcomes Safety outcomes Quality of life and other Patient-reported Outcomes Biomarkers for efficacy and safety
Study Design	RCT
Language restrictions	None
Abbreviations: OS – overall survival, PFS – progression-free survival, RCT – randomised controlled trial	

Despite this broad inclusion of comparators the company did not include best supportive care in the eligibility criteria, which is listed as a comparator in the NICE final scope [8] potentially limiting the number of connections in the network informing the NMA. However, RCTs that investigated the listed comparators against placebo/best supportive care were identified and included in the network if they met all other criteria. Therefore, all relevant evidence is likely to have been included.

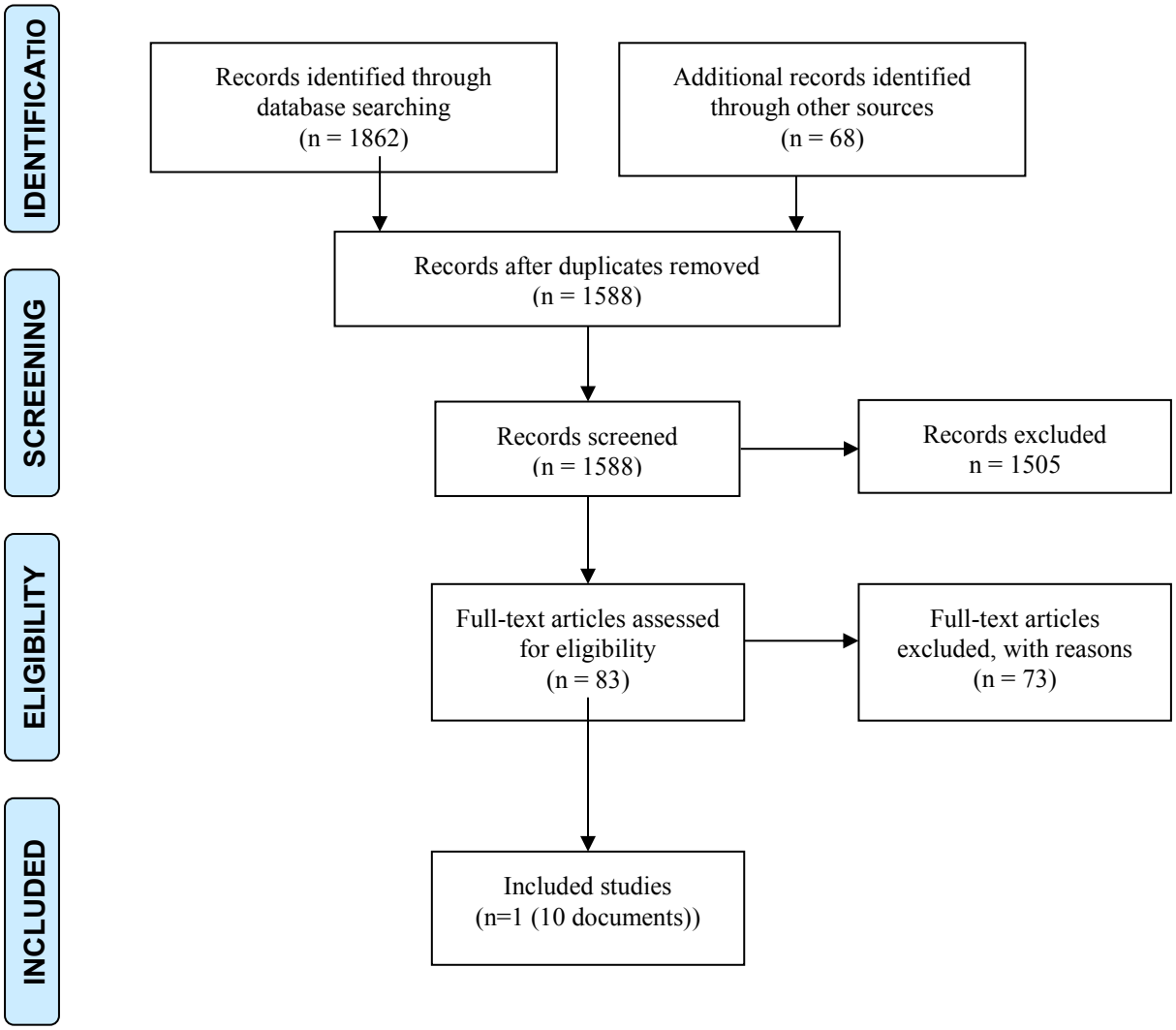
Overall, the ERG considers that the direct and NMA evidence review are likely to have identified all studies that are relevant to the NICE final scope [8] despite some discrepancies with regard to the definition of the disease state and the variation in language restrictions between the direct and indirect evidence search.

4.1.3 Critique of the screening process

The company provided details of the methods used to identify and screen clinical efficacy evidence for the direct and indirect evidence review. These methods are in line with those recommended by Centre for Reviews and Dissemination (CRD)[50] with initial record selection based on title and abstracts undertaken by two independent reviewers with a third party to resolve any discrepancies. All multiple publications from the same trial were included in the final list of articles providing they met the eligibility criteria.

For the direct evidence review a total of 1588 records were appraised, with 83 full text articles assessed for eligibility. Of these, 73 articles were excluded based on issues such as ineligible intervention, study design or insufficient detail concerning methodology. The remaining 10 articles all related to one RCT (METEOR), and were included in the final review. A flow diagram of the direct evidence search process is captured in Figure 5.

Figure 5: PRISMA flow diagram of direct evidence search (CS, pg 42, Figure 8)



The ERG notes that for the direct evidence search the company did not detail how many reviewers undertook the data extraction of the 10 records relating to the one RCT of interest or whether there was an independent third reviewer to identify any discrepancies. However, a thorough summary of the METEOR trial methods are presented in the CS (CS, Section 4.3) including trial design, population, sample size, treatment groups, primary and secondary outcomes, subgroups and the statistical methods used for trial data analysis.

For the indirect evidence review a total of 5579 records were appraised, 305 full text articles were assessed. Of these, 241 records were excluded due to issues including study type, population or intervention. A final 65 records were included relating to 19 studies. As outlined in Section 4.1.2 the company searched for a broad selection of comparators to create a wider evidence base for the NMA. The company acknowledge this evidence included comparators outside the NICE final scope as part of a global search. When focusing on relevant evidence for the comparators listed in the NICE final scope [8] the company excluded 10 studies. Subsequently a further four studies were excluded based on methodological criteria, shown in Table 8. The ERG considers that the reason for excluding these trials are valid. The final included records consisted of 10 records, which related to five RCTs. A flow diagram of the indirect evidence search process is presented in Figure 6.

Figure 6: PRISMA flow diagram for indirect evidence search (CS, pg 74, Figure 16)

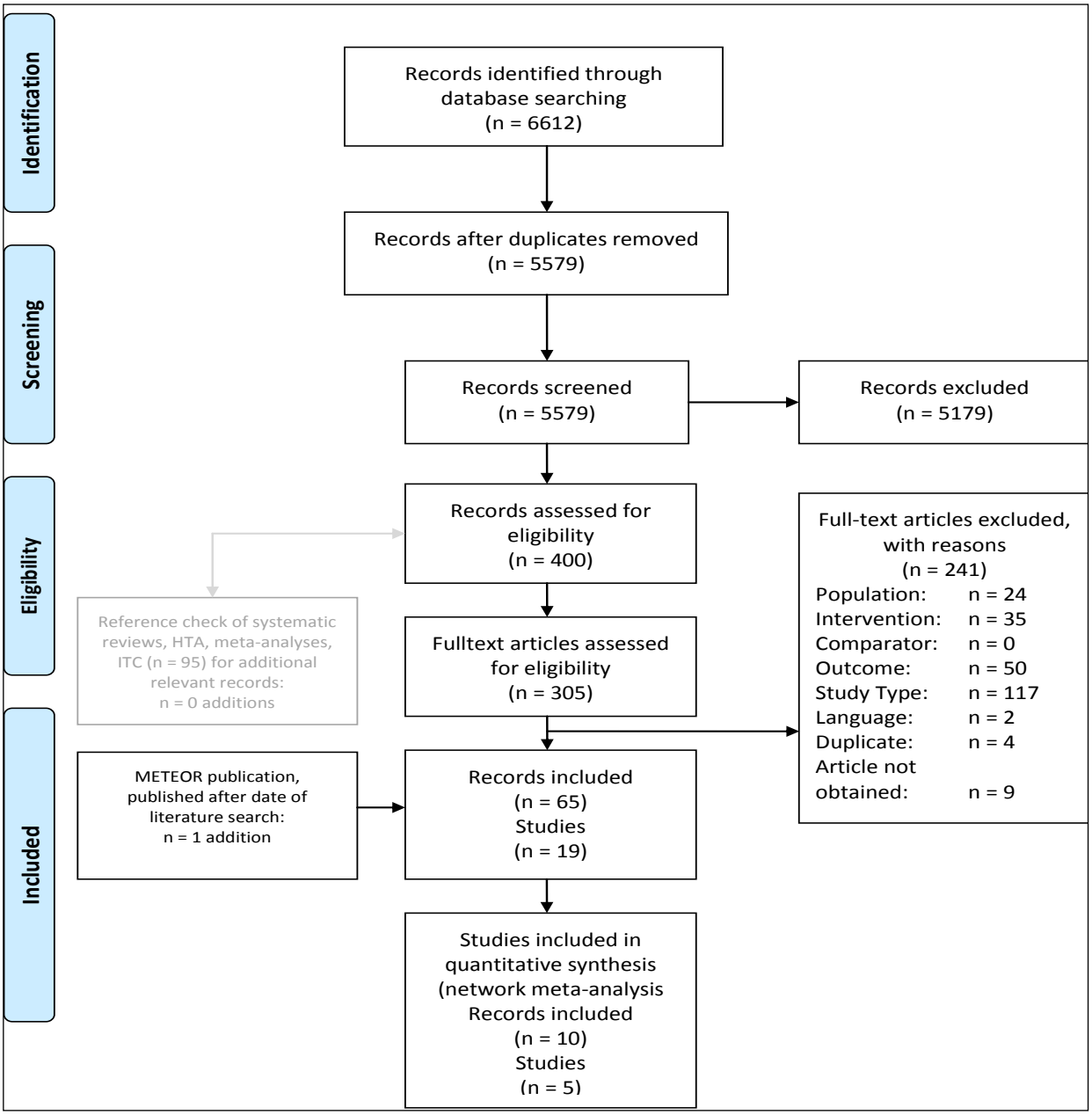


Table 8: Key methodological and clinical reasons for further exclusions (Adapted from CS, pg 77, Table 22)

Study	Key methodological and clinical parameters supporting exclusion
RECORD-3[51]	Sequential design and hence randomisation only for first-line treatment No PFS or OS data available for second line only
SWITCH[52]	Sequential design and hence randomisation only for first-line treatment Second line baseline characteristics not reported No OS data for second line
ESPN[53]	Only non-clear cell patients included No blinding details available
Ratain 2006 [54]	No information on prior VEGF therapies

Study	Key methodological and clinical parameters supporting exclusion
Abbreviations: PFS, progression-free survival; OS, overall survival; VEGF, vascular endothelial growth factor receptor.	

The final NMA network presented in the CS consisted of 4 studies that met the eligibility criteria outlined by the company; a summary is presented in Table 9.

Table 9: Final studies included in the indirect treatment comparison (Adapted from CS, pg 77, Table 23)

Study name	Design	Population	Treatment arms	Primary endpoint
METEOR [1, 49]	Phase 3 RCT Open-label Parallel group	Adult patients with clear cell mRCC who had progressed after at least one VEGF-targeted therapy	Cabozantinib Everolimus	PFS
RECORD-1 [55]	Phase 3 RCT Double-blind Cross over	Adult patients with clear cell mRCC who had documentation of progressive disease during or within 6 months of stopping sunitinib and/or sorafenib (prior therapy with cytokines and/or VEGF inhibitors also permitted)	Everolimus Placebo	PFS
CheckMate025[56]	Phase 3 RCT Open-label Parallel group	Adult patients with clear cell mRCC who had progressed after one or two previous regimens of antiangiogenic therapy	Nivolumab Everolimus	OS
TARGET[57]	Phase 3 RCT Double-blind Cross over	Adult patients with clear cell mRCC which had progressed after one systemic treatment within the previous 8 months not including VEGF pathway inhibitors	Sorafenib Placebo	OS
AXIS[58]	Phase 3 RCT Double blind Parallel group	Adult patients with clear cell mRCC who had progressed despite first-line systemic therapy (Sunitinib, bevacizumab plus interferon-alfa, temsirolimus or cytokines)	Axitinib Sorafenib	PFS
Abbreviations: mRCC, metastatic renal cell carcinoma; OS, overall survival; RCT, randomised controlled trial; PFS, progression-free survival; VEGF, vascular endothelial growth factor receptor.				

For the NMA evidence search the company did not outline in detail the screening process, with no information concerning the number of reviewers that undertook data extraction or whether a third independent reviewer was consulted on discrepancies and how consensus was reached.

In summary, the ERG considers that it is unlikely relevant trials have been missed and the data extracted from the included trials is relevant to inform the analysis of clinical efficacy of cabozantinib compared with the listed relevant comparators outlined by the NICE final scope. [8]

4.1.4 Quality assessment

4.1.4.1 Quality assessment of METEOR

The company provided an assessment of the quality for the METEOR trial[1] using criteria issued by University of York Centre for Reviews and Dissemination (CRD) [50]. This included domains assessing,

randomisation, concealment, group traits, blinding, drop-outs, outcomes and type of analysis. Each of these domains was assessed with 'yes, no or not clear' and additional qualitative justifications, this is summarised in Appendix 10.1.

The ERG carried out an independent assessment of quality of METEOR, which is presented alongside the company's quality assessment in Appendix 10.1. The ERG's quality assessment is in line with the company's assessment suggesting that the METEOR study is of good quality. METEOR had robust randomisation and allocation concealment procedures, resulting in well-balanced baseline characteristics between treatment groups. There was evidence of unbalanced drop-outs between the trial groups, with a higher proportion of patients discontinuing treatment in the everolimus group compared to the cabozantinib group. The reason for discontinuation for both groups was most commonly due to disease progression, clinical deterioration and adverse events (discussed more in Section 4.2.1). Intention to treat analysis was used for all key primary and secondary outcomes. The ERG notes that a modified intention to treat analysis for progression free survival (PFS) was carried out, primary end point ITT (PITT). The PITT analysis included the first 375 patients enrolled and randomised in the study rather than the total population which was 658 patients, with the company's rationale to prevent over representation of early progressed patients. The ERG notes that the PITT analysis is of limited use compared to the ITT analysis for the purpose of decision-making. (Further discussion in Section 4.2.3).

The ERG highlights that METEOR was an open label trial. The company states that this was to, "allow appropriate management of adverse events" (CS, pg 60, Table 13). The ERG considers that management of adverse events through dose reductions is common practice in clinical trials and that this could have been done while maintaining blinding to the treatments in METEOR. The ERG consulted clinical experts who reported despite adverse events being common with both cabozantinib and everolimus they should not have interfered with the use of blinding in METEOR.

4.1.4.2 Quality assessment of trials included in the NMA network

The five trials included in the NMA (shown in Table 9) were assessed for trial quality by the company using the recommended guidance by the University of York Centre for Reviews and Dissemination [50]. Of the five trials included in the NMA, three had unclear randomisation and allocation concealment procedures (TARGET, CheckMate 025, RECORD-1) and three trials were open label (METEOR, CheckMate 025, AXIS). Each trial had adequate quality for the remaining domains with no unexpected imbalance in dropouts, results for all outcomes reported and intention to treat analysis provided.

The ERG conducted an independent assessment of quality for the five RCTs included in the NMA, this is presented in Appendix 10.1. Overall the ERG agrees with the company's quality assessment of the trials. However, the ERG notes that the number of patients who discontinued treatment were imbalanced

in three of the trials (METEOR, TARGET, and RECORD-1) and that randomisation and allocation concealment seems to have been adequate in all but TARGET, for which these were unclear.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The company conducted a systematic review of all available and eligible evidence identifying one trial, METEOR[1], which compared cabozantinib with everolimus in patients with advanced clear-cell renal cell carcinoma, who had been previously treated with at least one VEGF-TKI. The METEOR trial compared cabozantinib 60 mg orally once per day with everolimus 10mg orally once per day, a listed comparator in the NICE final scope. [8] As discussed in Section 3.3, the company were unable to provide head-to-head evidence supporting the efficacy of cabozantinib compared to the other comparators in the NICE final scope: axitinib, nivolumab and best supportive care. To account for this lack of head-to-head evidence the company presented the results from an NMA which included all of the comparators specified in the NICE scope. The NMA is discussed further in Section 4.4 of the ERG report. The primary outcome of the METEOR trial was progression free survival (PFS) assessed using a modified ITT analysis referred to as the primary intention to treat population (PITT) (further details see Section 4.2.3). Both secondary outcomes, objective response rate (ORR) and overall survival (OS) used an intention to treat analysis (ITT). The outcomes provided by the company are those listed in the NICE final scope and confirmed by the ERG clinical experts as the most relevant to the disease area.

4.2.1 Trial conduct

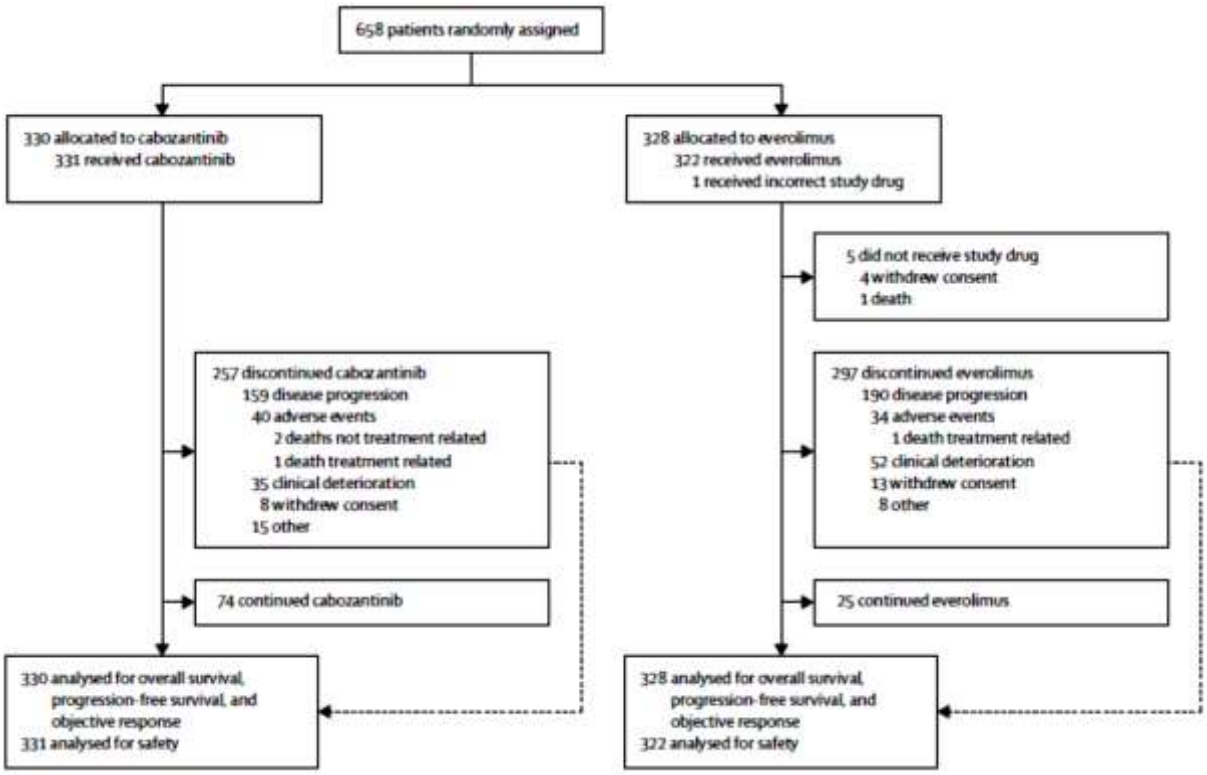
METEOR was an open-label, phase III trial conducted in 173 centres in 25 different countries. The proportion of recruitment in each continent was: 35% North America, 49% Europe, 13% Asia Pacific/Australia and 1.8% in Latin America. 3% of trial patients receiving cabozantinib were recruited in the UK compared to 4.9% patients receiving everolimus.

The first patient was recruited on 8th August 2013 and final data cut-off was on 31st December 2015. The ERG notes that there is no information regarding the recruitment period reported in the CS or CSR. Patients were eligible if they were 18 years or older and had advanced or metastatic renal cell carcinoma, with a clear-cell component. Patients must have received prior treatment with at least one VEGF-TKI and there was no limit to the number of prior anticancer therapies including cytokines, chemotherapy, monoclonal antibodies, including those targeting VEGF, programmed death 1 (PD-1) receptor or its ligand PD-L1. Patients were eligible if their Karnofsky performance status score was at least 70%, indicating a better performance, and they had adequate organ and bone marrow function. Exclusion criteria included previous therapy with an mTOR inhibitor or cabozantinib, and a history of uncontrolled clinically significant illness.

Amendments to the trial protocol were presented as supplementary material of the key publication for the METEOR trial.[59] The company outline the addition of a maintenance phase as a major amendment to the trial protocol. On completion of the main study endpoints, patients could continue to receive the study treatment if they experience a clinical benefit, until they met the criteria for treatment discontinuation, however they were not able to switch treatments during this period. During this phase patients were monitored for periodic safety assessments and tumour assessments as part of a standard care. The ERG notes that based on the median duration of treatment exposure (8.3 months for those in the cabozantinib group and 4.4 months for those in everolimus group) patients recruited between August 2013 and April 2014 prior to the protocol amendment may not have had the opportunity to continue treatment in the maintenance phase. The company does not provide details of the potential number of patients that fall within this pre-protocol amendment cohort.

The company provided a Consolidated Standards of Report Trials (CONSORT) diagram (Figure 7), to outline the participant flow of those taking part in the METEOR trial.

Figure 7: CONSORT diagram of participant flow in METEOR (Adapted from CS, pg 55, Figure 10).



In METEOR, 658 patients were randomised (330 to cabozantinib, 328 to everolimus), comprising the ITT population. A total of 564 patients (85.7%) discontinued treatment with uneven dropout rates

between the treatment groups (257 [78%] patients in cabozantinib group, 297 [91%] patients in the everolimus group). Patients in the everolimus group had a higher number of drop-outs, the majority of which were due to disease progression (64%) followed by clinical deterioration (18%) or adverse events (11%). Patients in the cabozantinib group mainly dropped out due to disease progression (58%) however compared to the everolimus group a higher proportion had adverse events (16%) and a lower proportion due to clinical deterioration (14%).

Patients in the trial were randomised in a 1:1 ratio to receive open-label cabozantinib 60mg orally once daily or 10 mg everolimus orally once daily. Randomisation was stratified by the number of prior VEGF-TKI treatments (1 or ≥2) and by Memorial Sloan Kettering Cancer Center (MSKCC) risk group (number of risk factors 0, 1, 2 or 3). Patients were randomised using a central interactive voice web response system. Study personnel were not aware of the treatment allocation details. However, due to the open label design of the trial investigators and patients were aware of which study intervention was received. As discussed earlier in Section 4.1.4, the company specify that the open label design was required to manage adverse events. The ERG dispute that the trial needed to be open label due to management of adverse events through dose reduction, when this could have been done in a blinded design.

Treatment duration was described by the company as, "Subjects received treatment for as long as they continued to experience clinical benefit in the opinion of the investigator (including after progression), or until there was unacceptable toxicity or the need for subsequent anticancer treatment, or any other reason for treatment discontinuation." (CS, pg 48, Table 11). The median treatment exposure for cabozantinib was 8.3 months, and 4.4 months for everolimus.

The company reported that treatment cross-over was not allowed and that dose modifications were permitted for both cabozantinib and everolimus. Cabozantinib could be reduced to 40 mg and then 20 mg, everolimus could be reduced to 5 mg and then 2.5 mg. Reasons for dose reduction included unacceptable toxicity, and doses could be modified at any time during the study. 62% of patients that received cabozantinib had a dose reduction whereas 25% of patients that received everolimus had their dose reduced. The reported median dose for cabozantinib was 43mg and for everolimus was 9mg.

The primary outcome of METEOR[1] was PFS, which was analysed using the PITT population, which comprised of the first 375 randomised patients. This outcome was assessed by an independent review committee using the RECIST 1.1 for tumour assessment every 8 weeks for the first 12 months and then 12 weeks thereafter. The company also provided PFS in the full ITT population as a post-hoc analysis. The secondary outcome was overall survival, using the intention to treat population of 658 patients. Survival was assessed every 8 weeks (± 7 days) after the post-treatment follow-up visit. Objective response rate was also a secondary outcome and was defined as the proportion of subjects for whom

the best overall response at the time of data cut off was complete response or partial response, as assessed by the independent review committee that occurred at the same assessment period as the PFS assessment.

Additional outcomes recorded in METEOR included measures of quality of life (QoL) using the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-19) and the EQ-5D-5L. The FKSI-19 is a self-report questionnaire measuring disease-related symptoms on a 5-point scale, 1 being "not at all" and 4 "very much". The total score and four-disease related symptoms subscales (FKSI-DRS-Physical, FKSI-DRS-Emotional, FKSI-Treatment Side Effects and FKSI-Function/Well-Being) were calculated. Total scores, subscale scores and change from baseline value were compared for each treatment group. The EQ-5D-5L is a questionnaire assessing of health status in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). The percentage of patients in each of the five dimensions was compared between treatment groups at both baseline and each visit during treatment. The proportion of patients in each level, Level 1 being 'no problem' to Level 5 'extreme problem were compared by treatment group. Both questionnaires were administered at baseline prior to the first dose of the study treatment and subsequently every 4 weeks for 6 months followed by once every 8 weeks thereafter. These assessments occurred regardless of study treatment given, dose reductions or discontinuation, and were continued until the date of the last tumour imaging assessment. The ERG notes that the use of a self-reported scale can be problematic within an open label trial as patients are aware what intervention they are receiving and may respond to the questionnaires in a biased way depending on the treatment they are receiving; therefore some caution should be taken when considering these results.

Safety analyses were performed on the safety population (331 in cabozantinib group and 322 in the everolimus group), these were patients that had received at least one dose of study treatment. Adverse event information was collected at study visits and could also be collected any time over the phone or by subject reporting. Details of adverse event seriousness, severity grade and relationship to study treatment was assessed by the investigators. Adverse events in both treatment groups were managed with supportive care and dose modifications.

The ERG considers the METEOR trial to be well conducted but considers it important to highlight that its open label design adds potential bias, particularly to self-reported health-related quality of life (HRQoL) measures. This is less of an issue for the other outcomes of the trial such as ORR and PFS that were assessed by a blinded independent review committee therefore removing any bias through knowledge of treatment allocation. Overall survival was assessed by unblinded investigators, however as the company outline, due to the objective nature of the measure there is little scope for bias.

4.2.2 Baseline characteristics

The baseline characteristics for METEOR are summarised in Table 10. They are presented for both the PITT population used for the primary outcome of PFS as well as the ITT population used for secondary outcomes. METEOR was a multi-centre trial, with 49% of patients enrolled in Europe and approximately 4% in the UK. The baseline characteristics appear to be balanced between the two intervention groups.

The ERG's clinical advisors confirmed the population in METEOR to be reflective of UK clinical practice. They also noted that the trial contained a high proportion of patients with an ECOG performance status of 0 (67%) and that this would be reflective of the fitter patients found in current practice. The ERG notes that the company have provided limited data concerning number of patients that had received, 1, 2 or ≥3 prior therapies. Based on the inclusion criteria, patients were eligible if they had received prior therapies excluding mTORs or cabozantinib. The majority of patients in METEOR had received only 1 prior therapy (70%). The most frequent prior therapy was sunitinib with 64% of patients in the cabozantinib ITT population receiving it compared to 62% of patients in the everolimus ITT population. Pazopanib was the second most common prior therapy with 44% of those in the cabozantinib ITT group compared to 41% in the everolimus ITT group. Sunitinib and pazopanib are the recommended first line treatments by NICE [28] therefore these prior therapies are in line with those used in the UK.

Table 10. Baseline characteristics of patient's in METEOR (Adapted from CS, pg 56, Table 12 and additional data provided by company at clarification stage)

Characteristic	**PITT**		**ITT**	
	Cabozantinib N= 187	**Everolimus N= 188**	**Cabozantinib N= 330**	**Everolimus N= 328**
Age — yr				
Median (range)	62	61	63	62
Range	36–83	31-84	32-86	31–84
Sex — no. (%)				
Male	142 (76)	130 (69)	253 (77)	241 (73)
Female	45 (24)	57 (30)	77 (23)	86 (26)
Not reported	0	1 (<1)	0	1 (<1)
Geographic region — no. (%)				
Europe*	83 (44)	84 (45)	167 (51)	153 (47)
North America	76 (41)	64 (34)	118 (36)	122 (37)
Asia–Pacific	25 (13)	36 (19)	39 (12)	47 (14)
Latin America	3 (2)	4 (2)	6 (2)	6 (2)
Race — no. (%)†				
White	157 (84)	147 (78)	269 (82)	263 (80)
Asian	12 (6)	20 (11)	21 (6)	26 (8)
Black	4 (2)	2 (1)	6 (2)	3 (<1)
Other	10 (5)	6 (3)	19 (6)	13 (4)
Not reported	4 (2)	12 (6)	15 (5)	22 (7)
Missing data	0	1 (<1)	0	1 (<1)
ECOG performance-status score — no. (%)‡				
0	129 (69)	116 (62)	226 (68)	217 (66)

1	58 (31)	72 (38)	104 (32)	111 (34)
MSKCC prognostic risk category — no. (%)§				
Favourable	80 (43)	83 (44)	150 (45)	150 (46)
Intermediate	80 (43)	75 (40)	139 (42)	135 (41)
Poor	27 (14)	30 (16)	41 (12)	43 (13)
Prior VEGF tyrosine kinase inhibitors — no. (%)				
1	137 (73)	136 (72)	235 (71)	229 (70)
2	42 (22)	49 (26)	84 (25)	91 (28)
≥3	8 (4.3)	3 (1.6)	11 (3.3)	8 (2.4)
Previous systemic therapy — no. (%)				
Sunitinib	114 (61)	113 (60)	210 (64)	205 (62)
Pazopanib	87 (47)	78 (41)	144 (44)	136 (41)
Axitinib	28 (15)	28 (15)	52 (16)	55 (17)
Sorafenib	11 (6)	19 (10)	21 (6)	31 (9)
Bevacizumab	1 (<1)	7 (4)	5 (2)	11 (3)
Interleukin-2	11 (6)	13 (7)	20 (6)	29 (9)
Interferon alfa	6 (3)	13 (7)	19 (6)	24 (7)
Nivolumab	9 (5)	11 (6)	17 (5)	14 (4)
Radiotherapy — no. (%)	56 (30)	61 (32)	110 (33)	108 (33)
Nephrectomy — no. (%)	156 (83)	153 (81)	282 (85)	279 (85)

Abbreviations ECOG, Eastern Cooperative Oncology Group; ITT, intention to treat; MSKCC; Memorial Sloan Kettering Cancer Center; PITT, primary-end point intention to treat; VEGF, vascular endothelial growth factor receptor.

Information about the number of prior therapies patients have received is important for judging the applicability of the trial data to the company's suggested positioning of cabozantinib as a second-line therapy in the current treatment pathway. At the clarification stage the company provided data concerning the number of patients that had received 1, 2 or ≥3 prior therapies. These revealed that although the majority of patients had received 1 or 2 prior therapies (~97%) there was a minority of patients, 3.3% in the cabozantinib group and 2.4% everolimus group that had received 3 or more prior VEGF-TKI therapies.

4.2.3 Description and critique of statistical approach used

The company discuss their statistical analysis methods in Section 4.4 of the CS (CS, pg 51) and a summary is provided in Table 11.

The METEOR trial was designed to provide adequate power to detect a statistically significant difference for both the primary outcome of PFS and the secondary outcome of OS. In the planned analysis for PFS, 259 events were required to provide 90% power to detect a HR of 0.667 (5 months in the everolimus group and 7.5 months in the cabozantinib group). This design required a minimum observed effect, in order to result in a statistically significant difference, of 27.8% (HR 0.783) in PFS from 5 to 6.39 months during 259 observed events in 375 subjects in the study. The planned analysis for OS was based on a single interim analysis during the primary analysis of PFS. A total of 408 deaths were required to provide 80% power to detect a HR of 0.75 (15 months in the everolimus group and 20 months in the cabozantinib group). The minimum observed effect, in order to result in statistical significance difference, of 22.5% (HR 0.816) in OS from 15 to 18.38 months. A total of 640 subjects

(325 per treatment group) were required to observe the number of events during the trial duration of 21 months.

The primary outcome of PFS was assessed using the PITT population, comprised of the first 375 randomised patients in the trial rather than the full trial ITT population. The company rationale for using the PITT population rather than the total ITT was based on the total sample size of the trial being larger than required to detect a significant change in PFS. The company argue using a large sample size would result in patients that progress early being over represented or those who progress late would be under represented. The ERG highlights that the use of the PITT analysis provides limitations compared to the ITT analysis when considering decision-making. The ERG acknowledges that the company did provide PFS results using the ITT as a post-hoc analysis, which provides transparency regarding the difference in the PFS results. The secondary outcome measures of the trial, OS and ORR were assessed using the ITT population which compromised of 658 randomised patients. The safety population, was used to conduct safety analyses in the trial and compromised of all patients who received at least one dose of the trial intervention.

Planned analyses for PFS, OS and ORR were carried out at data collected until the data cut-off point, May 2015. However, OS analysed at this interim period was found to not meet the significance boundary (HR 0.67; 95% CI: 0.51 to 0.89; p=0.005 49% information fraction: critical p value ≤0.0019) defined by the Lan-DeMets O-Brien-Fleming alpha spending function. Therefore, an unplanned secondary analysis was carried out for OS at a later data cut off time point, December 2015. This provided a minimum of 13 months follow-up from the last patient enrolment.

Patients were censored on the date of their last tumour assessment for those that received subsequent anti-cancer therapy before experiencing an event or had not experienced an event at the time of data cut-off (May 2015). Patients that had missed two or more tumour assessments followed by an event were censored to the most recent tumour assessment before the missed assessments. For OS, patients that were alive at the time of data cut-off (December 2015) had their duration of OS censored at the date last known to be alive. The ERG considers these methods of censoring and managing missing data appropriate.

Pre-specified subgroup analyses were carried out by the company, these included the number of prior VEGF-TKI therapy and Memorial Sloan Kettering Cancer Center (MSKCC) or Heng prognostic factors. An additional post-hoc analysis of OS was carried out for patients that had only received either sunitinib or pazopanib as prior VEGF-TKI therapy.

Overall, the ERG considers the statistical approach taken by the company for the secondary outcomes to be appropriate.

Table 11: Summary of statistical analysis in METEOR (reproduced from CS, pg 53, Section 4.4)

Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Treatment with cabozantinib will improve overall survival compared to everolimus in patients with advanced RCC	OS and PFS estimated with stratified log-rank test with randomisation stratification factors. Median Duration of PFS and OS corresponding 95% CI and landmark proportions estimated using Cox regression model, adjusting for randomisation stratification factors. Proportional hazards assumption evaluated by visual inspection of log-log plots. Analysis of ORR used ITT. Hypothesis testing using 2-sided chi-squared test at 0.01 alpha level. Point estimates and differences in response rates and CI were provided. Subgroup analyses for PFS and OS were pre-specified: Prior VEGF-TKI treatment, prognostic score. Additional subgroup of prior treatment of either sunitinib or pazopanib. CI and p values provided with unadjusted HRs.	The sample size was calculated in order to compare the PFS and OS between subjects randomised to receive cabozantinib and subjects randomised to receive everolimus. For PFS the final analysis was planned to take place after 259 events providing 90% power to detect a HR of 0.667 (5 months in everolimus arm vs 7.5 months in cabozantinib arm) with a 2-sided significance level of 5%. For OS, an initial single interim analysis was planned alongside primary analysis of PFS. A total of 408 death provide 80% power to detect HR of 0.75 (15 months in everolimus arm vs 20 months in cabozantinib arm) using 2-sided significance level of 4%. This planned interim analysis did not meet significance boundary (HR 0.67; 95% CI 0.51-0.89; p=0.005; 49% information fraction: critical p value ≤0·0019) therefore second interim analysis was carried out, with critical p value to achieve significance 0·0163 or lower. A total of 650 patients (325 per treatment arm) were to be randomised to ratio of 1:1 for study duration of 21 months (17 months to observe PFS events among 375 patients and 36 months to observe deaths for OS among 650).	For patients who were alive at the time of data cutoff or who were permanently lost to follow up, duration of OS was censored at the date the subject was last known to be alive. For PFS patients who had received subsequent anti-cancer therapy before experiencing an event or had not experienced an event at the time of data cutoff were censored on the date of last tumour assessment. Patients who had missed two or more scheduled tumour assessments followed by an event were censored on the date of their most-recent tumour assessment prior to the missing assessments. PFS censoring triggers also applied to ORR.
Abbreviations in table: CI, confidence interval, HR, hazard ratio; ITT, intention to treat; KM, Kaplan Meier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RCT, randomised controlled trial; VEGFF-TKI, Vascular endothelial growth factor receptor Tyrosine kinase inhibitor			

4.2.4 Summary statement

In summary, the ERG considers that the company's systematic review of the clinical literature followed recommended methodological practices. One Phase III randomised controlled trial, METEOR, was identified that directly evaluated the efficacy of cabozantinib compared to everolimus for treating advanced renal cell carcinoma. The METEOR trial was a well conducted trial; however due to its open

label design there is the potential for bias particularly for subjective outcomes including HRQoL (where patients in the cabozantinib group may have overestimated their HRQoL). The baseline characteristics appear to be well balanced between trial groups and the trial population was considered broadly representative of patients seen in current UK clinical practice. The outcomes assessed in the trial included PFS, OS, ORR and HRQoL, which are clinically relevant in addressing the decision problem as outlined in the final scope issued by NICE.[8] The statistical analyses carried out was appropriate for the secondary outcomes, OS and ORR using an intention to treat analysis (ITT). For the primary outcome PFS, the use of the primary end point intention to treat analysis (PITT) has limited use with regards to decision-making (further discussed in Section 4.2.3). Due to limited head-to-head data, comparisons between key comparators were determined using indirect evidence from a NMA, further details on this are discussed in Section 4.4. The ERG considers the trial conduct and statistical analyses to be of a high standard despite the open-label design and choice to use a modified ITT population for the primary outcome of the trial.

4.3 METEOR clinical effectiveness results

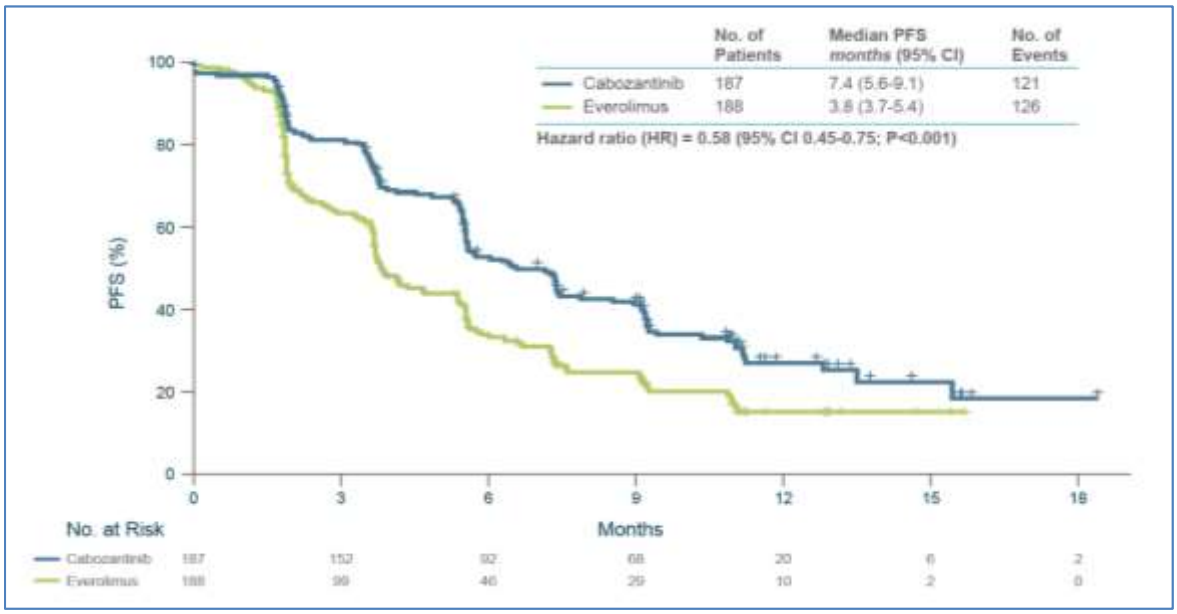
The results of METEOR, the only study providing direct clinical evidence for cabozantinib within the CS, are discussed in this Section. The ERG consider it important to highlight that the PFS results for both the PITT (first 375 randomised subjects) and ITT populations (all 658 randomised subjects) were presented in the CS, whereas the OS and ORR results were presented for only the ITT population. The data cut offs also varied slightly amongst the outcomes with it being 22 May 2015 for PFS and ORR, and 31 December 2015 for OS. The ERG considers these analyses and data sets to be the most appropriate given the statistical analysis plan for METEOR and the available data at the time of completion of the CS.

4.3.1 PFS (primary endpoint of METEOR)

4.3.1.1 PITT population

METEOR achieved its primary objective of cabozantinib prolonging PFS as assessed by the independent radiology review committee (IRC). PFS in METEOR was statistically significantly longer with cabozantinib compared to everolimus and the median PFS was 7.4 months vs 3.8 months, respectively (HR 0.58; 95% CI: 0.45 to 0.75; p-value <0.001) (Figure 8).

Figure 8. METEOR Kaplan-Meier plots of PFS for the PITT population (Reproduced from the CS, page 61, Figure 11)

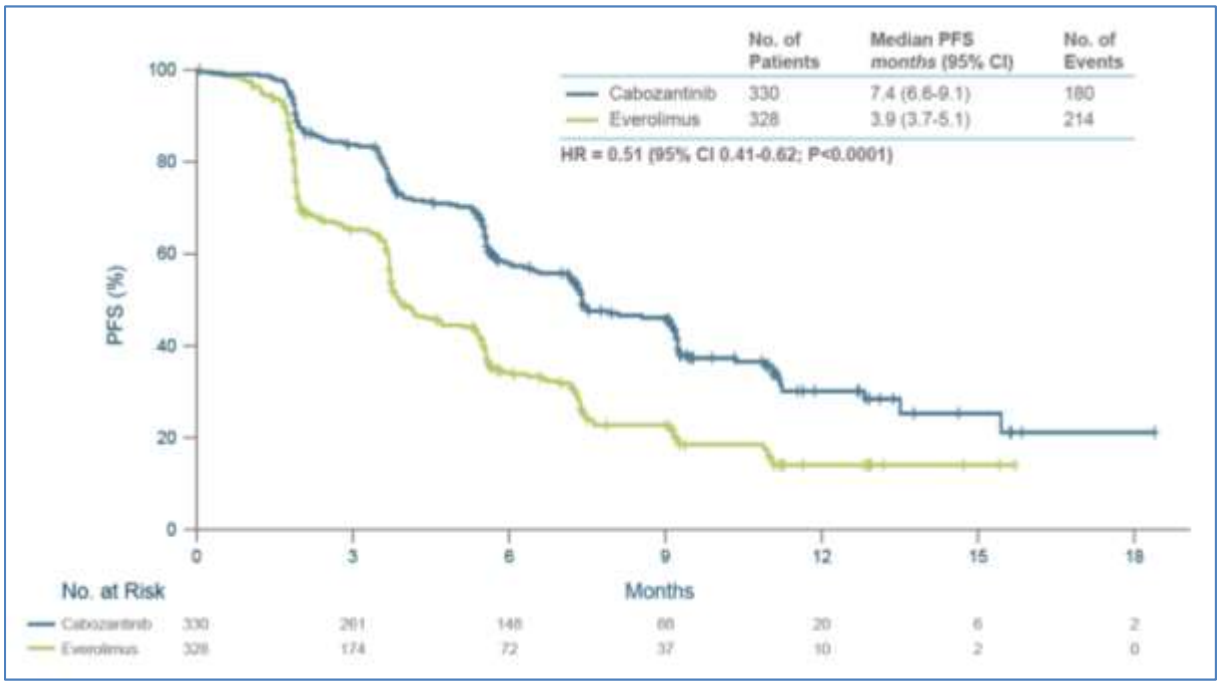


Source: Choueiri et al 2015[49]

4.3.1.2 ITT population

A similar clinical benefit to that observed for PFS in the PITT population of METEOR was also observed in the ITT population. The median PFS was 7.4 months in the cabozantinib group vs 3.9 months in the everolimus group and again it was statistically significant, favouring cabozantinib (HR 0.51; 95% CI: 0.41 to 0.62; p<0.0001) (Figure 9).

Figure 9. METEOR Kaplan-Meier plots of PFS for the ITT population (Reproduced from the CS, page 62, Figure 12)

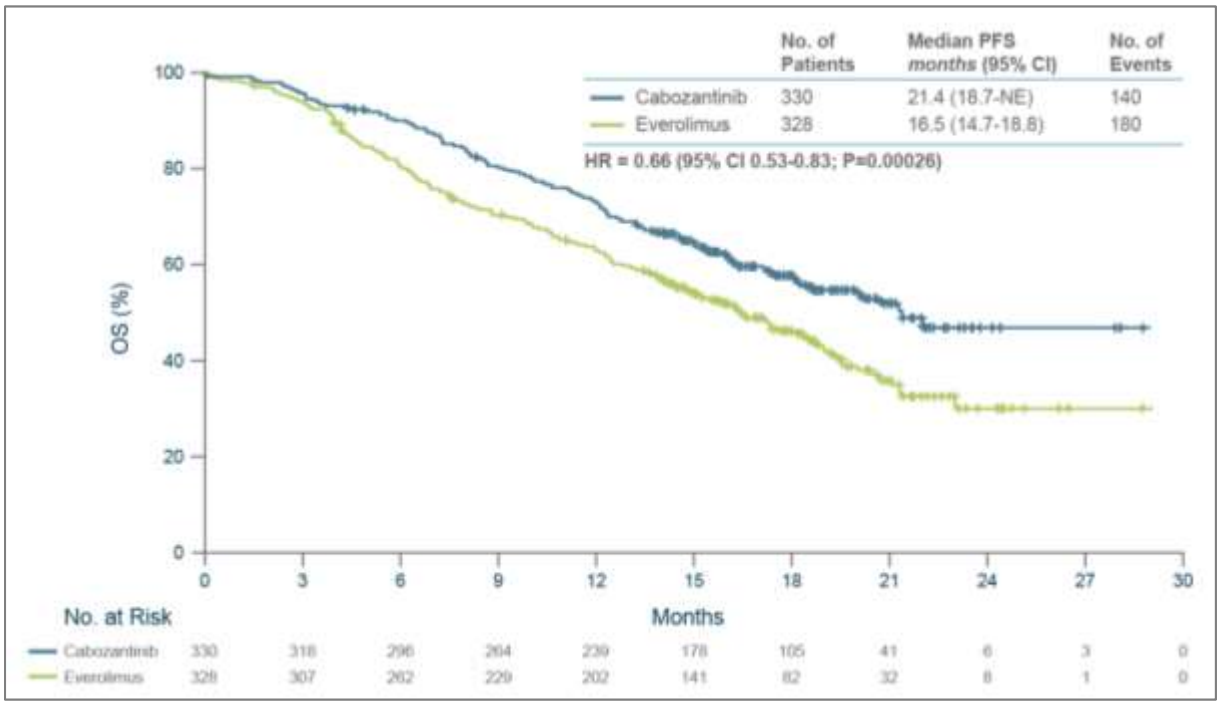


Source: Choueiri et al 2016[1]

4.3.2 Overall survival

Cabozantinib was associated with a statistically significantly longer median overall survival (OS) of 4.9 months compared to everolimus (HR 0.66; 95% CI: 0.53 to 0.83; p=0.00026). The median OS was 21.4 months (95% CI: 18.7 to not estimable) in the cabozantinib group and 16.5 months (14.7 to 18.8) in the everolimus group (Figure 10). The median duration of follow-up for OS was 18.7 months (interquartile range [IQR] 16.1 to 21.1) in the cabozantinib group and 18.8 months (IQR 16.0 to 21.2) in the everolimus group.

Figure 10. METEOR Kaplan-Meier plots of OS for the ITT population (Reproduced from the CS, page 63, Figure 13)



Source: Choueiri et al 2016[1]

The Kaplan-Meier landmark estimates at 6, 12, 18, and 24 months presented in the CS also suggest that at each time point there is a greater proportion of patients estimated to be alive in the cabozantinib group compared with the everolimus group (48% versus 31% at 24 months) (Table 12).

Table 12. Kaplan-Meier landmark estimates of survivial in METEOR (Adapted from the CS, page 63, Figure 13)

Landmark	**Estimate of % of patients alive (95% CI)**	
	Cabozantinib N=330	**Everolimus N=328**
6 months	91 (87-93)	81 (76-85)
12 months	73 (68-79)	63 (58-78)
18 months	58 (53-64)	47 (41-52)
24 months	48 (38-55)	31 (23-39)

Source: Choueiri et al 2016 (supplementary appendix)[59]
Abbreviations: CI, confidence interval.

4.3.3 Objective response rate

The objective response rate (ORR) was also statistically significantly higher with cabozantinib compared with everolimus (as per independent radiology review committee assessment [IRC]). The ERG notes that no one achieved a complete response in either trial group and considers this may be due to the nature of the population being advanced RCC. However, 17% of patients in the cabozantinib group and 3% in the everolimus group achieved a partial response (p<0.0001) (Table 13).

Table 13. ORR and response rates in METEOR for the ITT population METEOR (Adapted from the CS, page 64, Table 15)

	Cabozantinib N=330	**Everolimus N= 328**
ORR, % (95% CI)	17 (13-22)*	3 (2-6)
Complete response, n (%)	0	0
Partial response, n (%)	57 (17)	11 (3)
Stable disease, n (%)	216 (65)	203 (62)
Progressive disease, n (%)	41 (12)	88 (27)
Not evaluable or missing n (%)	16 (5)	26 (8)

Source: Choueiri et al 2016[1, 59]
* p<0.001 compared to Everolimus
Abbreviations: ORR, objective response rate.

The median time to achieving an objective response (as per Independent Radiological Review) was 1.91 months (95% CI: 1.6 to 11) in the cabozantinib group compared with 2.14 months (95% CI: 1.9 to 9.2 months) in the everolimus group. An objective response was achieved earlier in patients treated with cabozantinib compared to with everolimus.

4.3.4 Health Related Quality of Life

As described in Section 3.4, both the FKSI-19 and EQ-5D quality of life tools were used to capture HRQoL in METEOR. The results suggest that HRQoL is similar with cabozantinib treatment when compared to everolimus treatment. Detailed results for each of the HRQoL tools are presented below.

4.3.4.1 FKSI-19

The FKSI-19 total score estimated mean change from baseline was similar for cabozantinib compared with everolimus (-3.48 and -2.21, respectively [Table 14]). There were also no clinically meaningful differences (defined as effect size ≥ 0.5; effect size = (treatment difference in mean change from baseline scores) / (pooled SD for both groups for baseline values), [Sloan *et al*. 2005]) between treatment groups in the FKSI-total and three subscales of Disease-Related Symptoms (DRS)-Physical, DRS-Emotional, and Function/Well-Being. However, for the Treatment Side Effects (TSE) subscale there was a clinically significant difference (effect size [ES] -0.621) with cabozantinib associated with a lower overall score compared to everolimus (-2.416 and -0.814, respectively). On the TSE subscale,

diarrhoea and nausea were worse for cabozantinib (ES -0.77 and -0.34, respectively) and the ERG notes that these are frequent AEs for VEGF-TKIs.

The company reported that the FKSI-19 scores at the end of treatment were approximately seven points lower than baseline in each group. The ERG notes that the company also reported that the end of treatment was generally associated with disease progression and thus it could be expected that HRQoL would be lower.

Table 14. Changes from baseline in FKSI-19, repeated measures analysis for the METEOR ITT population (Adapted from the CS, pages 66–67, Table 16)

	Cabozantinib N = 330			Everolimus N = 328			Difference in Mean Change[a]	Pooled SD	p-value[a]	Effect Size[b]
	n	LSMean	SD	n	LSMean	SD				
DRS-Physical	[redacted]	-1.093	[redacted]	[redacted]	-1.386	[redacted]	[redacted]	[redacted]	[redacted]	0.046
Lack of energy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Losing weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Short of breath	[redacted]	0.029	[redacted]	[redacted]	-0.271	[redacted]	[redacted]	[redacted]	[redacted]	0.295
Fevers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bone pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coughing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weak all over	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood in my urine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Good appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sleeping well	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DRS-Emotional	[redacted]	0.398	[redacted]	[redacted]	0.393	[redacted]	[redacted]	[redacted]	[redacted]	0.004
Worry condition will worsen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Side Effects (TSE)	[redacted]	-2.416	[redacted]	[redacted]	-0.814	[redacted]	[redacted]	[redacted]	[redacted]	-0.621
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.340
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-0.767
Side effects of treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Function/Well-Being (FWB)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Able to work	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Enjoy life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Content with quality life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Score	[redacted]	-3.483	[redacted]	[redacted]	-2.214	[redacted]	[redacted]	[redacted]	[redacted]	-0.130

Source: METEOR Clinical Study Report[60]
A positive mean change (higher score) indicates improved health-related quality of life status.
a Derived from the prespecified repeated-measures mixed-effects model analysis of covariance for all measures.
b Effect size ≥ 0.5 (if applicable) is deemed clinically meaningful (Sloan et al 2005). Effect size = (treatment difference in mean change from baseline scores) / (pooled SD for both groups for baseline values).
Abbreviations: DRS, disease-related symptoms; FKSI, Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index; ITT, intent-to-treat; LSMean, least squares mean; SD, standard deviation.

4.3.4.2 EQ-5D-5L

The company reported in the CS that there were no clinically significant treatment differences in EuroQol (EQ)-visual analogue scale (VAS) or EQ-Index scores between the cabozantinib and everolimus groups in METEOR (Figure 11 and Table 15). The ERG agrees that the results presented in the CS suggest no clinically significant treatment difference in EQ-5D score between cabozantinib and everolimus.

Figure 11. Mean change from baseline in EQ Index Score for the METEOR ITT Population (Reproduced from the CS, page 65, Figure 14)

Table 15. EQ VAS and EQ-5D-5L index scores: change from baseline, repeated measures analysis (Adapted from the CS, page 68, Table 17)

	Cabozantinib (N = 330)		**Everolimus (N = 328)**		**Difference in Mean Change[a]**	**Pooled SD**	**p-valuea**	**Effect Size[b]**
	n	**LS Means (SD)**	**N**	**LS Means (SD)**				
VAS	[redacted]	-1.32 ([redacted]	[redacted]	-1.27 ([redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Index Score	[redacted]	-0.02 ([redacted]	[redacted]	-0.02 ([redacted]	[redacted]	[redacted]	[redacted]	-0.009

Source: METEOR Clinical Study Report[60]
A higher score indicates better health-related quality of life.
a Derived from the prespecified repeated-measures mixed-effects model analysis of covariance for all measures.
b Effect size ≥ 0.5 (if applicable) is deemed clinically meaningful (Sloan et al 2005). Effect size = (treatment difference in mean change from baseline scores) / (pooled SD for both groups for baseline values).

4.3.5 Subgroup analyses

The company provided subgroup analyses based on prior therapy and prognostic score although only results for OS were presented in the main text of the CS. It was reported in the CS that all pre-specified

subgroups in METEOR demonstrated consistently longer OS and PFS with cabozantinib compared with everolimus (HR < 1). The OS and PFS results for the subgroups missing from the main text of the CS were provided in one of its appendices (CS, Appendix 7). The ERG notes that the results of many of the subgroup analyses for PFS and OS failed to reach statistical significance although there was a trend demonstrated in favour of cabozantinib over everolimus in terms of improving OS and PFS across the various subgroups. The results of those subgroups of most importance in addressing the NICE final scope are discussed further below (Section 4.3.5.1 and 4.3.5.2).

4.3.5.1 Number and duration of prior VEGF-TKI therapies

OS was consistently longer with cabozantinib compared with everolimus irrespective of the number of prior VEGF-TKIs or the duration since first treatment with a VEGF-TKI (Figure 12). The OS benefit of cabozantinib compared with everolimus was statistically significant in the subgroup of people with only 1 prior VEGF-TKI (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.50 to 0.85) [redacted]

The ERG notes that for the subgroup of people with 2 or more prior VEGF-TKIs there was no statistically significant difference between cabozantinib and everolimus for OS (HR 0.73, 95% CI: 0.48 to 1.10) although the trend was in favour of cabozantinib. In terms of PFS, based on the ITT population, cabozantinib was associated with a statistically significant benefit compared with everolimus in both the subgroup of patients with one prior VEGF-TKI (HR 0.52, 95% CI: 0.41 to 0.66) and the subgroup with two or more VEGF-TKIs (HR 0.51, 95% CI: 0.35 to 0.74).

Figure 12. OS subgroup results based on number and duration of prior VEGF-TKI therapy (ITT population) (Adapted from the CS, page' 69, Figure 15)

In addition, the company reported the results of a post-hoc ITT subgroup analysis for people who only received prior VEGF-TKI therapy which was with sunitinib and for the equivalent subgroup for pazopanib. Both of these post-hoc subgroups suggested a trend in OS benefit with cabozantinib compared to everolimus although only the prior sunitinib subgroup reached statistical significance (median OS cabozantinib vs sunitinib 21.4 months vs 16.5 months, HR 0.66, 95% CI: 0.47 to 0.93;

median OS cabozantinib vs pazopanib 22.0 months vs 17.5 months, HR 0.66, 95% CI: 0.42 to 1.04). The ERG considers it important to highlight that these are post hoc subgroups and should be interpreted with caution due to the risk of bias associated with post hoc analyses and issues with statistical multiplicity with multiple subgroup analyses.

4.3.5.2 Prognostic Score

In terms of prognostic score, the ERG considers the results to be more inconclusive although the HRs do suggest a trend favouring cabozantinib over everolimus in terms of improving OS irrespective of baseline MSKCC or Heng risk category (Table 16). However, the difference was only statistically significant in the group 0 and 1 MSKCC subgroups and in the IMDC (Heng) 1 risk group (Table 16).

Table 16. OS by baseline risk group (Adapted from the CS, page 70, Table 18)

	Cabozantinib		Everolimus		Median OS Cabozantinib vs everolimus	HR (95% CI)
	N	events	N	events		
MSKCC Risk group						
0 (Favourable)	150	48	150	66	[redacted]	0.66 (0.46, 0.96)
1 (Intermediate)	139	64	135	79	[redacted]	0.67 (0.48, 0.94)
2 or 3 (Poor)	41	28	43	35	[redacted]	0.65 (0.39, 1.07)
IMDC (Heng) risk group						
0 (Favourable)	66	14	62	17	[redacted]	0.70 (0.34, 1.41)
1-2 (Intermediate)	210	89	214	121	[redacted]	0.65 (0.49, 0.85)
3-6 (Poor)	54	37	52	42	[redacted]	0.74 (0.48,1.15)

Source: Choeuiri et al 2016[1], METEOR Clinical Study Report[60]
Abbreviations: IMDC, International Metastatic RCC Data Consortium; MSKCC; Memorial Sloan Kettering Cancer Center; NE, not estimable.

4.3.6 Adverse effects

Safety data presented in the CS from the METEOR study were based on the 31 December 2015 data cut-off and the safety population of the trial.

As discussed in Section 4.2.1, the median duration of treatment exposure was 8.3 months in the cabozantinib group and 4.4 months in the everolimus group in METEOR. The patients in METEOR were more likely to have a dose reduction with cabozantinib compared to with everolimus (number of patients with any dose reduction: 62% and 25%, respectively). However, the median daily dose was lower than the standard recommended doses for both cabozantinib (43mg instead of 60mg) and everolimus (9mg instead of 10mg).

The treatment emergent adverse events (TEAEs) observed with cabozantinib were consistent with those of other VEGF-TKI treatments for advanced RCC. The proportion of patients experiencing an adverse event (AE) was the same for both the cabozantinib and everolimus treatment groups (92% [Table 17]) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%, [Table 17]).

The most common TEAEs of any grade in the cabozantinib group compared with the everolimus group were diarrhoea (75% vs 28%), fatigue (59% vs 47%), nausea (52% vs 30%), decreased appetite (47% vs 36%) and palmar-plantar erythrodysaesthesia syndrome (PPES, 42% vs 6%). The company reported that the majority of the TEAEs were managed through study drug dose reductions. The ERG considers that this thus suggests the TEAEs were generally treatment related. The TEAEs that were most likely to lead to permanent discontinuation of cabozantinib were reported to be decreased appetite and fatigue. These were the most common TEAEs with everolimus and so were not unique to cabozantinib. However, there was a higher overall incidence of TEAEs with cabozantinib compared to everolimus and more people experienced grade 3 TEAEs with cabozantinib compared to with everolimus. The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus), fatigue (11% vs 7%, cabozantinib vs everolimus), and PPES (8% vs 1%, cabozantinib vs everolimus). There were fewer grade ≥3 TEAEs with everolimus and anaemia was the only grade ≥3 TEAE that occurred in over 10% of patients although it was more common with everolimus than cabozantinib (6% vs 17%, cabozantinib vs everolimus).

Table 17. Treatment emergent adverse events reported as Grade 1-2 in ≥10% in either treatment group in METEOR (Adapted from the CS, pages 101–102, Table 42)

	Cabozantinib (N=331)			Everolimus (N=322)		
	Grade 1-2	**Grade 3**	**Grade 4**	**Grade 1-2**	**Grade 3**	**Grade 4**
Any adverse event	70 (21%)	210 (63%)	25 (8%)	103 (32%)	167 (52%)	26 (8%)
Diarrhoea	206 (62%)	43 (13%)	0	85 (26%)	7 (2%)	0
Fatigue	159 (48%)	36 (11%)	0	130 (40%)	24 (7%)	0
Nausea	158 (48%)	15 (5%)	0	92 (29%)	1 (<1%)	0
Decreased appetite	146 (44%)	10 (3%)	0	111 (35%)	3 (1%)	0
Palmar-plantar erythrodysaesthesia syndrome	115 (35%)	27 (8%)	0	16 (5%)	3 (1%)	0
Vomiting	106 (32%)	7 (2%)	0	44 (14%)	3 (1%)	0
Weight decreased	105 (32%)	9 (3%)	0	42 (13%)	0	0
Constipation	89 (27%)	1 (<1%)	0	64 (20%)	1 (<1%)	0
Dysgeusia	80 (24%)	0	0	30 (9%)	0	0
Hypothyroidism	76 (23%)	0	0	1 (<1%)	1 (<1%)	0
Hypertension	73 (22%)	49 (15%)	0	14 (4%)	12 (4%)	0
Dysphonia	68 (21%)	2 (1%)	0	16 (5%)	0	0
Cough	67 (20%)	1 (<1%)	0	107 (33%)	3 (1%)	0
Stomatitis	65 (20%)	8 (2%)	0	71 (22%)	7 (2%)	0
Mucosal inflammation	60 (18%)	5 (2%)	0	64 (20%)	10 (3%)	1 (<1%)
Dyspnoea	56 (17%)	10 (3%)	0	82 (26%)	11 (3%)	3 (1%)
Aspartate aminotransferase increased	55 (17%)	5 (2%)	0	19 (6%)	1 (<1%)	0
Back pain	54 (16%)	8 (2%)	0	41 (13%)	7 (2%)	0
Rash	52 (16%)	2 (1%)	0	92 (29%)	2 (1%)	0
Asthenia	49 (15%)	15 (5%)	0	46 (14%)	8 (2%)	0
Abdominal pain	48 (15%)	12 (4%)	0	27 (8%)	5 (2%)	0
Alanine aminotransferase increased	47 (14%)	7 (2%)	1 (<1%)	20 (6%)	1 (<1%)	0
Pain in extremity	46 (14%)	5 (2%)	0	31 (10%)	1 (<1%)	0

Muscle spasms	45 (14%)	0	0	17 (5%)	0	0
Arthralgia	43 (13%)	1 (<1%)	0	46 (14%)	4 (1%)	0
Headache	43 (13%)	1 (<1%)	0	42 (13%)	1 (<1%)	0
Anaemia	42 (13%)	19 (6%)	0	73 (23%)	53 (17%)	0
Dizziness	41 (12%)	1 (<1%)	0	21 (7%)	0	0
Dyspepsia	40 (12%)	1 (<1%)	0	15 (5%)	0	0
Oedema peripheral	39 (12%)	0	0	70 (22%)	6 (2%)	0
Hypomagnesaemia	38 (12%)	6 (2%)	10 (3%)	5 (2%)	0	0
Dry skin	37 (11%)	0	0	35 (11%)	0	0
Proteinuria	37 (11%)	8 (2%)	0	28 (9%)	2 (1%)	0
Flatulence	33 (10%)	0	0	7 (2%)	0	0
Insomnia	32 (10%)	0	0	33 (10%)	1 (<1%)	0
Pyrexia	31 (9%)	3 (1%)	0	57 (18%)	2 (1%)	0
Pruritus	27 (8%)	0	0	48 (15%)	1 (<1%)	0
Blood creatinine increased	17 (5%)	1 (<1%)	0	39 (12%)	0	0
Hypertriglyceridaemia	17 (5%)	4 (1%)	0	31 (10%)	7 (2%)	3 (1%)
Hyperglycaemia	15 (5%)	2 (1%)	1 (<1%)	46 (14%)	16 (5%)	0
Epistaxis	14 (4%)	0	0	46 (14%)	0	0

Source: Choueiri et al 2016[1]

The ERG notes that the total incidence of grade ≥3 TEAEs was higher for cabozantinib compared with everolimus (71% vs 60%, cabozantinib vs everolimus), although the incidence of serious TEAEs of grade ≥3 was similar between both treatment groups (39% vs 40%, cabozantinib vs everolimus [Table 18]). The most common serious TEAE with cabozantinib was abdominal pain (3%) and with everolimus it was anaemia (3%).

There were 51 deaths (Grade 5 TEAEs) in METEOR and it was reported in the CS that most of these were a result of disease progression. However, there were three deaths that were investigator assessed as treatment-related although only one of these was in the cabozantinib treatment group (Table 18).

Table 18. Grade ≥ 3 serious adverse events (Adapted from the CS, page 103, Table 43)

	Cabozantinib (n=331)	**Everolimus (n=322)**
Grade ≥3 serious adverse events, n (%)	130 (39)	129 (40)
Most common Grade ≥3 serious adverse events, n (%)		
Abdominal pain	9 (3)	3 (1)
Pleural effusion	8 (2)	7 (2)
Pneumonia	7 (2)	13 (4)
Pulmonary embolism	7 (2)	1 (<1)
Anaemia	5 (2)	10 (3)
Dyspnoea	4 (1)	10 (3)
Deaths during the adverse event reporting period, n (%)*	26 (8)	25 (8)
Deaths assessed as treatment-related	1 (not otherwise specified)	2 (one aspergillus infection and one pneumonia aspiration)

Source: Adapted from Choueiri et al 2016[1]
* Grade 5 AEs were classified as deaths

4.3.7 Summary of clinical effectiveness data from METEOR

- PFS in METEOR was statistically significantly longer with cabozantinib compared to everolimus and the median PFS was 7.4 months vs 3.8 months, respectively (HR 0.58; 95% CI: 0.45 to 0.75; p-value <0.001). A similar clinical benefit to that observed for PFS in the PITT population of METEOR was also observed in the ITT population (HR 0.51; 95% CI: 0.41 to 0.62; p<0.0001).
- Cabozantinib was associated with a statistically significantly longer median overall survival (OS) of 4.9 months compared to everolimus (HR 0.66; 95% CI: 0.53 to 0.83; p=0.00026).
- The objective response rate (ORR) was statistically significantly higher with cabozantinib (17%; 95% CI 13 to 22) compared with everolimus (3%; 95% CI 2 to 6; as per independent radiology review committee assessment [IRC]).
- In terms of HRQoL, results for the estimated mean change from baseline in the FKSI-19 total score were similar for cabozantinib compared with everolimus (-3.48 and -2.21, respectively) and there was no clinically significant treatment difference in EQ-5D score between cabozantinib and everolimus.

- OS was consistently longer with cabozantinib compared with everolimus irrespective of the number of prior VEGFR-TKIs or the duration since first treatment with a VEGFR-TKI. The ERG considers the results based on prognostic score subgroups to be more inconclusive because they weren't statistically significant, although the HRs do suggest a trend favouring cabozantinib over everolimus in terms of improving OS irrespective of baseline MSKCC or Heng risk category.
- The proportion of patients experiencing an adverse event (AE) was the same for both the cabozantinib and everolimus treatment groups (92%) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%). The most common TEAEs of any grade in the cabozantinib group compared with the everolimus group were diarrhoea (75% vs 28%), fatigue (59% vs 47%) and nausea (52% vs 30%). The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus) and fatigue (11% vs 7%, cabozantinib vs everolimus).

4.4 Critique of the network meta-analysis (NMA)

The company conducted a network meta-analysis (NMA) due to the absence of head-to-head trials comparing cabozantinib with axitinib, nivolumab, and BSC in patients with advanced RCC who have progressed after previous VEGF-TKI treatment. The studies included in the NMA were identified via a standard systematic review process which included a systematic literature review. The methods used to identify the studies included in the NMA are described in detail in Section 4.1. The company reported that the review was conducted from a global perspective and as a result it included additional comparator treatments to those specified in the NICE final scope for this STA. A summary of the inclusion and exclusion criteria used for the NMA are presented in Table 19.

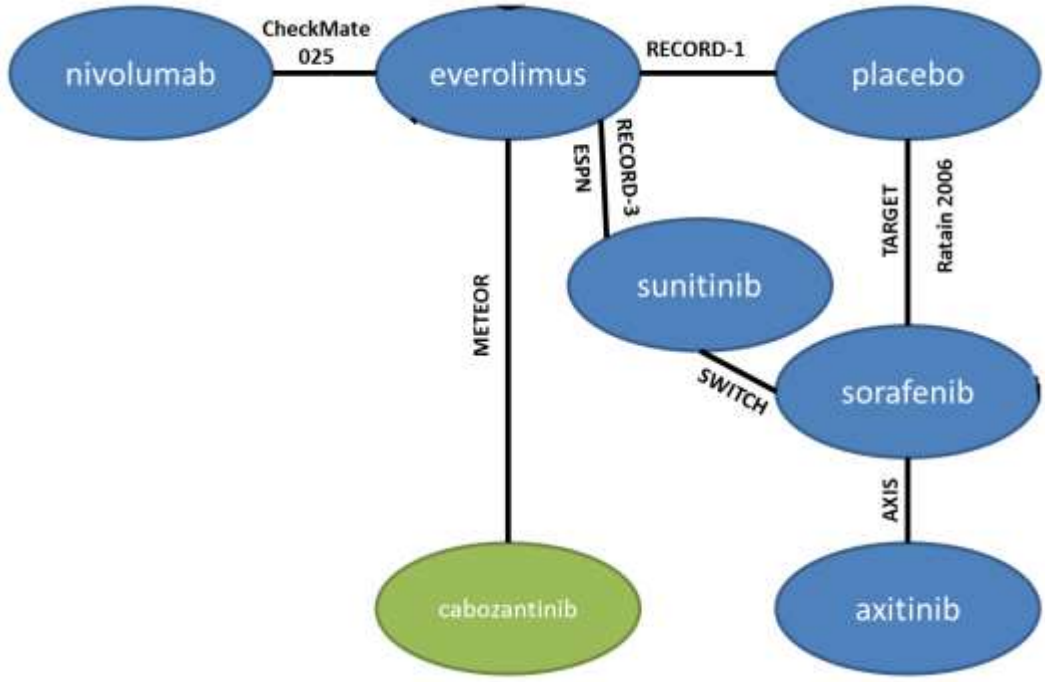
Table 19. Summary of inclusion and exclusion criteria used for the NMA (Adapted from the CS, page 73, Table 20)

	Inclusion Criteria	**Exclusion Criteria**
Population	Patients with previously treated advanced or metastatic renal cell carcinoma	Patients <18 years of age Healthy subjects Animal studies
Intervention	The following interventions in the second- (and further-) line setting: Cabozantinib (Cabometyx®▼) Axitinib (Inlyta®) Everolimus (Afinitor®) Sorafenib (Nexavar®) Sunitinib (Sutent®) Lenvatinib (Lenvima®) Nivolumab (Opdivo®)	Interventions in the first-line setting
Comparators	Any, including placebo and BSC	Radiotherapy, surgery and other non-pharmaceutical treatments

Outcomes	OS PFS	Patient-reported outcomes Biomarker results Safety results
Trial Design	RCT Systematic reviews, meta-analyses, HTAs were screened for bibliographies only	Non-RCT Comments, letters, editorials Non-systematic reviews
Timeframe	All publication years	
Language restrictions	English French German Italian Spanish	Publications with abstract in English but full text in language other than listed in inclusion criteria will not be included but listed.
Abbreviations: OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.		

A total of 65 publications, referring to 19 different studies, were included based on the criteria in Table 19. After limiting the comparators in the inclusion criteria to those in the NICE final scope or those providing an intermediate link between one of the other comparators, a further 10 studies were excluded. This left 9 studies for potential inclusion in the NMA (Figure 13).

Figure 13. Potential evidence network for NMA (Adapted from the CS, page 76, Figure 17)



The company reported that a further four studies (RECORD-3[61], SWITCH[52], ESPN[53] and Ratain et al. 2006[54]) were excluded due to methodological or clinical reasons (Table 20). The final NMA included 10 publications relating to five studies (Table 21).

Table 20. Company's rationale for the exclusion of four studies on methodological or clinical grounds (Adapted from the CS, page 77, Table 22)

Study	Key methodological and clinical parameters supporting exclusion
RECORD-3[61]	Sequential design and hence randomisation only for first-line treatment No PFS or OS data available for second line only
SWITCH[52]	Sequential design and hence randomisation only for first-line treatment Second line baseline characteristics not reported No OS data for second line
ESPN[53]	Only non-clear cell patients included No blinding details available
Ratain 2006[54]	No information on prior VEGF therapies

Abbreviations: PFS, progression-free survival; OS, overall survival; VEGF, vascular endothelial growth factor receptor.

The ERG agrees with the company's exclusion of these studies, particularly RECORD-3 and SWITCH as they don't present suitable data for inclusion in the NMA. If SWITCH is excluded then there is no benefit to including ESPN in the network as sunitinib becomes a satellite treatment that doesn't links into the network elsewhere. The only study which the ERG considers could have been included, is Ratain 2006. However, the ERG agrees with the company's decision to exclude it because it doesn't report whether patients had prior VEGF therapies, which is a requirement with cabozantinib. It was conducted between 2002 and 2004 and so was before VEGF inhibitors had become established as treatments in RCC so it is unlikely that all patients would have had prior VEGF therapy especially as only 89% had actually received a prior systemic anticancer therapy. It is also a relatively small study with only 65 patients, does not report data for overall survival and does not report hazard ratio (HR) or Kaplan-Meier plots for the PFS data. The ERG thus concludes that it's omission from the NMA was acceptable.

The final five trials included in the NMA were METEOR, AXIS, Checkmate 025, RECORD-1 and TARGET. They were all RCTs although there were differences between the trials in blinding, cross-over and prior therapies. Table 21 provides a summary of each of the studies and the differences between the studies is discussed further in the text below.

Table 21. Studies included in the company's NMA (Adapted from the CS, page 77, Table 23)

Study name	Design	Population	Treatment groups	Primary endpoint
METEOR[1]	Phase 3 RCT Open-label Parallel group	Adult patients with advanced RCC that has progressed after prior VEGF tyrosine kinase inhibitor therapy and must have had radiographic progression during treatment or within 6 months after the most recent dose of a VEGF inhibitor.	Cabozantinib Everolimus	PFS
RECORD-1[2]	Phase 3 RCT Double-blind	Adult patients with clear cell mRCC who had documentation of progressive disease during or within 6 months of stopping sunitinib and/or sorafenib (prior therapy with	Everolimus Placebo	PFS

	Cross over	cytokines and/or VEGF inhibitors also permitted)		
CheckMate 025[56]	Phase 3 RCT Open-label Parallel group	Adult patients with clear cell mRCC who had progressed after one or two previous regimens of antiangiogenic therapy	Nivolumab Everolimus	OS
TARGET[4]	Phase 3 RCT Double-blind Cross over	Adult patients with clear cell mRCC which had progressed after one systemic treatment within the previous 8 months not including VEGF pathway inhibitors	Sorafenib Placebo	OS
AXIS[5]	Phase 3 RCT Double blind Parallel group	Adult patients with clear cell mRCC who had progressed despite first-line systemic therapy (Sunitinib, bevacizumab plus interferon-alfa, temsirolimus or cytokines)	Axitinib Sorafenib	PFS
Abbreviations: RCT, randomised controlled trial; mRCC, metastatic renal cell carcinoma; PFS, progression-free survival; OS, overall survival.				

The company reported in the CS (CS, page 78) that the NMA was planned primarily on the efficacy endpoints of OS and PFS. Their rationale for this was that they are key outcomes of interest in RCC to clinicians and patients and are consistently selected as primary and secondary efficacy endpoints in RCC trials. The ERG agrees that PFS and OS are key outcomes but considers that the other outcomes (response rates, HRQoL and adverse events) requested in the NICE final scope are also important and should have been presented for all comparators specified in the NICE final scope.

The company reported that, "In order to assess the feasibility of performing an NMA, data availability for OS and PFS HRs and Kaplan-Meier curves were first assessed" (CS, page 78, Section 4.10.2) . In addition, it was reported in the CS that previous NICE technology appraisals were used alongside the journal publications of the studies in the NMA to try and source data for the outcomes where possible. A summary of this assessment is provided in Table 22. RECORD-1 and TARGET were both designed as cross-over studies and it was reported that pre-crossover results were extracted for OS. PFS as determined by an independent review panel was also extracted in preference to investigator assessed PFS, although only investigator assessed PFS was available from Checkmate025.

Table 22. Summary of the OS and PFS HRs and KM plots available from the studies in the NMA (Adapted from the CS, page 79, Table 24)

	OS ITT		**OS Cross-over adjusted**		**PFS Independent review committee**		**PFS Investigator assessed**	
	HR (95% CI)	**KM source in reference**	**HR (95% CI)**	**KM source in reference**	**HR (95% CI)**	**KM source in reference**	**HR (95% CI)**	**KM source in reference**
METEOR	0·66 (0.53–0.83)[1]	Figure 2[1]	Not applicable	Not applicable	0.51 (0.41, 0.62)[1]a	Figure 4[1]	Not applicable, IRC PFS available	Not applicable, IRC PFS available
RECORD-1	0.87 (0.65, 1.15)[2]	Figure 6A[2]	0.60 (0.22, 1.65)[62]	Figure 5[62]	0.30 (0.22, 0.40)[55]	Figure 2[55]	Not applicable, IRC PFS available	Not applicable, IRC PFS available
CheckMate 025	0.73 (0.57, 0.93)[56]	Figure 1[56]	Not applicable	Not applicable	Not available	Not available	0.88 (0.75, 1.03)[56]	Figure 2B[56]
TARGET	0.88 (0.74, 1.04)[4]	Figure1A[4]	0.78 (0.62, 0.97)[4]	Figure 1B[4]	0.44 (0.35, 0.55)[57]	Figure 2C[57]	Not applicable, IRC PFS available	Not applicable, IRC PFS available
AXIS**	0·997 (0.78, 1.27)[58]	Figure 2B[58]	Not applicable	Not applicable	0.741 (0.573 - 0.958)[5]	Figure 2C[5]	Not applicable, IRC PFS available	Not applicable, IRC PFS available

Note: ** prior-sunitinib group results reported.
[a] METEOR ITT population used for PFS instead of PITT (primary intention to treat).
Sources: [2]Motzer et al. 2010, [62]Korhonen et al. 2012, [55]Motzer et al. 2008, [56]Motzer et al. 2015, [4]Escudier et al. 2009, [57]Escudier et al. 2007, [58]Motzer et al. 2013, [5]Rini et al. 2011.
Abbreviations: OS, overall survival; ITT, intent to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier.

The economic model submitted as part of this STA also required time to treatment discontinuation (TTD) data although only METEOR and Checkmate 025 reported median treatment duration data and TTD Kaplan-Meier (KM) curves suitable for inclusion in this analysis (Table 23). The other studies (RECORD-1, TARGET and AXIS) all reported median treatment duration data but no KM curves and so they were not included in the TTD NMA.

Table 23. Time on treatment data availability for the studies in the NMA (Adapted from the CS, page 80, Table 25)

	Time on treatment	
	Median treatment duration	**KM source in reference**
METEOR	Cabozantinib: 8.3 months (CS, Table 80) Everolimus: 4.4 months (CS, Table 80)	CS, Figure 23
RECORD-1	Everolimus: 141 days[(2)] Placebo: 60 days[(2)]	Not available
CheckMate 025	Nivolumab: 5.5. months[(56)] Everolimus: 3.7 months[(56)]	Figure 39[(43)]
TARGET	Sorafenib: 25.6 weeks[(4)] Placebo: 15.7 weeks[(4)]	Not available
AXIS**	Axitinib: 6.4 months[(58)] Sorafenib: 5.0 months[(58)]	Not available

Note: ** prior-sunitinib group results reported.
Sources: [(2)]Motzer et al. 2010, [(56)]Motzer et al. 2015, [(4)]Escudier et al. 2009, [(58)]Motzer et al. 2013, [(43)]NICE STA in development [GID-TA10037] Manufacturer submission. 2016.
Abbreviations: CS, company submission; OS, overall survival; ITT, intent to treat; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; KM, Kaplan-Meier.

The company assessed the similarity of the studies for each outcome of the NMAs based on study design, prior therapies and prognostic score at baseline (Table 24). The availability of subgroup results for PFS and OS endpoints was also captured in Table 24.

Table 24: Assessment of similarity between studies in the NMAs and availability of outcomes and subgroup results (Adapted from the CS, page 81, Table 26)

	Study type	**Prior therapies**	**Prognostic score (MSKCC)**	**Subgroup results available by**
METEOR[(1)]	Phase 3 RCT Double blind Open-label Parallel group	1 prior VEGF Cabozantinib: 71% Everolimus: 70% 2+ prior VEGF Cabozantinib: 29% Everolimus: 30%	Favourable: 43-44% Intermediate: 40-43% Poor: 14-16% Missing: 0%	Patient level data available
RECORD-1[(2)]	Phase 3 RCT Double blind Cross-over	1 prior VEGF Everolimus: 74% Placebo: 74% 2+ prior VEGF Everolimus: 26% Placebo: 26%	Favourable: 28-29% Intermediate: 56-57% Poor: 14-15% Missing: 0%	Prognostic score: Yes Type of prior therapies: Number of prior therapies: No Cross-over adjusted: Yes
CheckMate 025[(56)]	Phase 3 RCT Double blind Open-label Parallel group	1 prior VEGF Nivolumab: 72% Everolimus: 72% 2 prior VEGF Nivolumab: 28% Everolimus: 28%	Favourable: 35-36% Intermediate: 49% Poor: 15-16% Missing: 0%	Prognostic score: Yes Type of prior therapies: No Number of prior therapies: Yes* Cross-over adjusted: NA
TARGET[(4)]	Phase 3 RCT	No prior VEGF therapy was	Favourable: 45-53% Intermediate: 47-55%	Prognostic score: No Type of prior therapies: No

	Study type	Prior therapies	Prognostic score (MSKCC)	Subgroup results available by
	Double blind Cross-over	received among patients.	Poor: NR Missing: NR	Number of prior therapies: No Cross-over adjusted: Yes
AXIS[5]	Phase 3 RCT Double blind Parallel group	1 prior treatment***	Favourable: 28% Intermediate: 36-37% Poor: 33% Missing: 2-3%	Prognostic score: No Type of prior therapies: Yes*** Number of prior therapies: No Cross-over adjusted: NA

*KM plot available in Nivolumab NICE appraisal, Company response to clarification questions. Appendix A8, Figure 2-5 on page 301-304.
**All patients received one previous systemic first-line regimen (sunitinib-based, bevacizumab plus interferon-alfa-based, temsirolimus-based, or cytokine based regimen) prior to study drug. 35% of patients received cytokine-based regimes.
***Subgroup is available by type of prior therapy (e.g. Sunitinib as first line treatment).
Abbreviations: BSC, best supportive care; RCT, randomised controlled trial; PFS, progression free survival; IRC, independent review committee assessed; INV; investigator assessed; vs, versus; NA, not applicable; NR, not reported.

The structure of the network for the OS and PFS NMAs is presented in Figure 14 and the equivalent network for TTD is presented in Figure 15.

Figure 14: Evidence network for OS and PFS NMAs (Reproduced from the CS, page 82, Figure 18)

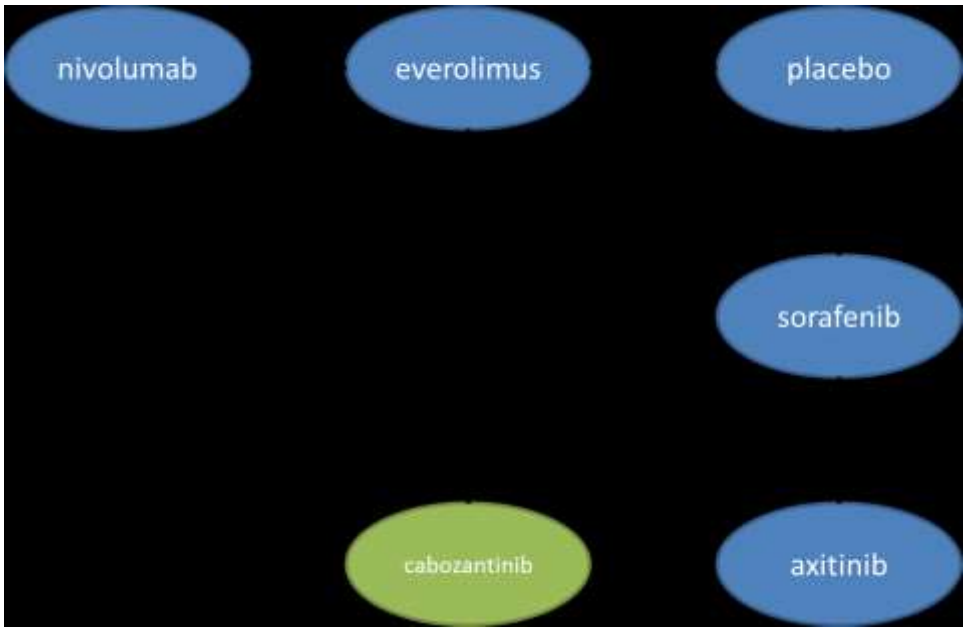
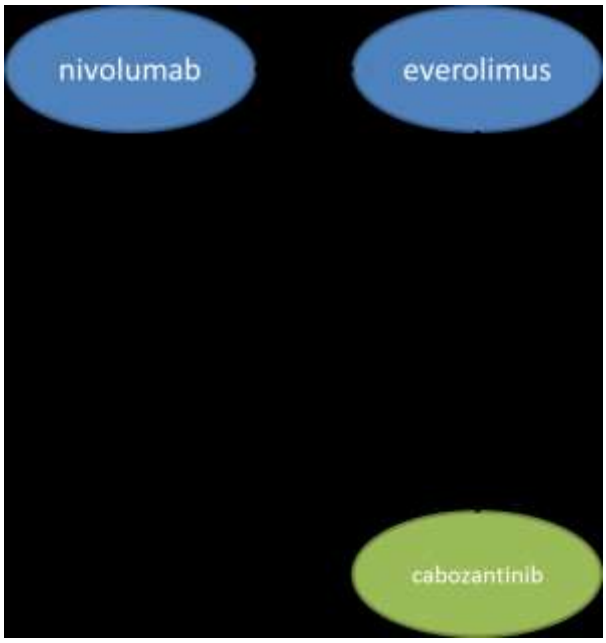


Figure 15: Evidence network for the TTD NMA (Reproduced from the CS, page 82, Figure 19)



As noted by the company, there were considerable differences between the included trials in the NMA in terms of the presence/absence of cross-over design, number and type of prior therapies, and baseline prognostic scores (Table 24).

RECORD-1 and TARGET both allowed cross-over following initial randomised study drug treatment discontinuation and thus cross-over adjusted results were sought to minimise the inherent bias associated with the cross-over treatment effect in line with the DSU Technical Support Document 16 (Treatment Switching).[63] The only cross-over adjusted data reported in TARGET was from the simple censoring of all placebo cross-over patients at the point prior to cross-over. The ERG notes that this censoring means the PFS results are unlikely to be affected by cross-over although the OS data will be affected as patients will likely of been censored earlier than if it wasn't a cross-over study. The ERG notes that at the cross-over censoring point in TARGET only 41% of the protocol defined 540 deaths had been observed. The pre-crossover results are thus immature due to this early censoring and the alternative ITT results would be biased due to the cross-over of patients in the placebo arm to sorafenib. The ERG notes the lack of IPD from TARGET and so it is not possible to conduct an analysis using a more formal crossover adjustment but the ERG also considers any estimate made through the link of TARGET in the NMA (i.e. the estimates of OS for axitinib) is likely to be unreliable. The results of RECORD-1 were reported using the rank-preserving structural failure time (RPSFT) model published by Korhonen et al[64] to adjust for the cross-over effect. The RPSFT model requires additional censoring of patient level data and so the precision of the HR estimate is

lower than that for the ITT estimate. However, the method is preferable to censoring of patients at time of crossover therefore for the purpose of the NMA the estimated HR using the RPSFT model in RECORD-1 was selected.

The ERG also notes that subsequent active treatments received in the other trials in the NMA are also potential sources of bias. In Checkmate025, 55% of patients in the nivolumab group and 63% in the everolimus group received subsequent systemic therapy. The most common subsequent therapy was everolimus for those in the nivolumab arm (26%) and it is unclear whether anyone in the everolimus arm received subsequent therapy with nivolumab. The ERG also notes that when Motzer *et al.* reported the overall survival results for AXIS, they highlighted that, "Analysis of overall survival might have been confounded by subsequent active treatments, which were given to the majority of patients who discontinued study treatment".[5] In METEOR similar proportions of patients in the everolimus group and the cabozantinib group were reported to have received subsequent systemic anticancer treatment after study treatment discontinuation (55% vs 50%; cabozantinib and everolimus, respectively) although of these 29% in the cabozantinib group received everolimus and 2% in the everolimus group received cabozantinib. The ERG considers the subsequent active treatments used in all of the trials in the NMA to be a potential source of bias for the estimates of overall survival although the resulting direction of bias for each treatment is unclear. The ERG notes that the company sought cross-over adjusted data from RECORD-1 and TARGET but the ERG does not consider the company to have addressed potential bias from subsequent active therapies in the other studies in the NMA.

The company's summary of the difference in number and types of prior therapies at baseline between the studies in the NMA is presented in Box 12.

Box 12. Overview of prior treatments in the studies in the NMA (Adapted from CS, page 84, Section 4.10.2)

In the METEOR study patients were included in the study if they had received at least one previous VEGF-TKI (there was no limit to the number of previous treatments).

In CheckMate025 patients were eligible to participate if they had received one or two previous regimens of antiangiogenic therapy.

In RECORD-1, previous therapy with sorafenib, sunitinib or both was allowed.

The TARGET study included patients if they had progressed after one systemic treatment within the previous 8 months.

AXIS study patients had received one previous systemic first line regimen with a sunitinib-based, bevacizumab plus interferon-alfa-based, temsirolimus-based, or cytokine based regimen, which reflected regimens with regulatory approvals at the time of the study design. In the NMA the prior-

sunitinib population was included as this was considered more comparable than prior cytokine-based regimens. For CheckMate025, results stratified by number of prior therapies received were reported in the ongoing nivolumab NICE STA although results were not reported by type of prior therapies. For RECORD-1 stratified estimates were available for PFS, but not OS. In the TARGET study publication no subgroup data were identified that stratified results by number/type of prior therapies. The AXIS study reported results by type of first-line therapy.
Abbreviations: PFS, progression-free survival; OS, overall survival; STA, single technology appraisal.

The ERG notes that prior treatment was a stratification factor in AXIS and thus the use of the prior-sunitib subgroup in the NMA maintains the randomisation from the trial. The ERG thus considers the subgroup use from AXIS in the NMA to be reasonable.

The data available on the number of previous therapies received in the METEOR, CheckMate025, RECORD-1, and AXIS studies are:

- METEOR: PFS and OS data (HR and 95% CI) by number of prior VEGF-TKIs (1, ≥ 2);
- CheckMate025: PFS data only (HR and 95% CI) by number of prior VEGF-TKIs (one/two);
- RECORD-1: PFS data only (HR, no 95% CI) by type of prior therapy (sorafenib/sunitinib/both);
- AXIS: PFS and OS (HR and 95% CI) by type of prior therapy (sunitinib regimen/bevacizumab regimen [PFS only]/temsirolimus regimen [PFS only]/cytokine regimen).

The company reported that due to the differences between the studies and the availability of data it was not possible to analyse the NMA results for the subgroup according to either prior type of therapy or prior number of therapies. In addition, although MSKCC prognostic score status at baseline was reported in all bar the AXIS study, there company reported there was insufficient reporting of PFS and OS data by MSKCC subgroup to enable any subgroup analyses by baseline prognostic score in the NMA.

The ERG consider it important to highlight that in response to clarification questions the company did provide a comparison of the one prior VEGF therapy subgroup from METEOR with the other comparators in the decision problem (i.e. second line cabozantinib). However, the ERG consider this analysis to be flawed because the comparator trials used in the NMA for this analysis contained patients with varying numbers of prior VEGF therapies and so were not the same population as the METEOR subgroup (i.e. second line patients) . The results of this analysis are thus subject to bias which the ERG consider would likely be favouring cabozantinib.

The company also reported in their clarification responses that a comparison of cabozantinib with all the comparators in the NICE decision problem using the METEOR subgroup of patients whom had received two prior lines of therapy with at least one VEGF (i.e. third line cabozantinib) was not feasible due to the lack of comparability with the other trials in the NMA. The ERG agrees with this decision although the ERG considers suitable subgroup data from some of the other trials in the network may be available. However, the ERG is unable to comment further on this issue due to limitations on time.

4.4.1 Quality assessment of studies in the NMA

The company provided quality assessments of each clinical trial in the NMA in an appendix of the CS (CS, Appendix 9) and reported that they were carried out by two assessors. The company concluded that the demographic and baseline characteristics were balanced between the treatment groups in all of the included studies. The company considered randomisation was carried out appropriately in only two studies (METEOR and AXIS) and for the remaining three studies (TARGET, RECORD-1 and CheckMate025) there was insufficient information to make a judgement. The company also considered there to be no unexpected imbalances in dropouts between study groups in any of the five studies and that they all reported ITT analysis with appropriate methods to account for missing data. The absence of double blinding in METEOR, AXIS and CheckMate025 was raised as a concern in the CS in terms of the resulting data quality. The ERG conducted its own quality assessment of the NMA studies and this, along with the company's assessment is presented in Appendix 10.1. In summary, the ERG generally agrees with the company's assessment although the ERG considers METEOR, TARGET and RECORD-1 to all have an imbalance in the number of dropouts, with more in the comparator study arms. The ERG agrees with the company's concerns around blinding and the open label trial design used in METEOR, AXIS and CheckMate025. The ERG also notes all of the included studies allowed subsequent active therapies with the type of therapy and the number of patients going on to receive these varying between the trial arms and being another potential source of bias in the NMA.

4.4.2 NMA data analysis methodology

The company considered two methods for comparing OS, PFS and TTD in the NMA: one based on the HRs and the other on the parametric curves (Kaplan-Meier). The method based on the HRs required a proportional hazard (PH) assumption to hold within each trial comparing a pair of comparators. The company digitally extracted the information from the relevant Kaplan-Meier plots (applying the algorithm from Guyot et al[65] and re-generated the patient-level data using the programming language R[66] to test whether the proportional hazards assumption was violated. The results of this assessment of PH for OS and PFS are presented in Table 25, and in Figure 16 for TTD from Checkmate 025. In summary, the PH assumption only held across the pairwise comparisons in METEOR, RECORD-1 and AXIS.

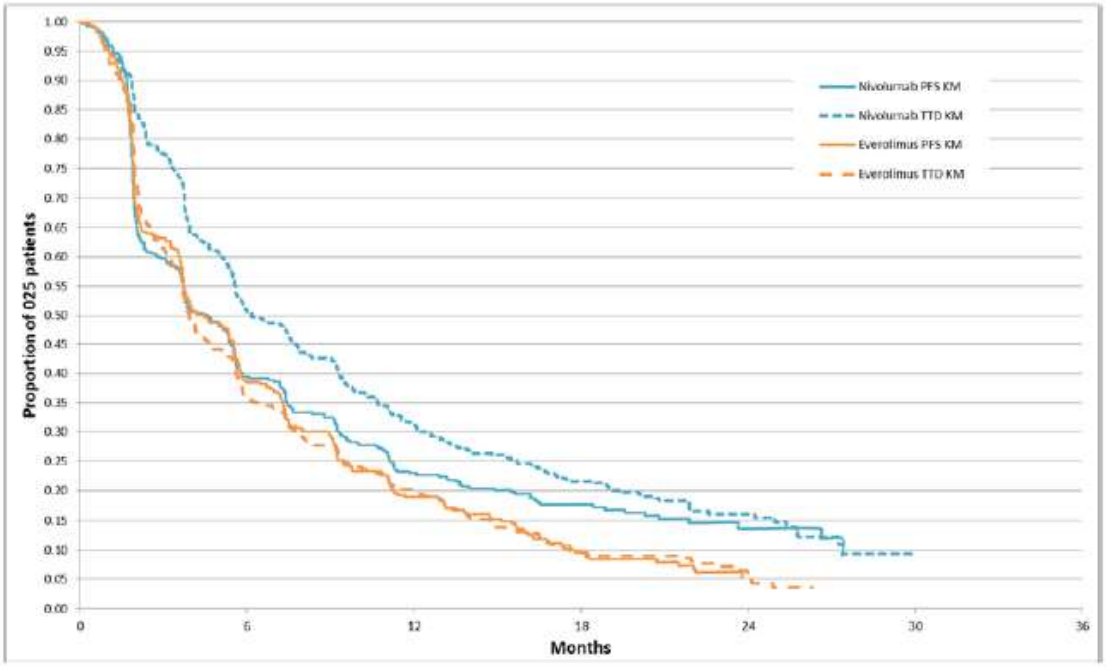
Table 25: Assessment of the proportional hazards assumption for OS and PFS for each study in the NMA (Adapted from the CS, page 90, Table 32)

Study Name	Base case cross-over adjustment		Sensitivity analysis ITT		Proportional hazards assumption holds?		Comments
	OS	PFS	OS	PFS	OS	PFS	
METEOR	Patient level data				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).
RECORD-1	Figure 5[62]	Figure 2[55]	Figure 6A[2]	Figure 2[55]	Yes	Yes	
CheckMate 025	Figure 1[56]	0.88 (0.75, 1.03)[56]	Figure 1[56]	Figure 2B[56]	No	No	
TARGET	Figure 1B[4]	Figure 2C[57]	Figure1 A[4]	Figure 2C[57]	No	No	
AXIS	Figure 2B[58]	Figure 2C[5]	Figure 2B[58]	Figure 2C[5]	Yes	Yes	

References: [62]Korhonen 2012, [2]Motzer et al 2010, [56]Motzer et al 2015, [57]Escudier 2007, [4]Escudier 2009, [5]Rini et al 2011, [55]Motzer et al 2009, [58]Motzer et al 2013

The digitalised KM plot for nivolumab from Checkmate 025 for PFS and TTD is presented in Figure 16.

Figure 16: Nivolumab KM PFS and TTD data from CheckMate025 (Reproduced from the CS, page 90, Figure 20)



Key: KM, Kaplan-Meier; PFS, progression-free survival; TTD, time to treatment discontinuation.

Source; Figure 39 from BMS submission. Nivolumab NICE appraisal [GID-TA10037][43]

The company reported that an NMA based on parametric curves was a more suitable method than that based on HRs given that the PH assumption does not hold for the TARGET and CheckMate 025 studies for any of the outcomes. The company went on to utilise a Bayesian NMA method based on parametric survival models and implemented it as described by Ouwens et al. 2010.[67]

The NMA was implemented with five parametric survival functions: log-normal, log-logistic, Weibull, Gompertz and exponential distributions, on the PFS and OS data. A generalised gamma distribution was not implemented due to technical reasons relating to WinBUGS. Each survival function used a specific underlying hazard function over time, h(t). Further details on the methodology used by the company is reported in Box 13. The ERG considers that a limitation of this approach is that it produces a family of survival curves for all treatments in the network; i.e. all results are either log-normal or log-logistic or Weibull or Gompertz or exponential. This simplification means that the goodness of fit statistics refer to the "average fit" across the network. That is, the distribution chosen may not fit any individual treatment well but, on average, that family of curves fits the network of treatments best. This limitation is discussed further in Section 5.

Box 13. Overview of the methodology used in the NMA (Reproduced from CS, pages 92–93, Section 4.10.4)

The digitised PFS or OS curves, S(t), from the identified studies were parameterised using the following five underlying survival functions over time:

$$S(t) = \begin{cases} \exp(-\lambda t^{\gamma}), & \text{for Weibull distribution,} \\ \exp\left(-\frac{a}{b}(\exp(bt)-1)\right), & \text{for Gompertz distribution,} \\ \frac{1}{1+at^{b}}, & \text{for log-logistic distribution,} \\ \Phi\left[-\frac{\log(t)-\alpha}{\beta}\right], & \text{for log-normal distribution,} \\ \exp(-\lambda t), & \text{for Exponential distribution,} \end{cases}$$

where Φ is the cumulative distribution of the standard normal distribution.

The algorithm of the NMA, presented in equation (1) in [CS] Appendix 12 could be programmed since the explicit formulas for hazard functions were available. The MCMC algorithm, presented in [CS] Appendix 12 was applied to estimate the parameters of the NMA model, i.e. parameters μ for the "baseline" treatment as well as those μ+δ for the other treatments relative to the "baseline" treatment. The survival functions were then estimated based on the posterior mean/median of those parameters, specific for treatments.

Abbreviations: NMA, network meta-analysis; PFS, progression-free survival; OS, overall survival.

The assumption of transitivity was tested for each survival distribution with details of the methods used for this reported in Appendix 11 of the CS. The company reported in the CS that the model parameters for each survival curve were estimated using a Markov Chain Monte Carlo (MCMC) method in

WinBUGS[68] that was run for 50,000 iterations with the first 25,000 iterations discarded as "burn-in". Convergence of the chains was confirmed using the Gelman-Rubin statistic.[69] Both fixed and random effects models were conducted and all networks were adjusted to the baseline of the METEOR study. The ERG is unable to comment on the appropriateness of the adjustment to the baseline of METEOR because details in the CS were limited.

4.4.3 NMA model fit and heterogeneity

Fixed and random effects models were run for both OS and PFS and compared for data fitting. The goodness-of-fit of the model prediction to the observed IPD was measured by computing the posterior mean residual deviance, Dbar.[70] The deviance information criteria (DIC) was then calculated and used to provide a measure of model fit for each outcome (Table 26, Table 27 and Table 28). The DIC was similar for both the fixed effects and random effects models (note that random effects model data were not reported in the CS for TTD). The company decided to use the fixed effect models for the primary NMA analyses with the rationale that they, "provided as good estimates as random effect models but were more stable, faster to run and provided good data fit" (CS, page 94, Section 4.10.5). As only a single study informs each within trial pairwise comparison, the ERG considers the use of the fixed effects model to be a pragmatic approach.

Table 26: Model fit statistics with OS (Adapted from the CS, page 93, Table 33)

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Residual deviance (Dbar)	4364.9	4364.8	4443.8	4344.0	4314.5	4314.3	4293.8	4293.4	4535.8	4536.3
Effective number of parameters (pD)	20.0	19.7	19.6	20.1	20.0	19.9	20.2	19.8	9.8	10.2
Deviance information criteria (DIC)	4384.9	4384.5	4463.4	4464.1	4334.5	4334.2	4314.0	4313.2	4545.6	4546.5
Abbreviations: FR, fixed effects; RE, random effects										

Table 27: Model fit statistics with PFS (Adapted from the CS, page 93, Table 34)

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Residual deviance (Dbar)	6355.8	6355.3	6456.8	6456.3	6047.7	6047.9	5987.3	5987.0	6599.7	6600.1
Effective number of parameters (pD)	19.7	20.0	19.8	19.8	19.9	19.9	20.2	19.9	9.9	10.2
Deviance information criteria (DIC)	6375.5	6375.3	6476.6	6476.1	6067.6	6067.8	6007.5	6006.9	6609.6	6610.3
Abbreviations: FE, fixed effects; RE, random effects										

Table 28. NMA model fit statistics for the fixed effects model for TTD (Adapted from the CS, page 97, Table 38)

Model fit statistics	Weibull	Gompertz	Log-logistic	Log-normal	Exponential
Residual deviance (Dbar)	2761.2	2767.1	2638.9	2597.5	2775.6
Effective number of parameters (pD)	7.6	7.7	7.8	7.8	4.0
Deviance information criteria (DIC)	2768.8	2774.8	2646.7	2605.3	2779.6

4.4.4 NMA results

The model with the lowest DIC was selected as the best fitting to the data and this was the log-normal fixed effects model. The NMA results for OS, PFS and TTD using the log-normal fixed effects model and the adjustment to the baseline from METEOR are presented in Figure 17, Figure 18 and Figure 19, respectively. The results of the NMA suggest that cabozantinib prolongs OS and PFS compared to axitinib, BSC (represented by placebo), everolimus and nivolumab. Median PFS and OS results also suggest cabozantinib has the greatest benefit compared with each of the comparators and median TTD was longer with cabozantinib compared with everolimus and nivolumab (9 months vs 5 months and 7.4 months respectively [Table 29]).

Figure 17: Averaged OS adjusted to the baseline from METEOR study, fixed effects (log-normal) (Adapted from the CS, page 98, Figure 21)

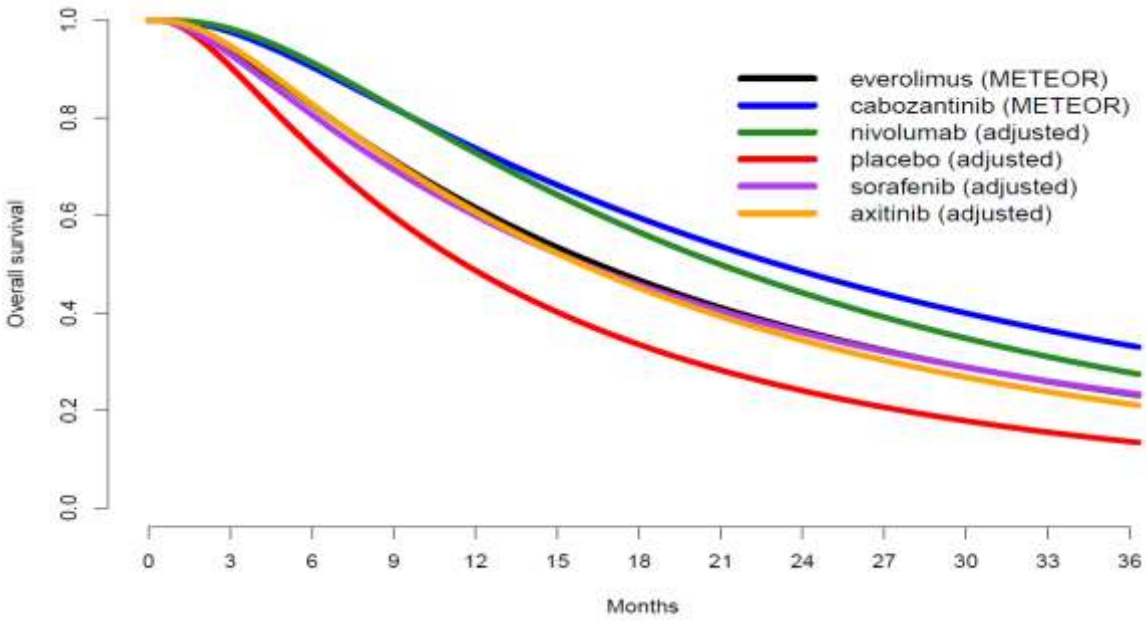


Figure 18: Averaged PFS adjusted to the baseline from METEOR study, fixed effects (log-normal) (Adapted from the CS, page 98, Figure 22)

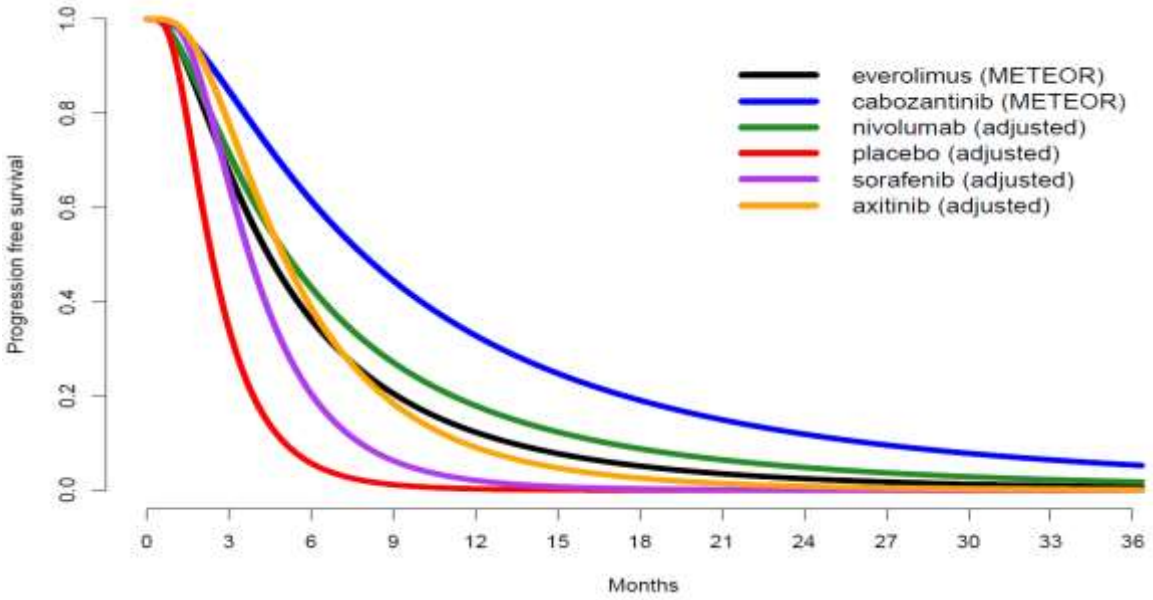


Figure 19: Averaged TTD adjusted to the baseline from METEOR study, fixed effects (log-normal) (Reproduced from the CS, page 99, Figure 23)

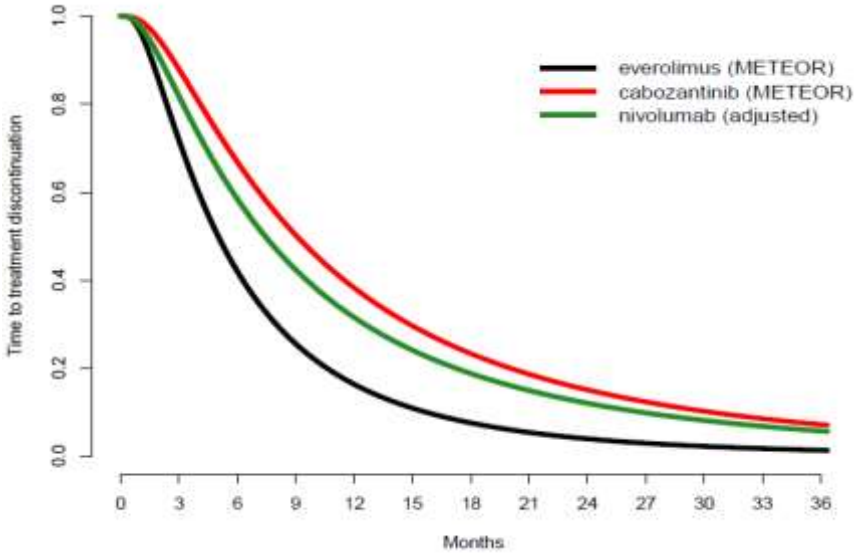


Table 29: Median OS, PFS and TTD results based on the log-normal function (Adapted from the CS, pages 99–100, Table 39 and Table 40)

	NMA result – log-normal function		
	Median OS (months)	**Median PFS (months)**	**Median TTD (months)**
Cabozantinib	22.9	7.8	9.0
Axitinib	15.7	4.9	N/A
Everolimus	16.3	4.4	5.0
BSC	11.5	2.4	N/A
Nivolumab	20.8	5.1	7.4
Abbreviations: BSC, best supportive care; OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation.			

The results of the company's sensitivity analyses using the ITT (un-adjusted) OS population were presented in Appendix 16. Of the CS.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG has concerns that the company's NMA results may be unreliable as a result of the heterogeneity of the trials included in the network, the lack of cross-over free OS data for TARGET and the use of immature OS data for TARGET. The ERG is particularly concerned about the overall survival estimate for axitinib generated by the company NMA as it is only linked into the network via TARGET. TARGET was a placebo-controlled trial and if it is assumed that sorafenib is likely to be more effective than placebo; utilising immature survival data is likely to underestimate the benefit of sorafenib over placebo. The results of AXIS show similar efficacy for axitinib and sorafenib and so the potential underestimating of OS in TARGET means that the survival benefit for axitinib will similarly be underestimated in the company's NMA. In addition, the ERG considers that the impact of subsequent active treatments in AXIS is highly likely to bias the estimated treatment effect for OS with differences between treatment groups in OS likely to be minimised as a result of cross-over. The ERG thus consider that the impact of not using mature and crossover-free OS data for TARGET and not adjusting for subsequent active treatments in AXIS is likely to minimise any relative benefit for axitinib compared to sorafenib in the network.

The ERG's clinical experts report that they would expect similar if not slightly better efficacy with axitinib when compared to everolimus. The ERG have conducted an exploratory analysis to explore the impact of assuming axitinib and everolimus have equal efficacy. This assumption is further supported by the results from a weight-adjusted indirect comparison of everolimus and axitinib using data from AXIS and RECORD-1, which showed similar median PFS for the two treatments.[71] The ERG analysis enables the exclusion of TARGET from the NMA as it is no longer required to provide a link between axitinib and the other comparators. The remaining comparators in the ERG's NMA were: cabozantinib, nivolumab, placebo and everolimus.

The ERG took the pragmatic decision to use a fixed effect model as there was no evidence available to inform the between trial heterogeneity. The ERG selected a fixed effects model for its NMA due to the limited data points for each treatment in the network. In addition, the ERG have assumed proportional hazards hold for OS for all treatments in the network as it appears to be only in the first 6 weeks in Checkmate 025 when this assumption appears to be violated. The ERG have selected HR as the summary statistic for all analyses and have used everolimus as the baseline. Similar to the company's approach, all analyses were conducted using WinBUGS and the ERG used a Bayesian Markov chain Monte Carlo (MCMC) simulation. As Bayesian statistical inference provides the probability that an estimate will take a particular value, results are presented with a 95% Credible Interval (CrI) rather than

a 95% Confidence Interval (CI). The OS results of the ERG's NMA are presented in Table 30. They show a similar treatment ranking to that seen in the company's NMA with cabozantinib having a statistically significant increase in OS compared to everolimus (HR 0.65; 95% Credible Interval [CrI] 0.53 to 0.83).

Table 30. HRs for OS generated by the ERG's NMA

Treatment	OS		
	HR	95% Credible Interval	
		Lower	Upper
Everolimus	Baseline	N/A	N/A
(Axitinib)	1.00	N/A	N/A
Cabozantinib	0.675	0.53	0.83
Nivolumab	0.74	0.57	0.93
Placebo	1.89	0.60	4.47
Abbreviations: HR, hazard ratio; OS, overall survival.			

The ERG also conducted an exploratory analysis for PFS assuming proportional hazards, although the ERG acknowledges that they do not hold for all the studies in the network and thus the results of this analysis should be interpreted with caution. The results of the ERG analysis of PFS were in keeping with the results of the company's NMA with a statistically significant increase in PFS for cabozantinib (HR 0.51; 95% CrI: 0.41 to 0.63) compared to everolimus (Table 31).

Table 31. HRs for PFS generated by the ERG's exploratory NMA

Treatment	PFS		
	HR	95% Credible Interval	
		Lower	Upper
Everolimus	Baseline	N/A	N/A
(Axitinib)	1.00	N/A	N/A
Cabozantinib	0.51	0.41	0.63
Nivolumab	0.88	0.75	1.03
Placebo	3.37	2.46	4.47
Abbreviations: HR, hazard ratio; PFS, progression free survival.			

The HRs generated by the ERG's NMA were then applied to the Weibull curve fitted to the everolimus arm of METEOR for the assessment of cost-effectiveness. The median values for OS are presented in Table 32 and those for the exploratory analysis of PFS are in Table 33. The results of the ERG's NMA are generally in keeping with those from the company's NMA. Cabozantinib is associated with the longest median PFS and OS in both the company's and ERG's NMA although the OS estimate is slightly lower in the ERG's analysis. The estimates for OS and PFS for placebo (BSC) from the ERG's NMA are slightly lower compared to those from the company's NMA. This supports the ERG's view that the inclusion of TARGET in the company's NMA is likely to have led to an overestimation of placebo and hence an underestimation in the efficacy of axitinib compared to everolimus.

Table 32. Estimated median OS for the ERG's NMA results and the company's NMA results

Treatment	Median OS (months)	
	Company's NMA	ERG's NMA
Cabozantinib	22.9	22.0
Axitinib	15.7	16.3
Everolimus	16.3	16.3
Placebo	11.5	10.1
Nivolumab	20.8	20.4
Abbreviations: NMA, network meta-analysis; OS, overall survival.		

Table 33. Estimated median PFS for the ERG's exploratory NMA and the company's NMA results

Treatment	Median PFS (months)	
	Company's NMA	ERG's NMA
Cabozantinib	7.8	7.8
Axitinib	4.9	4.7
Everolimus	4.4	4.7
Placebo	2.4	1.9
Nivolumab	5.1	5.2
Abbreviations: NMA, network meta-analysis; PFS, progression free survival.		

4.6 Conclusions of the clinical effectiveness section

- Marketing Authorisation was granted on 9 September 2016 for the use of cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior VEGF-targeted therapy.
- The clinical evidence presented in the company's submission (CS) for cabozantinib is derived from the METEOR phase III open-label randomised controlled trial. METEOR compared cabozantinib with everolimus in patients with advanced clear-cell renal cell carcinoma, who had been previously treated with at least one VEGF-TKI. The ERG considers METEOR to be a well-designed and conducted trial, and is of the view that the trial is reflective of English clinical practice.
- Safety and clinical efficacy results of METEOR are relevant to the decision problem as outlined in the NICE final scope for this STA and those considered by the ERG's clinical experts to be the key ones for patients with advanced RCC. All relevant comparators as specified in the NICE final scope for this STA were considered within the CS.
- PFS in METEOR was statistically significantly longer with cabozantinib compared to everolimus and the median PFS was 7.4 months vs 3.8 months, respectively (HR 0.58; 95% CI: 0.45 to 0.75; p-value <0.001).
- Cabozantinib was associated with a statistically significantly longer median overall survival (OS) of 4.9 months compared to everolimus (HR 0.66; 95% CI: 0.53 to 0.83; p=0.00026).

- The objective response rate (ORR) was statistically significantly higher with cabozantinib compared with everolimus (as per independent radiology review committee assessment [IRC]).
- In terms of HRQoL, results for the estimated mean change from baseline in the FKSI-19 total score were similar for cabozantinib compared with everolimus (-3.48 and -2.21, respectively) and there was no clinically significant treatment difference in EQ-5D score between cabozantinib and everolimus.
- OS was consistently longer with cabozantinib compared with everolimus irrespective of the number of prior VEGFR-TKIs or the duration since first treatment with a VEGFR-TKI. The HRs also suggest a trend favouring cabozantinib over everolimus in terms of improving OS irrespective of baseline MSKCC or Heng risk category.
- The proportion of patients experiencing an adverse event (AE) was the same for both the cabozantinib and everolimus treatment groups (92%) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%). The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus) and fatigue (11% vs 7%, cabozantinib vs everolimus).
- The company conducted a survival curve-based network meta-analysis (NMA) with five RCTs (METEOR, AXIS, Checkmate 025, RECORD-1 and TARGET) due to the absence of head-to-head trials comparing cabozantinib with axitinib, nivolumab, and BSC. However, there were differences between the trials in terms of the presence/absence of cross-over design, number and type of prior therapies, and baseline prognostic scores.
- The ERG has concerns that the company's NMA results were unreliable as a result of the heterogeneity of the trials included in the network, the lack of cross-over free OS data for TARGET and the use of immature OS data for TARGET. The ERG is particularly concerned about the overall survival estimate for axitinib generated by the company NMA as it is only linked into the network via TARGET.
- The results of the company's NMA suggest that cabozantinib prolongs OS and PFS compared to axitinib, BSC (represented by placebo), everolimus and nivolumab.
- The ERG conducted a conservative exploratory analysis to explore the impact of assuming axitinib and everolimus have equal efficacy. This analysis enables the exclusion of TARGET from the NMA. The results of the ERG's NMA show a similar treatment ranking to that seen in the company's NMA with cabozantinib having the lowest HR for OS compared to everolimus and cabozantinib is associated with a statistically significant increase in OS (HR 0.65; 95% Credible Interval [CrI] 0.527 to 0.825). The results of the ERG's NMA are generally in keeping with those of the company's NMA.

4.6.1 Summary of clinical issues

- The open label design of METEOR may be a potential source of bias particularly, for subjective outcomes including HRQoL (where patients in the cabozantinib group may have overestimated their HRQoL). The company states that it was open label to, "allow appropriate management of adverse events". The ERG considers that management of adverse events through dose reductions is common practice in clinical trials and that this could have been done while maintaining blinding to the treatments in METEOR.
- There was an omission of TRAEs reporting from METEOR in the CS. In addition, comparison of HRQoL, response rates and adverse effects for cabozantinib and axitinib, nivolumab or best supportive care were not presented in the CS.
- The ERG does not consider the METEOR data for the subgroup of people with two or more prior VEGFR-TKIs to address the NICE decision problem for the potential third line positioning of cabozantinib in the advanced RCC treatment pathway. This is because the comparator in METEOR is everolimus and the ERG's clinical experts report it is mainly used at second line and infrequently, if at all at third line. The ERG therefore consider the key comparator's for cabozantinib at third line to be BSC and nivolumab.
- The ERG does not consider the company to have provided suitable subgroup data by line of therapy for the comparison of cabozantinib with the axitinib, nivolumab and BSC in the NICE final scope for the potential second or third line positioning of cabozantinib. This is because the comparator trials used in the NMA for second line cabozantinib contained patients with varying numbers of prior VEGFR therapies and so were not the same population as the METEOR subgroup (i.e. second line patients). The company provided no analysis for the third line position.
- The ERG has concerns that the company's NMA results may be unreliable as a result of the heterogeneity of the trials included in the network, the lack of cross-over free OS data for TARGET and the use of immature OS data for TARGET. The ERG is particularly concerned about the OS estimate for axitinib generated by the company NMA. In addition, the ERG considers that the impact of subsequent active treatments in AXIS is highly likely to bias the estimated treatment effect for OS, with differences between treatment groups in OS likely to be minimised as a result of cross-over.

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 for cabozantinib for treating advanced renal cell carcinoma (RCC) in adults who have received at least one prior VEGF-targeted therapy. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© EXCEL based economic model. Table 34 summarises the location of the key economic information within the company's submission (CS).

Table 34. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	5.1
Model structure	5.2.2
Technology	5.2.3
Clinical parameters and variables	5.3
Measurement and valuation of health effects and adverse events	5.4
Resource identification, valuation and measurement	5.5
Results	5.7
Sensitivity analysis	5.8
Subgroup analysis	5.9
Validation	5.10
Strengths and weaknesses of economic evaluation	5.11
Abbreviations used in table: MS, manufacturer's submission.	

5.2 Summary of the company's key results

The company's base case results for the trial-based model comparing cabozantinib with everolimus are given in Table 35, and the NMA-based model results comparing cabozantinib with axitinib, everolimus, best supportive care (BSC) and nivolumab are given in Table 36.

Table 35. Base case results for cabozantinib compared to everolimus based on the METEOR trial (CS, page 151, Table 77)

Drug	Total costs	Total QALYs	Total life-years	Incremental cabozantinib versus			ICER versus cabozantinib
				Costs	QALYs	Life years	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 36. Pairwise analysis cost-effectiveness results based on the NMA (adapted from CS, page 151-152, Table 77 and 79)

Treatment	Cost	LYs	QALYs	Incremental costs Cabozantinib versus	Incremental LYs Cabozantinib Versus comparator	Incremental QALYs Cabozantinib Versus comparator	ICER Cabozantinib Versus comparator (£/QALY)
Cabozantinib	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

The results of the probabilistic sensitivity anlayses for each of the comparators in the NMA-based model is given in Table 37 to Table 40, respectively.

Table 37. Mean results of PSA of cabozantinib compared to axitinib (CS, page 164, Table 89)

Treatment	Costs	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

Table 38. Mean results of PSA of cabozantinib compared to everolimus based on METEOR trial (CS, page 165, Table 91)

Treatment	Cost	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

Table 39. Mean results of PSA of cabozantinib compared to BSC (CS, page 165, Table 92)

Treatment	Cost	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

Table 40. Mean results of PSA of cabozantinib compared to nivolumab (CS, page 164, Table 90)

Treatment	Costs	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic review (SR) of the literature to identify published cost-effectiveness studies relevant to advanced RCC. The company provided an overview of the cost-effectiveness search in the company submission (CS, Section 5.1), with details of the search strategy provided an appendix (CS, Appendix 17). The search strategy and terms used to identify cost-effectiveness studies are reasonable and utilised search filters from the University of York Centre for Reviews and Dissemination (CRD) website.[72] Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

The search aimed to identify cost-effectiveness analysis studies in advanced RCC. Search terms combined disease related terms (advanced RCC) and terms for study design (economic models or economic burden). The search was restricted to the years 2006-2016 based on a published HTA report which reported that no relevant publications were identified prior to 2006.[73]

The following electronic databases were searched:

- Medline (includes Medline in Process and other non-indexed citations with status: publisher, in-data review or Pubmed-not-Medline);
- Embase;
- NHS Economic Evaluation Database (EED);
- Health Technology Assessment (HTA) Database.

In addition to electronic databases, the company searched the NICE website for ERG reports, manufacturer submissions and relevant documents for appraisals of drugs used to treat second-line metastatic RCC.

A total of 635 studies were identified in the electronic database search and the full text of 85 citations were reviewed following abstract appraisal. After full text appraisal, 39 studies were excluded for the following reasons: "Duplicates" (n=1); "Intervention" (n=1); "Outcomes" (n=8); "Population" (n=8); "Publication type" (n=3); "Study type" (n=13); "Outstanding" (n=3); "Unclear" (n=3).

The inclusion and exclusion criteria applied in the search for each criterion are reported in Table 41. The quality of the included studies was assessed using the guidelines for authors and peer reviewers of economic submissions to the BMJ.[74] The ERG considers that it is unlikely that the company missed any published studies reporting economic evaluations relevant to the decision problem.

Table 41. Inclusion and exclusion criteria used in systematic literature review for cost-effectiveness studies (CS, pg 110, Table 45)

Criteria	Inclusion	Exclusion
Population	Adult patients with RCC (advanced / metastatic, previously treated)	Animal studies, paediatric population and other indications
Intervention	Cabozantinib, everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib, BSC	Other non-pharmacological therapies
Comparator	Cabozantinib, everolimus, axitinib, nivolumab, sorafenib, sunitinib, lenvatinib, BSC	As above
Outcomes	Cost-effectiveness Methods and Results (e.g. total costs, costs per life year gained, costs per QALY gained, ICER, ICUR)	Other outcomes
Study design	Cost-effectiveness /cost-utility studies	-
Language	No restrictions. English, German, French, Spanish and Italian (publications in other languages will be listed, and only abstracts in English included)	-
Publication type	Full-text publications, conference proceedings	Mere animal studies Letter, Editorial, Notes, Historical article
Abbreviations in table: BSC, best supportive care; QALY quality adjusted life year; ICER, incremental cost effectiveness ratio, ICUR, incremental cost utility ratio; RCC, renal cell carcinoma.		

5.4 Overview of company's economic evaluation

The company submitted a *de novo* economic model developed using Microsoft Excel® that evaluated cabozantinib in two separate analyses. The first analysis was a trial-based analysis comparing cabozantinib with everolimus, using effectiveness data obtained solely from the METEOR trial.[1] In

the following sections of this document, this will be referred to as the trial-based model. The second analysis compared cabozantinib with everolimus, axitinib, nivolumab and best supportive care (BSC) as pairwise comparisons, and the effectiveness data was derived from a network meta-analysis (NMA) based on various trials (See Table 42).[2-5] The NMA, along with the trials included, is described in detail in Section 4.4. In the following sections of this document this will be referred to as the NMA-based model. The comparators in each of the economic analyses are outlined in Table 42.

Table 42. Summary of the comparisons in the company's model

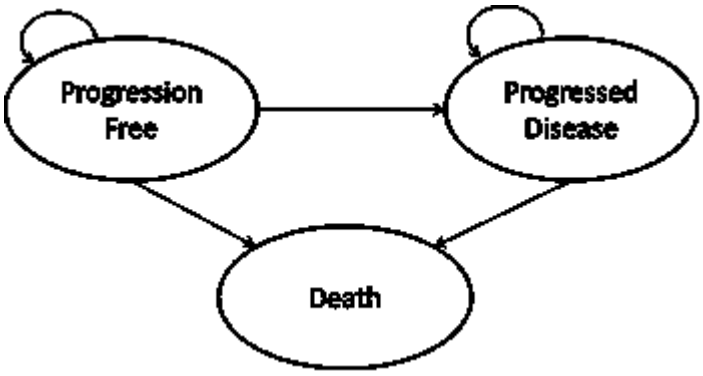
Model	Intervention	Comparator	Trial(s)
Trial-based model	Cabozantinib	Everolimus	METEOR. [1]
NMA-based model	Cabozantinib	Everolimus, axitinib, nivolumab, BSC.	METEOR, AXIS, CheckMate 025, TARGET, RECORD-1. [1-5]
Abbreviations in table: BSC, best supportive care; NMA, network meta-analysis.			

5.4.1 Model structure

In this section, the ERG presents a description of the modelling approach taken by the company. Further discussion and a critique of the company's approach are given in Section 5.5.

The company provided a single *de novo* economic model developed in Microsoft Excel® for the two analyses presented. A partitioned survival structure was used with three health states: progression-free, progressed disease, and death, as represented in Figure 20.

Figure 20 Model structure (CS, page 114, Figure 25)



The company justified this approach as being one that has been used in previous health economic analyses, including NICE technology assessments in metastatic RCC, such as TA219, TA333 and TA417; the latter was in development at the time of the company's submission for cabozantinib.

The model consists of discrete 4-weekly cycles, at each of which the cohort of patients is modelled to capture changes between health states, as well as changes to treatments given. This cycle length was justified as reflecting the frequency of physician visits in the METEOR study. The time horizon of the model is 30 years to allow almost all patients to reach the state of death, and half-cycle corrections were used to obtain more accurate estimation of progression-free survival (PFS), overall survival (OS) and time to treatment discontinuation (TTD). All patients start in the progression-free state and remain there until their disease progresses or they die. Once a patient's disease progresses, they move to the progressed disease state where they remain until death.

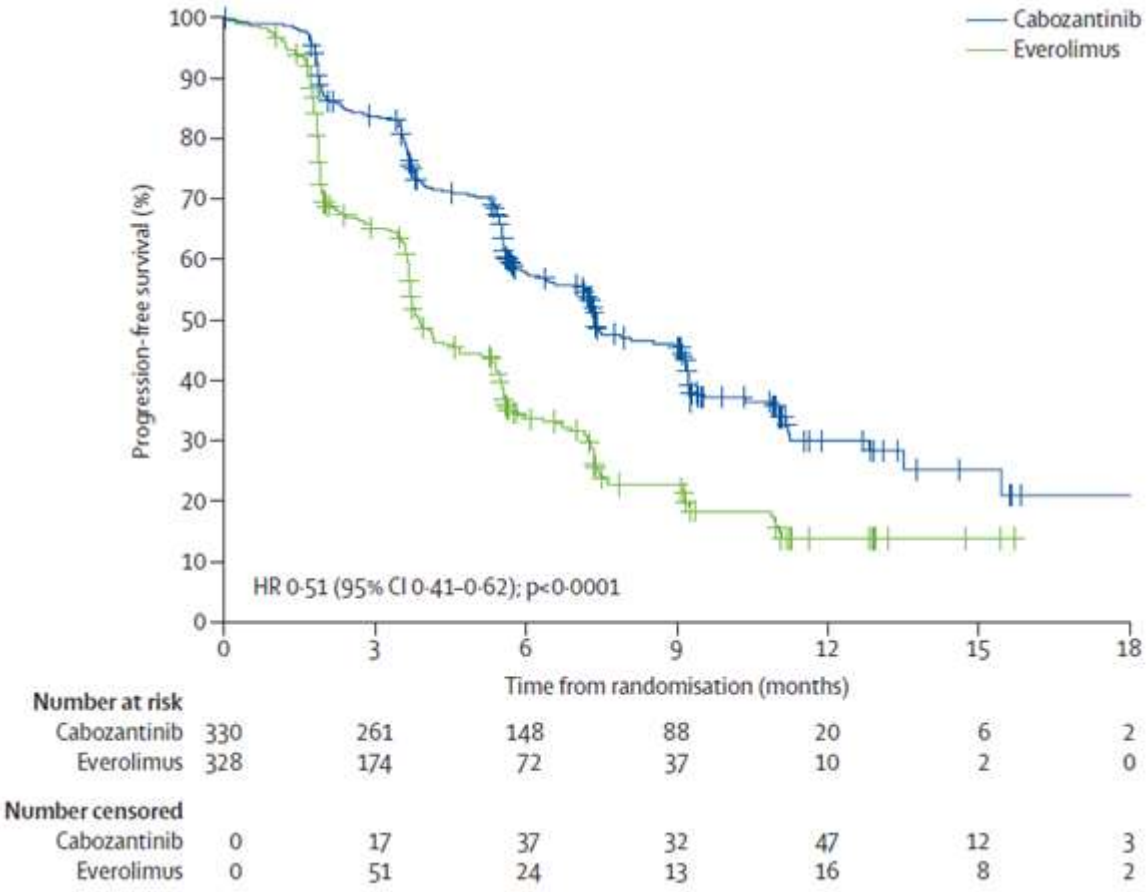
5.4.2 Treatment effectiveness

The effectiveness of each treatment in the model is largely captured by the proportion of patients in each of the health states at any given model cycle, i.e. a less effective treatment will see a quicker progression of patients from the progression-free health state through to post-progression health state and to the death state. In general terms, the number of patients in the progression-free health state at any given model cycle is estimated directly from PFS data for the relevant treatment and comparator. The same approach is used to estimate the number of people entering the death state at any given model cycle, instead using OS data for each treatment. To estimate the number of people in the post-progression health state, the difference between the proportion of people in the OS and PFS health states was taken. This section outlines the data used to estimate PFS and OS for each treatment in both the trial-based model and the NMA-based model, as well as how TTD and PFS data were used to estimate the number of people who remain on the initial active treatment at any given model cycle. Any treatment effectiveness relating to QoL is discussed in Section 5.4.4.

5.4.2.1 Progression free survival (PFS)

For the trial-based model, the Kaplan-Meier (KM) data based on the ITT population from the METEOR trial for PFS (including the number of patients at risk and number of censored patients) are shown in Figure 21. In the METEOR trial, PFS for cabozantinib and everolimus was assessed by an IRC (independent radiology committee). For the NMA-based model, KM data were regenerated from the KM plots in each of the trials included in the NMA. Further details of the NMA are given in Section 4.4.

Figure 21: Kaplan-Meier plot of PFS for ITT population (CS, Figure 27)



Abbreviations in figure: HR, hazard ratio; CI, confidence interval.

The company assessed assumptions of proportional hazards (PH) and accelerated failure time (AFT) of the patient level data for PFS from the METEOR trial data as well as the regenerated KM data used in the NMA. This was done by generating scaled Schoenfeld residual plots, log-cumulative hazard plots and using a chi-squared hypothesis test to assess PH, and by generating quantile-quantile (Q-Q) plots to assess AFT (CS, Appendix 10). The results of the chi-squared tests for each trial in the NMA are given in Table 43, and the company's overall assessment of PH is given in Table 44.

Table 43. Therneau and Grambsch test results for proportional hazards assumption (Clarification response to B6)

Study Name	Rho	Chi-Square	P-value
METEOR	-0.0966	3.56	0.0593
AXIS	-0.00421	0.00405	0.949
CheckMate 025	-0.0811	4.1	0.043
RECORD-1	-0.04	0.39	0.532
TARGET	0.218	26.7	2.36e-07

Table 44. Proportional hazards for PFS (adapted from CS, page 90, Table 32)

Study Name	Proportional hazards assumption holds?	Comments
METEOR	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).
RECORD-1	Yes	
CheckMate 025	No	
TARGET	No	
AXIS	Yes	

Based on these plots and the p-value generated from the chi-squared test (p = 0.059), the company found the PH assumption holds for PFS in the METEOR trial, but this was not the case across all of the other trials in the NMA, and as such, a HR-based NMA was not deemed to be appropriate by the company. Instead, an NMA based on the parameters of independently fitted parametric survival curves was implemented. For the trial-based model, despite PH appearing to hold in the METEOR trial, the company chose to use independently fitted curves for cabozantinib and everolimus to align with the methodology employed for the NMA results.

In order to determine the most appropriate distribution to extrapolate the data beyond the trial period of 18 months, the company explored the following distributions as outlined in the NICE DSU Technical Support Document 14 [(7)]: exponential; Weibull; Gompertz; log-logistic; log-normal; and the generalised Gamma.

The company stated that the SMEEP algorithm from the NICE DSU Technical Support Document 14 was used to determine the distribution with the best fit to the KM data. [(7)] For each distribution and treatment arm for each trial, the company calculated the Akaike Information Criterion (AIC), the corrected AIC (AICC) and the Bayesian Information Criterion (BIC) statistics (reported in Table 45 and Table 46 for cabozantinib and everolimus, respectively). Based on these statistical tests, the log-logistic distribution provided the best fit for the cabozantinib treatment arm and the log-normal was the best fit for the everolimus arm. In addition to the statistical tests, the company stated that distributions were validated by practising NHS Oncologists for clinical plausibility. Given that the best fitting distributions were different for the cabozantinib and everolimus arms of METEOR, and that NICE DSU 14 document [(7)] advises that fitting different distributions to treatment arms within the same trial should be avoided, the company decided to separately fit a log-logistic distribution to both treatment arms of METEOR. The company did not test the model using a log-normal fit to both arms.

Table 45. Model fit statistics for independently fitted PFS data from METEOR study – cabozantinib (CS, page 125, Table 52)

Model	AIC	Model	AICC	Model	BIC
Log-logistic	1205.81	Log-logistic	1205.85	Log-logistic	1213.41
Weibull	1213.37	Weibull	1213.41	Weibull	1220.97
Gamma	1209.01	Gamma	1209.08	Log-normal	1220.40
Log-normal	1212.02	Log-normal	1212.05	Gamma	1219.61
Gompertz	1229.14	Exponential	1229.17	Exponential	1236.74
Exponential	1238.40	Gompertz	1238.41	Gompertz	1242.20
Abbreviations: AIC, Akaike's information criteria; AICC, corrected Akaike's information criteria; BIC, Bayesian information criteria.					

Table 46. Model fit statistics for independently fitted PFS data from METEOR study – everolimus (CS, page 125 Table 53)

Model	AIC	Model	AICC	Model	BIC
Log-normal	1165.83	Log-normal	1165.87	Log-normal	1173.42
Gamma	1167.55	Log-logistic	1167.61	Log-logistic	1175.16
Log-logistic	1167.58	Gamma	1167.62	Gamma	1178.93
Weibull	1197.33	Weibull	1197.37	Weibull	1204.92
Gompertz	1219.26	Exponential	1219.30	Gompertz	1224.42
Exponential	1220.63	Gompertz	1220.64	Exponential	1226.85
Abbreviations: AIC, Akaike's information criteria; AICC, corrected Akaike's information criteria; BIC, Bayesian information criteria.					

For the NMA-based model, regenerated KM data based on the included trials was used in the NMA described in Section 4.4, to fit parametric curves adjusted to the baseline of the everolimus arm of METEOR, to estimate and extrapolate the relative PFS for the additional comparators axitinib, nivolumab and BSC. The same distributions were tested as in the trial-based model, however, the company stated that the generalised gamma distribution could not be used for the NMA-based model due to an inability to implement the method with this distribution in WinBUGS. As the NMA requires all trials to be fitted using the same family of parametric curve, the goodness-of-fit was assessed as a global fit for each family. This means that there is no statistic given for the goodness-of-fit of a particular curve to its respective trial data. The global goodness-of-fit was tested using the Deviance Information Criterion (DIC) and the results of these tests are given in Table 47.

Table 47. NMA model fit statistics for PFS (CS, page 93, Table 34)

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Residual deviance (*Dbar)*	6355.8	6355.3	6456.8	6456.3	6047.7	6047.9	5987.3	5987.0	6599.7	6600.1
Effective number of parameters (p^D)	19.7	20.0	19.8	19.8	19.9	19.9	20.2	19.9	9.9	10.2
Deviance information criteria (*DIC*)	6375.5	6375.3	6476.6	6476.1	6067.6	6067.8	6007.5	6006.9	6609.6	6610.3

Abbreviations in table: FE, fixed effects; RE, random effects

Based on the lowest of these values, the company chose to use the log-normal distribution to estimate PFS for all comparators in the base case of the NMA-based model. Figure 22 presents the PFS curves based on the log-normal distribution for all treatment options included in the cost-effectiveness model. Table 48 presents the median PFS estimates generated by the NMA for all treatment options.

Figure 22. Base case PFS curves, all treatment options (CS, pg 98, figure 22)

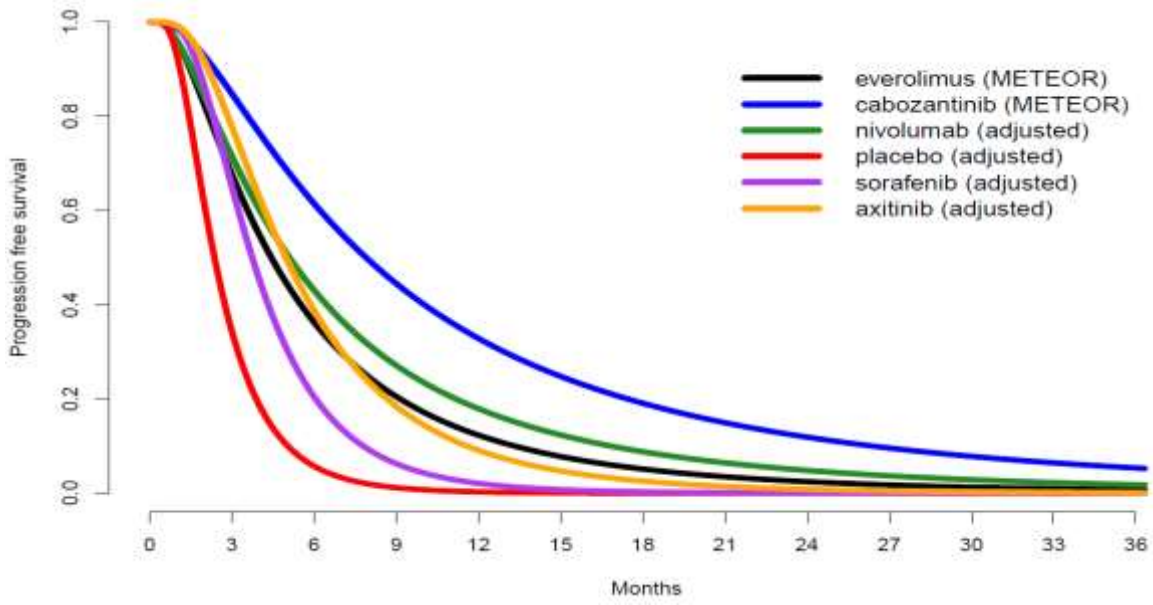


Table 48. Median PFS results (NMA) for all treatment options based on log-normal distribution (CS, pg 99, table 39)

Treatment	Median PFS (NMA log-normal function)
Cabozantinib	7.8
Axitinib	4.9
Everolimus	4.4
BSC	2.4
Nivolumab	5.1

The company performed scenario analyses on the impact of using alternative distributions for the NMA comparators on the ICER. The results of these are given in Section 5.6.2.

In response to clarification questions, the company also applied a range of PH models on the METEOR trial data, using the exponential, Weibull and Gompertz distributions as the underlying survival distribution. The resulting hazard ratios (HRs) are given in Table 49.

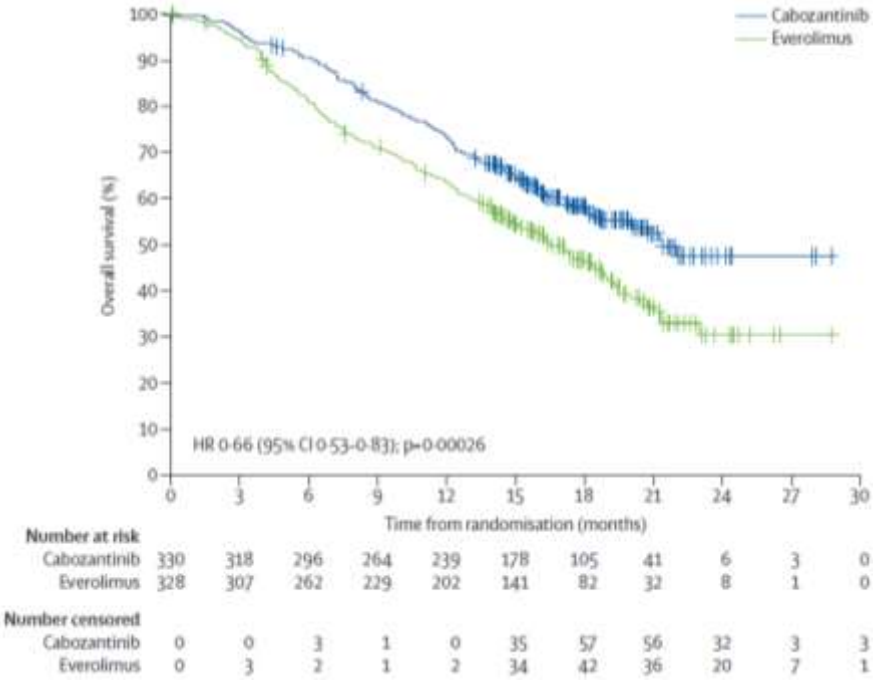
Table 49. PFS estimated HRs from PH models (Clarification response to B8)

Underlying distribution	HR (cabozantinib versus everolimus)
Exponential	0.5559
Weibull	0.5028
Gompertz	0.5275

5.4.2.2 Overall survival (OS)

For the trial-based model, KM data for OS from the ITT population of the METEOR trial were provided for the comparison of cabozantinib with everolimus. This data is plotted in Figure 23, along with the data for the number at risk and the number censored below the graph. For the NMA-based model, KM data were regenerated from KM plots from each of the trials included in the NMA. Further details of the NMA are given in Section 4.4.

Figure 23. Kaplan-Meier curves for overall survival in METEOR (ITT population)



Source: Choueiri et al. 2016[1]

The assumptions of PH and AFT were tested on both the METEOR trial data and the regenerated KM data used in the NMA, using Schoenfeld residual plots, log-cumulative hazard plots and chi-squared hypothesis tests for PH, and quantile-quantile plots for AFT. The results of the chi-squared tests for each trial are given in Table 50 and the company's overall assessment of whether proportional hazards holds or not is shown in Table 51.

Table 50. Therneau and Grambsch test results for proportional hazards assumption (Clarification response to B6)

Study Name	Rho	Chi-Square	P-value
METEOR	-0.0466	0.692	0.406
AXIS	-0.0217	0.121	0.728
CheckMate025	0.11	4.72	0.0298
RECORD-1	-0.0939	1.54	0.215
TARGET	0.102	5.8	0.016

Table 51. Proportional hazards for OS (adapted from CS, page 90, Table 32)

Study Name	Proportional hazards assumption holds?
METEOR	Yes
RECORD-1	Yes
CheckMate025	No
TARGET	No
AXIS	Yes

The company found that PH did not apply across all trials in the NMA, so they chose to use independently fitted curves for the NMA based model, as the methods used for the NMA allowed for this flexibility (See Section 4.4 for more detail). For the METEOR trial, the company believed that the PH assumption did hold, but despite this, they chose to use independently fitted curves to align with the methodology employed for the NMA results.

To extrapolate the OS data for use in the economic model, the company fitted independent parametric survival curves to each arm of the METEOR trial. The following parametric models were tested to fit to the patient level data from METEOR: exponential, Weibull, Gompertz, log-logistic, log-normal and the generalised gamma, and these models were each assessed to select the best fitting model using the SMEEP algorithm as described in the NICE DSU Technical Support Document 14.[7] This included using the AIC, AICC and BIC statistics, a visual inspection of the curves and a comparison of the extrapolated estimates against external data sources, which included a long-term follow up study in second-line advanced RCC.[75] The plausibility of different extrapolations was also assessed by oncologists who practised within the NHS in England, based on a visual inspection of the curves. The most appropriate model was selected by considering all of the factors described above.

For the NMA-based model, regenerated KM data based on the included trials was used in the NMA described in Section 4.4, to fit parametric curves adjusted to the baseline of the everolimus arm of METEOR, to estimate and extrapolate the relative overall survival for the additional comparators axitinib, nivolumab and BSC. The same distributions were tested as in the trial-based model, however, the company stated that the generalised gamma distribution could not be used for the NMA-based model due to an inability to implement the method with this distribution in WinBUGS. The METEOR trial was also included in the NMA-based model so there is an additional comparison for cabozantinib against everolimus as part of the NMA-based model results. Model fit was assessed using DIC as a global estimate for each of the distributions when fitted to all trials concurrently, in the same way described for PFS in Section 5.4.2.1.

The AIC and BIC statistics for the fitted curves for cabozantinib in the METEOR trial are given in Table 52 and for the everolimus arm, the equivalent values are given in Table 53. Based on these

statistics, the best fitting model for the cabozantinib arm of METEOR was the log-logistic distribution and for the everolimus arm it was a Weibull distribution that had the best fit, closely followed by the log-logistic. This is indicated by the lowest value of the AIC and BIC statistics. The company chose to use the log-logistic distribution for both arms in the trial-based model base case, to avoid having different shaped models for the comparison, which the company believed was not recommended, based on the NICE DSU Technical Support Document 14.[7] This was supported by the oncologists consulted by the company who agreed that it provided the best fit. The company did not test the model using the Weibull distribution for each arm as an alternative, and provided no justification for choosing the log-logistic over the Weibull for the base case.

Table 52. AIC and BIC statistics for independently fitted OS data from the METEOR study – cabozantinib (CS, page 122, Table 50)

Model	AIC	Model	AICC	Model	BIC
Log-logistic	1254.15	Log-logistic	1254.19	Log-logistic	1261.75
Weibull	1256.13	Weibull	1256.17	Weibull	1263.73
Gamma	1256.53	Gamma	1256.60	Log-normal	1267.93
Log-normal	1257.92	Log-normal	1257.95	Gamma	1265.52
Gompertz	1264.42	Exponential	1264.455	Exponential	1272.017
Exponential	1274.41	Gompertz	1274.43	Gompertz	1278.21

Table 53. AIC and BIC statistics for independently fitted OS data from the METEOR study – everolimus (CS, page 122, Table 51)

Model	AIC	Model	AICC	Model	BIC
Weibull	1487.54	Weibull	1487.57	Weibull	1495.12
Log-logistic	1487.61	Log-logistic	1487.65	Log-logistic	1495.20
Gamma	1488.23	Gamma	1488.30	Gamma	1499.60
Log-normal	1492.45	Log-normal	1492.49	Log-normal	1500.04
Gompertz	1493.90	Exponential	1493.94	Exponential	1501.49
Exponential	1503.30	Gompertz	1503.31	Gompertz	1507.09

The results of the global goodness-of-fit test for the parametric OS curve fitting for the NMA-based model are given in Table 54. Based on the DIC statistics, the log-normal distribution had the best global fit for the METEOR, AXIS, TARGET, RECORD-1 and CheckMate 025 regenerated KM data. [1-5] The log-normal was therefore chosen for the base case in the NMA-based model for the pairwise comparisons of cabozantinib against axitinib, nivolumab and BSC.

Table 54. NMA model fit statistics for OS (CS, page 93, Table 33)

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	FE	RE	FE	RE	FE	RE	FE	RE	FE	RE
Residual deviance (Dbar)	4364.9	4364.8	4443.8	4344.0	4314.5	4314.3	4293.8	4293.4	4535.8	4536.3
Effective number of parmeters (pD)	20.0	19.7	19.6	20.1	20.0	19.9	20.2	19.8	9.8	10.2

Deviance information criteria (DIC)	4384.9	4384.5	4463.4	4464.1	4334.5	4334.2	4314.0	4313.2	4545.6	4546.5
Abbreviations in table: FE, fixed effects; RE, random effects										

In response to clarification questions, the company also applied a range of PH models on the METEOR trial data, using the exponential, Weibull and Gompertz distributions as the underlying survival distribution. The resulting HRs are given in Table 55.

Table 55. OS estimated HRs from PH models (Clarification response to B8)

Underlying distribution	HR (cabozantinib versus everolimus)
Exponential	0.6879
Weibull	0.6731
Gompertz	0.6762

5.4.2.3 Time to treatment discontinuation

Where data were available, TTD data was used to determine the proportion of patients remaining on the initial active treatment at any given model cycle. This is to reflect the fact that patients receiving active treatment can continue to do so beyond progression according to the treatment stopping rules in the marketing authorisations (MA) of each drug. The proportion of patients receiving treatment at any point of time in the model, as determined by the TTD data, is then used to calculate treatment-related costs (i.e. treatment acquisition and administration).

In the trial-based model, the company used parametric survival analysis to extrapolate TTD, adopting the same approach taken for OS, and PFS. Parametric survival curves were fitted independently to both the cabozantinib and the everolimus arms of the METEOR trial, using the same standard distributions as per the PFS and OS analysis (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal and, generalised gamma). Each parametric distribution was assessed for goodness-of-fit to the data in both arms of the METEOR trial. The company reported using the SMEEP algorithm to determine the most appropriate distribution to use in the line with the NICE DSU Technical Support Document 14.[7] Best model fit was selected based on the following criteria: AIC and BIC statistics, visual inspection and the plausibility of different extrapolations according to oncologists currently practising within the NHS in England that were consulted by the company.

The AIC and BIC statistics are reported in Table 56 and Table 57, for cabozantinib and everolimus respectively. The company reports that both the log-logistic and log-normal models were considered to fit the KM data well but the log-normal had the lowest AIC, AICC and BIC and so this was used in the company's base case for the trial-based model. The company did not test using the log-logistic as an alternative for both arms or the closely second best fitting Gamma distribution for both arms.

Table 56. AIC and BIC statistics for independently fitted TTD data from METEOR study for cabozantinib (CS, page 126, Table 54)

Model	AIC	Model	AICc	Model	BIC
Log-logistic	1793.71	Log-logistic	1793.75	Log-logistic	1801.32
Gamma	1793.82	Gamma	1793.89	Gamma	1805.22
Log-normal	1792.67	Log-normal	1792.71	Log-normal	1800.28
Weibull	1805.85	Weibull	1805.88	Weibull	1813.45
Gompertz	1820.54	Gompertz	1820.58	Gompertz	1828.14
Exponential	1824.54	Exponential	1824.55	Exponential	1828.34

Table 57. AIC and BIC statistics for independently fitted TTD data from METEOR study for everolimus (CS, page 126, Table 55)

Model	AIC	Model	AICc	Model	BIC
Log-normal	1701.25	Log-normal	1701.28	Log-normal	1708.80
Gamma	1701.76	Gamma	1701.83	Gamma	1713.08
Log-logistic	1707.81	Log-logistic	1707.85	Log-logistic	1715.36
Weibull	1747.55	Weibull	1747.58	Weibull	1755.09
Exponential	1753.65	Exponential	1753.66	Exponential	1757.42
Gompertz	1755.60	Gompertz	1755.64	Gompertz	1763.15

For the NMA based model, in addition to the data from the METEOR trial, TTD data were only available for nivolumab from the CheckMate 025 trial.[3] The data from these two trials was used in an NMA to estimate parametric TTD curves for nivolumab adjusted to the everolimus group of METEOR. The same standard distributions were used as per the PFS and OS analysis for the NMA-based model (i.e. exponential, Weibull, Gompertz, log-logistic, log-normal). The DIC statistics were used to assess the global goodness-of-fit for each distribution tested in the model. The results are shown in Table 28.

Table 58. Model fit statistics (TTD)

Model fit statistics	Weibull	Gompertz	Log-logistic	Log-normal	Exponential
Residual deviance (Dbar)	2761.2	2767.1	2638.9	2597.5	2775.6
Effective number of parameters (pD)	7.6	7.7	7.8	7.8	4.0
Deviance information criteria (DIC)	2768.8	2774.8	2646.7	2605.3	2779.6

The log-normal distribution was selected to fit the curves for cabozantinib, everolimus and nivolumab in the NMA as it was determined to be the best fitting based on the lowest DIC statistic. The company stated that the log-normal distribution was also chosen for the ERG's preferred model in TA417.[76]

The adjusted TTD curves used in the NMA-based model are shown in Figure 24, and the median TTD estimated from these curves is summarised for cabozantinib, everolimus and nivolumab in Table 59.

Figure 24. Averaged TTD adjusted to the baseline from METEOR study, fixed effects (log-normal)

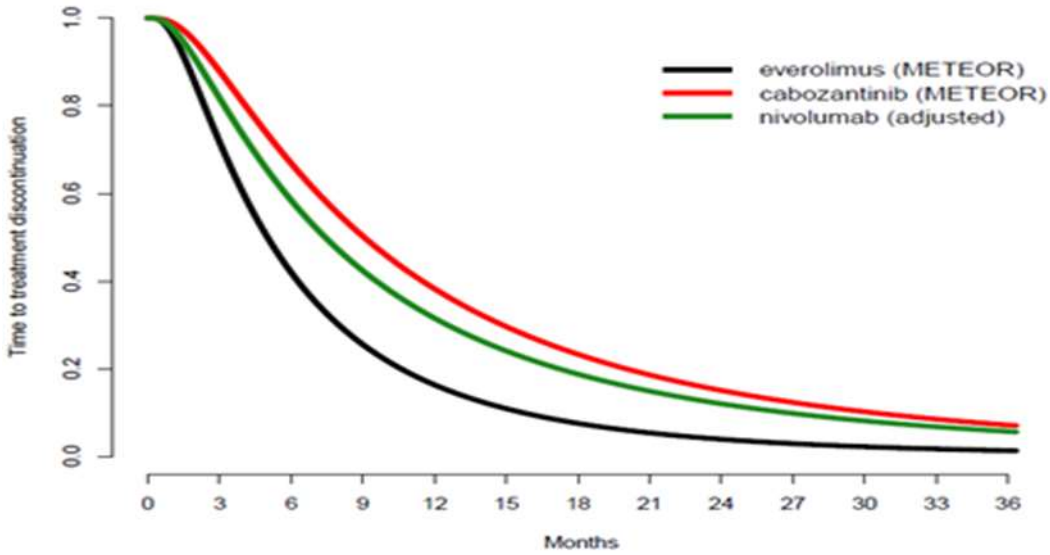


Table 59. Median TTD results based on the Log-normal function

Treatment	Adjusted median TTD (months)
Cabozantinib	9.0
Everolimus	5.0
Nivolumab	7.4
Key: TTD, time to treatment discontinuation	

Due to the lack of available TTD data for axitinib, the company used the PFS curves derived from the NMA to estimate treatment-related costs for axitinib.

5.4.3 Adverse events

The company included treatment-emergent Grade 3 or Grade 4 adverse events observed in at least 5% of any of the trial populations. The adverse events considered in the model are anaemia, diarrhoea, fatigue, hypertension, and palmar-plantar erythrodysaesthesia syndrome (PPE).

The rates assumed for cabozantinib and everolimus are based on those observed in the METEOR trial.[1] The rates assumed for axitinib were obtained from the drug's Summary of Product Characteristics (SPC), which contains pooled data on frequency of adverse events across clinical trials. The names of the trials from which the data was obtained are not stated in the document.[77] No source of rates of treatment-emergent adverse events for nivolumab was identified, therefore treatment-related adverse event rates were used instead.[3] The rates of adverse events assumed in the model for all the comparators are presented in Table 60.

Table 60. Rates of adverse events assumed in the model

Adverse Event	Cabozantinib[1]	Everolimus[1]	Axitinib[77]	Nivolumab[3]
	N=331	N=322	N=672*	N=406
Anaemia	5.7%	16.5%	1.6%	1.7%
Diarrhoea	13.0%	2.2%	10.2%	1.2%
Fatigue	10.9%	7.5%	10.9%	2.5%
Hypertension	14.8%	3.7%	23.0%	0.0%
Palmar-plantar erythrodysaesthesia syndrome	8.2%	0.9%	7.6%	0.0%

Patients in the cabozantinib, and everolimus groups of the METEOR trial experienced an average of 1.17 and 1.15 episodes of adverse events, respectively. Each episode lasted for a duration of approximately 19 days on average. Therefore, patients in the model are assumed to have 1.16 adverse event episodes (i.e. the average across the two trial arms), with each episode lasting 4 weeks (one model cycle). These assumptions did not vary according to treatment arm in the model.

The resource use and costs associated with management of adverse events have been incorporated in the model as reported in Section 5.4.5.3. A utility decrement was assumed for patients in the model when they are experiencing adverse events as described in Section 5.4.4.

5.4.4 Health-related quality of life

In this section, the ERG reports the sources of health related quality of life (HRQoL) data used in the cost-effectiveness analysis, and how it was translated in to quality adjusted life years (QALYs) in the model, as reported in Section 5.4 of the CS.

5.4.4.1 Systematic literature review of Health-related quality of life

The company performed a systematic review of the literature to identify HRQoL studies that reported health state utility values (HSUVs), in particular EQ-5D values, for advanced/metastatic Renal Cell Carcinoma (mRCC). Searches were conducted in Medline, Embase, NHS Economic Evaluation database and the HTA database for relevant publications during the 2006-2016 publication period. The company stated the reason for the restriction in timeframe was because a HTA report published by the Peninsula Technology Assessment Group (PenTAG) in 2008 did not identify any relevant publications before 2006.[78] The NICE website was also searched for relevant evidence review group reports, manufacturer's submissions and other relevant documents associated with second line mRCC. The search strategy used for each database is reported in Appendix 19 of the CS. Table 61 details the inclusion/ exclusion criteria used for the review.

Table 61. Inclusion/ exclusion criteria for HRQoL systematic literature review

Criteria	Include	Exclude
Population	Adult patients with RCC	Paediatric population and other indications

Intervention	Surgical intervention, non-pharmacological therapy or not best supportive care	-
Comparator	No restriction	-
Outcomes	HRQoL outcomes: EQ-5D utilities. Utilities derived from generic preference-based instruments such as the SF-36, SF-12, SF-6D, HUI2 or HUI3. Utilities derived using mapping algorithms. Mapping algorithms.	Other outcomes
Study type	Clinical and observational studies, Economic evaluations, utility analysis, Systematic reviews, meta-analysis, HTA reports (No restrictions, with exception of case reports and case series - they will be excluded)	-
Language	No restrictions. English, German, French, Spanish and Italian (publications in other languages will be listed, and only abstracts in English included)	-
Publication type	Full-text publications, conference proceedings	-
Abbreviations: RCC, Renal Cell Carcinoma; HRQoL, Health Related Quality of Life; HTA, Health Technology Assessment		

In total, the search identified 4,178 papers of which 571 were duplicates. Abstracts were reviewed for 3,607 papers, of which 3,282 papers were excluded using the criteria outlined in Table 61 and 325 papers went to the next stage of screening. From the next stage, 50 papers were selected for inclusion and were as follows:

- 5 guidance documents;
- 19 reviews;
- 8 full text quality of life (QoL) studies and clinical;
- 10 full text economic evaluations;
- 8 conference abstracts and posters.

Out of the 50 papers reviewed, the company state that only evidence from the original QoL/ clinical studies served as a source to extract data for the cost-effectiveness model. The company state that data were extracted by a reviewer and any uncertainties were discussed with a second reviewer. Details of the data extraction are presented in Table 62.

Table 62. Summary list of HRQoL studies (CS Appendix 19)

Study	Country	Population	Intervention	Sample size	Index/Scale	Health states	Mean utility score	
(79)	International	Mean age Sunitinib 61 (27-87) years IFN-alfa 60(34-85) years Male /female 71/29% Race: white: 94.40%	Sunitinib 50mg&day IFN-alfa	Sunitinib 50mg&day N=375 total (US group N=179 EU group N= 135) IFN/alfa N=375 (US group N=168 EU group N= 139)	EQ-5D	Sunitinib mean value across all available post-baseline observations / US cohort /European cohort	0.75 / 0.77 / 0.72	
						IFN-alfa mean value across all post-baseline observations /US cohort /European cohort	0.69 / 0.75 / 0.71 Statistical significance for the difference for sorafenib vs IFN-alfa, p-value <0.0078 / 0.7127 / 0.2467	
(80)	International	Mean age Pazopanib 56.9+/-10years Placebo 56.9+/-11 years Male Pazopanib 197% Placebo 109% Treatment naïve patients Pazopanib n=155% Placebo n=78%	Pazopanib Placebo	Pazopanib N=289 Placebo N=145	EQ-5D	Baseline – pazopanib mean (SD)	0.72	0.25
						Baseline - placebo	0.73	0.24
						week 6 - pazopanib	0.71	0.22
						week 6 - placebo	0.72	0.30
						Week 12 - pazopanib	0.70	0.25
						week 12- placebo	0.75	0.23
						Week 18 - pazopanib	0.71	0.26
						Week 18 - placebo	0.76	0.22
						Week 24 - pazopanib	0.71	0.24
						Week 24 - placebo	0.76	0.23
						Week 48 - pazopanib	0.79	0.20
						Week 48 - placebo	0.80	0.24
(81)	International	mRCC with prior systemic therapy Axitinib Median age 61 (20-82); Male 73% Sorafenib 61 (22-80)/Male 71%	Axitinib Sorafenib	Axitinib n=361 Sorafenib n=362	EQ-5D	Axitinib treatment,	0.71	
						Sorafenib	0.69	
						Difference	0.02 (95%CI:-0.01-0.05), p-value 0.1903	

(82)	International	Advanced or metastatic mRCC, histological confi rmation of advanced renal cell carcinoma with a clear-cell component, measurable disease	Nivolumab 3mg/kg Everolimus 10mg	Nivolumab N=362 Everolimus N=344	EQ-5D	Nivolumab [baseline, mean (SD)]	0.78	0.24
						Everolimus [baseline, mean (SD)]	0.78	0.21
						Difference in mean change from baseline to endpoint (Nivolumab vs everolimus)	0.04	95%CI: 0.02-0.07, p=0.0003
(83)	France, Italy, UK, Germany, Finland.	mRCC, 67% men; 72% EPOG PS, 0; 28 % EPOG PS, 1; No. of metastatic sites 0 or 1: 26% ≤2: 74%	Pazopanib 80mg/day Washout period Sunitinib 50mg/daily	N=168	EQ-5D	Mean utility score (SD)	0.77 (0.24)	
(84)	UK	mRCC	Various	100 people (general public)	EQ-5D	Stable disease no AE	0.795 (95%CI: 0.761 - 0.830)	
						Disease progression	0.355 (95%CI: 0.299 - 0.412)	
						Stable with anaemia grade 3	0.676 (95%CI: 0.630 - 0.722)	
						Stable with diarrhoea stage 1-2	0.690 (95%CI: 0.641 - 0.738)	
						Stable with diarrhoea stage 3	0.534 (95%CI: 0.482 - 0.586)	
						Stable with fatigue stage 1-2	0.751 (95%CI: 0.710 - 0.792)	
						Stable with fatigue stage 3	0.591 (95%CI: 0.543 - 0.639)	
						Stable with PPE stage 3	0.469 (95%CI: 0.414 - 0.524)	
						Stable with mucositis stage 1-2	0.726 (95%CI: 0.681 - 0.771)	
						Stable with mucositis stage 3	0.526 (95%CI: 0.476 - 0.575)	

						Stable with nausea stage 1-2	0.635 (95%CI: 0.587 - 0.683)
						Stable with nausea stage 3	0.540 (95%CI: 0.594 - 0.690)
						Stable with hypertension stage 3	0.642 (95%CI: 0.594 - 0.690)
(85)	US	Poor prognosis advanced RCC patients (stage IV or recurrent disease), KPS ≥60	Temsirolimus IFN-alfa	Temsirolimus, N=209 IFN-alfa, N=207	EQ-5D	Baseline mean utility score (SD)	0.62 (0.24)
(86)	International	Naïve mRCC patients	Temsirolimus alone IFN-alfa alone Combination of Temsirolimus & IFN- alfa	N=260 upon progression N=230 after grade 3 or 4 AE N=278 TWIST	EQ-5D	Baseline- temsirolimus (median)	0.689
						Baseline- IFN-alfa (median)	0.656
						Baseline-combination of temsirolimus & IFN-alfa	0.689
						Time with serious toxicity (TOX) (median)	0.585
						Time after progression (REL) (median)	0.587
						Time after progression (REL) (median) [* EQ-5D scores were pooled across all treatment groups for each of the three health states]	0.689

Abbreviations in table: mRCC, metastatic renal cell carcinoma; IFN-alfa, Interferon alfa; US, United States; EU, Europe; UK, United Kingdom; AE, adverse event; EQ-5D, EuroQol 5 dimension; SD, standard deviation

The company also searched for NICE submissions for the key comparators axitinib, everolimus and nivolumab and extracted data are presented in Table 63.

Table 63. Summary list of NICE submissions for key comparators (CS, pg 130)

Key comparator	State	Utility value	Comments
Axitinib – AXIS study (TA333)	Progression free	0.692	Average EQ5D index score for those visits without progression, SD 0.275
	Progressed	0.610	Mean utility at the end of treatment for all patients, SD 0.316
Everolimus (TA219)	Progression free without AE	0.758	Peninsula Technology Assessment Group (2008). SD 0.03
	Progression free with AE	0.708	-0.05 disutility associated with dyspnoea health state utility in advanced non-small cell lung cancer (Doyle et al, 2008)
	Progressed disease	0.683	Peninsula Technology Assessment Group (2008). SD 0.04
Nivolumab (TA417)	Progression free nivolumab	0.800	CheckMate025 study
	Progressed nivolumab	0.730	CheckMate025 study
	Progression free everolimus	0.760	CheckMate025 study
	Progressed everolimus	0.700	CheckMate025 study
	Progression free BSC	0.690	Assumption from TA333
	Progressed BSC	0.610	Assumption from TA333
	Pneumonitis	-0.150	Medical oncologist opinion
	Diarrhoea	-0.100	Medical oncologist opinion
	Anaemia	-0.081	Medical oncologist opinion
	Pneumonia	-0.130	Medical oncologist opinion

Abbreviations in table: AE, Adverse event; BSC, Best supportive care; SD, Standard deviation.

In Section 5.4.3 of the CS, the company considered disutility values associated with AEs for the overall analysis of HRQoL. From the literature review four sources of disutility values for AEs were identified and are presented in Table 64. These values were used as part of a scenario analysis for post progression utility estimates.

Table 64. Summary of available utility values for the cost-effectiveness model (CS, pg 132, Table 63)

State	Axitinib (TA333)	Everolimus (TA219)	Nivolumab (TA417)	Swinburn et al (2010)
Progression free	0.692	0.758	0.800	0.795
Progressed	0.610	0.683	0.730	0.355
AE disutility	NA	-0.050	See details in Table 63	See details in Table 62
Abbreviations in table: AE, Adverse event.				

5.4.4.2 Modelling approach for METEOR EQ-56D-5L data

The Health state utility values (HSUVs) for all health states regardless of treatment arm applied in the company's base case are based on EQ-5D-5L data obtained in the METEOR trial and are presented in Table 84.

Table 65. HSUVs used in cost-effectiveness model

Health State	Utility value
Progression free	0.817
Progressed	0.777
AE disutility	-0.055
Abbreviations in table: AE, Adverse event.	

The company compared the estimates obtained from the systematic literature review (Table 64) with the utility estimates generated from the METEOR trial (Table 65), but decided to use the estimates generated from the METEOR trial. The company's justification for this decision is presented in Box 14. The company states the utility estimates related with axitinib (obtained from the AXIS trial) are based on the US version of the EQ-5D and may not be generalizable to the UK population.

Box 14. Company justification for HSUVs (CS, pg 134, Section 5.4.4)

Given the difficulties in combining utility estimates from different sources, including differences in trial populations and/or elicitation methods the base case analysis uses utility values derived directly from the METEOR trial for all comparisons. A scenario analysis is provided using alternative post-progression utility estimates. The average decrement across published estimates derived directly from patients using EQ-5D was used in this scenario.
Abbreviations in Box: EQ-5D, EuroQol-5 dimensions

EQ-5D-5L Questionnaires were completed prior to patient's clinic visits and up to 30 days after final administration of study drug. The company provided completion rates of EQ-5D-5L questionnaires at each time point in Section 5.4.1 of the CS. The mean EQ-5D-5L score for patients without disease progression in the METEOR trial was 0.817 (standard error = 0.003).

Analysis of the EQ-5D-5L data by treatment arm was performed using a repeated measure mixed effect model (See Section 4.3.4). The analysis found that there was no statistically significant difference in HRQoL according to the treatment group. Two further regression models controlling for progression status and AEs were run to assess the impact of these variables on HRQoL. The results of the model are presented in Table 66.

Table 66. Mixed procedure model - progression status and adverse events (CS, pg 128)

Effect	Progress	Adverse Events	Estimate	Pr > |t|
Intercept			0.2498	<.0001
BASE			-0.3400	<.0001
Progress	Yes		-0.0399	<.0001
Progress	No	Yes	0	
Adverse events		No	-0.0552	<.0001
Adverse events			0	

The company's model estimated that the decrement associated with patients experiencing disease progression was 0.04, resulting in a post-progression HSUV of 0.777. A scenario analysis was carried for post progression utility estimates based on the average utility decrements found in the published literature, which is reported in Section 5.4.4.1 (Table 64) of this report.

The company estimated AE utility decrement was -0.06 for all patients regardless of treatment arm. In the cost-effectiveness model the comparator specific AE impact was calculated by weighting the AE utility decrement by the proportion of patients experiencing a grade 3/4 AE (only for grade 3/4 AEs where ≥ 5% of the treatment population experienced the event). The company assumed that the duration of an AE was 4 weeks (one model cycle) based on the average AE duration of 19 days observed in the METEOR trial. The number of grade 3/4 treatment emergent AEs (TEAEs) episodes used in the model to estimate the overall utility decrement was 1.16 as observed in the METEOR trial.

5.4.5 Resources and costs

The company carried out a systematic literature review to identify studies reporting resource utilisation and costs incurred for the management of advanced RCC. An overview of the search was provided in Section 5.5.5 of the CS, and the search terms and results were reported in Appendix 20.

The following databases were searched:

- Medline (includes Medline in Process and other non-indexed citations with status: publisher, in-data review or Pubmed-not-Medline);

- Embase;
- NHS Economic Evaluation Database;
- HTA Database.

In addition to searching electronic databases, the company hand searched NICE submission/appraisal data to identify relevant information. In total, 3,760 papers were identified through the electronic searches. After abstract review, a total of 243 publications selected for full-text screening. Of those, 139 studies were excluded for the following reasons; "Intervention" (n=13); "Outcomes" (n=32); "Population" (n=32); "Publication type" (n=5); "Study type" (n=57); "Unclear" (n=3); "Unavailable" (n=1); "Outstanding" (n=3). A total of 97 studies were finally included, of which 10 were European studies. The inclusion and exclusion criteria applied are presented in Table 67, and the included European studies are summarised in Table 68.

Table 67. Inclusion and exclusion criteria applied in systematic literature review for resource use and costs (CS, pg 145, Table 75)

Criteria	Inclusion	Exclusion
Population	Adult patients with RCC (advanced / metastatic, previously treated)	Animal studies, Paediatric population and other indications
Intervention	Not restricted	-
Comparator	Not restricted	-
Outcomes	Cost data: Direct medical cost (e.g. medication, physician visits, hospitalization, etc.) Direct non-medical cost (e.g. paid caregiver time, etc.) Indirect cost Resource utilisation data: Number of hospitalisations, rehabilitations, etc.	Other outcomes
Study design	Various study types	-
Language	English, German, French, Spanish and Italian (publications in other languages will be listed, and only abstracts in English included)	-
Publication type	Full-text publications, conference proceedings	Mere animal studies Letter, Editorial, Notes, Historical article
Abbreviations in table: RCC, renal cell carcinoma.		

Table 68. Summary of included studies reporting resource use and costs (CS, Appendix 21, pg 203-207)

Author, Year	Type of study	Aim of the study	Study description	Country	Therapy	Resource use	Cost outcomes
Anonymous 2006(Bevacizumab HTA database 2006)	Technology brief	To provide an early assessment of a new or emerging technology.	NR	UK	Bevacizumab (BEV)/Interferon-alfa (IFN) vs No treatment	NR	**Cost of treatment and follow-up:** BEV cost of £1,652 per fortnightly infusion assuming wastage
Ballali *et al*., 2013	Cost-effectiveness analysis	To evaluate the impact of multitargeted tyrosine kinase inhibitors (TKI) considering 1st and 2nd line treatment for a full period of 3 years in the eligible patients of Veneto Region	A Markov state decision model was selected to evaluate the cost impact of sunitinib and sorafenib use for a lapse of time of three years in Veneto public hospitals considering transition probabilities from three different states, and by comparing the expected deaths and the monthly survival rates in treatment and no-treatment groups	Italy	Sunitinib and Sorafenib	NR	**Cost of treatment reported as cumulative for the 1st and 2nd line therapy, Mean (90%CI)** **Cumulative cost at 6th month** Sunitinib + Sorafenib:€ 2,633,573 (€ 1,039,632 -€ 3,539,720) **Cumulative cost at 12th month** Sunitinib + Sorafenib: € 3,800,899 (€ 1,545,855 - € 5,100,104) **Cumulative cost at 18th month** Sunitinib + Sorafenib: € 4,056,495 (€ 1,697,715 - € 5,429,808) **Cumulative cost at 24th month** Sunitinib + Sorafenib: € 4,079,500 (1,722,720 - 5,462,528) **Cumulative cost at 30th month** Sunitinib + Sorafenib: €4,080,409 (€1,722,720 - €5,4625,28) **Cumulative cost at 36th month** Sunitinib + Sorafenib: €4,080,411 (€1,722,720 - € 5,462,528)

Botteman *et al.*, 2011	Cost-effectiveness analysis	To assess the cost-effectiveness of Zolendronic acid(ZOL) adopting a French, German, and United Kingdom government payer perspective	The model is based on a post hoc retrospective analysis of a subset of patients with RCC who were included in a larger randomized clinical trial of patients with bone metastases secondary to a variety of cancers	France, Germany and United Kingdom	ZOL vs Placebo	**Resource use associated with ZOL administration in UK:** Physician time 11.12 min Pharmacy technician time 10.58min Nurse time 44.25min Needle 2 pieces Gauze 2 pieces Alcohol swab 2 Syringe 2 pieces Set of gloves 3 pieces Medical tape 1 piece Sample tubes 2pieces Disposable IV set 1 piece Thermometer cover 1 piece	**Costs of AE (skeletal-related events) in UK:** Vertebral fractures €189 Non-vertebral fractures €6,158 Radiation therapy to bone €468 Surgery to bone €3,346 Spinal cord compression €5,060 **Total cost per ZOL infusion €270.86, includes:** Cost of ZOL €218.32 Administration cost (ZOL) €47.68 Supplied cost €4.86
Hoyle *et al.*, 2010	Cost-effectiveness analysis	To estimate the cost-effectiveness of sorafenib versus best supportive care (BSC) for second-line treatment of advanced renal cell carcinoma from the perspective of the UK National Health Service.	A Markov-type decision analytic model was developed to estimate the cost effectiveness of sorafenib.	UK	Sorafenib vs BSC	**Resource use :** **PFS medical management** Sorafenib: 1 outpatient consultation/month ; 1 CT scan/3months; 1 blood test /month BSC: 1 GP visit/month; 1CT scan /6months; 1 blood test/month **PD medical management:** Sorafenib and BSC: 1GP visit/month; 1.5 community nurse visits /month Pain medication (morphine sulphate)/day	**Cost per 6-week model cycle, Mean (SE)**: Progression-free survival (PFS) medical management BSC: £81 (£3) Sorafenib: £223 (£9) **Progressive Disease (PD) medical management** BSC and Sorafenib: £435 (£22)
Liniker *et al.*, 2013	Retrospective cost	This study is a retrospective cost attribution	All patients entered into oncology (non-	UK	Multiple	NR	**Cost associated with treatment of renal cell cancer**

	attribution analysis	analysis to quantitate the treatment costs associated with cancer clinical trial protocols conducted over a 2 year period.	haematology) clinical trials involving investigational medicinal products in 2009 and 2010 in a single UK institution were identified. The trial protocols on which they were treated were analysed to identify the treatment costs for the experimental arm(s) of the trial and the equivalent SOC had the patient not been entered in the trial				**IVA-Doxorubicin + maintenance VC**: £6393 Bevacizumab: £5144 Docetaxel: £2337 Cetuximabþchemo-RT: £2000 Bevacizumab and ECX: £1519 Bevacizumab±carboplatinþ + paclitaxel: £1310 Aflibercep + docetaxel: £1186 GemCap + chemo-RT: £1134 ECX: £859 Capecitabine: £848 SIR-Spheres and OxMdG: £803 Bevacizumab + FEC-T: £459 Bevacizumab, or bevacizumab + low dose IFN, or bevacizumab + standard dose IFN: £206 Cisplatin + capecitabine + streptozocin: £126 Cetuximab + OxMdG: £83 Dalteparin + SOC: £25 Exemestane: £3 Celecoxib + SOC: £0 Pravastatin + SOC: £0 Sorafenib 1 year or 3 years :£0 Bevacizumab + capecitabine: : -£23 Faslodex + Arimidex, or Faslodex: -£40 Panitumumab + EOX: -£1000 GemCap + GV1001 (concomitant), or GV1001 then GemCap: -£1037 Temozolomide: -£1520

							OxMdG 12 weeks: -£3178 Trastuzumab 6 months: -£6005
Paz-Ares *et al.*, 2010	Cost-effectiveness analysis	To investigate the cost-effectiveness of sunitinib (50 mg⁄day, schedule 4⁄2) vs. best supportive care (BSC) in patients with cytokine refractory mRCC, from the perspective of the Spanish National Health Service	A Markov model compared the cost-effectiveness (taking into account drugs; medical visits; laboratory tests; X-rays; terminal care; adverse event management) of sunitinib and BSC across three disease states: no progression, survival with progression and death from mRCC or other causes	Spain	Sunitinib vs BSC	**Medical visits:** Sunitinib: First 3 months Six oncologist (EC) external consultation. (once every 15 days) Remainder One oncologist EC⁄1.5 months BSC: One visit every month: • 50% oncologist EC⁄cycle • 25% palliative care staff EC • 25% home visits from a qualified nurse Monitoring: Sunitinib: First 3 months Six biochemistry and full blood test (once every 15 days) Remainder: One biochemistry and full blood test⁄1.5 months One abdominal CT scan⁄3 months One pelvic CT scan⁄3 months One initial chest X-ray BSC: One biochemistry and full blood test⁄1.5 months Two abdominal CT scans in total Two pelvic CT scans in total One initial chest X-ray	**Unit cost:** Oncology EC: €85.96 Palliative EC: €41.37 Home nurse visit: €29.72 Full blood test and biochemistry: €37.77 Abdominal⁄pelvic CT scan: €31.83 Chest X-ray: €31.47 Terminal care: Chronic care⁄palliative care unit : €216.91 **Adverse event cost (unit cost)** Anaemia: €337.71 Thrombocytopenia: €586.97 Abdominal pain: €52.98 Diarrhoea: €52.98 Vomiting: €0.44 Fatigue €0.00 Tumour haemorrhage: €639.81 Tumour embolism: €77.74 Palliative radiotherapy (cost⁄month): €212.73 ZOL 4 mg⁄month: €244.8 Sunitinib: 50 mg⁄day (65%patients):€ 4,760 37Æ5 mg⁄day (32%patients):€3,570 25 mg⁄day (3%patients): € 2,380 BSC: Ibuprofen 1.2 g⁄day: €0.15 Morphine: €0.12 Megestrol acetate: 2.71

Petrou *et al.*,2014	Feasibility study (of introducing a value-based pricing scheme)	To assess the feasibility of introducing a value-based pricing scheme of pharmaceuticals in Cyprus and explore the integrative framework.	A probabilistic Markov chain Monte Carlo model was created to simulate progression of advanced RCC for comparison of sorafenib to standard best supportive	Cyprus	Sorafenib compared vs BSC	**PFS management:** **Sorafenib:** 1 specialist visit/month/1 CT scan/3 months/blood test/month 40, **BSC:** 1 GP visit/month; 2 nurses / month; 1 psychologist /month **PD management** **Sorafenib and BSC:** GP visit/month; 2 nurses / month; 1 psychologist /month	**Sorafenib (PFS)** **Specialist visit : €40** **1GP+2nurse+1psycologist visit: €70** Annual costs related to hypertension: 3 visits € 60 CT scan: **€** 256 (every 3 months) Hospitalization: **€135 daily** **Blood test (full blood count, liver function, SGPT, SGOT and creatine): €157**
Petrou *et al.*, 2014	Cost-effectiveness analysis	To assess the cost effectiveness of sorafenib as a second line treatment of advanced renal cell carcinoma compared to standard best supportive care (BSC) in Cyprus.	A probabilistic Decision analytic Markov Model was created to simulate disease progression and data from landmark trials were used	Cyprus	Sorafenib vs BSC	**PFS management:** **Sorafenib:** 1 specialist visit/month/1 CT scan/3 months/blood test/month **BSC:** 1 GP visit/month; 1 CT scan (every 6 months) **PD management** **Sorafenib and BSC:** GP visit/month; 2 nurses / month; 1 psychologist /month	**Specialist visit : €40** **1GP: €20** **1GP +2nurse+1psycologist visit: €70** Annual costs related to hypertension: 3 visits € 60 Sorafenib (PFS management): CT scan: **€** 256 (every 3 months) BSC (PFS management): CT scan: **€** 256 (every 6 months)
Petrou *et al.*, 2015	Cost-effectiveness analysis	To estimate the cost-effectiveness of axitinib versus sorafenib, for the second-line treatment of renal cell carcinoma.	A literature review for evidence synthesis was performed and a probabilistic Markov Model was employed to simulate disease progression	Cyprus	Axitinib vs Sorafenib	NR	**Medical activity (treatment, follow-up and AE management), unit cost**: Hospitalization: €135 /day) FBC: €13 U&E: €52 Specialist visit: €30 CT SCAN: 256 (quarterly) Euros Proteinuria analysis €72 Blood tests: €210

Purmonen *et al.*, 2008	Cost-effectiveness analysis, cost utility analysis	To analyze the cost-effectiveness of sunitinib as second-line therapy for cytokine-refractory mRCC compared with current routine clinical practice in Finland (ie, BSC, including palliative biochemotherapy) .	A probabilistic decision-analytic model was developed to estimate the cost-effectiveness of sunitinib. Data were gathered from clinical trials, literature sources, and expert opinions, as well as from a local sample (n =39) from 2 university hospitals in Finland	Finland	Sunitnib vs BSC	**Medications: (frequency, number, %)** IFN-alfa /Cancer medication/ bisphosphonates/analgesics 0 - 33 (85%)/15 (38%)/32 (82%)/9 (23%) 1 - 6 (15%)/12 (31%)/5 (13%)/12 (31%) 2 - 0/7 (18%)/2 (5%)/6 (15%) ≥3 – 0/5 (13%)/ 0/12 (31%) **Imaging examinations (frequency, number, %)** Radiography/CT/Sonography/MRI 0 - 12 (31%)/24 (61%)/25 (64%)/36 (92%) 1 - 11 (28%)/10 (26%)/8 (20%)/3 (8%) 2 - 3 (8%)/2 (5%) 3 - 3 (8%)/3 (8%)/0 ≥4 - 10 (25%)/2 (5%)/2 (5%)/0 **Health care service units (frequency, number, %)** Ward Care Days (University hospital)/HC Center/Outpatient visits 0: 10 (26%)/19 (49%)/14 (36%) 1-5: - 6 (15%)/2 (5%)15 (38%) 6 - 10: 6 (15%)/2 (5%)/6 (15%) 11 - 19: 12 (32%)/3 (8%)/3 (8%) ≥2O: 5 (13%)/13 (34%)/1 (3%) Radiotherapy days 0: 23 (59%) 1-5: - 2 (5%) 6 - 10: 6 (15%)	**Cost, Mean (SE), (2005)** **Sunitinib arm** Month 1:€ 545 (€114) Months 2-3: €324 (€68) Months >3: €201 (€42) **Drug costs per month**: €3,748 **Total cost BSC arm**: €1,339 Expected mean cost in BSC: €5,543

						11 - 19: 3 (8%) ≥2O: 5 (13%)	

Abbreviations in table: AE, adverse event; BEV, bevacizumab; BSC, best supportive care; CI, confidence interval; CT, computerised tomography; ECX, epirubucin combined with cisplatin and capecitabine; EOX, epirubicin combined with oxaliplatin and capecitabine; GemCap, gemcitabine and capecitabine; HC, health centre; IFN, interferon; mRCC, metastatic renal cell carcinoma; MRI, magnetic resonance imaging; NR, not reported; OxMdG, Oxaliplatin, 5-Fluorouracil &. Folinic Acid; PD, progressed disease; PFS, progression-free survival; SE, standard error; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; SOC, standard of care; TKI, tyronase kinase inhibitor; ZOL, zolendronic acid.

5.4.5.1 Pharmacological costs

The pharmacological costs considered in the model are treatment acquisition, and treatment administration costs. The acquisition costs for the intervention and comparators are summarised in Table 69.

Table 69. Acquisition costs for intervention and comparators

Treatment	Vials/tablets per pack	Formulation	Cost (per pack) UK list price	Source
Cabozantinib	28	20/40/60	£4,800	BNF[87]
Everolimus	30	10	£2,673	BNF[87]
Axitinib	56	5	£3,517	BNF[87]
Nivolumab	1 1	40 100	£439 £1,097	MIMS[88]
Abbreviations in table: BNF, British National Formulary; mg, milligram; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service.				

In order to estimate total drug costs, TTD data from the METEOR trial was used to inform the proportions of patients in the cabozantinib and everolimus arms receiving treatment at each time point in the model.[89] TTD for nivolumab was estimated based on data from TA417.[36] However, no published TTD curves were identified from the AXIS trial for axitinib, therefore patients in the axitinib arm were assumed to stop treatment upon progression. The PFS distribution generated from the NMA was used to calculate treatment costs for axitinib.

Drug doses assumed in the model, and costs per cycle are summarised in Table 70. Patients in the model are assumed to receive 100% of the doses of cabozantinib to reflect the flat price of cabozantinib which does not vary according to formulation (i.e. 20 mg or 40 mg or 60 mg). The dose of cabozantinib in the trial could be reduced from 60 mg per day to 40 mg per day, and then to 20 mg per day if required.[89]

Table 70. Drug formulation, dose and total cost per 4-weeks model cycle for comparators

Drug	Dose	Frequency	Relative dose intensity, % (SE)	Total cost per cycle
Cabozantinib	60/40/20 mg	daily	100.0 (0.0)*	£4,800.00
Everolimus	10 mg	daily	83.9 (1.1)[a]	£2,093.41
Axitinib	10 mg	daily	102.0 (1.9)[b]	£3,587.34
Nivolumab	3 mg/kg	Every 2 weeks	97.5 (9.8)[c]	£5,146.15
Abbreviations in table: kg, kilogram; mg, milligram; SE, standard error.				

Patients in the everolimus arm of the model are assumed to receive 83.1% of the planned doses to reflect the proportion of doses received in the METEOR trial.[89] The RDI assumed for axitinib and nivolumab is 102.0% and 97.5%, respectively. These values are based on the published literature, and have been used in previous NICE appraisals (TA417 and TA333).[5, 76, 90] In the base case analysis, drug wastage

was not included for nivolumab, but was estimated to be 8.5%. A description of how this value was calculated is presented in Box 15.

Box 15. Calculation of wastage for nivolumab (CS, pg 136)

The percent wastage was estimated to be 8.5% by comparing the exact recommended weight-based dosage for patients to the total drug acquisition required given the availability of the 40 mg or 100 mg nivolumab vials. The wastage estimate was obtained using the weight distribution of patients in the METEOR trial (average 80.19 kg).
Abbreviations in box: kg, kilogram; mg, milligram.

Nivolumab is the only treatment that is assumed to incur an administration cost, since it is administered intravenously while the rest of the comparators are taken orally. A cost of £152 per administration is applied for nivolumab, resulting in an administration cost of £304 per model cycle.

Patient access schemes for the comparators have not been applied to the acquisition costs of the comparators dues to being commercial in confidence.

5.4.5.2 Disease management costs

The costs associated with the management of RCC are included in the model. Resource use was estimated based on input from clinicians practising in the UK. Disease management costs differed according to progression status (i.e. PFS or PD), as reported in Table 71.

Prior to progression, patients are assumed to have a visit with a consultant or a specialist nurse every 6 weeks, and to have a GP visit every 8 weeks. After progressing patients are assumed to have more frequent GP and community nurse visits (i.e. every 4 weeks).

In terms of investigations, patients are assumed to have CT scans every 12 weeks before progression, and none after progression. Patients in the model have blood tests every 6 weeks before progression, and every 4 weeks after progression.

A one-off cost reflecting end of life care in the last four weeks of life is applied to all patients who die in the model. This cost was estimated based on a published paper assessing end of life costs in the UK.[91]

Table 71. Costs associated with disease management (CS, pg 141, Table 71)

Disease state	Resource	Frequency	Unit cost	Source of unit costs
Progression-	GP visit	Every 8 weeks	£54.00	General practitioner - unit costs. PSSRU (2015) Section 10.8

free				p177
	CT scan	Every 12 weeks	£129.00	NHS National Tariff Payment System 2016-17. Tariff RA14Z
	Blood test	Every 4 weeks	£54.00	NHS Trust and PCT combined Reference Costs: the main schedule 2014-15. Code DAPS05 (Haematology)
	Consultant/ specialist nurse (50:50)	Every 6 weeks	Consultant: £93.00 Nurse specialist: £65.00 Average: £79.00	NHS National Tariff Payment System 2016-17. Consultant (tariff WF01A): Nurse specialist (community), 1 hour patient's time. PSSRU (2015) Section 10.4 p172
Progression	GP visit	Every 4 weeks	£54.00	General practitioner - unit costs. PSSRU (2015) Section 10.8 p177
	Community nurse visit	Every 4 weeks	£65.00	Nurse specialist (community), 1 hour patient's time. PSSRU (2015) Section 10.4 p172
	Blood test	Every 6 weeks	£54.00	NHS Trust and PCT combined Reference Costs: the main schedule 2014-15. Code DAPS05 (Haematology)
End of life costs	Various	One-off cost during last 4 weeks of life	£5,912.39	Georghiou T, Bardsley M. Exploring the cost of care at the end of life. 2014. Table 4: summary costs of hospital care http://www.inflation.eu/inflation-rates/great-britain/historic-inflation/cpi-inflation-great-britain.aspx. Access on 9th Aug, 2016.
Abbreviations in table: CT, computerised tomography; GP, general practitioner; NHS, National Health Service; PCT, primary care trust; PSSRU, Personal and Social Services Unit.				

5.4.5.3 Adverse event costs

The costs of management of adverse events are included in the model. The rates of adverse events were based on rates observed in the METEOR trial (for cabozantinib and everolimus)[(1)], in the CheckMate 025 trial[(3)] (for nivolumab), and rates reported across different trials presented in axitinib's SPC as described in Section. 5.4.3. The resource use and costs assumed for the management of each adverse event are presented in Table 72.

Table 72. Treatment-emergent adverse events management resource use assumed in the model (CS, pg 144, Table 74)

Adverse Event	Resource Use Assumption	Total Costs
Anaemia	25% inpatient hospitalisation 75% day-case visit 1 blood transfusion	£593.00
Diarrhoea	1 inpatient hospitalisation	£426.00
Fatigue	1 outpatient visit	£93.00
Hypertension	Amilodipine 5 mg once a day for 4 weeks 5% inpatient hospitalisation + 95% outpatient visits(4 visits)	£656.00
PPE	1 outpatient visit corticosteroid cream (clobetasol) for 50 days	£101.00
Abbreviations in table: mg, milligram; PPE, Palmar-plantar erythrodysaesthesia syndrome		

5.4.5.4 Subsequent therapy costs

Patients are assumed to receive subsequent therapy upon treatment discontinuation, with no delay between discontinuation and proceeding to the next treatment. The proportions of treatments, and durations assumed are presented in Table 73 and Table 74, respectively and are based on data from the pivotal trials (i.e. METEOR for cabozantinib and everolimus, AXIS for axitinib and CheckMate 025 for nivolumab). The doses and costs of subsequent therapies in the model are summarised in Table 75.

Table 73. Distribution of subsequent treatments following treatment discontinuation (CS, pg 140, Table 69)

Initial treatment	Subsequent Treatment					
	Axitinib	Everolimus	Sunitinib	Sorafenib	Pazopanib	BSC
Cabozantinib	17.00%	29.00%	5.20%	0.00%	0.00%	49.00%
Axitinib	0.50%	39.0%	8.50%	16.00%	8.50%	28.00%
Everolimus	27.00%	0.00%	10.00%	9.50%	6.70%	47.00%
Nivolumab	24.20%	25.6%	6.80%	6.30%	9.0%	28.00%
BSC	0.00%	0.00%	0.00%	0.00%	0.0%0	100.00%
Abbreviations in table: BSC, best supportive care. Sources: METEOR study (Choueiri et al 2016)[1] AXIS study (Rini et al 2011)[5] CheckMate 025 study (Motzer et al 2015)[3]						

Table 74. Duration of subsequent treatments (CS, pg 140, Table 70)

Subsequent treatments	Duration in days	Source
Axitinib	220.80	NICE technology appraisal guidance [TA333][90]
Cabozantinib	231.80	METEOR Trial (Ipsen METEOR patient level data. 2016)
Everolimus	167.60	METEOR Trial (Ipsen METEOR patient level data. 2016)
Sunitinib	118.70	Hutson,T.E. et al. 2014[92]
Sorafenib	180.70	NICE technology appraisal guidance [TA333][90]
Pazopanib	109.60	Rautiola,J. et al. 2014[93]

Table 75. Subsequent therapy dosage and costs (CS, pg 139, Table 68)

Drug	Formulation (mg)	Cost per pack, £	Vials/ tabs per admin	Vials/ tabs per pack	Dose, mg	Weekly frequency	Relative dose intensity, % (SE)	Total cost per cycle, £
Sorafenib	200	2,980.47[87, 88]	4.00	112	800	7	100.00**	2,980.47
Sunitinib	50	3,138.80[87]	1.00	28	50	4.7 *	100.00**	2,092.53
Pazopanib	400	1,121.00[87]	1.00	30	800	7	100.0**	2,092.53

Abbreviations in table: mg, milligrams.
* Sunitinib is given in 6 weeks cycles of 4 weeks of treatment followed by a rest period of 2 weeks;
** Assumed 100% for subsequent therapies

5.4.6 Discounting

The company used an annual discount rate of 3.5% for both costs and QALYs. The discount was applied after the first year (i.e. from cycle 14 onwards). A sensitivity analysis was performed around this discount, which was varied from 0% to 5%. The results are given in Section 5.6.2.

5.4.7 Sensitivity analysis

The company carried out a series of sensitivity analyses to test the robustness of the results to changes in assumptions and parameter values. The analyses were both deterministic (one-way parameter variations and scenario analyses) and probabilistic. The sensitivity analyses performed and their results are summarised in Section 5.6.2.

5.4.8 Model validation

In section 5.10 of the CS, it is reported that clinical outputs of the model were validated with UK clinical oncologists and the cost-effectiveness model was validated by economists who were not involved in the development of the model. The company provided an overview of the routines carried out by the economists for the input data validation and technical validation. These are presented in Table 76.

Table 76: Model validation routines

Input data validation routines	Technical validation routines
Rationale for inclusion of particular data sources	Detection of coding errors
Data sources checked against original source	Sheet by sheet testing, including macros
Distributions and parameters to represent uncertainty	Check formulas on each input cell and how the linking of data to the variables/engines is done.
Data adjustments: • Mathematical transformations, treatment of outliers, treatment of missing data, data synthesis, calibration, etc.	Check model parameters, testing of dropdown menus, names of cells, and all switches, including all sensitivity analyses
	Check if any elements seem redundant
	Check intended functionality of macros versus actual functionality, and for interpretability
	Run model with extreme values
	Movement of patients through the model
	Additional checks: • Suggestions for optimisation for speed and accuracy, if relevant • Absence of bugs • Logical code structure • Appropriate transition of the conceptual model • Appropriateness of data and model

The company also reports to have consulted with oncologists currently practising within the NHS in England regarding the appropriateness of the OS, PFS and TTD survival curve extrapolations (section 5.3 of the CS).

5.5 Critique of the company's economic evaluation

5.5.1 NICE reference case checklist

Table 77 and Table 78 summarise the ERG's quality assessment of the company's economic evaluation. Table 77 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 scope outlined in Section 3. Table 78 summarises the ERG's appraisal of the quality of the company's de novo economic model using the Philips checklist. [94]

Table 77. NICE reference case checklist for the base case analysis

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.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D-5L.
Benefit valuation	Time-trade off or standard gamble	Not reported.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes. EQ-5D-5L UK algorithm used.
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; PSS, Personal and Social Services; QALY, quality-adjusted life year; STA, single technology appraisal..

Table 78. Phillip's 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 advanced, previously treated RCC and has been validated by oncologists treating RCC in the UK.
S4: Structural assumptions	The chosen structure is appropriate, and reflects the clinical stopping rules for all the active interventions with patients being able to receive treatment after progression if deemed clinically beneficial.
S5: Strategies/ comparators	Cabozantinib was compared to everolimus, axitinib, nivolumab and best supportive care (BSC).
S6: Model type	The model type used for the cost-effectiveness analysis was a partitioned survival (area under the curve) model.
S7: Time horizon	A lifetime horizon of 30 years was used, considered sufficient to capture all the relevant costs and benefits associated with advanced, previously treated RCC.
S8: Disease states/pathways	The model included three health states: progression-free survival on treatment (PFS)), post-progression survival (PPS) and death. Treatment duration was captured independently from disease progression, as treatment could be continued even if a patient has progressed. The health states considered are deemed appropriate and sufficient to capture all the outcomes and costs.
S9: Cycle length	A cycle length of 28 days (4 weeks) was chosen to reflect the frequency of physician visits in the METEOR trial, which was deemed by the ERG to be a longer cycle length than expected for the disease area. However, to account for the long cycle lengths, a half cycle correction was applied, which is considered an appropriate adjustment estimate the outcomes more accurately.
Data	
D1: Data identification	The main source of evidence was the phase III METEOR trial comparing cabozantinib against everolimus and the NMA for axitinib, nivolumab and BSC. Relative treatment effectiveness was obtained from these two sources of data. Resource use was estimated by clinicians currently practicing in the UK and costs were obtained from PSSRU and the NHS England National Tarrifs. .[6, 95, 96]
D2: Pre-model data analysis	Survival analysis was performed for the head-to-head trial data for cabozantinib and everolimus and a network meta-analysis (NMA) was carried out using regenerated digitized Kaplan-Meier data for PFS, OS and TTD (where available) for axitinib, nivolumab and BSC to estimate parametric survival curve parameters. Both analyses were clearly stated in the CS. The ERG notes that the company used the proportionality of the hazards as a decision criterion for selecting an appropriate NMA methodology and choosing to fit independent curves for the METEOR data.
D2a: Baseline data	Baseline data were informed by the METEOR trial and were considered appropriate for the model population. However, according to the ERG's clinical experts the population in METEOR are reflective of UK clinical practice, but the trial contained a high proportion of patients with an ECOG performance status of 0 (67%) and that this would be reflective of the fitter patients found in current practice.
D2b: Treatment effects	Treatment effects on OS, PFS and TTD were modelled using independent treatment-specific parametric curves to estimate the proportion of patients in each health state, extrapolated until the end of the time horizon.

Dimension of quality	Comments
	Treatment effectiveness data for cabozantinib and everolimus was obtained from the METEOR trial [1]. A network meta-analysis was carried out to estimate the survival curves of axitinib, nivolumab and BSC. The ERG consider the methods applied to the trial-based model for the estimation of treatment effectiveness to be fairly reasonable. However, there is a lack of clarity in the justification for the choice of parametric curve fitted for each outcome, and other plausible alternatives were not fully considered or tested as scenario analyses. For the NMA-based model, the fitting of survival curves for each outcome is severely limited by the requirement to have a single distribution applied to all comparators, with only the parameters of the curves varying. This resulted in very poorly fitting curves in some cases, which causes the inherent relative treatment effect between these independently fitted curves to be very unreliable. This of course causes the results of the NMA-based model to be very uncertain.
D2c: Costs	All costs were clearly stated. Resource use is estimated for the base case analysis mainly based on the company's clinical expert input. NHS England National Tariffs and PSS costs are used where available, in line with the NICE reference case.[6, 95, 96] The ERG's clinical experts disagreed with the inclusion of GP visits prior to progression, stating that patients are more likely to be seen by consultants during this period every 4 weeks on average instead. In addition, the clinical experts noted that hospital costs associated with hypertension may be an overestimate and that sorafenib should not be a subsequent therapy option in the model as it is not reimbursed by the NHS. Costs of adverse events associated with subsequent therapies were not included in the model.
D2d: Quality of life weights (utilities)	The Health state utility values (HSUVs) for all health states regardless of treatment arm applied in the company's base case are based on EQ-5D-5L data obtained in the METEOR trial. Analysis of the EQ-5D-5L data by treatment arm was performed using a repeated measure mixed effect model. Disutility associated with AEs was considered separately in the model. Treatment specific AE impact was calculated by weighting the average AE utility decrement by the proportion of patients experiencing a grade 3/4 AE (only for grade 3/4 AEs where ≥ 5% of the treatment population experienced the event).
D3: Data incorporation	Data incorporation was generally appropriate. The ERG identified a structural error in the use of PFS instead of TTD to calculate active treatment costs. However this error was corrected at the clarification stage by the company.
Assessment of uncertainty	
D4a: Methodological D4b: Structural	Methodological and structural uncertainty was adequately explored for each individual analysis in the model. The electronic model allowed a high degree of flexibility as several options were incorporated to allow varying methodological and structural assumptions.
D4c: Heterogeneity	The trial data used to estimate PFS, OS and TTD is based on the ITT population, which includes patients with 1, 2 or more previous therapies. Subgroup analysis was not adequately performed to estimate results for the second- and third-line subgroups in the treatment pathway separately.
D4d: Parameter	Parametric uncertainty was adequately explored through deterministic sensitivity analyses and a probabilistic sensitivity analysis around the base case.
Consistency	
C1: Internal consistency	The model was internally consistent, with the exception of the error in the use of PFS instead of TTD to calculate active treatment costs.

Dimension of quality	Comments
C2: External consistency	The model was assessed for externally consistency, as the extrapolated landmark estimates of survival from the NMA and METEOR results were assessed by clinical experts. The concluded that the survival results were plausible.
Abbreviations used in table: OS, overall survival; PFS, progression free survival; TTD, time to discontinuation; NMA, network meta-analysis; RCC, renal cell carcinoma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; ERG, evidence review group; AE, adverse events.	

5.5.2 Modelling approach and model structure

The ERG consider the company's model to have an appropriate structure that is largely similar to other published oncology models. However, the company's original submission contained an error in the calculation of subsequent treatment costs, which led to patients in the model receiving subsequent treatment immediately after progression while the initial treatment was still being received. The company corrected this error in response to clarification questions and the company's corrected base case results are given in Section 6.1.

5.5.3 Population

The population considered in the economic model was adults with advanced RCC who had been previously treated with at least one VEGF-inhibitor, which is in line with the population specified in the NICE final scope. [8]

According to the ERG's clinical experts, and as already described in Section 3.1 of this report, the population in METEOR are reflective of UK clinical practice. However, the clinical experts noted that the METEOR trial contained a high proportion of patients with an ECOG performance status of 0 (67%) and that this would be reflective of the fitter patients found in current practice.

In Section 3.3 of the CS (Figure 5 and Figure 6), cabozantinib is positioned as a second-line treatment, but the company also state that it can be used in the third-line setting, and this was therefore requested by NICE in the final scope.[8] As mentioned previously, patients in the economic model have had at least one VEGF-inhibitor. However, the company does not present any subgroup analysis for patients who have received 1, 2 or ≥3 prior therapies, as they state the relative treatment effect is equivalent. The ERG requested additional data on the number and type of prior systemic anti-cancer therapies during the clarification stage, which were subsequently provided by the company. The data indicated that although the majority of patients had received 1 or 2 prior therapies (~97%) there was a minority of patients, 3.3% in the cabozantinib arm and 2.4% everolimus arm that had received 3 or more prior VEGF-TKI therapies.

The key issue in not considering these subgroups in the economic model regardless of whether the treatment effectiveness is equivalent, is that the baseline inputs in the model are likely to differ and thus impact on the ICER. As such the ERG requested a separate base case analyses for the 2nd and 3rd line treatment for advanced RCC of cabozantinib compared with all relevant comparators based on these subgroups. The company responded to the request stating that outcomes obtained from the NMA (OS, PFS and TTD) were only feasible for the subgroup of patients with only 1 prior VEGF-TKI and presented a new base case for the second line treatment for advanced RCC of cabozantinib compared with only with comparators from the NMA. Results of the new NMA base case analysis are presented in Table 79, alongside results from the original NMA base case analysis. The results indicate that changing the population to patients who have received only one prior therapy has a large impact on the ICER, however, these results are unreliable as the comparator arms from the regenerated KM data are based on the ITT populations and not the subgroups.

Table 79. 2nd line treatment – NMA base case ICERs vs original base case ICERs

Treatment	New NMA base case ICER	Original NMA base case ICER
Cabozantinib	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost effectiveness ratio; NMA, network meta-analysis

No second or third line treatment base case analyses for the METEOR trial were provided by the company and as such the ERG is uncertain about what the impact of the different subgroups would be on the ICER.

5.5.4 Interventions and comparators

The intervention and comparators considered in the economic analysis were cabozantinib, everolimus, axitinib, nivolumab and BSC. These are in line with the interventions and comparators included in the NICE final scope for this STA.[8]

The modelled treatment regimen was 60mg orally once every day for cabozantinib, 10mg orally once every day for everolimus, 5mg orally twice per day for axitinib and 3mg/kg by intravenous infusion every two weeks. These regimens are in line with what was reported in the METEOR, CheckMate 025 and AXIS trials, as well as the recommended doses for everolimus, axitinib and nivolumab.

The company included the relative dose intensity in the model to account for variations from the planned drug dose received, ensuring representative costing for drug acquisition. This is described further in Section 5.4.5.

Time on treatment was modelled using parametric survival distributions. Time to discontinuation (TTD) data from the METEOR trial were used for time on treatment with cabozantinib and everolimus; TTD for nivolumab was obtained from [3]. PFS data were used for axitinib as TTD data were unavailable. In line with the CS, TTD is discussed as part of the treatment effectiveness in Section 5.4.2.3.

5.5.5 Treatment effectiveness

The ERG consider the methods applied to the trial-based model for the estimation of treatment effectiveness to be fairly reasonable. However, there is a lack of clarity in the justification for the choice of parametric curve fitted for each outcome, and other plausible alternatives were not fully considered or tested as scenario analyses.

For the NMA-based model, the fitting of survival curves for each outcome is severely limited by the requirement to have a single distribution applied to all comparators, with only the parameters of the curves varying. This resulted in very poorly fitting curves in some cases, which causes the inherent relative treatment effect between these independently fitted curves to be unreliable. This causes the results of the NMA-based model to be uncertain, as the estimation and extrapolation of PFS and, in particular, OS, are extremely influential on the ICER.

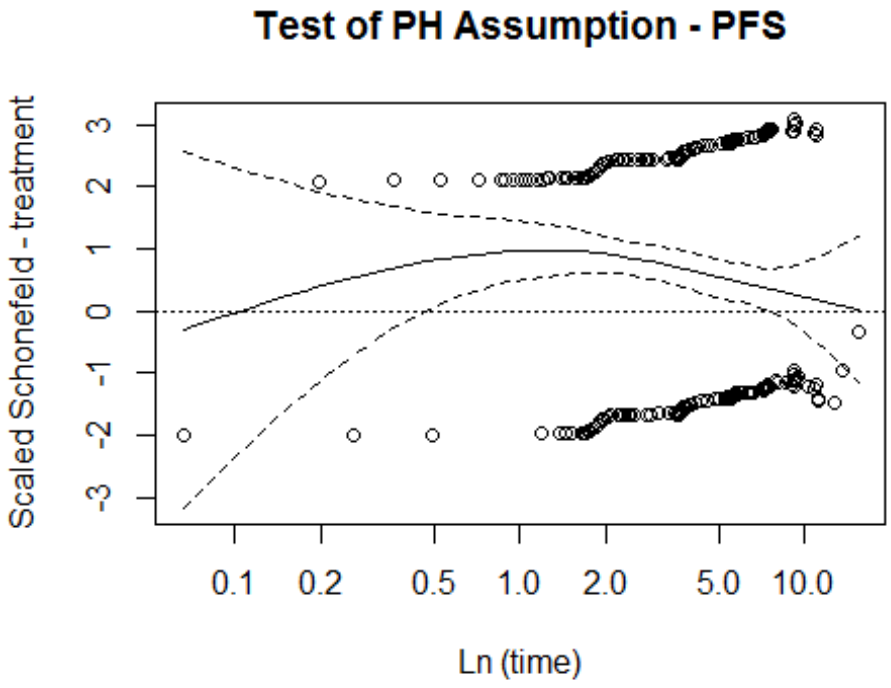
The remainder of this section will go into further detail about the issues identified by the ERG relating to the outcomes of PFS, OS and TTD and the effect any limitations or uncertainties could have on the overall model results.

5.5.5.1 Progression-free survival

For the estimation and extrapolation of PFS for the trial-based model, the company chose to use the log-logistic distribution for both treatment groups based on assessment of goodness-of-fit using the AIC, AICC and BIC statistics, and visual inspection by UK practising oncologists as described previously in Section 5.4.2.1. However, the statistics indicated that the log-logistic was only the best fit for the cabozantinib data, while the log-normal was the best fit for the everolimus data. The ERG would have preferred to see more justification as to why the log-normal was not chosen for both arms or at least tested as a scenario analysis.

As an assessment of PH, the company provided a plot of scaled Schoenfeld residuals as shown in Figure 25. The ERG consider that this plot does not provide any clear evidence of non-proportionality of hazards and therefore believe that this is in line with the company's conclusion that a PH assumption holds.

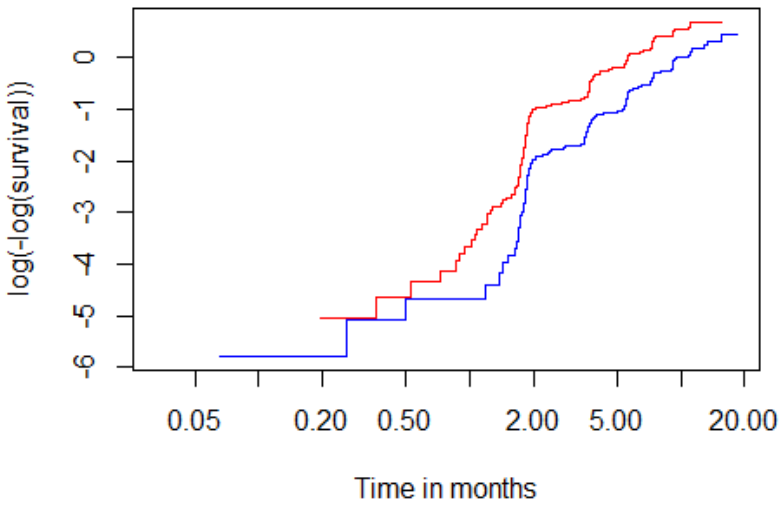
Figure 25. Schoenfeld residuals for assessing PH assumption for PFS (CS, Appendix 10)



At clarification stage, a log-cumulative hazard plot against log time for the METEOR trial was requested by the ERG, to determine whether PH assumptions holds and whether the hazard rates for the METEOR trial are indicative of a particular distribution, and thus, make a judgement on the appropriateness of the log-logistic distribution used by the company. This plot is presented in Figure 26. After a visual inspection of this log-cumulative hazard plot, the ERG consider the company's conclusion that a PH assumption does hold to be reasonable. The ERG notes a clear deviation from linearity within the first two months; however, beyond two months, the two plotted lines appear to have a linear trend with approximately constant separation, indicating proportional hazards. In the ERG's opinion, the violation of PH in the first two months is unlikely to have any meaningful impact on the survival estimation and also, therefore, on the model results. The ERG consider that it would have been appropriate to apply a jointly fitted PH model to the METEOR trial data for PFS. After clarification

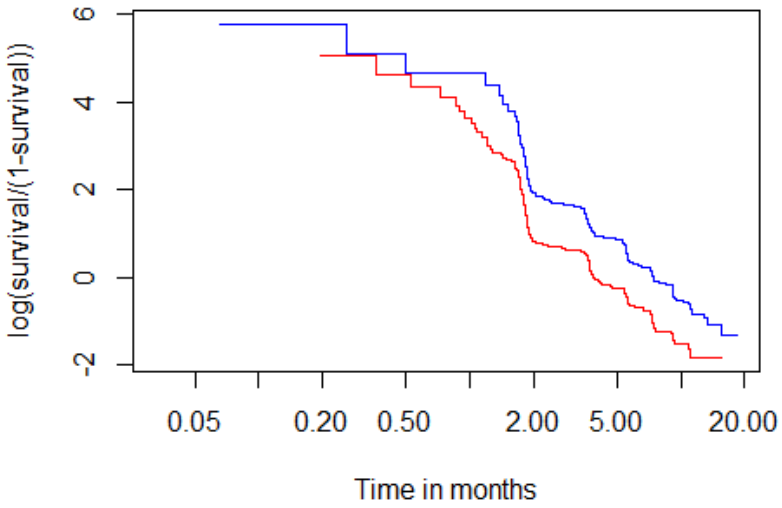
questions, the company provided a scenario analysis based on a PH model for PFS (and OS) and the results of this are given in Section 6.2.

Figure 26. Log cumulative hazard plots: METEOR PFS (Clarification response to B4)



The decision to fit independent curves to the METEOR trial did not appear to be logical given the assessment of PH; however, the ERG considers this method to be just as reliable given that it does not require any assumptions of relative treatment effect to hold. The ERG considers the company's choice of the log-logistic distribution to be reasonable based on the log-survival odds plot against log time shown in Figure 27. This shows approximate linearity between log odds of survival and log time for each arm of the METEOR trial, with the same deviation from linearity in the first two months as seen with the PH assessment. Again, this deviation is unlikely to have a meaningful effect on the estimation of survival probabilities and also, therefore, on the model results.

Figure 27. Log(survival function / (1-survival function)) plots versus Log(time) – PFS (Clarification response to B4)



In the original CS, the company did not provide the different survival curves with KM plots superimposed for visual inspection, only the AIC/AICC/BIC statistics. During the clarification stage, the ERG requested these and the company provided the additional graphs which are presented in Figure 28 and Figure 29 for cabozantinib and everolimus, respectively.

Figure 28. Comparison of KM data and fitted curves – PFS cabozantinib (Clarification resposne to B3)

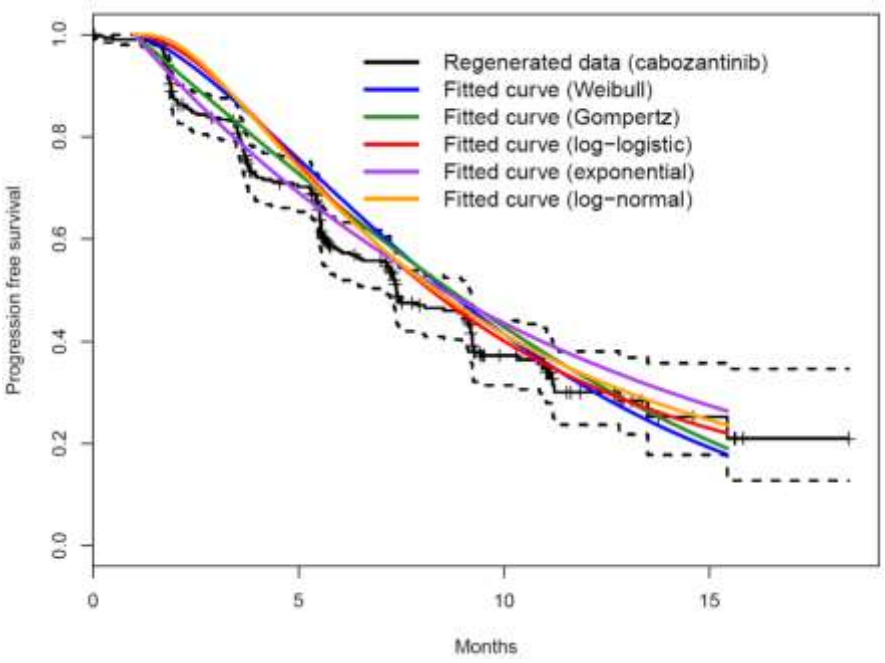
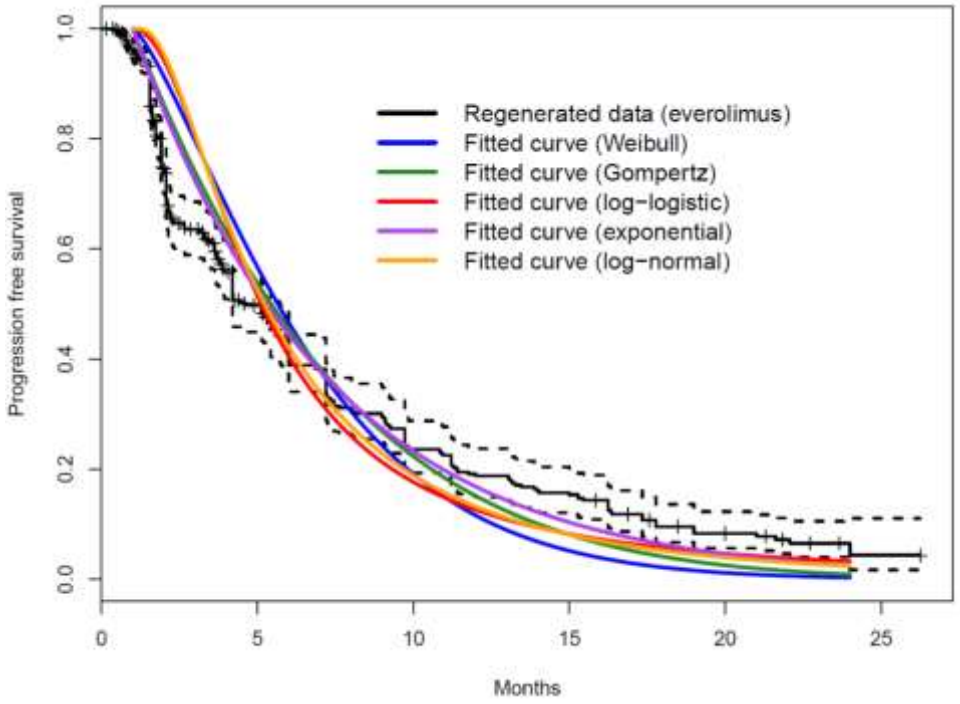


Figure 29. Comparison of KM data and fitted curves – PFS everolimus (Clarification resposne to B3)



Based on visual inspection, the ERG found that none of the survival curves fit the KM data well, but found that of the available distributions for use, the Weibull and log-logistic curves seemed to be a better fit for both cabozantinib and everolimus. The ERG verified survival estimates of the METEOR PFS extrapolated data (Table 80) with clinicians who confirmed that the estimates were clinically plausible. The ERG determines that the use of the log-logistic is reasonable based on visual inspection of the log-cumulative hazard plots, survival curves compared to the KM data and the AIC/AICC/BIC statistics. As there is much uncertainty around the distributions due to poor fit to any one distribution, the ERG conducted a sensitivity analysis to assess the impact on the ICER of changing the distributions in Section 6.2.

Table 80. Fitted progression-free log-logistic extrapolated PFS estimates - METEOR

Landmark	Estimate of % of progression-free patients	
	Cabozantinib	Everolimus
6 months	60	33
12 months	30	12
18 months	17	6
24 months	11	3
36 months	6	2
48 months	3	1

60 months	2	1
120 months	0	0

The company state that two potential methods for the NMA were assessed for use in generating PFS for axitinib, nivolumab and BSC, one based on HRs and the other on regenerated parametric curves. The company state the availability of data was sufficient to use either method, but chose to use the regenerated parametric curve method as this did not require the PH assumption to hold for each comparator. The company did test for PH for each comparator by performing Therneau and Grambsch chi-squared tests and determined that, for nivolumab and placebo, the assumption did not hold. At clarification stage, the ERG requested log-cumulative hazard plots (Figure 30 to Figure 33) to visually inspect for PH as these were not provided in the original CS. The ERG's visual inspection of the plots supports the findings of the statistical tests except that based on the plot for axitinib the PH assumption may not hold. Based on the findings that PH does not hold for all comparators, the ERG considers the regenerated parametric curve NMA method for PFS to be a reasonable approach.

Figure 30. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – axitinib (AXIS) PFS (Clarification response to B5)

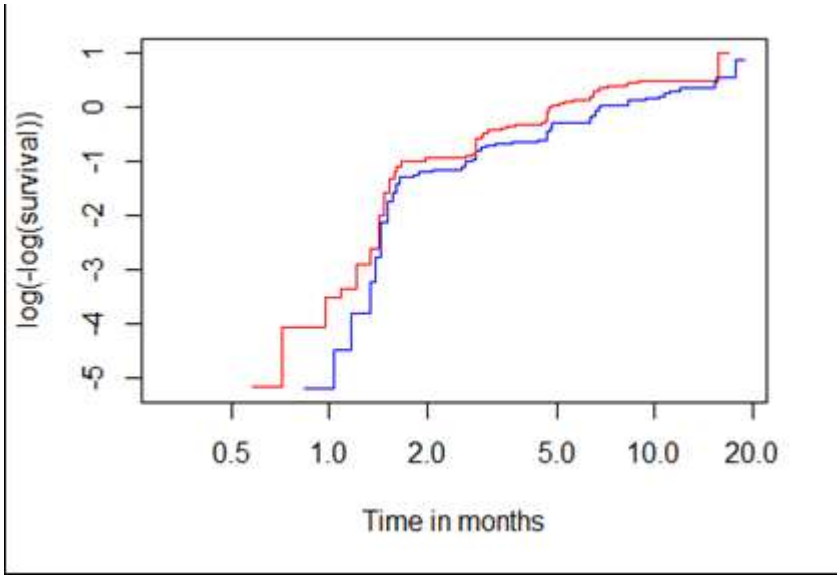


Figure 31. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – nivolumab (CheckMate025) PFS (Clarification response to B5)

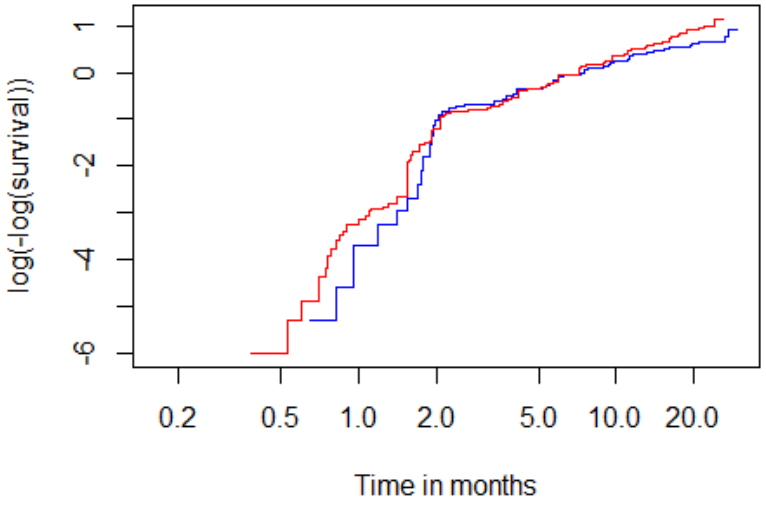


Figure 32. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – everolimus (RECORD-1) PFS (Clarification response to B5)

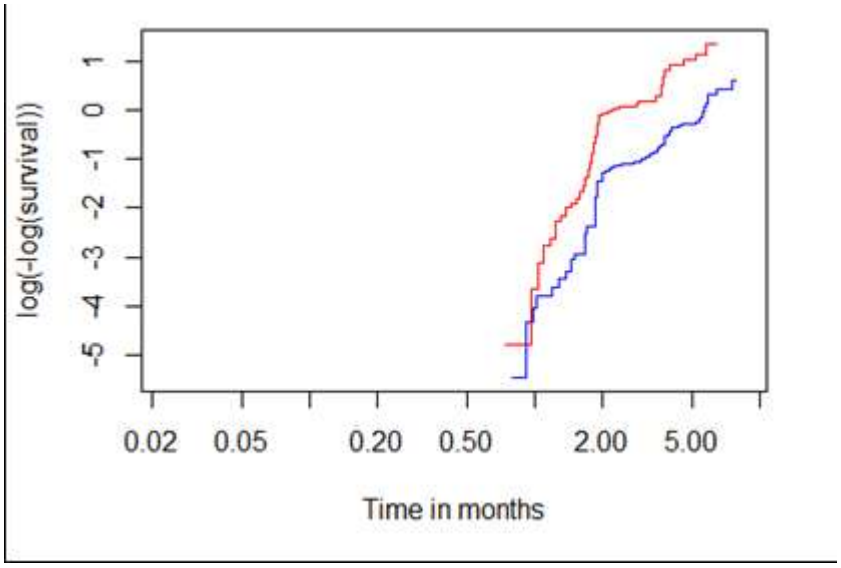
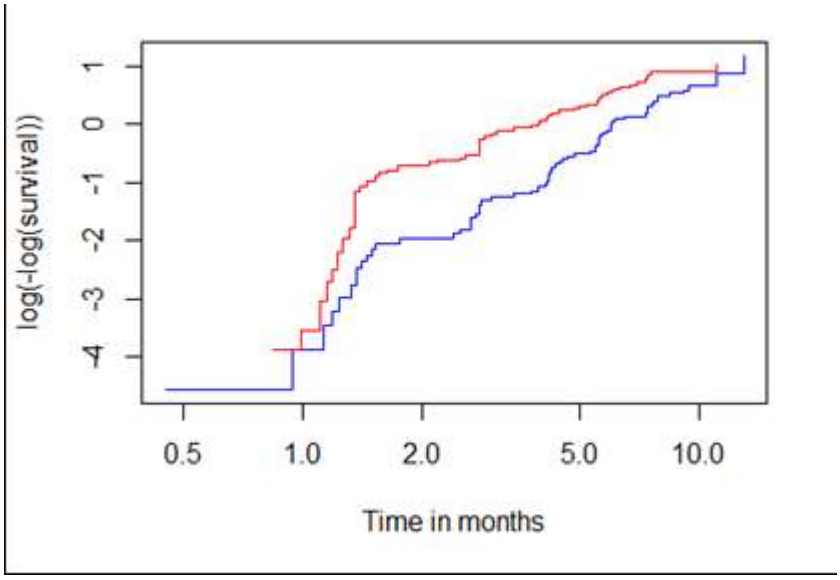


Figure 33. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – BSC (TARGET) PFS (Clarification response to B5)



The company ran statistical tests to assess the distributions for goodness-of-fit to the regenerated data and found the log-normal to be the best global fit. However, the ERG considers this method to be unreliable, as the goodness-of-fit for some, or even all comparators using a single distribution may be poor. This was shown when the fitted curves were superimposed on the respective KM plots. To account for the effect of the uncertainty around the choice of distributions on the ICER, the company conducted sensitivity analysis for each distribution considered (See Section 5.6.2). The scenario analysis found there was significant variation in the ICER depending on the chosen distribution.

At the clarification stage, the ERG requested the graphs of the survival curves with superimposed KM plots to visually inspect goodness-of-fit to all distributions under consideration. These graphs are presented in Figure 34 to Figure 36.

Figure 34. Comparison of re-generated KM data and fitted curves – PFS axitinib (Clarification response to B3)

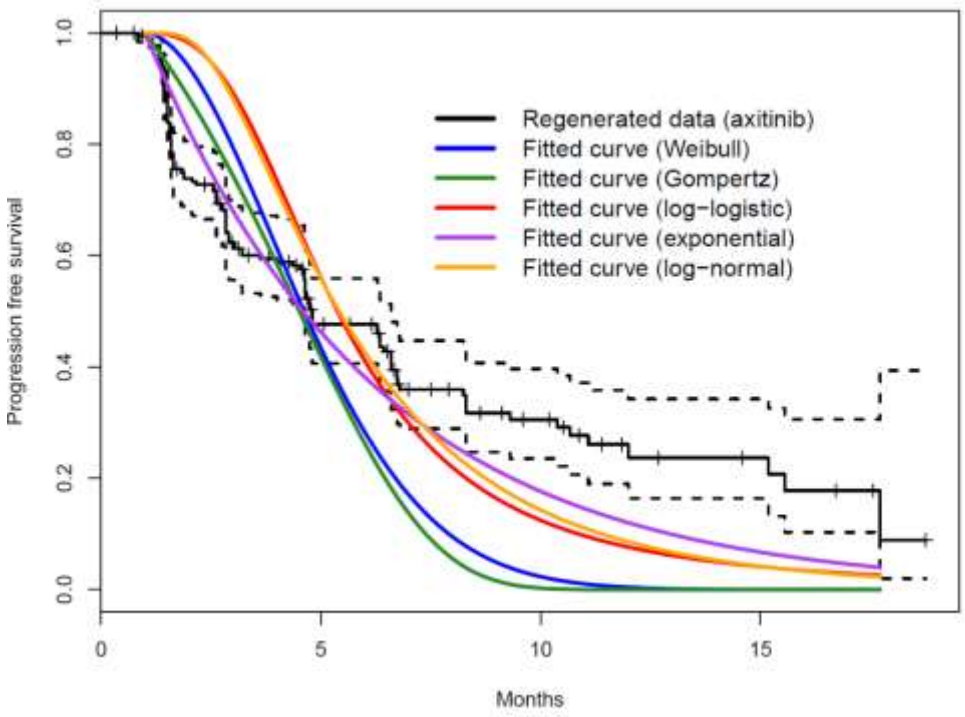


Figure 35. Comparison of re-generated KM data and fitted curves – PFS nivolumab (Clarification response to B3)

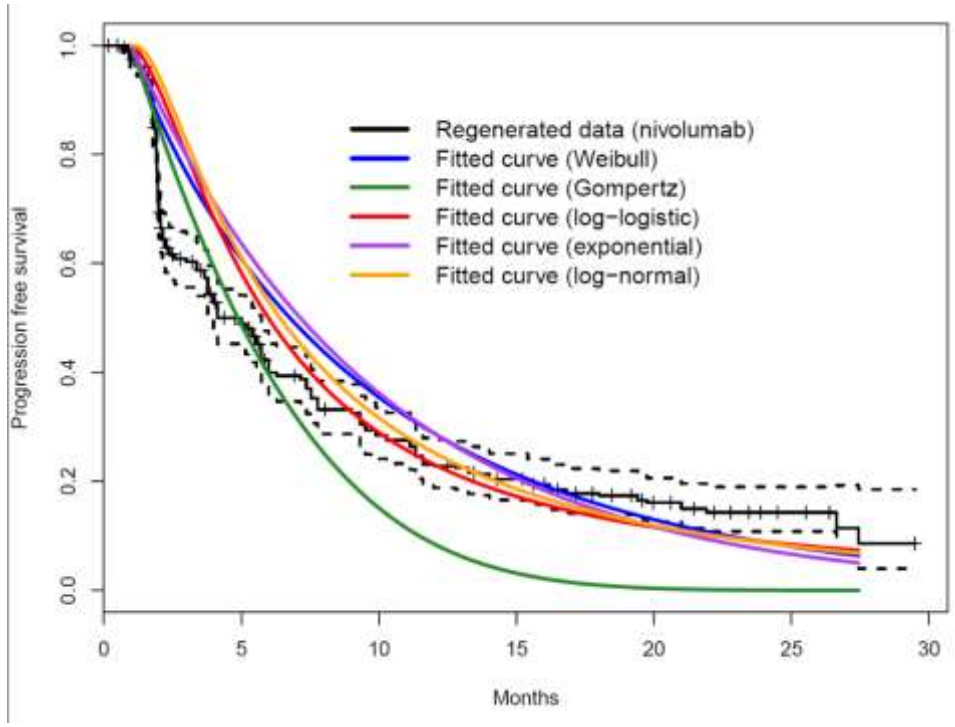
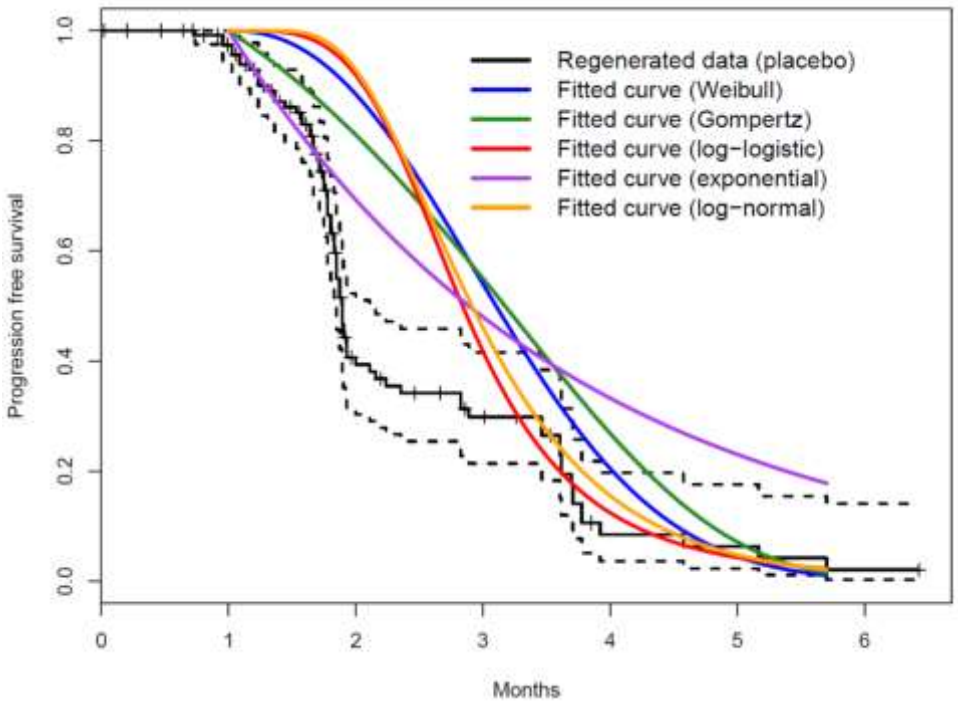


Figure 36. Comparison of re-generated KM data and fitted curves – PFS placebo (Clarification response to B3)



The ERG considers that all of the assessed survival curves, including the log-normal distribution, had a visually poor fit to the regenerated KM data. However, the ERG validated the company's extrapolated survival estimates at various time points (see Table 81) with clinicians, who considered that the estimates produced were clinically plausible. The ERG considers the choice of log-normal distribution to be reasonable based on the results of the statistical tests for goodness-of-fit and the validation of the extrapolated survival estimates with clinicians. However, the results need to be treated with caution as the chosen distribution visually had a poor fit to the KM data and as such could cause the cost-effectiveness estimates to be unreliable. This is reflected in sensitivity analyses conducted by the company (See Section 5.6.2).

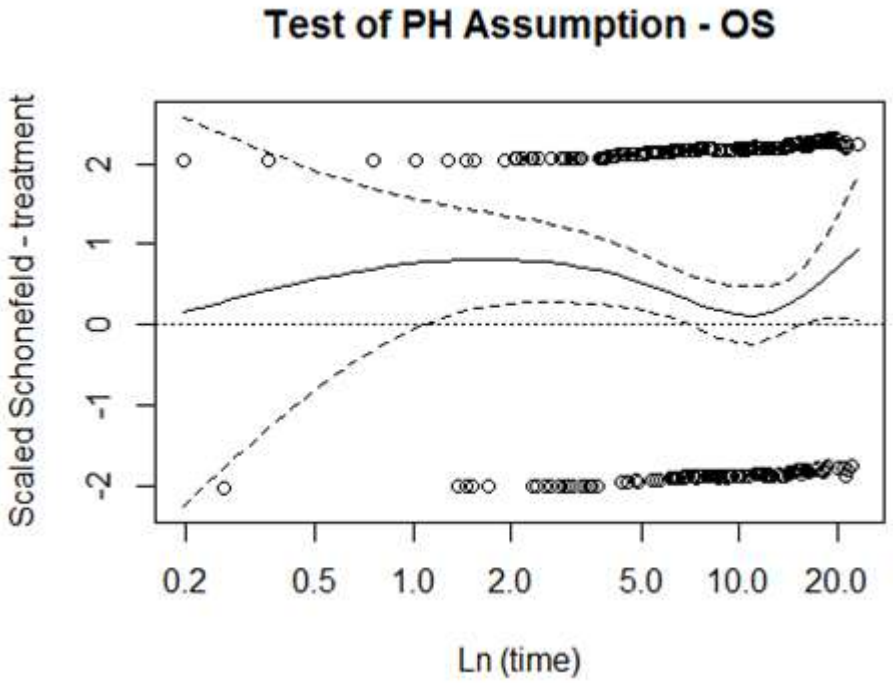
Table 81. Fitted progression-free log-normal extrapolated PFS estimates – NMA

Landmark	Estimate of % of progression-free patients	
	12 months	36 months
Cabozantinib	33	5
Nivolumab	18	2
Everolimus	12	1
Axitinib	9	0
BSC	0	0

5.5.5.2 Overall survival

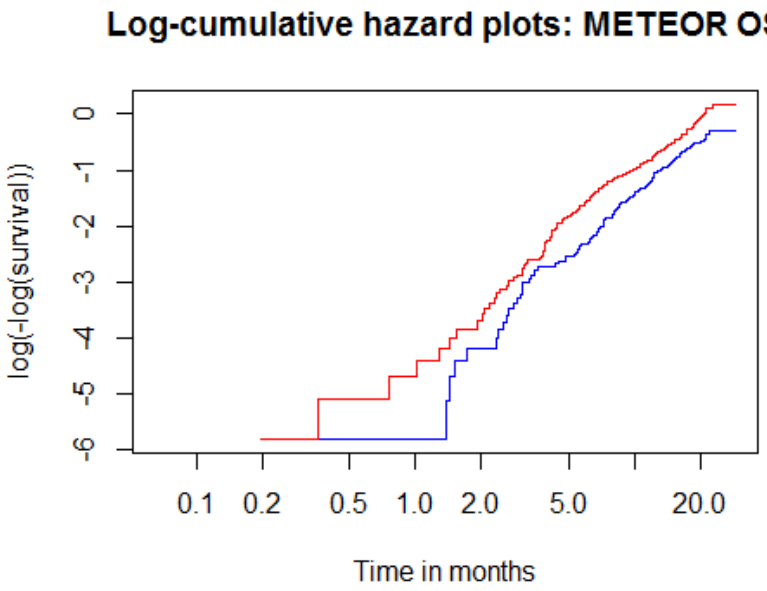
In the estimation and extrapolation of OS data for the trial-based model, the company chose to use independently fitted parametric curves for each arm of the METEOR trial. This was despite the company deducing that a PH model could have been implemented, as the data did not violate this assumption. This was shown by a chi-squared test resulting in a p-value of 0.406, meaning that, at a threshold of 0.05, the null hypothesis that hazards are proportional is not rejected. In addition to the chi-squared test, PH was also assessed by scaled Schoenfeld residual plots, as shown in Figure 37. This plot does not show clear evidence of a non-zero slope and therefore does not show that the PH assumption is violated.

Figure 37. Schoenfeld residuals for assessing PH assumption for OS (CS, Appendix 10)



In response to clarification questions, the company provided a log-cumulative hazard plot for the OS data in the METEOR trial, shown in Figure 38. This plot shows that for cabozantinib and everolimus in the METEOR trial, the log-cumulative hazard plots are close to being parallel, indicating that the hazards for each treatment are approximately proportional. The plot also shows an approximate linearity between log-cumulative hazard and log-time for each treatment arm, which is a characteristic of the Weibull distribution.

Figure 38. Log-cumulative hazard plot – OS (Clarification response to B4)



When assessing the visual fit of the curves as seen in Figure 39 and Figure 40 for cabozantinib and everolimus, respectively, there appears to be very little difference between the curves. For both cabozantinib and everolimus, the exponential curve seems to stand out as the poorest fitting model as it seems to underestimate the KM data initially, whereas the other curves, although slightly overestimating the KM data, appear to have a closer fit.

Figure 39. Comparison of re-generated KM data and fitted curves – OS cabozantinib (Clarification resposne to B3)

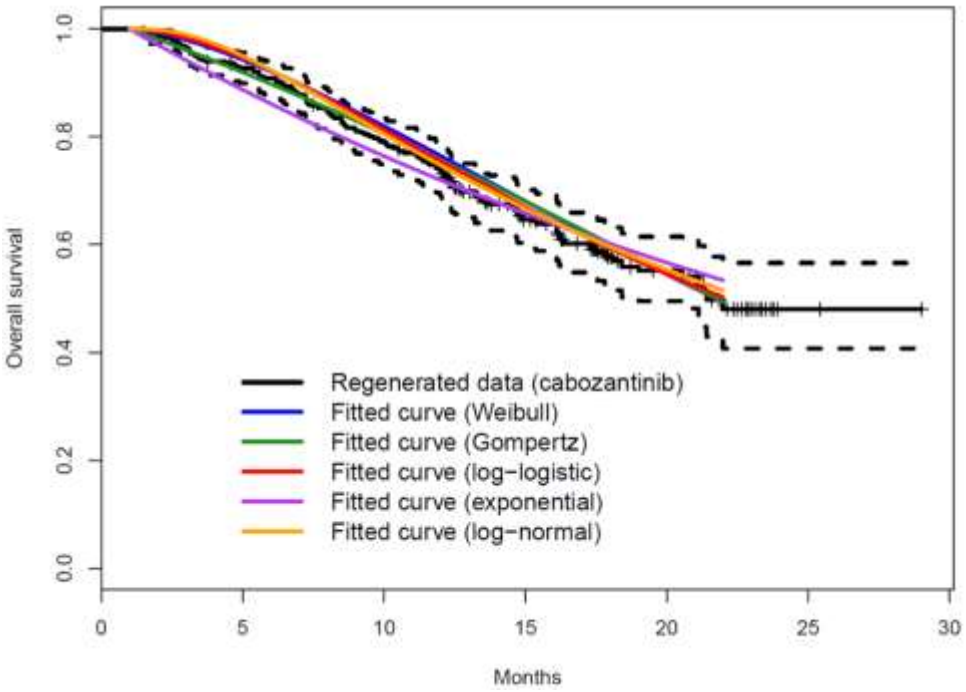
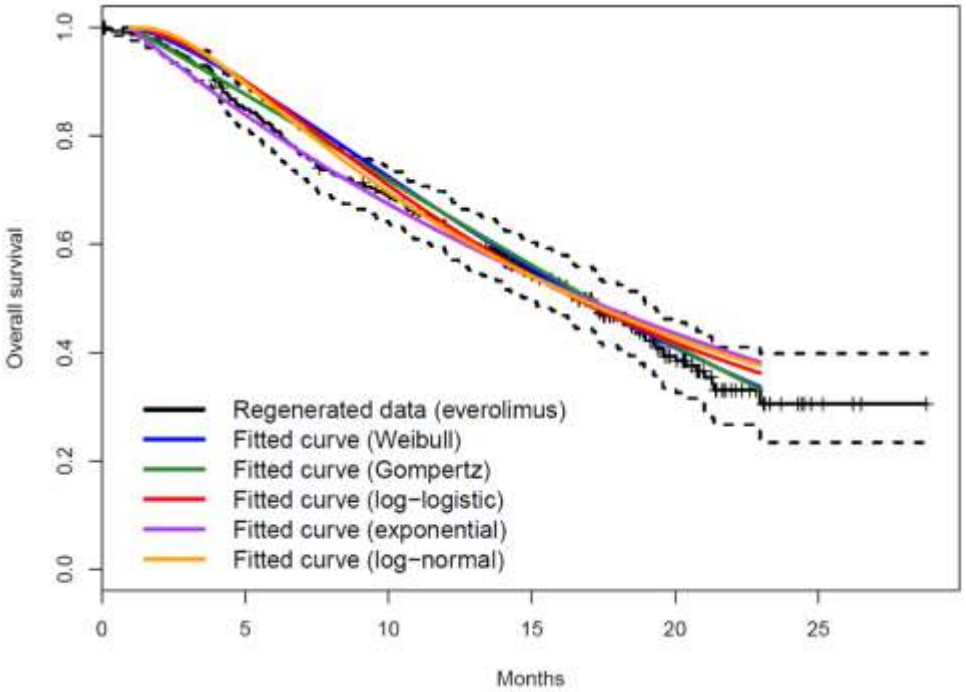


Figure 40. Comparison of re-generated KM data and fitted curves – OS everolimus (Clarification resposne to B3)



The ERG considers the company's initial approach to fitting separate overall survival curves to the METEOR trial data to be reasonable, given that it is a flexible modelling approach that does not require any assumptions for the relative treatment effect. The ERG agrees with the company's decision to use a treatment and comparator curve from the same family of parametric survival distributions; however, the ERG believe that the choice of the log-logistic distribution has not been fully justified.

The company stated that the log-logistic distribution provided the best fit to the cabozantinib group, and the Weibull distribution provided the best fit to the everolimus group, based on AIC and BIC statistics. While choosing one distribution for the two groups is justified, the company did not appear to fully consider the Weibull as the choice for each arm instead of the log-logistic. The ERG considers the Weibull distribution to be a suitable choice given that the log-cumulative hazard plots are indicative of the hazard functions of a Weibull distribution and not of a log-logistic, due to the linearity between log-cumulative hazard and log time. The results of a scenario analysis around the company's base case using the Weibull distribution for the OS curves is given in Table 82. This shows a greatly increased ICER of [redacted] per QALY compared to the company's corrected base case ICER of [redacted] per QALY based on the log-logistic OS curves.

Table 82. Company's base case results for cabozantinib compared to everolimus based on the METEOR trial using a Weibull OS curve

Drug	Total costs	Total QALYs	Total life-years	Incremental cabozantinib versus			ICER versus cabozantinib
				Costs	QALYs	Life years	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

For the NMA-based model, parametric curves were derived from an NMA, which directly estimated the parameters of each curve for each treatment compared in the model. This is discussed in more detail in Section 4.4. Although each curve was fitted to each trial group independently, a major limitation of the approach taken is that only a single distribution was used for each group. When applying parametric curves to different treatment groups in the economic model, it is justified to use the same distribution, as discussed previously. However, to choose the best fitting distribution for the curves, the assessment was based on a global measure; the DIC goodness-of-fit statistic, for the fit of all curves in the NMA. This gives no indication of how well a particular curve fits the data of a particular trial group, but only highlights which single distribution provides the best fitting set of curves for all treatments in

comparison to using another distribution to fit all curve. This method is therefore a potential source of high parameter uncertainty, as the relative treatment effect in each trial is determined by the parameters estimated by this global model. If each comparator has a badly fitted curve, then the relative effect between the two curves is unreliable, and this effect will be propagated throughout the model when applied across the NMA network, causing the results of the NMA-based model to be potentially unreliable. The KM plots with superimposed parametric curves for comparison are given in Figure 41, Figure 42, Figure 43 and Figure 44, for axitinib, nivolumab, placebo and sorafenib, respectively.

Figure 41. Comparison of regenerated KM data and fitted curves – OS axitinib (Clarification response to B3)

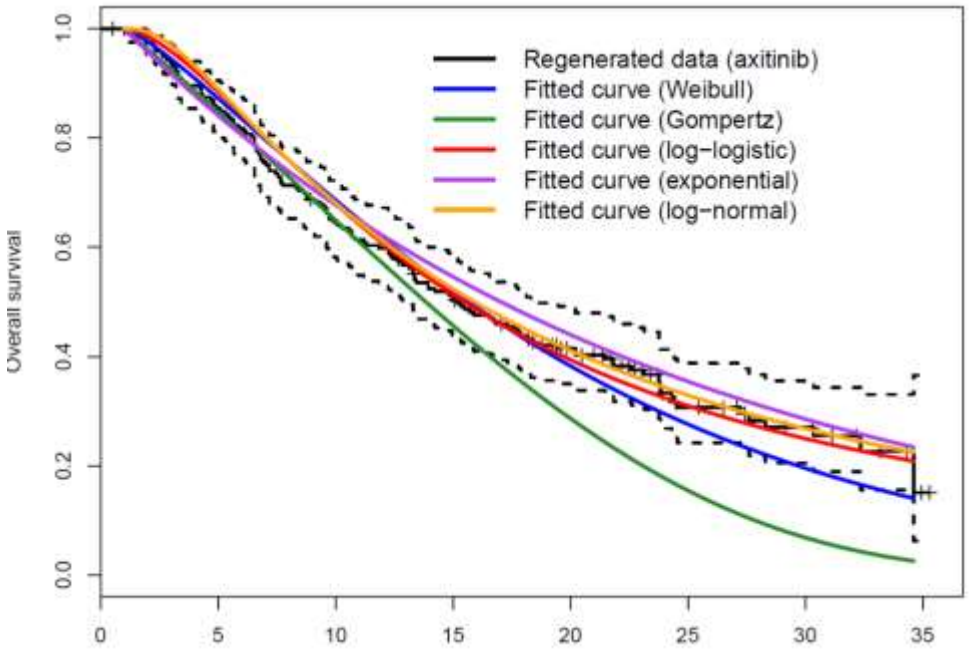


Figure 42. Comparison of re-generated KM data and fitted curves – OS nivolumab (Clarification response to B3)

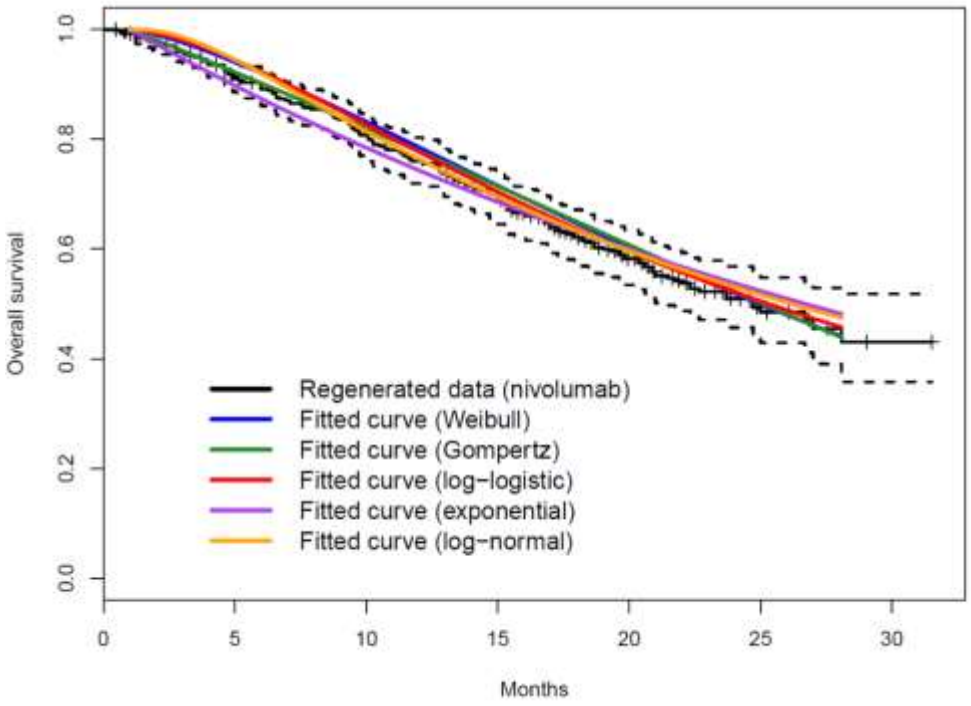


Figure 43. Comparison of re-generated KM data and fitted curves – OS placebo (Clarification response to B3)

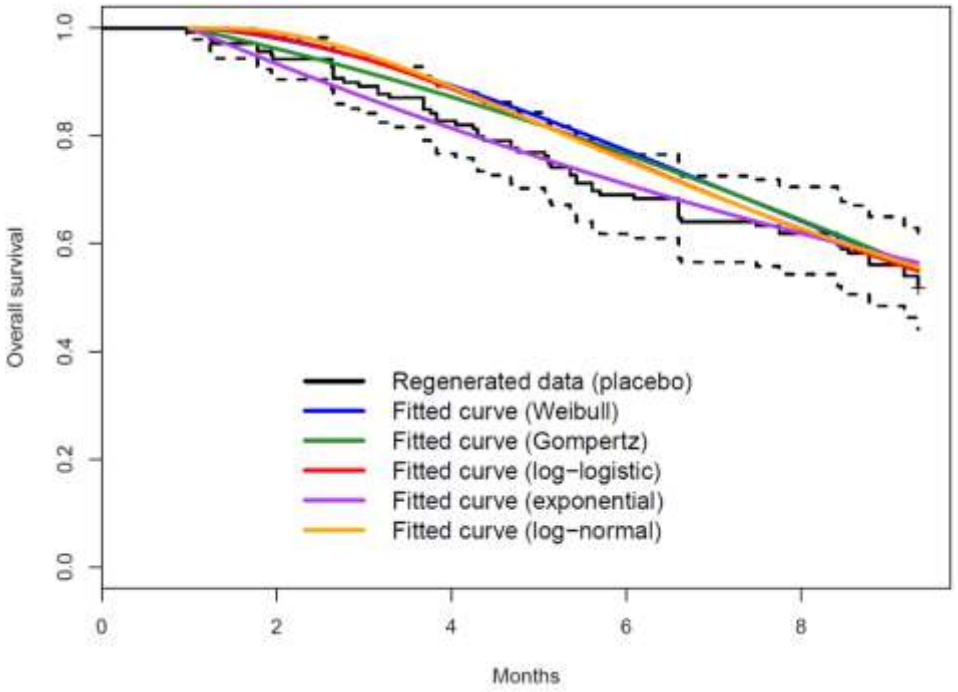
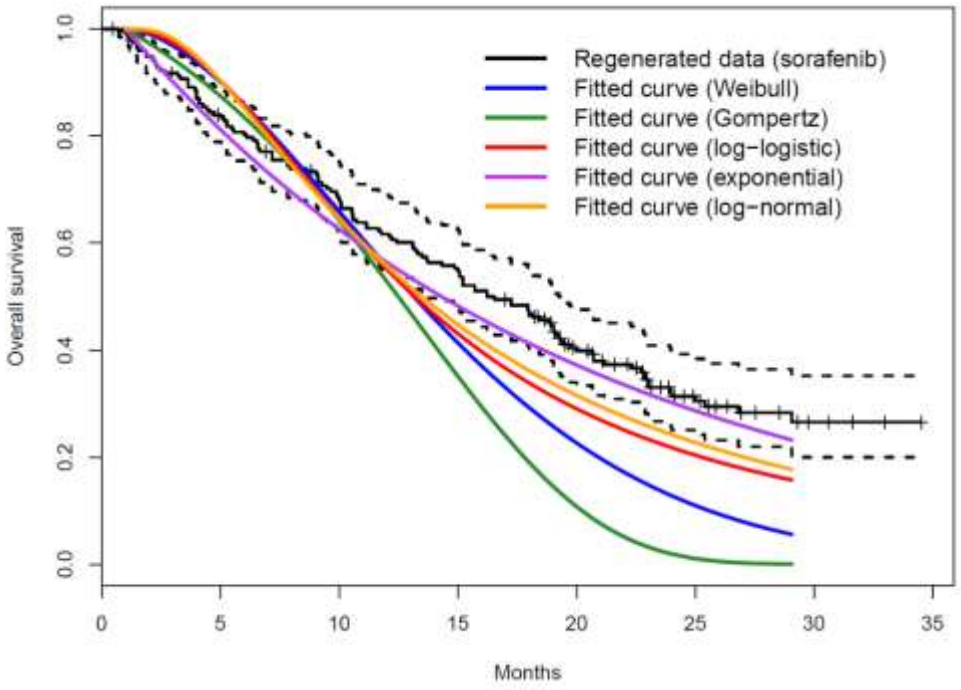


Figure 44. Comparison of re-generated KM data and fitted curves – OS sorafenib (Clarification response to B3)



Although the company's chosen model, the log-normal distribution, shows a good visual fit for axitinib and nivolumab, this isn't the case for sorafenib and placebo. Furthermore, none of the curves appear to give a good visual fit to the sorafenib KM plot. This causes uncertainty on the relative treatment effect of a comparison with axitinib, as axitinib is adjusted to the everolimus arm of METEOR via sorafenib and placebo in the NMA network.

Another key source of uncertainty in the estimation of OS in the NMA based model is that KM plots with superimposed curves for the everolimus arms of RECORD-1 and CheckMate 025 were not provided by the company for a visual fit assessment. These trial arms impact on the relative effectiveness of all comparators, as everolimus forms the link between cabozantinib and all other comparators in the NMA network. There also appeared to be a reduced performance for everolimus in METEOR compared to CheckMate 025 and RECORD-1, so a good fit for each everolimus group in the NMA is therefore essential for retaining a reliable relative treatment effect between all the adjusted independently fitted curves. The ERG, however, were unable to identify a reason for the difference in performance, and clinical experts noted that patients in the METEOR trial had a better prognosis than those in CheckMate 025 and RECORD-1, but performed less well on everolimus. The ERG considered this to be an issue that the company could not have addressed.

Given the limitations of the company's method for estimating survival curves, in particular for the axitinib comparison, the ERG considered an alternative approach used in the recently published TA417; that is, to assume the OS for axitinib is equivalent to that of everolimus. Under this assumption, which was validated by clinical experts, the network required to provide estimates for the other comparators does support a PH assumption for OS (assuming the initial 6 weeks of CheckMate 025 does not have an important impact). The ERG consider this to be a more reliable comparison than that provided by the company. The ERG therefore conducted an NMA to estimate HRs for each comparator (except axitinib) relative to the everolimus arm of the METEOR trial. The resulting HRs are given in Table 83 and the results of the ERG base case using this data are provided in Section 6.

Table 83. Estimated HRs from the ERG's NMA (relative to everolimus)

Treatment	HRs (95% CrI)
Cabozantinib	0.665 (0.527, 0.825)
Axitinib	1.000[a]
Everolimus	Baseline
BSC	1.888 (0.603, 4.472)
Nivolumab	0.735 (0.570, 0.934)

Abbreviations in table: BSC, best supportive care; HR, hazard ratio.
[a] axitinib was assumed to be equivalent to everolimus.

5.5.5.3 Time to treatment discontinuation

In the ERG's opinion, the approach taken by the company to estimate TTD may be reasonable, however the company did not provide details on how they followed the SMEEP algorithm in the NICE DSU Technical Support Document 14. [7]

The ERG identified an error in the way that TTD was applied in the economic model for cabozantinib, nivolumab, and everolimus. According to the CS, patients in the model continue to subsequent therapy directly after discontinuing treatment and therefore TTD should determine the proportion of patients who go on to subsequent therapy except in the case of axitinib. However, while TTD data was indeed used to determine the proportion of patients on initial treatment in the model, patients receive subsequent therapy as soon as they progress and not based on the TTD curves. Therefore, the proportion of patients who continue to receive initial treatment in the model after progressing, simultaneously incur the cost of subsequent therapy which in turn leads to a overestimation of costs.[7] This error was corrected by the company after clarification questions and the results of the company's corrected base case are given in Section 6.1.

The ERG also considered whether the approach taken for the NMA-based model was suitable given that the TTD for the comparator treatments may not be correlated across treatment groups, in which case the adjustment made to the everolimus group of the METEOR trial may not be applicable. The ERG considers an alternative approach that assumes a within group relationship between TTD and PFS may be more suitable; however, the ERG were not able to test this as a scenario within the timeframe of this appraisal.

5.5.6 Adverse events

The company estimated costs and utility decrements due to TEAEs for each comparator only if the TEAE occurred in 5% or more of the respective trial population. However, the company did not provide a justification for primarily including TEAEs in the analysis instead of treatment-related adverse events (TRAEs). TEAEs are any adverse events that occur after initiation of treatment, while TRAEs are events which are believed by investigators to be associated with treatment. Using TEAEs led to an inconsistency as the only data available for nivolumab was for TRAEs, however, because of the 5% restriction, the number of TRAEs for nivolumab was zero.

Furthermore, no justification was provided for the 5% threshold which seems high for Grade 3/4 adverse events. The ERG tested the impact of changing the threshold for including adverse events to 0.5% instead of 5% on the cost-effectiveness results. The ICERs differed from the company's reported ICERs by -£162, £866, £1205, and £1,983 per QALY compared to nivolumab, everolimus, axitinib and BSC, respectively.

The ERG's clinical experts confirmed that adverse events that are expected to have an impact on resource use, and the quality of life of patients have been considered in the model. The ERG considers the company's approach to estimating the mean number of episodes and duration of each episode to be reasonable, given the lack of available data for the comparators.

5.5.7 Health-related quality of life

The HSUVs used in the cost effectiveness model for PFS, PPS and AEs were based on EQ-5D-5L data collected from the METEOR trial. The data were analysed using a repeated measure mixed-effect model with co-variates for treatment arm, progression status and AEs. The ERG notes that the company provided the EQ-5D-5L questionnaire completion rates in Section 5.4.1 of the CS.

5.5.7.1 Health-state utility values

The HSUVs for all health states regardless of treatment arm applied in the company's base case are based on METEOR data and are presented in Table 84 alongside estimates obtained from the systematic literature review. The ERG's clinical experts suggested that the estimates of utility for progression-free and progressed states calculated using the METEOR data are higher than expected in clinical practice. A widely reported utility study [97] estimates that the average UK general population utility for people aged 55-64 is 0.80. This value compared with the METEOR estimate for the progression-free health state (0.817), suggests that a patient with mRCC has better HRQoL than someone of a similar age who is disease free. The ERG's clinical experts believe that in clinical practice, patient utilities for these states would be closer to those given for axitinib in TA333. Therefore, the ERG ran a scenario analysis using the TA333 utility values in the economic analysis. Results of the analysis are report in Section 6.2 of this report.

Through regression analysis, the company found that that treatment had no significant effect on patient utility and therefore applied the same utility values for all treatment arms. The company also considered disutility associated with AEs separately. The ERG considers that using the same utility values for progression-free and progressed health states for all treatment arms is appropriate given that disutility associated with AEs for each treatment arm are analysed separately and would be the main driver for any differences in HRQoL between treatments.

Table 84. Summary of available utility values for the cost-effectiveness model (CS, pg 132, Table 63)

State	METEOR	Axitinib (TA333)	Everolimus (TA219)	Nivolumab (TA417)	Swinburn *et al* 2010[84]
Progression free	0.817	0.692	0.758	0.800	0.795
Progressed	0.777	0.610	0.683	0.730	0.355
AE disutility	-0.055	NA	-0.050	See details in Table 63	See details in Table 62
Abbreviations in table: AE, Adverse event.					

To assess the impact of changing the HSUVs in the final ICER, the company performed a scenario analysis (reported in Section 6.2) using the average utility value decrement associated with the progressed health state (0.072 vs 0.04) obtained in the systematic literature review. The scenario analysis reported by the company (CS, page 168, Table 94) revealed that increasing the utility decrement associated with progression had minimal impact on the ICER.

5.5.7.2 Adverse events disutility values

The company calculated the overall AE-related decrement in utility values for each treatment arm by weighting the AE utility decrement (-0.06) by the proportion of patients experiencing an AE (only for AEs where ≥ 5% of the treatment population experienced an event) by treatment arm. Weighted values are reported in Table 85. For nivolumab, the weighted disutility is 0 as there were no AEs where ≥ 5% of the treatment population experienced an event.

Table 85. Weighted disutility values for AEs associated with treatment

Treatment	Weighted AE disutility
Cabozantinib	-0.03
Everolimus	-0.02
Axitinib	-0.03
Nivolumab	0.00

The ERG considers the calculation of the weighted utility appropriate to reflect the differences in the toxicity profile for each treatment arm. However the initial AE utility decrement used by the company may be underestimating the impact of AEs on patients' QoL when compared with values from the literature review. In Section 5.4.3 of the CS, the average disutility values reported in the literature is 0.17 versus 0.06 found in the METEOR trial. In addition, the ERG's clinical experts commented that the toxicity profile was high for cabozantinib and would expect that HRQoL would be significantly impacted. The ERG assessed the impact of changing the AE-related utility decrement in the base case model to the average disutility value from the literature and found the impact on the ICER to be minimal.

5.5.8 Resources and costs

Resource use is estimated for the base case analysis mainly based on the company's clinical expert input. NHS England National Tariffs and PSS costs are used where available, in line with the NICE reference case.[6, 95, 96] The ERG checked that prices are correctly inflated when necessary, and that discounting is applied in the model appropriately. The formulae are generally correct and sound in the electronic model.

The ERG's clinical experts disagreed with the inclusion of GP visits prior to progression, stating that patients are more likely to be seen by consultants during this period every 4 weeks on average instead. The company carried out a scenario analysis, in which resource use assumed in the company's base case analysis in the nivolumab appraisal (TA417).[36] However, the company's base case assumptions surrounding resource use in TA417 were deemed by the ERG to not reflect clinical practice since GP visits were included and consultant visits were excluded.

The resource use assumed for the management of adverse events is broadly reflective of what would happen in UK clinical practice, according to the ERG's clinical experts. However, the experts stated that they would generally not admit patients to hospital for hypertension, and that a 25% rate of hospitalisation for anaemia may be an overestimate unless it's the only way some patients would be able to receive a blood transfusion. Furthermore, the costs of adverse events that patients experience from subsequent therapy lines have not been incorporated in the model. It is unclear what the impact including these costs will have in relative cost-effectiveness across the treatment arms.

The ERG's clinical experts disagreed with the inclusion of sorafenib as a subsequent therapy option in the model, since it is not reimbursed in the UK. The company carried out a scenario analysis in which subsequent therapy costs were removed from the model, which is reported in Section 5.6.2.

5.6 Results included in company's submission

5.6.1 Base case results

In this section, the ERG presents the results of the base case analysis of the cost-effectiveness of cabozantinib compared to axitinib, everolimus, nivolumab, and BSC. The company carried out a base case analysis for cabozantinib compared to everolimus based on the results of the METEOR trial. For all other comparators efficacy estimates generated from the NMA described in Section 4.4 are used. An additional scenario using NMA data for the comparison of cabozantinib to everolimus was also carried out.

5.6.1.1 Base case results based on the METEOR trial

The results of the pairwise analysis of cabozantinib compared to everolimus based on efficacy inputs from the METEOR trial, are presented in Table 86.

According to the company's analysis, cabozantinib is expected to extend life by approximately [redacted], compared to everolimus with a gain of an average of [redacted] QALYs per patient. The resultant incremental cost-effectiveness ratio when cabozantinib is compared to everolimus is [redacted] per QALY gained.

Table 86. Base case results for cabozantinib compared to everolimus based on the METEOR trial (CS, page 151, Table 77)

Drug	Total costs	Total QALYs	Total life-years	Incremental cabozantinib versus			ICER versus cabozantinib
				Costs	QALYs	Life years	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

5.6.1.2 Base case results based on the NMA

The results of the pairwise analysis based on the NMA are presented in Table 87. According to this analysis, cabozantinib is expected to extend survival by [redacted], [redacted], and [redacted] months compared to BSC, axitinib, and nivolumab, respectively. Cabozantinib is predicted to increase quality adjusted life-years (QALYs) by [redacted], [redacted], and [redacted] on average compared to axitinib, nivolumab, and BSC, respectively. The incremental cost-effectiveness ratios of cabozantinib relative to axitinib, nivolumab, and BSC are [redacted], [redacted] and [redacted] per QALY, respectively.

In the scenario comparing cabozantinib to everolimus based on the NMA cabozantinib extends life by approximately 8 months, corresponding to a gain of an average of [redacted] QALYs per patient. Therefore, using efficacy values from the NMA instead of directly from the METEOR trial reduces the ICER by [redacted] ([redacted] per QALY) to [redacted] per QALY.

Table 87. Pairwise analysis cost-effectiveness results based on the NMA (adapted from CS, page 151-152, Table 77 and 79)

Treatment	Cost	LYs	QALYs	Incremental costs Cabozantinib versus	Incremental LYs Cabozantinib Versus comparator	Incremental QALYs Cabozantinib Versus comparator	ICER Cabozantinib Versus comparator (£/QALY)
Cabozantinib	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

The QALY gain for all the comparators disaggregated by health state is summarised in Table 88. The majority of QALYs in the model are accrued after progression, reflecting the length of time spent in that state. However, the proportion of incremental gain in QALYs for patients receiving cabozantinib relative to all the comparators is higher during the PFS health state. The percentage of incremental gain attributed to PFS ranges from [redacted] (versus BSC) to [redacted] (versus nivolumab) across the comparisons. As patients were assigned the same utility values regardless of treatment arm prior to and after progression, this incremental gain reflects the predicted prolongation of PFS in patients receiving cabozantinib compared to other treatment options.

Table 88. QALY gain according to health state (CS, page 157-160, Table 81-84)

Health state	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	Nivolumab (4)	BSC (5)	Absolute increment (% increment)			
						1 vs 2	1 vs 3	1 vs 4	1 vs 5
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: BSC, best supportive care; PFS, progression-free survival; PPS, post-progression survival; LY, life year ; QALY, quality-adjusted life year.									

A summary of the costs in the model disaggregated by health state is presented in Table 89. The disaggregated costs show that for all the comparators with the exception of BSC, a higher proportion of the overall costs is incurred prior to progression particularly for cabozantinib and nivolumab. PFS costs associated with cabozantinib and nivolumab constitute [redacted] and [redacted], of total costs, respectively, and nearly all (i.e. greater than [redacted]) of these costs can be attributed to pharmacological costs. For treatments that are assumed to incur costs for adverse events, the total cost of managing the events is very low ranging from [redacted] for everolimus to [redacted] for axitinib, corresponding to [redacted] to [redacted] of overall costs, respectively. The costs of subsequent therapies in the model are highest for nivolumab, and are the main driver for the difference in overall costs compared to cabozantinib. The total cost of end of life services were similar across all treatment arms since all patients who die were assumed to use these services, and by the end of the time horizon nearly all patients are dead.

Table 89. Costs disaggregated by health state (CS, page 160-162, Table 85-88)

Cost component	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	Nivolumab (4)	BSC (5)	Increment			
						1 vs 2	1 vs 3	1 vs 4	1 vs 5
PFS									
Treatment acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS									
Subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of life	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Costs*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; PFS, progression-free survival; PPS, post-progression survival; LY, life year ; QALY, quality-adjusted life year.

Note: *, these values are reported incorrectly in the CS.

5.6.2 Sensitivity analysis

In this section, the ERG presents the deterministic one-way sensitivity analyses (OWSAs) and probabilistic sensitivity analyses (PSAs), as well as the scenario analyses carried out by the company. The company provided the results of these sensitivity analyses and scenario analyses in Section 5.8.2 and Section 5.8.3 of the CS for the comparison between cabozantinib and axitinib. The mean results of the pairwise PSAs conducted for cabozantinib against axitinib, in addition to the cost-effectiveness plane showing the cloud of PSA simulations for cabozantinib compared to axitinib, are reported in Section 5.8.1 of the CS. The PSA results for the other comparisons (i.e. cabozantinib compared to nivolumab, everolimus and BSC) are reported in Appendix 23 of the CS.

Scenario analysis

The company carried out a series of scenario analyses, to test the impact on changing assumptions in the model surrounding:

- Discount rates;
- Time horizon;
- Overall survival (curve fit);
- Progression-free survival (curve fit);
- Time on treatment (curve fit);
- Utility values;
- Costs.

The results of the scenario analyses for the pairwise comparisons of cabozantinib compared to axitinib, everolimus, BSC, and nivolumab are presented in Table 90. The scenario analyses show that the cost-effectiveness results across all comparisons are most sensitive to assumptions surrounding the model selected to fit overall survival data. Furthermore, the results for cabozantinib compared to nivolumab are very sensitive to assumptions surrounding subsequent therapies received, with nivolumab no longer dominated by cabozantinib when subsequent therapy costs are removed and when proportions of patients assumed is based on the opinion of UK clinicians.

Table 90. Scenario analysis results (adapted from CS, page 168, Table 94)

Parameter	Base case assumption	Scenario analysis	Cabozantinib			
			vs axitinib ICER	vs everolimus ICER	vs BSC ICER	vs nivolumab ICER
Base case	-	-	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate (costs and utilities)	3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]
		0%	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon	30 years	15 years	[redacted]	[redacted]	[redacted]	[redacted]
		20 years	[redacted]	[redacted]	[redacted]	[redacted]
PFS curves	Log-normal for comparisons based on NMA	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]
		PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic for comparison based on the METEOR trial	PFS=log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
		PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]
OS curves: cross-over adjusted	Log-normal for comparisons based on NMA	OS=exponential	[redacted]	[redacted]	[redacted]	[redacted]
		OS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]
	Log-logistic for comparison based on the METEOR trial	OS=log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
		OS=Weibull	[redacted]	[redacted]	[redacted]	[redacted]
OS unadjusted study population (ITT)	OS=exponential	OS=exponential	[redacted]	[redacted]	[redacted]	[redacted]
	OS=gompertz	OS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]
	OS=log-logistic	OS=log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
	OS=log-normal	OS=log-normal	[redacted]	[redacted]	[redacted]	[redacted]
	OS=Weibull	OS=Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Time on treatment curves	TTD=log-normal	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]

		TTD=Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
		TTD=log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
		TTD=Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Utility value for PPS	0.777 (from METEOR trial)	0.745 (from published trials)t	[redacted]	[redacted]	[redacted]	[redacted]
Costs	Disease management cost (UK clinician's opinion)	Disease management cost (nivolumab TA submission)	[redacted]	[redacted]	[redacted]	[redacted]
	Subsequent treatment cost (based on published papers)	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]
	Subsequent treatment cost included	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]
	End-of-life cost included	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]
	Wastage included for nivolumab	Wastage excluded (nivolumab)	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; TA, technology appraisal; TTD, time-to-treatment discontinuation.						

One-way sensitivity analysis

The company carried out OWSAs to assess the impact on the cost-effectiveness results of the variation of the value of individual parameters. According to the OWSA results for cabozantinib compared to everolimus, axitinib, and BSC the three most influential parameters in the model are time horizon assumed, cost of cabozantinib, and the discount rate applied to the effects. The OWSA shows that the relative cost-effectiveness of cabozantinib compared to nivolumab is extremely sensitive to assumptions surrounding the costs of nivolumab (i.e baseline weight and RDI with a positive ICER obtained (i.e. nivolumab not dominated by cabozantinib). The results of the OWSAs are presented in Figure 45 to Figure 48.

Figure 45. OWSA of cabozantinib compared to everolimus (CS, Appendix 23, page 217)

Figure 46. OWSA for cabozantinib compared to axitinib (CS, page 167, Figure 39)

Figure 47. OWSA of cabozantinib compared to BSC (CS, Appendix 23, page 218)

Figure 48. OWSA of cabozantinib compared to nivolumab (ERG generated from company's model)

Probabilistic sensitivity analysis

The company performed a PSA to assess the joint parameter uncertainty around the base case results. All the parameters used in the model were varied except for treatment related costs for cabozantinib and BSC, and the AE cost for nivolumab, which was fixed at zero. The mean results of the PSAs across 5,000 iterations are presented in Table 91 to Table 94. The probabilistic ICERs for cabozantinib compared to everolimus (based on METEOR trial), and to BSC are in line with the deterministic ICERs, with a difference of £269 and £1,028 per QALY, respectively. The mean probabilistic ICER for cabozantinib compared to axitinib is higher by £3,625 per QALY than the deterministic ICER. The mean results of the PSA, show nivolumab to continue to be dominated by cabozantinib.

Table 91. Mean results of PSA of cabozantinib compared to axitinib (CS, page 164, Table 89)

Treatment	Costs	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

Table 92. Mean results of PSA of cabozantinib compared to everolimus based on METEOR trial (CS, page 165, Table 91)

Treatment	Cost	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

Table 93. Mean results of PSA of cabozantinib compared to BSC (CS, page 165, Table 92)

Treatment	Cost	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

Table 94. Mean results of PSA of cabozantinib compared to nivolumab (CS, page 164, Table 90)

Treatment	Costs	LYs	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]				
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

The scatterplots and cost-effectiveness acceptability curves (CEACs) for all of the pairwise comparisons are presented in Figure 49 to Figure 52, and Figure 53 to Figure 56, respectively. According to the scatter plots, there seems to be a non-negligible amount of parametric uncertainty surrounding the deterministic base case for cabozantinib compared to axitinib and nivolumab. The ERG reran the PSA for all the analyses, and found that cabozantinib is dominated by axitinib, and nivolumab in 12%, and 11% of the simulations, respectively.

According to the CEACs, at a willingness to pay (WTP) threshold of £20,000 per QALY, cabozantinib has a 0% probability of being cost-effective compared to axitinib, everolimus and BSC. At a WTP threshold of £40,000 per QALY the probability of cabozantinib being cost-effective against axitinib

increases to 15%, but remains 0% compared to everolimus and BSC. At a threshold of £50,000 per QALY, the company reported that the probability of cabozantinib being cost effective compared to axitinib was [redacted]

The probability of cabozantinib being cost-effective compared to nivolumab is 70% and 80%, at WTP thresholds of £20,000, and £40,000 per QALY, respectively.

Figure 49. Scatterplot for cabozantinib compared to axitinib (CS, pg 163, Figure 37)

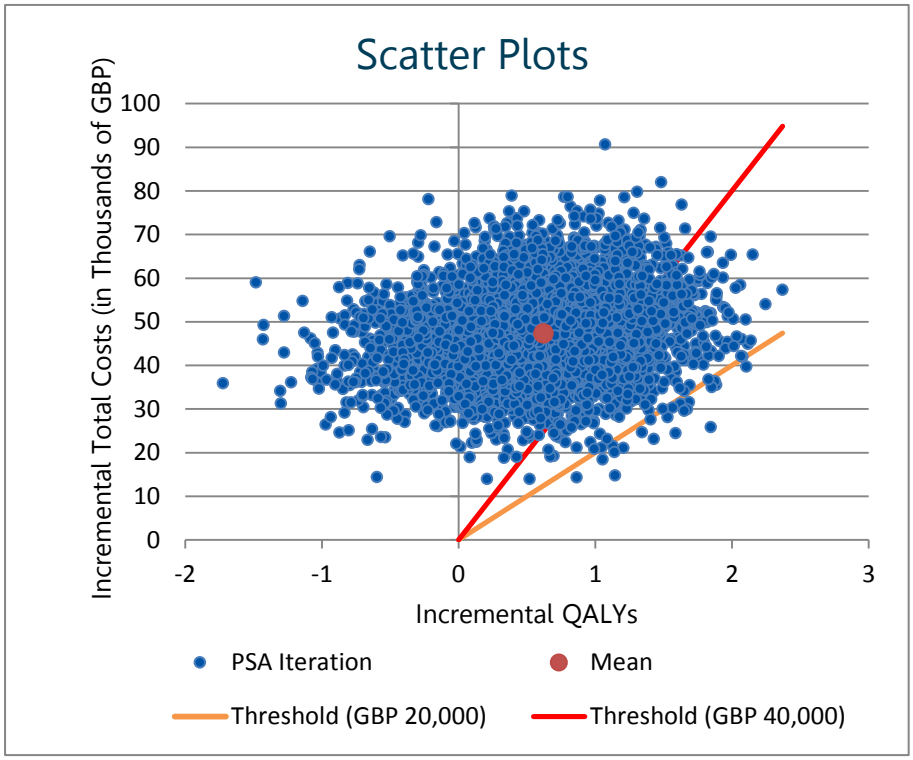


Figure 50.Scatterplot for cabozantinib compared to nivolumab (CS, Appendix 23, pg 214)

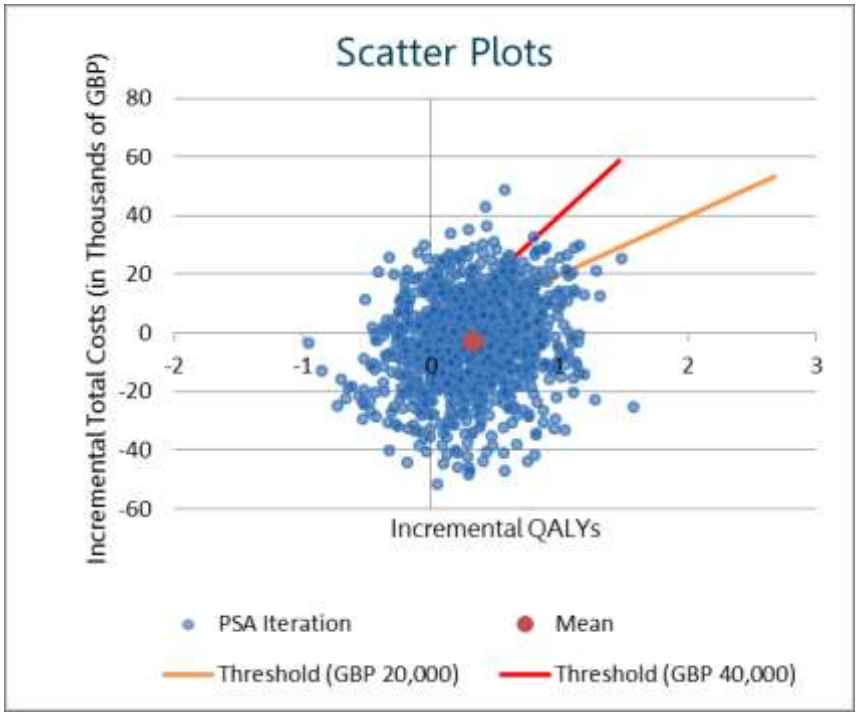


Figure 51. Scatterplot for cabozantinib compared to everolimus based on the METEOR trial (CS, Appendix 23, pg 215)

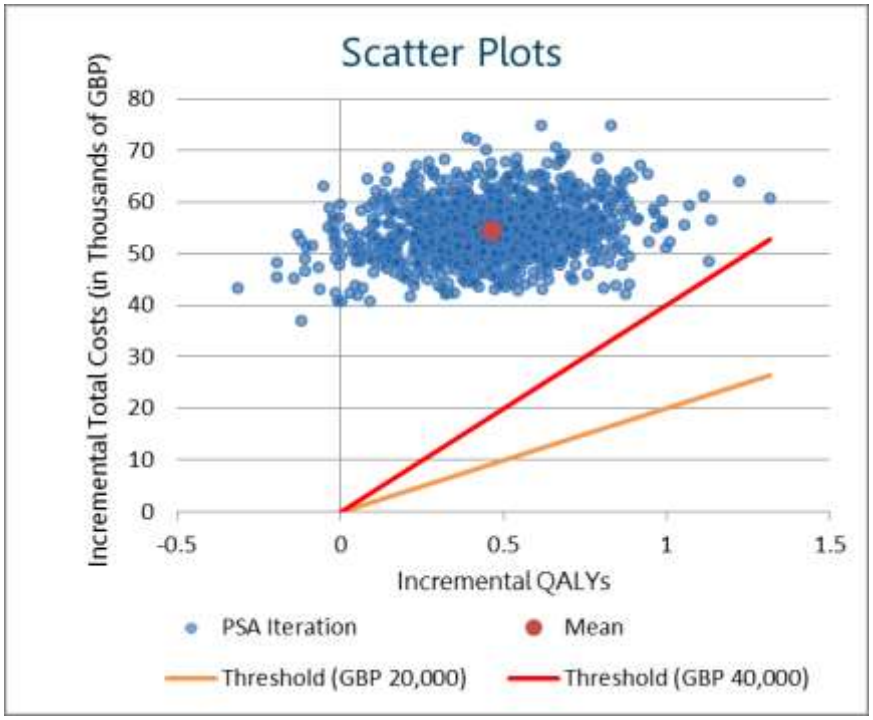


Figure 52. Scatterplot for cabozantinib compared to BSC (CS, Appendix 23, pg 216)

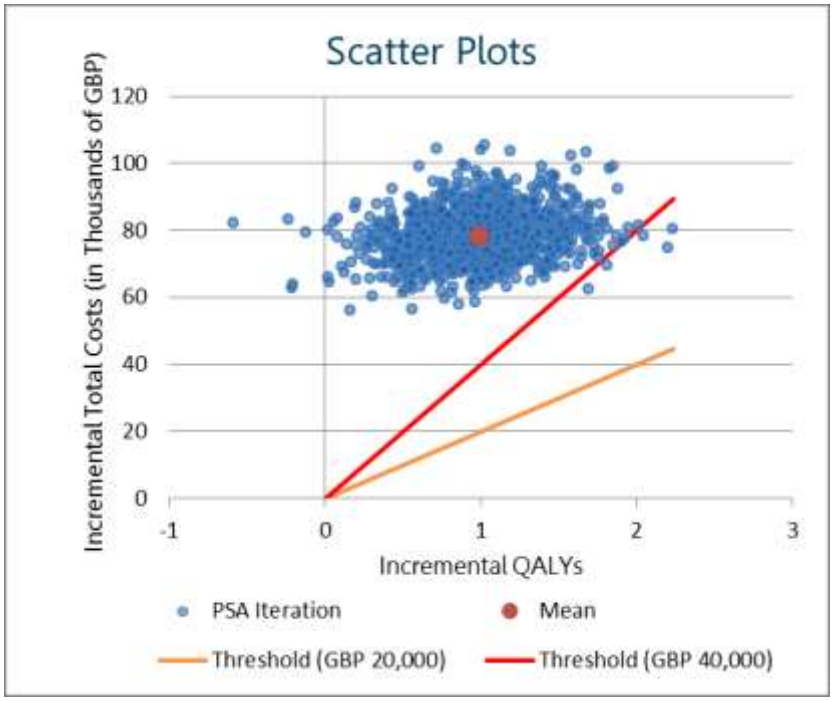


Figure 53. CEAC for cabozantinib compared to axitinib (CS, pg 164, Figure 38)

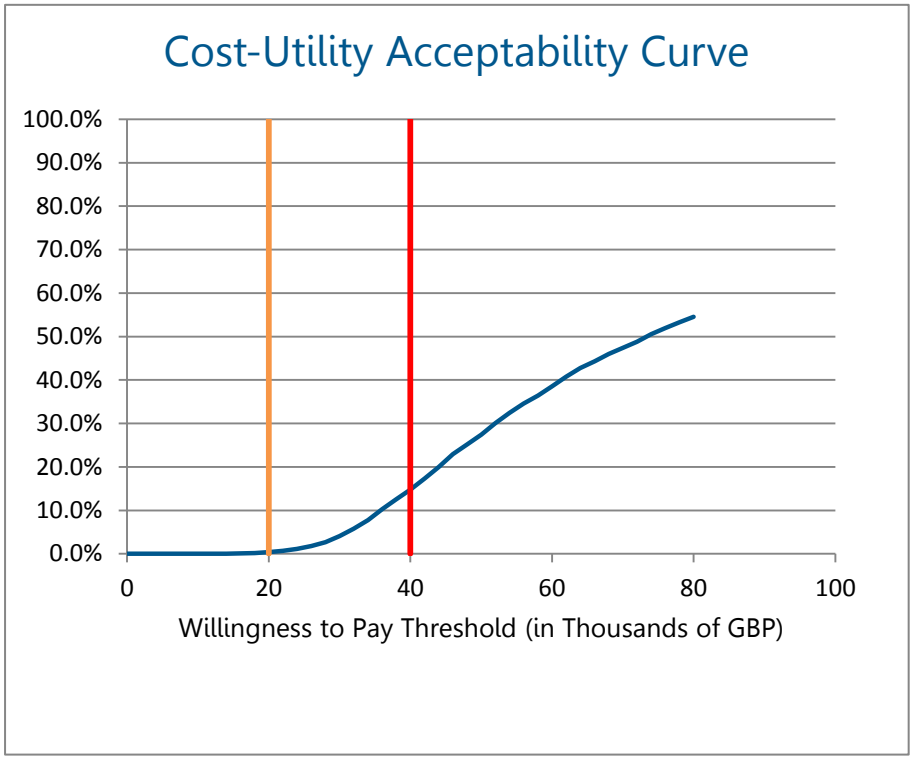


Figure 54.CEAC for cabozantinib compared to nivolumab (CS, Appendix 23, pg 214)

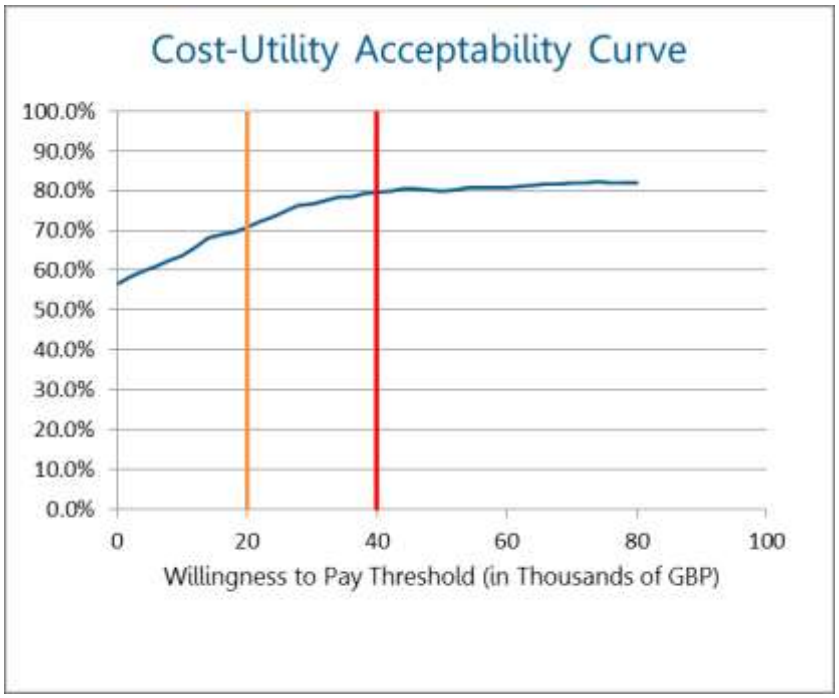


Figure 55. CEAC for cabozantinib compared to everolimus based on the METEOR trial (CS, Appendix 23, pg 215)

Figure 56. CEAC for cabozantinib compared to BSC (CS, Appendix 23, pg 216)

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The ERG identified only one error in the company's cost-effectiveness model, which was related to the use of the PFS data to calculate active treatment costs instead of the TTD data, which was stated as used in the CS. The company stated that the only comparator in the analysis that utilised PFS data was axitinib as TTD data were not available from the literature. At clarification stage, the issue was raised with the company, who provided an updated model with the error rectified. Corrected company base case results are presented in Table 95 and Table 96.

Table 95. Corrected company base case results – trial based analysis

Treatment	Cost	LYs*	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 96. Corrected company base case results – NMA based analysis

Treatment	Cost	LYs*	QALYs	Incremental costs cabozantinib versus	Incremental LYs cabozantinib versus	Incremental QALYs cabozantinib versus	ICER cabozantinib versus
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

6.2 ERG scenario analysis

In this section, the ERG explores the impact of the uncertainty surrounding several modelling assumptions on the model results using scenario analyses, based on the company's revised base case. The scenarios explored were selected based on the ERG's critique of the CS in Section 5.5. The ERG looks at the impact of alternative assumptions on:

1) **Overall survival model for trial based analysis**: In the base case analysis, the company used a log-logistic distribution to extrapolate OS based on goodness of fit statistics and clinical expert feedback. The log-logistic distribution proved only to be the best fit for cabozantinib, as for everolimus the Weibull distribution was deemed to be the best fit. However, the Weibull distribution followed second for goodness of fit to the cabozantinib data. The ERG explores a scenario extrapolating OS using the alternative Weibull distribution.

2) **Progression free survival model for trial based analysis**: Like with OS, cabozantinib had different distributions which proved to have a good fit to the data. The log-logistic distribution was a good fit to the cabozantinib data, and the log-normal distribution was a good fit to the everolimus data. However, for both treatment arms, the generalised gamma distribution followed second for goodness of fit. The company decided to use the log-logistic distribution for both treatment arms based on goodness of fit statistics and clinical expert feedback. The ERG explores two scenarios extrapolating PFS using the following alternative distributions:

   a) Log-normal distribution;

   b) Generalised gamma distribution.

   It should be noted that in Section 5.5.5.1, the ERG explored whether the log-normal distribution would be appropriate to use for extrapolation of PFS through visual inspections of the log-cumulative hazard plots. The conclusion of the assessment was that it would not be appropriate. However, a scenario exploring the distribution's use was included by the ERG as visual inspection of the log-cumulative plots carries a degree of uncertainty and thus it's impact on the ICER should it be deemed an appropriate distribution needs to be explored.

3) **A combination of scenario 1 and 2a.**

4) **A combination of scenario 1 and 2b.**

5) **PH modelling for both trial based and NMA analyses**: In Section 5.5.5, the ERG found the company's NMA methodology choice to be restrictive when deciding on the distribution with the best goodness-of-fit to the regenerated KM data for all comparators. In addition, the company chose to model the treatments in the METEOR trial independently, even though the PH assumption holds for the data. The ERG explores a scenario using PH modelling for OS (for the NMA analysis, refer to scenario 1a in Table 98). The choice for only testing the assumption on OS and not including

PFS is because a PH assumption for PFS is weaker and changing PFS has minimal impact on the ICER (see scenario 2a & b)

6) **Health state utility values**: The ERG's clinical experts stated that the HSUVs used in cost-effectiveness analysis were high and in clinical practice would be closer to the values found in the AXIS trial, which were 0.692 for PFS and 0.610 for PPS. The ERG explores the use of these values for both the trial based analysis and NMA analysis (refer to scenario 2 in Table 98)

7) **Resource costs**: The ERGs clinical experts believed the inclusion of GP costs was inaccurate, as Oncologists would typically be responsible for monitoring the patient. The ERG explores a scenario where GP costs are excluded from the trial based analysis and the NMA analysis (refer to scenario 4 in Table 98).

The results of the scenario analyses are reported in Table 97 and Table 98.

Table 97. ERG scenario analyses – trial based analysis

	Results per patient	Cabozantinib	Everolimus	Incremental value
0	**Company (corrected) base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
1	**Weibull distribution for OS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2a	**Log-normal distribution for PFS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2b	**Gamma distribution for PFS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
3	**Combination of scenario 1&2a**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
4	**Combination of scenario 1&2b**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]

	ICER			[redacted]
5a	**PH assumption for OS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
6	**HSUVs from AXIS trial**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
7	**Exclusion of GP costs**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

Abbreviations in table: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; HSUV, health state utility value; OS, overall survival; PFS, progression free survival; GP, general practitioner.

Table 98. ERG scenario analyses – NMA based analysis

	Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Nivolumab (5)	Incremental value (1-2)	(1-3)	(1-4)	(1-5)
0	**Company (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						[redacted]	[redacted]	[redacted]	[redacted]
1	**PH assumption for OS**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER						[redacted]	[redacted]	[redacted]	[redacted]
2	**HSUVs from AXIS trial**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER						[redacted]	[redacted]	[redacted]	[redacted]
3	**Exclusion of GP costs**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER						[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; HSUV, health state utility value; OS, overall survival; PFS, progression free survival; GP, general practitioner.

6.3 ERG base case ICER

In this Section the ERG presents the model results using its preferred modelling approaches and assumptions, as discussed and explored throughout the report. The ERG's base case included changes in the following assumptions:

1. Using the Weibull distribution to extrapolate OS for the trial based analysis.

2. Assuming PH holds for all comparators in the NMA and adopting a PH modelling approach for the NMA based analysis. Axitinib was assumed to be equivalent to everolimus to avoid violating PH for the TARGET trial in the network.

3. Assuming the HSUVs for PFS and PPS are 0.692 and 0.610 respectively. These reflect the values in the AXIS trial, which the ERG's clinical experts stated would be closer to what is seen in practice than the values obtained from the METEOR trial.

4. Inclusion of wastage costs for nivolumab due to the weight-based dosing regimen in the NMA analysis. In the CS, these were said to be included, but during clarification stage the company mistakenly omitted the wastage costs of nivolumab in their base case NMA analysis.

5. Exclusion of GP costs in line with the ERG's clinical expert opinion.

The ERG's base case ICER for the trial and NMA analyses are presented in Table 99 and Table 100.

Table 99: ERG's base case ICER – trial based analysis

Results per patient	Cabozantinib	Everolimus	Incremental value
Company (corrected) base case			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
Weibull distribution for OS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER (with all changes incorporated)			[redacted]
HSUV's from AXIS trial			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
ICER (with all changes incorporated)			[redacted]
GP costs excluded			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]

ICER (compared with base case)		[redacted]
ICER (with all changes incorporated)		[redacted]
ERG preferred base case ICER		[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PH, proportional hazards; HSUV, health state utility value; GP, general practitioner; ERG, evidence research group.

Table 100: ERG's base case ICER – NMA based analysis

Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Nivolumab (5)	Incremental value			
						(1-2)	(1-3)	(1-4)	(1-5)
Company (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						[redacted]	[redacted]	[redacted]	[redacted]
PH assumption for OS									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
HSUV's from AXIS trial									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab wastage included									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
GP costs excluded									
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)						[redacted]	[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)						[redacted]	[redacted]	[redacted]	[redacted]
ERG preferred base case ICER						[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PH, proportional hazards; HSUV, health state utility value; GP, general practitioner; ERG, evidence research group.

6.3.1 Scenario analysis for ERG base case

The ERG performed three scenarios on the ERG preferred base case to explore alternative, but equally plausible assumptions and the associated impact on the ICER. The scenarios performed are as follows:

1) **Alternative overall survival model for the trial based analysis**: The ERG's preferred distribution for the independent OS extrapolation of the METEOR trial data was the Weibull distribution. This distribution was determined in the company CS to be the best fit to the everolimus data and the cumulative hazard plots in Section 5.5.5 indicate a Weibull distribution to be appropriate. However, the log-logistic distribution, was the best fit for cabozantinib. The ERG explores a scenario around the preferred base case using the log-logistic distribution as per the company's base case choice for extrapolation of OS.

2) **PH modelling for trial based analysis**: The PH assumption for OS and PFS held for cabozantinib and everolimus in the METEOR trial, though it was not included in the ERG preferred base case as using PH, where appropriate, tends to be a simplification rather than a more accurate representation of the trial. However, PH can be more flexible as it allows the extension to using NMA-based results. In addition, exploring the PH assumption for the METEOR trial data, allows for validation of the ERG preferred base case for the NMA analysis. The ERG explores three scenarios around the preferred base case for the trial analysis by applying the PH assumption to extrapolate:

   a) OS;

   b) OS and PFS.

3) **PH modelling for NMA analysis:** The PH assumption for PFS was not included in the ERG preferred base case for the NMA as the assumption did not hold for all comparators in the NMA and in addition PFS was found not be a key driver in the model. The ERG explores a scenario including the PH assumption on the PFS curves for the preferred base case for the NMA analysis (scenario 1 in Table 102).

Table 101 and Table 102 presents the results of the scenario.

Table 101. Scenario analysis on ERG base case – trial based analysis

	Results per patient	Cabozantinib	Everolimus	Incremental value
0	**ERG preferred base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
1	**Log-logistic distribution for OS**			

	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2a	**PH assumption for OS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]
2b	**PH assumption for OS & PFS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			[redacted]

Abbreviations in table: ICER, incremental cost-effectiveness ratio; PFS, progression free survival; QALY, quality-adjusted life year; PH, proportional hazards; ERG, evidence research group.

Table 102. Scenario analysis on ERG base case – NMA based analysis

	Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Nivolumab (5)	Incremental value (1-2)	(1-3)	(1-4)	(1-5)
0	**ERG base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER						[redacted]	[redacted]	[redacted]	[redacted]
1	**PH assumption for PFS**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER						[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PFS, progression free survival; QALY, quality-adjusted life year; PH, proportional hazards; ERG, evidence research group.

7 END OF LIFE

The ERG notes that NICE end of life (EOL) supplementary advice should be applied when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

In Section 4.13 of the CS, the company present the case for cabozantinib meeting the end of life criteria. With regards to the first criteria, the company reported the median life expectancy with BSC is less than 12 months and less than 24 months with established standard care. From previous technology appraisals of second line treatments for advanced RCC, published literature and clinical expert opinion, it is established that the life expectancy for this patient population is poor and not likely to exceed 24 months.[36, 98, 99] Therefore, the ERG considers cabozantinib to satisfy the first criteria.

Data from the METEOR trial and the NMA were used to explore the second criteria and the results indicate that cabozantinib may offer an extension to life of approximately 5 months when compared to current NHS treatments (axitinib) and everolimus (see Table 103).

Table 103. Overall survival by treatment

Treatment	Median overall survival (months)	Difference
Cabozantinib	21.4	-
Axitinib	15.7	5.7
Everolimus	16.5	4.9
BSC	11.5	9.9
Nivolumab*	20.8	0.6

Lastly, the company's justification for satisfying the third criteria is that the anticipated size of the population who would be eligible for treatment with cabozantinib in 2017 would be approximately 1,000 patients.

8 OVERALL CONCLUSIONS

The clinical evidence presented in the company's submission (CS) for cabozantinib is derived from the METEOR phase III randomised controlled trial. METEOR compared cabozantinib with everolimus in patients with advanced clear-cell renal cell carcinoma, who had been previously treated with at least one VEGF-TKI. METEOR was a well-conducted trial, and it is reflective of English clinical practice although METEOR contained a high proportion of patients with an ECOG performance status of 0 (67%) which would be reflective of the fitter patients found in current practice. In addition, safety and clinical efficacy results of METEOR are relevant to the decision problem as outlined in the NICE final scope for this STA.

The company conducted a network meta-analysis (NMA) due to the absence of head-to-head trials comparing cabozantinib with axitinib, nivolumab, and best supportive care (BSC) in patients with advanced RCC who have progressed after previous VEGF-TKI treatment. Five RCTs were included in the NMA and there was substantial clinical heterogeneity among them including differences in subsequent therapies and cross-over, the number and type of prior therapies, and the baseline prognostic scores. The ERG has concerns that the company's NMA results were unreliable as a result of the heterogeneity of the trials included in the network, the lack of cross-over free OS data for TARGET and the use of immature OS data for TARGET. The ERG is particularly concerned about the likely underestimation of the overall survival estimate for axitinib generated by the company NMA as it is only linked into the network via TARGET.

The ERG notes that the company is positioning cabozantinib as a second and third line treatment option in advanced RCC. However, the ERG does not consider the METEOR trial level data for the subgroup of people with two or more prior VEGF-TKIs addresses the NICE decision problem for the potential third line positioning of cabozantinib in the advanced RCC treatment pathway. The ERG notes that the clinical pathway and the ERG's clinical experts suggest that everolimus is mainly used at second line and infrequently, if at all at third line. The ERG instead consider the key comparator's for cabozantinib at third line to be BSC and nivolumab. In addition, the ERG does not consider the company to have provided suitable subgroup data by line of therapy for the comparison of cabozantinib with the axitinib, nivolumab and BSC in the NICE final scope for the potential second or third line positioning of cabozantinib.

The economic evaluation was well presented, with the inputs and assumptions reported clearly in the company submission (CS). The electronic model design was sound, and the ERG did not encounter any

major difficulty to check and confirm that the methodologies were applied as stated in the CS and correctly implemented in the model. The company conducted an appropriate range of scenario analyses.

The ERG considers the company's economic analysis to have only partially fulfilled the final scope, as there was no subgroup analysis performed to estimate the cost effectiveness of cabozantinib as a second line and a third line therapy independently. In the ERG's opinion, the company's justification, that a similarity in the relative treatment effect at second and third line, is insufficient and does not infer that the cost effectiveness results will be equivalent.

The ERG was satisfied that the economic evaluation had considered all relevant comparators, including nivolumab, which, at the time of the submission was part of an on-going appraisal (TA417) and has since been approved (TA417). This involved two analyses using the METEOR trial data to estimate the cost effectiveness of cabozantinib compared to everolimus, and a second analysis based on a novel NMA approach to estimate the cost effectiveness of cabozantinib versus axitinib, nivolumab and best supportive care independently, as direct head-to-head trials were not available. The NMA also included the METEOR trial and thus incorporated an additional analysis for the comparison of cabozantinib and everolimus. However, the ERG is concerned at the potential lack of robust results for these comparators due to potentially serious limitations in the method used.

The key limitation in the estimation and extrapolation of the survival curve parameters for both progression-free survival (PFS) and overall survival (OS), was that a single family of distributions (e.g. log-normal) had to be applied to the data for all comparators. The assessment of goodness-of-fit (Deviance Information Criterion) was, therefore, a global measure that did not give an indication of the goodness-of-fit of a particular parametric curve to the data for a particular comparator. A visual assessment of these parametric curves and the plotted Kaplan-Meier (KM) data shows that some of the curves had a poor fit. The ERG considers this to be a serious limitation leading to potentially non-robust estimates of the ICER, and hence, caution must be taken when considering the results of this analysis.

For the METEOR trial-based economic evaluation, parametric curves were fitted independently to each group of the trial, which the ERG considers to be a suitable approach. However, when assessing the goodness-of-fit, the company provided no justification for the choice of distribution when there was discordance in the optimal fit across the two groups. The ERG agrees with the company's decision to apply the same family of distributions to each group, however, the choice between the two best fitting curves was not clear and the impact on the results by choosing the alternative curve proved to be great.

The ERG performed some analyses to reduce the uncertainty caused by the limitations in the company's analysis, which involved assuming that the OS of axitinib was equivalent to everolimus, allowing a hazard ratio based NMA to be performed on the remaining network of trials. This avoided the poorly fitted curves but adds a slight uncertainty in the violation of proportional hazards (PH) in the CheckMate 025 trial, when a PH assumption was tested across all trials. However, this violation in the CheckMate 025 trial only occurs in the first 6 weeks, and the ERG considers this to have a minor impact on the estimation of OS and, therefore, on the ICER for the comparison with nivolumab in the ERG's base case analysis. The assumption that the OS of axitinib is equivalent to everolimus was validated by clinical experts and provides a conservative estimate for the ICER of cabozantinib compared to axitinib.

Another key limitation of the analyses presented are that the patient access schemes for the comparator drugs have not been applied to the acquisition costs as they are commercial in confidence. This results in potentially seriously underestimated ICERs as the true cost of the comparator drugs to the NHS will be lower that the costs applied in the model.

Overall, the ERG considers the company's analysis to be well performed but with potentially serious limitations that lead to potentially unreliable results. The ERG considers the lack of a subgroup analysis in the economic evaluation to limit the conclusions that can be made for the cost-effectiveness of cabozantinib in each proposed position in the treatment pathway.

8.1 Implications for research

The only direct evidence for cabozantinib compared to the treatments identified in the NICE final scope is with everolimus (METEOR) and everolimus is not used frequently in the English treatment pathway for RCC. Nivolumab has recently been approved as a treatment option at second and third line, and axitinib is the pre-existing standard of care at second line, and best supportive care previously at third line. Therefore, robust direct evidence of cabozantinib compared with axitinib and nivolumab are needed in the treatment of patients with advanced/metastatic RCC who have received previous treatment, particularly for the second line positioning of cabozantinib.

Robust head-to-head trial data for the third line positioning of cabozantinib are also required to fully inform decision making regarding the third-line patient population. Ideally head-to-head trial data for cabozantinib compared to nivolumab and to best supportive care are required.

In addition, an economic analysis including all treatment options, such as in the context of a multiple technology assessment (MTA), should be performed once robust relative treatment effectiveness estimates are obtained for the second and third line RCC treatment options.

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10 APPENDICES

10.1 Quality assessment of RCTs

Table 104: Quality assessment of METEOR (adapted from CS, pg 57, Table 13)

METEOR	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Yes. Patients were randomised 1:1 ratio to receive cabozantinib or everolimus. Randomisation was stratified.	Yes. Randomisation was carried out using an IVRS. Patients were stratified by number of previous VEGF TKI treatments (1 or ≥2), MSKCC risk group (favourable, intermediate, or poor). Generation of randomization sequence not reported in main publication or CS.
Was concealment of treatment allocation adequate?	Yes. Treatment allocation was concealed using an interactive voice and web response system.	Yes. A central voice and web system was used to conceal allocation. Study personnel did not have access to list of patient blocks or block sizes.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes. Randomisation was stratified by MSKCC risk group and number of prior therapies for advanced RCC. Baseline characteristics seem similar between the trial arms
Were care providers, participants and outcome assessors blind to treatment allocation?	No. This was an open-label study. Patients and investigators were not masked to study treatment to allow appropriate management of adverse events.	No. Patients and investigators were not masked to study treatment. PFS and ORR was assessed by IRC who were blinded to treatment. OS was assessed by unblinded investigators.
Were there any unexpected imbalances in drop-outs between groups?	No	Yes. There was a higher proportion of discontinued patients in the everolimus group (91%) compared to the cabozantinib group (78%).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No. All outcomes specified in trial methods: PFS, OS, ORR and HRQoL, AE have been assessed and 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	Yes. Primary outcome PFS was analysed using a pre-specified PITT comprising the first 375 randomised patients. PFS was also analysed using the full ITT population. Overall survival used ITT analysis.

How closely do the RCT(s) reflect routine clinical practice?	The baseline characteristics of patients in the trial reflect those patients likely to receive cabozantinib in clinical practice. The outcomes measured are relevant to clinical practice.	Based on its clinical advisors, the ERG considers the patients in METEOR to broadly reflect clinical practice.

Abbreviations: AE, adverse events; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; MSKCC, memorial Sloan Kettering Cancer Center; IRC, independent review committee; ITT, intention to treat; IVRS, interactive voice response system; ORR, objective response rate; OS, overall survival; PITT, primary end point intention to treat; PFS, progression free survival; VEGF TKI,

Table 105: Quality assessment of TARGET (adapted from CS, Appendix 9, Table 5)

TARGET	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Not clear. 1:1 allocation with block size of four; stratification of patients by country and MSKCC prognostic score (low, intermediate); generation of randomization sequence unclear.	Not clear. Patients were reportedly randomisedin a 1:1 ratio, with a block size of four, to sorafenib or placebo. Patients were stratified by country and MSKCC prognostic score. Generation of randomization sequence not reported
Was concealment of treatment allocation adequate?	Not clear. No information.	Not clear. Trial was double-blind but methods of treatment allocation were not described.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographic and baseline characteristics were balanced between the sorafenib and placebo groups.	Yes. Randomisation was stratified by MSKCC risk group. Baseline characteristics seem similar between the trial arms
Were care providers, participants and outcome assessors blind to treatment allocation?	Yes. It was a double-blind study. Patients and investigators were masked to study treatment. A blinded independent data and safety monitoring committee assessed outcomes.	Yes. The trial was double-blind with patients and investigators unaware of allocation. Post-progression patients and investigators were aware of treatment allocation
Were there any unexpected imbalances in drop-outs between groups?	No. There were no unexpected imbalances in drop-outs between groups for efficacy or safety analyses.	Yes. There was a higher proportion of patients discontinuing treatment in the placebo group (75%) compared to the patients in the sorafenib group (63%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. There is no evidence suggesting that the authors measured more outcomes than have been reported.	No. Key outcomes outlined in the main publication were reported fully: OS, PFS, AE.
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. All randomized patients were included in the intent-to-treat population for efficacy analysis. Safety analysis was conducted using a safety set (all patients receiving at least study drug once).	Yes. ITT analysis was used for all key outcomes of interest. Analysis of safety was done on all patients who received at least one dose of study drug (safety analysis set)

Abbreviations: AE, adverse events; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; MSKCC, memorial Sloan Kettering Cancer Center; IRC, independent review committee; ITT, intention to treat; IVRS, interactive voice response system; ORR, objective response rate; OS, overall survival; PITT, primary end point intention to treat; PFS, progression free survival; VEGF TKI,

Table 106: Quality assessment of CheckMate 025 (adapted from CS, Appendix 9, Table 5)

CheckMate 025	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Not clear. 1:1 allocation with block size of four; stratification of patients according to region (United States or Canada, Western Europe, and the rest of the world), MSKCC prognostic risk group, and the number of previous antiangiogenic therapy regimes (one or two) for advanced renal cell carcinoma. Generation of randomization sequence unclear.	Yes. Patients were randomised in a 1:1 ratio using an interactive voice response system with a block size of 4. Stratified by region, MSKCC risk group, number of prior systemic therapies (1 or 2) for advanced RCC. Generation of randomization sequence unclear.
Was concealment of treatment allocation adequate?	Not clear. No information.	Yes. Treatment allocation was concealed using an interactive voice response system

Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographic and baseline characteristics were balanced between the nivolumab and everolimus groups.	Yes. Randomisation was stratified by MSKCC risk group and number of prior therapies for advanced RCC. Baseline characteristics seem similar between the trial arms
Were care providers, participants and outcome assessors blind to treatment allocation?	No. It was an open-label study. Patients and investigators were not blinded to study treatment.	No. The trial was open label with investigators and patients aware of treatment allocation.
Were there any unexpected imbalances in drop-outs between groups?	No. There were no unexpected imbalances in drop-outs between groups for efficacy or safety analyses.	No. Both groups showed similar number of discontinued patients; 339/410 (82.7%) patients discontinued nivolumab treatment and 369/411 (89.8%) discontinued everolimus treatment
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. There is no evidence suggesting that the authors measured more outcomes than have been reported.	No. Results were reported for all the main outcomes outlined listed in the publication; OS, ORR, PFS, QoL and AE.
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. All randomized patients were included in the intent-to-treat population for efficacy analysis.Safety analysis was conducted using a safety set (all patients receiving at least study drug once).	Yes. ITT analysis was used for all key outcomes. The safety analysis set (all patients receiving at least one dose of study drug) was used for AEs.
Abbreviations: AE, adverse events; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; MSKCC, memorial Sloan Kettering Cancer Center; IRC, independent review committee; ITT, intention to treat; IVRS, interactive voice response system; ORR, objective response rate; OS, overall survival; PITT, primary end point intention to treat; PFS, progression free survival; VEGF TKI,		

Table 107: Quality assessment of AXIS (adapted from CS, Appendix 9, Table 5)

AXIS	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Yes. Patients were stratified according to ECOG status (0 or 1) and type of previous treatment (i.e., regimen containing sunitinib, bevacizumab, temsirolimus, or cytokine), and then randomly assigned them (1:1) to receive either axitinib or sorafenib. Randomisation lists were generated from an independent randomisation group using a permuted block design of size four (two to axitinib and two to sorafenib) within each stratum.	Yes. Patients were randomised 1:1 to axitinib or sorafenib. Randomisation was stratified by ECOG performance status and previous treatment. Randomised lists were computer generated by an independent randomisation group with a permuted block design of size four within each stratum.
Was concealment of treatment allocation adequate?	Yes. A web-enabled centralised registration system concealed treatment allocation before registration and allowed centres to enrol patients directly. Patients and investigators were not masked to study treatment.	Yes. Web centralised registration system was used to conceal treatment allocation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Demographic and baseline characteristics were typical of a population with advanced RCC and were well balanced between the axitinib and sorafenib arm.	Yes. Patients were stratified according to ECOG performance status and previous treatment. Baseline characteristics seem similar between the trial arms

Were care providers, participants and outcome assessors blind to treatment allocation?	No. It was an open-label study. Patients and investigators were not masked to study treatment. Progression-free survival and objective response rate were assessed by a masked independent radiology review.	No. The trial was open label, patients and investigators were not masked to treatment. The radiologists who participated in the independent review committee assessment of PFS (the primary endpoint) were masked to group assignment.
Were there any unexpected imbalances in drop-outs between groups?	No. In the axitinib arm, 318/361 discontinued treatment (240 patients due to disease progression/relapse) and in sorafenib arm, 325/362 patients discontinued treatment (226 patients due to disease progression/relapse). There were no imbalances for drop-outs between groups for efficacy and safety analyses.	No. There was a similar proportion of patients who discontinued treatment in each treatment group
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. There is no evidence suggesting that the authors measured more outcomes than have been reported.	No. Results were reported for all main: PFS, OS, ORR, QoL, AEs
Did the analysis include an intention-to-treat analysis? If so was this appropriate and were appropriate methods used to account for missing data?	Yes. Efficacy was assessed in the intention-to-treat population. Safety was assessed in patients who received at least one dose of study drug.	Yes. ITT analysis was used for all key outcomes. The safety analysis set (all patients receiving at least one dose of study drug) was used for AEs.
Abbreviations: AE, adverse events; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; MSKCC, memorial Sloan Kettering Cancer Center; IRC, independent review committee; ITT, intention to treat; IVRS, interactive voice response system; ORR, objective response rate; OS, overall survival; PITT, primary end point intention to treat; PFS, progression free survival; VEGF TKI,		

Table 108: Quality assessment of RECORD-1 (adapted from CS, Appendix 9, Table 5)

RECORD-1	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Not clear. Patients were stratified according to a Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable vs intermediate vs poor risk) and previous anticancer therapy (one vs two previous VEGF receptor tyrosine kinase inhibitors). Patients were randomly assigned in a two to one ratio to everolimus or placebo with the use of permuted blocks of six (four to everolimus, two to placebo) within each stratum. Generation of randomization sequence unclear.	Yes. Randomisation was done centrally in a 2:1 ratio to everolimus and placebo via an interactive voice response system using a validated computer system, and was stratified by MSKCC prognostic score and previous anticancer therapy, with a permuted block size of six. Generation of randomization sequence unclear.
Was concealment of treatment allocation adequate?	Not clear. Treatment concealment method was not addressed.	Yes. Allocation concealment was carried out using central IVRS
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes. Baseline characteristics were well balanced between study groups.	Yes. Randomisation was stratified by MSKCC risk group and prior VEGF-TKI therapy. Baseline characteristics seem similar between the trial arms

Were care providers, participants and outcome assessors blind to treatment allocation?	Yes. Patient and investigator were blinded. Outcome analyses by independent review committee and by investigator review	Yes. Both patients and investigators were blinded treatment allocation. The primary outcome, PFS, was assessed by a ICR and study investigators
Were there any unexpected imbalances in drop-outs between groups?	No. There were no unexpected imbalances in drop-outs between groups for efficacy or safety analyses.	Yes. There was a higher proportion of patients that discontinued treatment in the placebo group (96%) compared to everolimus group (73%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No. There is no evidence suggesting that the authors measured more outcomes than have been reported.	No. The main outcomes were outlined and reported fully, including PFS, OS, QoL and AEs.
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. All randomly assigned patients were assessable for efficacy (intention-to-treat analysis). All patients receiving at least one dose of everolimus were eligible for safety analysis. Patients without tumour progression or death at the time of the data cut-off for the analysis or at the time of receiving an additional anticancer therapy were censored at their last date of adequate tumour evaluation.	Yes. ITT was used for all outcomes. The safety analysis set (all patients receiving at least one dose of study drug) was used for AEs.

Abbreviations: AE, adverse events; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; MSKCC, memorial Sloan Kettering Cancer Center; IRC, independent review committee; ITT, intention to treat; IVRS, interactive voice response system; ORR, objective response rate; OS, overall survival; PITT, primary end point intention to treat; PFS, progression free survival; VEGF TKI,

Cabozantinib for previously treated advanced renal cell carcinoma

Addendum

This report was commissioned by the NIHR HTA Programme as project number 16/10/09

BMJ Technology Assessment Group

Summary of the document

The ERG produced this addendum to provide the Committee with the results of the economic model (both company corrected and ERG base cases) with the confidential patient access scheme (PAS) for cabozantinib applied. The PAS equates to a [redacted] discount on the list price of cabozantinib. In addition, NICE requested the following additional analyses:

- Probabilistic sensitivity analysis (PSA) of the company's corrected base case with cabozantinib PAS discount applied;
- PSA of the ERG base case;
- Fully incremental analysis of the company base case (both list price and PAS for cabozantinib);
- Fully incremental analysis of the ERG base case (both list price and PAS for cabozantinib);
- Fully incremental analysis of the company base case PSA results (both list price and PAS for cabozantinib);
- Fully incremental analysis of the ERG base case PSA results (both list price and PAS for cabozantinib;
- ERG's scenario analyses around the ERG base case using the PAS discount for cabozantinib; and
- Treatment waning scenario for the ERG NMA-based base case.

The ERG reviewed the company's PAS submission and found that it the PAS had been implemented in the company's updated model correctly and that the results matched those produced by the ERG.

COMPANY'S BASE CASE

Table 1. Base case results for cabozantinib compared to everolimus based on the METEOR trial (CS, page 151, Table 77)

Drug	Total costs	Total QALYs	Total life-years	Incremental cabozantinib versus			ICER versus cabozantinib
				Costs	QALYs	Life years	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 2. Pairwise analysis cost-effectiveness results based on the NMA (adapted from CS, page 151-152, Table 77 and 79)

Treatment	Cost	LYs	QALYs	Incremental costs Cabozantinib versus comparator	Incremental LYs Cabozantinib Versus comparator	Incremental QALYs Cabozantinib Versus comparator	ICER Cabozantinib Versus comparator (£/QALY)
Cabozantinib	[redacted]	[redacted]	[redacted]				
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year							

ADDITIONAL WORK UNDERTAKEN BY THE ERG

Model corrections

Corrected company base case results with the incorporated cabozantinib PAS discount are presented in Table 3 and Table 4.

Table 3. Corrected company base case results – trial based analysis

Treatment	Cost	LYs*	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£78,557

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 4. Corrected company base case results – NMA based analysis

Treatment	Cost	LYs*	QALYs	Incremental costs cabozantinib versus	Incremental LYs cabozantinib versus	Incremental QALYs cabozantinib versus	ICER cabozantinib versus
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,118
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,404
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,019
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by cabozantinib

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

The results of the PSA for the company's corrected base case with the incorporated cabozantinib PAS discount are presented in Table 5 and Table 6.

Table 5. Corrected company base case results – trial based analysis (PSA)

Treatment	Cost	LYs*	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£79,347

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 6. Corrected company base case results – NMA based analysis (PSA)

Treatment	Cost	LYs*	QALYs	Incremental costs cabozantinib versus	Incremental LYs cabozantinib versus	Incremental QALYs cabozantinib versus	ICER cabozantinib versus
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,984
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£66,291
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,314
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by cabozantinib

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

A fully incremental analysis of the company's corrected base case based on the deterministic NMA analysis using list prices for all drugs is presented in Table 7.

Table 7: Full incremental analysis of comparators (deterministic, list prices)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

A fully incremental analysis of the company's corrected base case based on the PSA of the NMA analysis using list prices for all drugs is presented in Table 8.

Table 8: Full incremental analysis of comparators (PSA, using list prices)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

A fully incremental analysis company's corrected base case based on the deterministic NMA analysis using incorporating the cabozantinib PAS discount is presented in Table 9.

Table 9: Full incremental analysis of comparators (deterministic, cabozantinib PAS discount)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,354
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£68,404
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

A fully incremental analysis of the company's corrected base case based on the PSA of the NMA analysis using incorporating the cabozantinib PAS discount is presented in Table 10.

Table 10: Full incremental analysis of comparators (PSA, cabozantinib PAS discount)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,786
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£67,262
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

ERG base case ICER

The ERG's base case was based on the following assumptions:

1. Using the Weibull distribution to extrapolate OS for the trial based analysis.

2. Assuming proportional hazards (PH) hold for all comparators in the NMA and adopting a PH modelling approach for the NMA based analysis. Axitinib was assumed to be equivalent to everolimus to avoid violating PH for the TARGET trial in the network.

3. Assuming the health state utility values (HSUVs) for PFS and PPS are 0.692 and 0.610 respectively. These reflect the values in the AXIS trial, which the ERG's clinical experts stated would be closer to what is seen in practice than the values obtained from the METEOR trial.

4. Inclusion of wastage costs for nivolumab due to the weight-based dosing regimen in the NMA analysis. In the CS, these were said to be included, but during clarification stage the company mistakenly omitted the wastage costs of nivolumab in their base case NMA analysis.

5. Exclusion of GP costs in line with the ERG's clinical expert opinion.

The ERG base case results for the trial based analysis and the NMA based analysis with the incorporated cabozantinib PAS discount are presented in Table 11 and Table 12. A more detailed analysis of the individual and cumulative impact of each of the ERG's assumptions for the base case are presented in Table 13 and Table 14.

Table 11. Overview of ERG base case results – trial based analysis

Treatment	Cost	LYs*	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£121,897

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 12. Overview of ERG base case results – NMA based analysis

Treatment	Cost	LYs*	QALYs	Incremental costs cabozantinib versus	Incremental LYs cabozantinib versus	Incremental QALYs cabozantinib versus	ICER cabozantinib versus
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£78,410
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£98,166
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£79,186
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated by cabozantinib

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 13. ERG's base case ICER – trial based analysis

Results per patient	Cabozantinib	Everolimus	Incremental value
Company (corrected) base case			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			**£78,557**
Weibull distribution for OS			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£103,848**
ICER (with all changes incorporated)			**£103,848**
HSUV's from AXIS trial			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]

ICER (compared with base case)			**£94,080**
ICER (with all changes incorporated)			**£122,385**
GP costs excluded			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			**£78,039**
ICER (with all changes incorporated)			**£121,897**
ERG preferred base case ICER			**£121,897**

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PH, proportional hazards; HSUV, health state utility value; GP, general practitioner; ERG, evidence research group.

Table 14. ERG's base case ICER – NMA based analysis

Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Nivolumab (5)	Incremental value (1-2)	(1-3)	(1-4)	(1-5)
Company (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						**£46,118**	**£68,404**	**£57,019**	**Dominated by cabozantinib**
PH assumption for OS									
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)						**£66,391**	**£82,776**	**£66,055**	**Dominated by cabozantinib**
ICER (with all changes incorporated)						**£66,391**	**£82,776**	**£66,055**	**Dominated by cabozantinib**
HSUV's from AXIS trial									
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)						**£56,100**	**£82,600**	**£69,490**	**Dominated by cabozantinib**
ICER (with all changes incorporated)						**£78,978**	**£98,755**	**£79,889**	**Dominated by cabozantinib**
Nivolumab wastage included									
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)						**£46,118**	**£68,404**	**£57,019**	**Dominated by cabozantinib**
ICER (with all changes incorporated)						**£78,978**	**£98,755**	**£79,889**	**Dominated by cabozantinib**
GP costs excluded									
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)		**£45,498**	**£67,832**	**£56,389**	**Dominated by cabozantinib**
ICER (with all changes incorporated)		**£78,410**	**£98,166**	**£79,186**	**Dominated by cabozantinib**
ERG preferred base case ICER		**£78,410**	**£98,166**	**£79,186**	**Dominated by cabozantinib**
Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PH, proportional hazards; HSUV, health state utility value; GP, general practitioner; ERG, evidence research group.					

The results of the PSA on the ERG base case for the trial and NMA based analyses are presented in Table 15 and Table 16, respectively.

Table 15. Overview of ERG base case results – trial based analysis (PSA)

Treatment	Cost	LYs*	QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£124,556

Abbreviations used in the table: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 16. Overview of ERG base case results – NMA based analysis (PSA)

Treatment	Cost	LYs*	QALYs	Incremental costs cabozantinib versus	Incremental LYs cabozantinib versus	Incremental QALYs cabozantinib versus	ICER cabozantinib versus
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£76,037
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,216
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£90,794
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

A fully incremental analysis of the ERG's base case based on the deterministic NMA analysis using list prices for all drugs is presented in Table 17.

Table 17: Full incremental analysis of comparators (deterministic, list prices)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

A fully incremental analysis of the ERG's base case based on a PSA of the NMA analysis using list prices for all drugs is presented in Table 18.

Table 18: Full incremental analysis of comparators (PSA, list prices)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

A fully incremental analysis based of the ERG's base case based on the deterministic NMA analysis incorporating the cabozantinib PAS discount is presented in Table 19.

Table 19: Full incremental analysis of comparators (deterministic, cabozantinib PAS discount)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£61,071
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£98,166
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

A fully incremental analysis of the ERG's base case based on a PSA of the NMA analysis incorporating the cabozantinib PAS discount is presented in Table 20.

Table 20: Full incremental analysis of comparators (PSA, cabozantinib PAS discount)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£83,398
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£10,696,048
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£96,216
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

The results of the ERG's scenario analyses based on the cabozantinib PAS are presented in Table 21 and Table 22 for the trial-based model and the NMA-based model, respectively.

Table 21. Scenario analysis on ERG base case – trial based analysis

	Results per patient	Cabozantinib	Everolimus	Incremental value
0	**ERG preferred base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£121,897**
1	**Log-logistic distribution for OS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£93,459**
2a	**PH assumption for OS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£99,568**
2b	**PH assumption for OS & PFS**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER			**£102,729**

Abbreviations in table: ICER, incremental cost-effectiveness ratio; PFS, progression free survival; QALY, quality-adjusted life year; PH, proportional hazards; ERG, evidence research group.

Table 22. Scenario analysis on ERG base case – NMA based analysis

	Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	BSC (4)	Nivolumab (5)	Incremental value (1-2)	(1-3)	(1-4)	(1-5)
0	**ERG base case**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER						**£78,410**	**£98,166**	**£79,186**	**Dominant**
1	**PH assumption for PFS**									
	Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ICER						**£85,502**	**£101,605**	**£80,586**	**Dominant**

Abbreviations in table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PFS, progression free survival; QALY, quality-adjusted life year; PH, proportional hazards; ERG, evidence research group.

NICE requested the ERG to perform a scenario analyses around the ERG's base case whereby the HRs for OS relative to the everolimus group were gradually increased or decreased to 1 over a period of 12 months, starting from month 25. The results of this scenario are presented in Table 23 and Table 24 for based on list prices and including the cabozantinib PAS, respectively. Fully incremental analyses are also given in Table 25 and Table 26, respectively. The best supportive care (BSC) results required a correction due to an erroneous OS curve caused by the assumptions whereby the survival probability increased. The correction means that survival remains constant for a period of time and therefore may still be unreliable.

Table 23: Scenario with waning effect (deterministic, list prices)

Treatment	Cost	LYs*	QALYs	Incremental costs cabozantinib versus	Incremental LYs cabozantinib versus	Incremental QALYs cabozantinib versus	ICER cabozantinib versus
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 24: Scenario with waning effect (deterministic, cabozantinib PAS discount)

Treatment	Cost	LYs*	QALYs	Incremental costs cabozantinib versus	Incremental LYs cabozantinib versus	Incremental QALYs cabozantinib versus	ICER cabozantinib versus
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£156,221
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£199,856
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£129,195
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

Table 25: Full incremental analysis of waning effect scenario (list prices)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.							

Table 26: Full incremental analysis of waning effect scenario (cabozantinib PAS discount)

Treatment	Cost	LYs*	QALYs	Incremental			ICER
				Cost	LYs*	QALYs	
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£85,121
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£199,856
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.							

Cabozantinib for previously treated advanced renal cell carcinoma

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 16/10/09

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer'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
19	Typographical error in company name corrected and text relating to marketing authorisation amended
21	Percentage for the TEAE of nausea amended
29	Survival cures changed to survival curves.
35	Number of treatments not recommended for use by NICE amended
48	Average cost of a course of treatment marked as commercial in confidence as requested by company
78	Text describing pazopanib and sunitinib subgroup results amended
79	Percentages for the TEAEs of nausea and PPES amended
85	Percentage for the TEAE of nausea amended
137	In Table 69, cost (per) pack changed from £4,800 to £5,143 and vials/tablets per pack changed from 28 to 30 and figure for nivolumab planned dose in text changed from 83.1% to 83.9%.
147	'for nivolumab' added to the end of the following sentence: The modelled treatment regimen was 60mg orally once every day for cabozantinib, 10mg orally once every day for everolimus, 5mg orally twice per day for axitinib and 3mg/kg by intravenous infusion every two weeks.
148	'Check Mate 025' added to the end of the following sentence: Time to discontinuation (TTD) data from the METEOR trial were used for time on treatment with cabozantinib and everolimus; TTD for nivolumab was obtained from.
207	Typographical errors in company name corrected

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of cabozantinib, (CABOMETYX®; Ipsen) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of cabozantinib in the treatment of people who have received previous vascular-endothelial growth factor (VEGF)-targeted therapy for advanced renal cell carcinoma (RCC).

In 2016, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of cabozantinib following an accelerated review. Cabozantinib was granted Promising Innovative Medicine (PIM) status in July 2016. Marketing Authorisation was granted on 9 September 2016 for the use of cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior VEGF-targeted therapy.

The clinical evidence presented in the company's submission (CS) for cabozantinib is derived from the METEOR phase III randomised controlled trial. METEOR compared cabozantinib with everolimus in patients with advanced clear-cell renal cell carcinoma, who had been previously treated with at least one VEGF-TKI (tyrosine kinase inhibitor). The final scope issued by NICE specified the population of interest to be people who have received previous VEGF-targeted therapy for advanced renal cell carcinoma. The evidence review group (ERG) notes that over 70% of patients in METEOR had only received one prior VEGF-TKI and the remaining patients had received 2 or more prior VEGF-TKIs. The ERG considers the population in METEOR to be relevant to the decision problem.

The comparator in METEOR was everolimus. In the final scope issued by NICE, the comparators of interest were identified as axitinib, everolimus, nivolumab and best supportive care (BSC). All comparators were considered in the CS and are in keeping with those currently used in UK clinical practice.

All clinically relevant outcomes were reported in the CS for the comparison of cabozantinib with everolimus. However, the ERG notes the omission of treatment related adverse events (TRAEs) reporting from METEOR in the CS and that comparison of HRQoL, response rates and adverse effects for cabozantinib and axitinib, nivolumab or best supportive care are not presented in the CS. In addition, the ERG notes that the long term safety and efficacy of cabozantinib cannot be assessed from the data that are currently available.

The company also provided subgroup data by type of prior VEGF-TKI therapy, number of prior VEGF-TKI therapies, baseline Heng score and baseline MSKCC scores from METEOR as requested in the NICE final scope albeit for limited outcomes (PFS and OS only).

although the HRs do suggest a trend favouring cabozantinib over everolimus in terms of improving OS irrespective of baseline MSKCC or Heng risk category.

The proportion of patients experiencing an adverse event (AE) was the same for both the cabozantinib and everolimus treatment groups (92%) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%). The most common TEAEs of any grade in the cabozantinib group compared with the everolimus group were diarrhoea (75% vs 28%), fatigue (59% vs 47%) and nausea (53% vs 30%). The company reported that the majority of the TEAEs were managed through study drug dose reductions. The TEAEs that were most likely to lead to permanent discontinuation of cabozantinib were reported to be decreased appetite and fatigue. The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus) and fatigue (11% vs 7%, cabozantinib vs everolimus).

The company conducted a survival curve-based network meta-analysis (NMA) due to the absence of head-to-head trials comparing cabozantinib with axitinib, nivolumab, and BSC in patients with advanced RCC who have progressed after previous VEGF-TKI treatment. There were five trials included in the NMA: METEOR, AXIS, Checkmate 025, RECORD-1 and TARGET. They were all RCTs although there were differences between the trials in terms of the presence/absence of cross-over design, number and type of prior therapies, and baseline prognostic scores.

The results of the NMA suggest that cabozantinib prolongs OS and PFS compared to axitinib, BSC (represented by placebo), everolimus and nivolumab. The ERG has concerns that the company's NMA results were unreliable as a result of the heterogeneity of the trials included in the network, the lack of cross-over free OS data for TARGET and the use of immature OS data for TARGET. The ERG is particularly concerned about the overall survival estimate for axitinib generated by the company NMA as it is only linked into the network via TARGET. TARGET was a placebo-controlled trial and if it is assumed that sorafenib is likely to be more effective than placebo; utilising immature survival data is likely to underestimate the benefit of sorafenib over placebo. The results of AXIS show similar efficacy for axitinib and sorafenib and so the potential underestimating of OS in TARGET means that the survival benefit for axitinib will similarly be underestimated in the company's NMA.

1.2 Summary of cost effectiveness evidence submitted by the company

The company submitted a *de novo* economic model developed using Microsoft Excel® that evaluated cabozantinib in two separate cost-utility analyses. The first was a trial-based analysis comparing cabozantinib with everolimus, using effectiveness data obtained solely from the METEOR trial.[1] The second analysis compared cabozantinib with everolimus, axitinib, nivolumab and best supportive care (BSC) as pairwise comparisons, and the effectiveness data was derived from a network meta-analysis

efficacy with axitinib when compared to everolimus and so the ERG conducted a conservative exploratory analysis to explore the impact of assuming axitinib and everolimus have equal efficacy. This analysis enables the exclusion of TARGET from the NMA as it is no longer required to provide a link between axitinib and the other comparators. However, based on clinical advice, the assumption of equal efficacy to everolimus could potentially under-estimating the efficacy of axitinib. The remaining comparators in the ERG's NMA were: cabozantinib, nivolumab, placebo and everolimus.

The results of the ERG's NMA show a similar treatment ranking to that seen in the company's NMA with cabozantinib having the lowest HR for OS and cabozantinib is associated with a statistically significant increase in OS (HR 0.65; 95% Credible Interval [CrI] 0.527 to 0.825). The estimated median PFS and OS based on the ERG's NMA are generally in keeping with those estimated from the company's NMA.

Economic

The ERG performed a limited number of scenario analyses around the company's corrected base case for both the trial-based model and the NMA-based model. These were around the estimate and extrapolation of survival curves for PFS and OS; health state utility values used in the model; and resource use included in the overall costs.

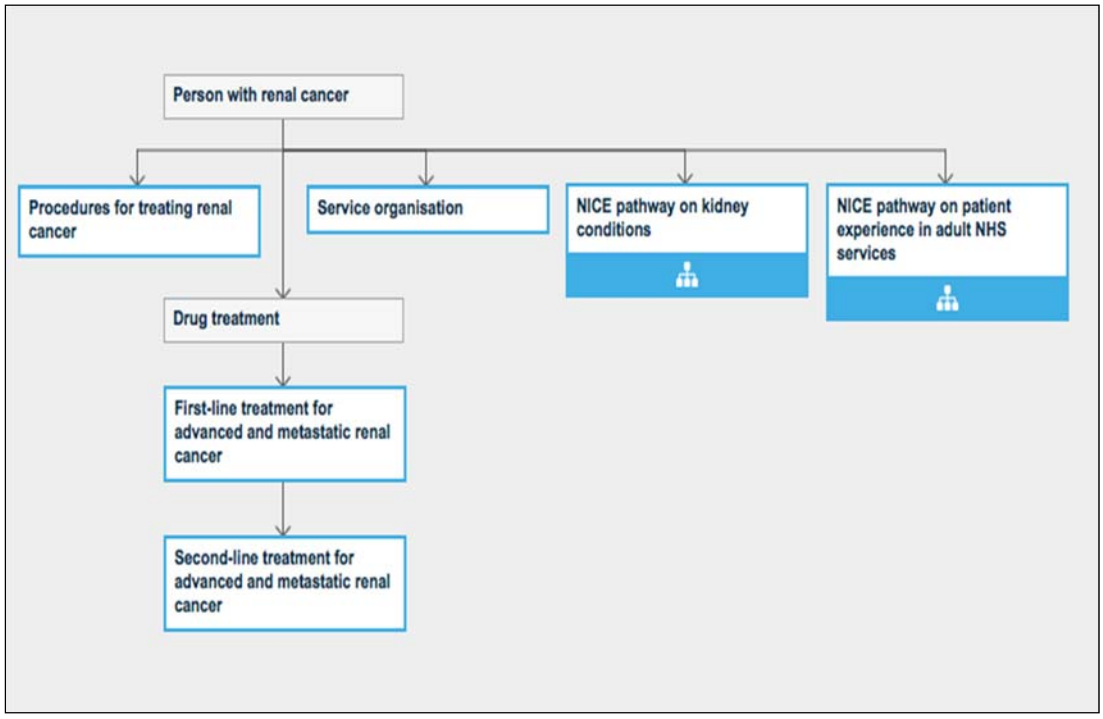
The following changes were made to both models, after consulting with clinical experts in renal cell carcinoma:

- Changing health state utility values to those from TA333;
- Removing the GP cost applied to the management of patients.

For the trial-based model, the OS survival curves were changed to the Weibull distribution as this was the best fitting curve to the everolimus group, and log-cumulative hazard plots indicated linearity between log-cumulative hazard and log time; a characteristic of the Weibull distribution.

For the NMA-based model, the OS curves were regenerated based on a hazard ratio (HR) based NMA performed by the ERG to estimate the HR for OS, for cabozantinib, nivolumab and BSC compared to everolimus. The HR for axitinib compared to everolimus was assumed to be equal to one due to concerns the ERG have about the company's NMA potentially underestimating survival with axitinib. The company's NMA included the TARGET trial (sorafenib vs placebo) as a link to the AXIS trial (axitinib vs sorafenib) but the OS results from TARGET are potentially confounded by patient cross-over. The TARGET trial also showed that the hazards between the two groups were not proportional, but this may have been a result of the confounding. The ERG's clinical experts consider that assuming

Figure 1. NICE pathway for renal cancer[28]



- Abbreviations: NHS, national health service; NICE, National Institute for Health and Care Excellence.

The recommended first and second line drug treatment options in the NICE treatment pathway for renal cancer are summarised in Box 7. The available first line options considered by NICE are pazopanib, sunitinib, bevacizumab, sorafenib and temsirolimus, of which the latter 3 drugs are not recommended by NICE. Axitinib, everolimus, sorafenib and sunitinib are the available treatment options considered for second line and the latter 3 drugs are not recommended for use by NICE. However, the ERG notes that everolimus is currently undergoing review by NICE in the cancer drugs fund (CDF) rapid reconsideration process (GID-TA10057), with guidance expected to be published in March 2017.[29]

Box 7. Company's summary of the NICE recommendations for first and second line therapy of advanced and metastatic RCC (Adapted from CS, pages 29–30, Section 3.3.1)

In summary NICE recommends:

- Sunitinib or pazopanib for the first-line treatment of patients with advanced and /or metastatic RCC with an ECOG performance status of 0 or 1 (TA169[30] and TA215[31])
- Axitinib for use in patients with advanced RCC after failure of treatment with a first-line TKI or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme (TA333[32]).

While everolimus is not recommended by NICE (TA219[33]), it is available via the Cancer Drugs Fund (CDF) for:

- People with RCC who have had prior treatment with only one previous TKI, and

The ERG notes that cabozantinib also has a similar FDA approval for the treatment of advanced RCC that was granted on 25 April 2016. The FDA approval is wider as it allows cabozantinib use in patients who have received prior antiangiogenic therapy and doesn't specify that this must be a VEGF-TKI.

The company reported in the CS that they are also planning to make submissions to the Scottish Medicines Consortium (SMC) in Q4 of 2016 and the National Centre for Pharmacoeconomics (NCPE) in the Republic of Ireland in early 2017 for further approvals for the use of cabozantinib in RCC.

Cabozantinib is an oral once daily treatment and the recommended dose is 60mg with treatment continuing until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Temporary interruptions or dose reductions may be made to manage adverse events. As discussed in Section 2.2, the company report that the introduction of cabozantinib will not require any changes to the existing NHS infrastructure and resources. The company also reported that any required dose reductions and treatment interruptions could be managed remotely via the telephone. The ERG's clinical advisors report that it is unlikely these would be managed remotely but that they would most likely be done in outpatient clinics, in keeping with that of the existing oral advanced RCC treatments. Further details on the administration of cabozantinib are reported in Table 5.

Table 5. Summary of prescribing information for cabozantinib and unit cost (Adapted from the CS, page 23, Table 4)

	Cost	**Source**
Pharmaceutical formulation	Film coated tablet	SmPC[46]
Acquisition cost (excluding VAT)	£5,143.00 for a 30 tablet pack	List price
Method of administration	Oral	SmPC[46]
Doses	20 mg, 40 mg and 60 mg	SmPC[46]
Dosing frequency	Once daily	SmPC[46]
Average length of a course of treatment	Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. Median duration of treatment with cabozantinib in the phase III pivotal trial (the METEOR study) was 8.3 months as of 31 December 2015.	SmPC[46] METEOR study[1]
Average cost of a course of treatment	[redacted]	Economic model
Anticipated average interval between courses of treatments	Not applicable – retreatment is not anticipated	
Anticipated number of repeat courses of treatments	Not applicable – retreatment is not anticipated	
Dose adjustments	Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of cabozantinib therapy. When dose reduction is necessary, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.	SmPC[46] (Table 1)
Anticipated care setting	Therapy with cabozantinib should be initiated by a physician experienced in the administration of anticancer medicinal	SmPC[46]

Figure 12. OS subgroup results based on number and duration of prior VEGF-TKI therapy (ITT population) (Adapted from the CS, page' 69, Figure 15)

In addition, the company reported the results of a post-hoc ITT subgroup analysis for people who only received prior VEGF-TKI therapy which was with sunitinib and for the equivalent subgroup for pazopanib. Both of these post-hoc subgroups suggested a trend in OS benefit with cabozantinib compared to everolimus although only the prior sunitinib subgroup reached statistical significance (median OS cabozantinib vs sunitinib [prior sunitinib subgroup] 21.4 months vs 16.5 months, HR 0.66, 95% CI: 0.47 to 0.93; median OS cabozantinib vs pazopanib [prior pazopanib subgroup] 22.0 months vs 17.5 months, HR 0.66, 95% CI: 0.42 to 1.04). The ERG considers it important to highlight that these are post hoc subgroups and should be interpreted with caution due to the risk of bias associated with post hoc analyses and issues with statistical multiplicity with multiple subgroup analyses.

4.3.5.2 Prognostic Score

In terms of prognostic score, the ERG considers the results to be more inconclusive although the HRs do suggest a trend favouring cabozantinib over everolimus in terms of improving OS irrespective of baseline MSKCC or Heng risk category (Table 16). However, the difference was only statistically significant in the group 0 and 1 MSKCC subgroups and in the IMDC (Heng) 1 risk group (Table 16).

Table 16. OS by baseline risk group (Adapted from the CS, page 70, Table 18)

	Cabozantinib		Everolimus		Median OS Cabozantinib vs everolimus	HR (95% CI)
	N	events	N	events		
MSKCC Risk group						
0 (Favourable)	150	48	150	66	[redacted]	0.66 (0.46, 0.96)

1 (Intermediate)	139	64	135	79	[redacted]	0.67 (0.48, 0.94)
2 or 3 (Poor)	41	28	43	35	[redacted]	0.65 (0.39, 1.07)
IMDC (Heng) risk group						
0 (Favourable)	66	14	62	17	[redacted]	0.70 (0.34, 1.41)
1-2 (Intermediate)	210	89	214	121	[redacted]	0.65 (0.49, 0.85)
3-6 (Poor)	54	37	52	42	[redacted]	0.74 (0.48,1.15)

Source: Choeuiri et al 2016[1], METEOR Clinical Study Report[60]
Abbreviations: IMDC, International Metastatic RCC Data Consortium; MSKCC; Memorial Sloan Kettering Cancer Center; NE, not estimable.

4.3.6 Adverse effects

Safety data presented in the CS from the METEOR study were based on the 31 December 2015 data cut-off and the safety population of the trial.

As discussed in Section 4.2.1, the median duration of treatment exposure was 8.3 months in the cabozantinib group and 4.4 months in the everolimus group in METEOR. The patients in METEOR were more likely to have a dose reduction with cabozantinib compared to with everolimus (number of patients with any dose reduction: 62% and 25%, respectively). However, the median daily dose was lower than the standard recommended doses for both cabozantinib (43mg instead of 60mg) and everolimus (9mg instead of 10mg).

The treatment emergent adverse events (TEAEs) observed with cabozantinib were consistent with those of other VEGF-TKI treatments for advanced RCC. The proportion of patients experiencing an adverse event (AE) was the same for both the cabozantinib and everolimus treatment groups (92% [Table 17]) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%, [Table 17]).

The most common TEAEs of any grade in the cabozantinib group compared with the everolimus group were diarrhoea (75% vs 28%), fatigue (59% vs 47%), nausea (53% vs 30%), decreased appetite (47% vs 36%) and palmar-plantar erythrodysaesthesia syndrome (PPES, 43% vs 6%). The company reported that the majority of the TEAEs were managed through study drug dose reductions. The ERG considers that this thus suggests the TEAEs were generally treatment related. The TEAEs that were most likely to lead to permanent discontinuation of cabozantinib were reported to be decreased appetite and fatigue. These were the most common TEAEs with everolimus and so were not unique to cabozantinib. However, there was a higher overall incidence of TEAEs with cabozantinib compared to everolimus and more people experienced grade 3 TEAEs with cabozantinib compared to with everolimus. The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus), fatigue (11% vs 7%, cabozantinib vs

- OS was consistently longer with cabozantinib compared with everolimus irrespective of the number of prior VEGFR-TKIs or the duration since first treatment with a VEGFR-TKI. The ERG considers the results based on prognostic score subgroups to be more inconclusive because they weren't statistically significant, although the HRs do suggest a trend favouring cabozantinib over everolimus in terms of improving OS irrespective of baseline MSKCC or Heng risk category.
- The proportion of patients experiencing an adverse event (AE) was the same for both the cabozantinib and everolimus treatment groups (92%) although there was a higher proportion of ≥ grade 3 AEs in the cabozantinib group (cabozantinib 71% and everolimus 60%). The most common TEAEs of any grade in the cabozantinib group compared with the everolimus group were diarrhoea (75% vs 28%), fatigue (59% vs 47%) and nausea (53% vs 30%). The most common grade ≥3 TEAEs with cabozantinib were hypertension (15% vs 4%, cabozantinib vs everolimus), diarrhoea (13% vs 2%, cabozantinib vs everolimus) and fatigue (11% vs 7%, cabozantinib vs everolimus).

4.4 Critique of the network meta-analysis (NMA)

The company conducted a network meta-analysis (NMA) due to the absence of head-to-head trials comparing cabozantinib with axitinib, nivolumab, and BSC in patients with advanced RCC who have progressed after previous VEGF-TKI treatment. The studies included in the NMA were identified via a standard systematic review process which included a systematic literature review. The methods used to identify the studies included in the NMA are described in detail in Section 4.1. The company reported that the review was conducted from a global perspective and as a result it included additional comparator treatments to those specified in the NICE final scope for this STA. A summary of the inclusion and exclusion criteria used for the NMA are presented in Table 19.

Table 19. Summary of inclusion and exclusion criteria used for the NMA (Adapted from the CS, page 73, Table 20)

	Inclusion Criteria	**Exclusion Criteria**
Population	Patients with previously treated advanced or metastatic renal cell carcinoma	Patients <18 years of age Healthy subjects Animal studies
Intervention	The following interventions in the second- (and further-) line setting: Cabozantinib (Cabometyx®▼) Axitinib (Inlyta®) Everolimus (Afinitor®) Sorafenib (Nexavar®) Sunitinib (Sutent®) Lenvatinib (Lenvima®) Nivolumab (Opdivo®)	Interventions in the first-line setting
Comparators	Any, including placebo and BSC	Radiotherapy, surgery and other non-pharmaceutical treatments

5.4.5.1 Pharmacological costs

The pharmacological costs considered in the model are treatment acquisition, and treatment administration costs. The acquisition costs for the intervention and comparators are summarised in Table 69.

Table 69. Acquisition costs for intervention and comparators

Treatment	Vials/tablets per pack	Formulation	Cost (per pack) UK list price	Source
Cabozantinib	30	20/40/60	£5,143	BNF[87]
Everolimus	30	10	£2,673	BNF[87]
Axitinib	56	5	£3,517	BNF[87]
Nivolumab	1 1	40 100	£439 £1,097	MIMS[88]
Abbreviations in table: BNF, British National Formulary; mg, milligram; MIMS, Monthly Index of Medical Specialties; NHS, National Health Service.				

In order to estimate total drug costs, TTD data from the METEOR trial was used to inform the proportions of patients in the cabozantinib and everolimus arms receiving treatment at each time point in the model.[89] TTD for nivolumab was estimated based on data from TA417.[36] However, no published TTD curves were identified from the AXIS trial for axitinib, therefore patients in the axitinib arm were assumed to stop treatment upon progression. The PFS distribution generated from the NMA was used to calculate treatment costs for axitinib.

Drug doses assumed in the model, and costs per cycle are summarised in Table 70. Patients in the model are assumed to receive 100% of the doses of cabozantinib to reflect the flat price of cabozantinib which does not vary according to formulation (i.e. 20 mg or 40 mg or 60 mg). The dose of cabozantinib in the trial could be reduced from 60 mg per day to 40 mg per day, and then to 20 mg per day if required.[89]

Table 70. Drug formulation, dose and total cost per 4-weeks model cycle for comparators

Drug	Dose	Frequency	Relative dose intensity, % (SE)	Total cost per cycle
Cabozantinib	60/40/20 mg	daily	100.0 (0.0)*	£4,800.00
Everolimus	10 mg	daily	83.9 (1.1)[a]	£2,093.41
Axitinib	10 mg	daily	102.0 (1.9)[b]	£3,587.34
Nivolumab	3 mg/kg	Every 2 weeks	97.5 (9.8)[c]	£5,146.15
Abbreviations in table: kg, kilogram; mg, milligram; SE, standard error.				

Patients in the everolimus arm of the model are assumed to receive 83.9% of the planned doses to reflect the proportion of doses received in the METEOR trial.[89] The RDI assumed for axitinib and nivolumab is 102.0% and 97.5%, respectively. These values are based on the published literature, and have been used in previous NICE appraisals (TA417 and TA333).[5, 76, 90] In the base case analysis, drug wastage

The key issue in not considering these subgroups in the economic model regardless of whether the treatment effectiveness is equivalent, is that the baseline inputs in the model are likely to differ and thus impact on the ICER. As such the ERG requested a separate base case analyses for the 2nd and 3rd line treatment for advanced RCC of cabozantinib compared with all relevant comparators based on these subgroups. The company responded to the request stating that outcomes obtained from the NMA (OS, PFS and TTD) were only feasible for the subgroup of patients with only 1 prior VEGF-TKI and presented a new base case for the second line treatment for advanced RCC of cabozantinib compared with only with comparators from the NMA. Results of the new NMA base case analysis are presented in Table 79, alongside results from the original NMA base case analysis. The results indicate that changing the population to patients who have received only one prior therapy has a large impact on the ICER, however, these results are unreliable as the comparator arms from the regenerated KM data are based on the ITT populations and not the subgroups.

Table 79. 2nd line treatment – NMA base case ICERs vs original base case ICERs

Treatment	New NMA base case ICER	Original NMA base case ICER
Cabozantinib	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]
BSC	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; ICER, incremental cost effectiveness ratio; NMA, network meta-analysis

No second or third line treatment base case analyses for the METEOR trial were provided by the company and as such the ERG is uncertain about what the impact of the different subgroups would be on the ICER.

5.5.4 Interventions and comparators

The intervention and comparators considered in the economic analysis were cabozantinib, everolimus, axitinib, nivolumab and BSC. These are in line with the interventions and comparators included in the NICE final scope for this STA.[8]

The modelled treatment regimen was 60mg orally once every day for cabozantinib, 10mg orally once every day for everolimus, 5mg orally twice per day for axitinib and 3mg/kg by intravenous infusion every two weeks for nivolumab. These regimens are in line with what was reported in the METEOR, CheckMate 025 and AXIS trials, as well as the recommended doses for everolimus, axitinib and nivolumab.

The company included the relative dose intensity in the model to account for variations from the planned drug dose received, ensuring representative costing for drug acquisition. This is described further in Section 5.4.5.

Time on treatment was modelled using parametric survival distributions. Time to discontinuation (TTD) data from the METEOR trial were used for time on treatment with cabozantinib and everolimus; TTD for nivolumab was obtained from Check Mate 025 [3]. PFS data were used for axitinib as TTD data were unavailable. In line with the CS, TTD is discussed as part of the treatment effectiveness in Section 5.4.2.3.

5.5.5 Treatment effectiveness

The ERG consider the methods applied to the trial-based model for the estimation of treatment effectiveness to be fairly reasonable. However, there is a lack of clarity in the justification for the choice of parametric curve fitted for each outcome, and other plausible alternatives were not fully considered or tested as scenario analyses.

For the NMA-based model, the fitting of survival curves for each outcome is severely limited by the requirement to have a single distribution applied to all comparators, with only the parameters of the curves varying. This resulted in very poorly fitting curves in some cases, which causes the inherent relative treatment effect between these independently fitted curves to be unreliable. This causes the results of the NMA-based model to be uncertain, as the estimation and extrapolation of PFS and, in particular, OS, are extremely influential on the ICER.

The remainder of this section will go into further detail about the issues identified by the ERG relating to the outcomes of PFS, OS and TTD and the effect any limitations or uncertainties could have on the overall model results.

5.5.5.1 Progression-free survival

For the estimation and extrapolation of PFS for the trial-based model, the company chose to use the log-logistic distribution for both treatment groups based on assessment of goodness-of-fit using the AIC, AICC and BIC statistics, and visual inspection by UK practising oncologists as described previously in Section 5.4.2.1. However, the statistics indicated that the log-logistic was only the best fit for the cabozantinib data, while the log-normal was the best fit for the everolimus data. The ERG would have preferred to see more justification as to why the log-normal was not chosen for both arms or at least tested as a scenario analysis.

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Cabozantinib for previously treated advanced renal cell carcinoma ID931

You are asked to check the ERG report from BMJ Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **6pm, 19 December 2016** 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 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 19, Section 1.1: Typographical error	'Ispen' need to be corrected to 'Ipsen'	Typographical error	The ERG thanks the company for highlighting this issue and has amended the text.

Issue 2 Clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 19, Section 1.1. The following ERG statement would benefit from further clarification: "In 2016, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of cabozantinib following an accelerated review as a result of it being granted Promising Innovative Medicine (PIM) status. Marketing Authorisation was granted on 9 September 2016 for the use of cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior VEGF-targeted therapy.	The accelerated review and granting of the PIM process are two separate processes. "In 2016, the Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion on the use of cabozantinib following an accelerated review ~~as a result of it being granted Promising Innovative Medicine (PIM) status~~. Cabozantinib was granted Promising Innovative Medicine (PIM) status in July 2016.Marketing Authorisation was granted on 9 September 2016 for the use of cabozantinib in the treatment of advanced renal cell carcinoma in adults following prior VEGF-targeted therapy.	Clarification	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.

Issue 3 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 30, Section 1.5 (Economic): Typographical error	'survival cures' need to be corrected to 'survival curves'	Typographical error	The ERG thanks the company for highlighting this issue. The proposed amendment has been made.

Issue 4 Typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 36, Section 2.2: Typographical error in the statement: "Axitinib, everolimus, sorafenib and sunitinib are the available treatment options considered for second line and the latter 2 drugs are not recommended for use by NICE"	The number '2' should be corrected to '3' as everolimus, sorafenib and sunitinib are not recommended for use.	Typographical error	The ERG thanks the company for highlighting this issue and has amended the text.

Issue 5 Data to be marked as commercial in confidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 49, Table 5; The average cost of a course of treatment is not marked as commercial in confidence.	The average cost of a course of treatment now needs to be marked as commercial in confidence.	A PAS will be submitted for DH approval and it is anticipated that this will be approved prior to or immediately after the first Appraisal Committee meeting. Mark up is required to avoid any potential back calculation from QALYs /ICERs calculated to the PAS discounted price.	The ERG thanks the company for highlighting this issue. The requested text has been marked as commercial in confidence.

Issue 6 Correction to cited TEAE figures

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 21, Section 1.2 Page 80, Section 4.3.6 Page 85, Section 4.3.7 The figures for the TEAEs of nausea and PPES cited in the text require amending to correlate with Table 17.	The following amendments needs to be made to ensure the figures cited in the text correlate with Table 17. Nausea ~~52%~~ 53% vs. 30% (pages 21,80 and 85) PPES ~~42%,~~ 43% vs. 6% (page 80)	The figures for the TEAEs of nausea and PPES cited in the text require amending to correlate with Table 17. Figures were incorrect in the original submission.	The ERG thanks the company for highlighting the factual errors. The proposed amendments have been made.

Issue 7 Amendment to text: Subgroup data by line of therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 28, Section 1.4.2 and Page 106, Section 4.6.1 The ERG report states: "The ERG does not consider the company to have provided suitable subgroup data by line of therapy for the comparison of cabozantinib with the axitinib, nivolumab and BSC in the NICE final scope for the potential second or third line positioning of cabozantinib. Page 147, Section 5.5.1, Table 78, D4c:Heterogenity	Please reconsider amending the text to accurately reflect that it was due to the lack of evidence in the published domain that a subgroup analysis by line of therapy could not be performed rather than the company not being able to provide a suitable/adequate analysis.	As explained in the manufacturer submission (Section 4.10.2 page 85) due to the lack of Kaplan Meier data across the network for all available comparators it was is not possible to conduct a robust NMA by prior therapy.	The ERG does not consider this to be a factual error.

The ERG report states: "Subgroup analysis was not adequately performed to estimate results for the second- and third-line subgroups in the treatment pathway separately"			

Issue 8 Amendment to text: Selection of OS parametric distribution

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 28, Section 1.4.2 (Economic) The ERG report states: "Applying the Weibull distribution would avoid the extended and potentially unrealistic tail in the resulting survival curve when using a log-logistic distribution" This is not supported by evidence.	Please reconsider amending the text specifically the statement around an "unrealistic" tail as this is not supported by evidence.	Ipsen is of the opinion that due to the lack of long term mortality evidence in RCC for patients using cabozantinib there is some uncertainty with regards to the most appropriate survival distribution. There is currently no evidence to suggest that cabozantinib patients would not follow a log-logistic distribution.	The ERG does not consider this to be a factual error.

Issue 9 Amendment to text: Sensitivity and scenario analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
The following areas do not reflect that fact that the required information was provided. Page 29, Section 1.4.2	Please reconsider amending the text to reflect that a range of scenario analyses to test the plausibility of different survival distributions were provided by Ipsen in their submission.	Ipsen provided scenario analyses which tested the plausibility of different survival distributions (Section 5.8.3 in company submission and Appendix16).	The ERG notes that each quote highlighted here by the company is in reference to the METEOR trial-based model analysis, for which no scenario analyses were presented in

(Economic) The ERG report states: “The lack of consideration of the Weibull was found to be a key source of uncertainty by the ERG” Page 119, Section 5.4.2.2 The ERG report states: “The company did not test the model using the Weibull distribution for each arm as an alternative” Page 120, Section 5.4.2.3 The ERG report states: “The company did not test using the log-logistic as an alternative for both arms or the closely second best fitting Gamma distribution for both arms” Page 147, Section 5.5.1, Table 78 and Page 150, Section 5.5.5 The ERG report states: “other plausible alternatives were not fully considered or tested as scenario analyses”			Section 5.8.3 nor Appendix 16. Therefore, the ERG does not consider this to be a factual inaccuracy.

Page 150, Section 5.5.5.1 The ERG report states: “The ERG would have preferred to see more justification as to why the log-normal was not chosen for both arms or at least tested as a scenario analysis” Page 163, Section 5.5.5.2 The ERG report states: “the company did not appear to fully consider the Weibull as the choice for each arm instead of the log-logistic”.			

Issue 10 Amendment to text: Resource use

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 29, Section 1.4.2 (Economic) The ERG report states: "For both models, the resource costs were considered to be unrealistic of UK clinical practice by the ERG based on clinical expert opinion."	Please reconsider amending the text specifically in regards to the use of the term "unrealistic".	Health resource utilisation in the company model was estimated by clinicians currently practicing in the UK. Ipsen is of the opinion that due to variability in clinical practice across the UK there might be differences in treatment pathways which might results in different health care resource utilisation estimates. The text should be amended to reflect this.	The ERG does not consider this to be a factual error.

Issue 11 Amendment to text: Utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 29, Section 1.4.2 (Economic) The ERG report states: "The ERG's clinical experts also believed that the utility values used were unrealistic and did not reflect the health states of patients in a real-world setting. When presented with alternative values from current NICE appraisals in renal cell carcinoma, the values used in TA333 were	Please reconsider amending the text specifically in regards to the use of the term "unrealistic". Proposed text is as follows: "The ERG's clinical experts also believed that the utility values used ~~were unrealistic and~~ did not reflect the health states of patients in a real-world setting. When presented with alternative values from current NICE appraisals in renal cell carcinoma, the values used in TA333 were considered a better reflection."	The utility estimates used in the company model were obtained directly from the METEOR trial and are representative of patients using cabozantinib. The utility values from TA333 are for the whole of AXIS population, including prior sunitinib and prior cytokine groups. The utility estimates for the prior cytokine group may differ from the prior VEGFR-group. Further the US tariffs were used to estimate these	The ERG does not consider this to be a factual error.

considered a better reflection."		utility values.	

Issue 12 Clarification: Sub group results

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 79 Section 4.3.5.1 The following results need to be clarified: '(median OS cabozantinib vs sunitinib 21.4 months vs 16.5 months, HR 0.66, 95% CI: 0.47 to 0.93; median OS cabozantinib vs pazopanib 22.0 months vs 17.5 months, HR 0.66, 95% CI: 0.42 to 1.04).	Text should be amended: "(median OS cabozantinib vs everolimus [prior sunitinib subgroup] 21.4 months vs. 16.5 months, HR 0.66, 95% CI: 0.47 to 0.93; median OS cabozantinib vs. everolimus [prior pazopanib subgroup] 22.0 months vs 17.5 months, HR 0.66, 95% CI: 0.42 to 1.04).	To clarify the results.	The ERG thanks the company for highlighting this issue and has amended the text as requested.

Issue 13 Factual inaccuracy: Pharmacological costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 139, Section 5.4.5.1. Table 69 The cost (per) pack list price for cabozantinib in Table 69 is incorrect	The cost (per) pack list price for cabozantinib needs to be corrected to £5,143.00.	To ensure the correct cost per pack for cabozantinib in the UK. Cabozantinib is only available in the UK in packs of 30 tablets with a list price of £5,143.00	The ERG thanks the company for highlighting this issue. The cost given in Table 69 was based on the values used in the model, realising that the cost per tablet is equivalent for the two values. To be in line with the quantities provided in the UK, we have amended the value in this

			table, as requested.

Issue 14 Factual inaccuracy: Dose intensity

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 139, Section 5.4.5.1. The ERG report states: "Patients in the everolimus arm of the model are assumed to receive 83.1% of the planned doses". This is incorrect	The figure in the ERG report of 83.1% is incorrect. Patients received 83.9% of the planned doses of everolimus in the METEOR trial.	To state the correct relative dose intensity for everolimus	The ERG thanks the company for highlighting this issue and has amended the text as requested.

Issue 15 Missing text

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 149, Section 5.5.4 'for nivolumab' appears to be missing from the following sentence "The modelled treatment regimen was 60mg orally once every day for cabozantinib, 10mg orally once every day for everolimus, 5mg orally twice per day for axitinib and 3mg/kg by intravenous infusion every two weeks"	The following amendment is proposed: "The modelled treatment regimen was 60mg orally once every day for cabozantinib, 10mg orally once every day for everolimus, 5mg orally twice per day for axitinib and 3mg/kg by intravenous infusion every two weeks <u>for nivolumab</u>"	To provide missing text	The ERG thanks the company for highlighting this issue and has amended the text as requested.

Issue 16 Missing text

Description of problem	Description of proposed amendment	Justification for amendment	ERG's response
Page 150, Section 5.5.4 Text is missing from the following sentence: "Time to discontinuation (TTD) data from the METEOR trial were used for time on treatment with cabozantinib and everolimus; TTD for nivolumab was obtained from[(3)]"	In order to provide the missing text the following amendment is proposed. "Time to discontinuation (TTD) data from the METEOR trial were used for time on treatment with cabozantinib and everolimus; TTD for nivolumab was obtained from Check Mate 025[(3)]"	To provide missing text	The ERG thanks the company for highlighting this issue and has amended the text as requested.