NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

The following documents are made available to the consultees and commentators:

1. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Ipsen
   - Kidney Cancer Support Network
   - Kidney Cancer UK

   Bristol-Myers Squibb

   The Department of Health – had no comments

   The Pfizer – had no comments

2. **Comments on the Appraisal Consultation Document from expert:**
   - Professor Robert Hawkins, Professor of Medical Oncology – Clinical expert, nominated by Ipsen

3. **Evidence review group critique of additional information submission by the company**
   - Critique
   - Addendum

Ipsen Ltd – Response to ACD consultation – 14 March 2017

ID931 – Cabozantinib for previously-treated advanced renal cell carcinoma

We appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for the above appraisal and to submit additional evidence to address the uncertainties and questions raised by the Appraisal Committee. We believe this additional evidence will reassure the Committee that cabozantinib is cost effective and should be recommended for use following the second Appraisal Committee meeting. In summary, we have:

- Simplified the Network Meta-Analysis (NMA)
- Incorporated the Committee's preferred assumptions and implemented these throughout our analyses
- Investigated different methods to estimate overall survival (OS)
- Reviewed our results in light of evidence on the natural course of the disease
- Provided additional evidence on OS from the METEOR trial
- Applied a revised patient access scheme (PAS)

Further details are provided below and in Sections 1 and 2. Details of factual inaccuracies and typographical errors are provided in Section 3.

Executive summary

The ACD states that the Committee's preferred analyses would exclude best supportive care (BSC), incorporate better fitting survival curves, assume axitinib and everolimus were equally effective, and remove subsequent treatments not available in England. The preferred analyses would also include updated costs (including nivolumab wastage and excluding GP costs) and utilities (age-adjusted and revised decrements for adverse events [AEs]). In presenting the revised results, the Committee also preferred an incremental cost effectiveness analysis, probabilistic cost effectiveness estimates, exploration of better survival for nivolumab and a breakdown of the survival benefits of cabozantinib before and after progression.

In the original Ipsen submission, the lognormal parametric function fitted the METEOR trial data the best and, therefore, was used in the base case analyses. As suggested by the Committee, we have explored more flexible survival functions proposed by Jansen[1]. We found that at least one of the fractional polynomial functions fit the trial data better. We revised the NMA assuming that axitinib and everolimus are of equal effectiveness, which allowed us to use a simpler evidence network. Using this new approach resulted in lower overall average survival with each treatment: to [redacted] months with cabozantinib; [redacted] with nivolumab; [redacted] with axitinib; and [redacted] for everolimus. Average progression-free survival (PFS) also reduced to [redacted] months for cabozantinib and [redacted] for both axitinib and everolimus. The PFS results for nivolumab were higher than expected and exceeded overall survival at an average of [redacted] months and a median of [redacted]. Given the clinical implausibility of this outcome, we conducted a scenario analysis using the lognormal model for PFS and this produced an average PFS of [redacted] months for nivolumab (median of [redacted] months). As requested by the Committee, we also undertook a scenario analysis applying the general population mortality rate to 50 per cent of nivolumab patients. This increased average survival with nivolumab to [redacted] months. Overall, the better fitting survival curve showed that cabozantinib provides an additional OS benefit of greater than three months compared with axitinib and everolimus, and approximately two or more months compared with nivolumab.

Compared with our original approach, the statistical fit to trial data of at least one of the more flexible survival functions was improved. However, the Committee also requested that modeled survival be considered in light of evidence on the natural course of the disease. We found that, beyond the trial period, this new approach predicts that only 4.9% of patients treated with

everolimus would still be alive at five years. This is inconsistent with a recently published study by Ruiz-Morales (2016) showing that approximately 10% of second-line RCC patients treated were still alive at five years. This cohort of over 3,000 patients previously treated with either pazopanib or sunitinib, were similar to the METEOR trial population and approximately 50 to 70 % received either everolimus or axitinib as second line therapy. Similarly, clinical experts consulted during the NICE appraisal of nivolumab predicted that 10 to 12 % of second line RCC patients would be alive after five years (section 4.14 of the nivolumab Final Appraisal Determination). As such, we explored an alternative approach to modelling survival using the better-fitting fractional polynomial curves for the trial period and the lognormal curves beyond the end of the trial. Visually, this improved the fit with the Ruiz-Morales Kaplan-Meier curve for second-line RCC patients, whilst retaining the better fitting curves for the trial period. This approach increased average survival to [redacted] months with cabozantinib, [redacted] months with nivolumab, and [redacted] months with axitinib/everolimus.

Overall, the different extrapolation methods produce average survival estimates ranging from [redacted] to [redacted] months for cabozantinib, [redacted] to [redacted] months for nivolumab and [redacted] to [redacted] months for axitinib/everolimus. The fractional polynomial approach appears not to be consistent with evidence on the natural course of RCC, producing low estimates of survival, whereas other methods have been explored producing higher estimates. The most clinically plausible estimates may lie somewhere in between these two extremes and so all approaches were included in the economic modelling to assess the impact on cost effectiveness.

We incorporated the revised survival curves into the model and updated the costs and utility estimates. We excluded GP costs pre-progression and included nivolumab wastage in our analysis. We assumed that the patients in the model receiving sorafenib as subsequent treatment would receive axitinib instead, with the associated costs and effectiveness. Utilities were age-adjusted as preferred by the Committee, and a scenario analysis undertaken using the largest utility decrement for adverse events found using a systematic literature review conducted for the original submission (not included in main analysis as little impact on the cost per QALY). In addition to these model revisions, we have agreed with the Department of Health a revised PAS with a [redacted] discount on the list price for cabozantinib.

Compared with axitinib and everolimus at current list prices, the cost per QALY based on the fractional polynomial curves were [redacted] and [redacted] respectively without the revised PAS for cabozantinib. We also calculated the cost per QALYs assuming a hypothetical range of discounts as a proxy for the confidential discounts available for axitinib and everolimus, ranging between [redacted] and [redacted]%. The with-PAS cost per QALYs for cabozantinib versus axitinib vary between £35,010 and £50,842, and for everolimus between £59,600 and £68,542. Using the fractional polynomial function for the trial period and the lognormal function beyond the trial, the with-PAS cost per QALYs for cabozantinib compared with axitinib range from £25,759 to £39,516, when comparator prices are between [redacted] and [redacted]% lower. Compared with everolimus, the cost per QALYs vary by discount level from £49,072 to £56,278 respectively. Compared with nivolumab, cabozantinib (with PAS) is cheaper and more effective (dominant) in the majority of scenarios, varying different survival functions, applying general population mortality to nivolumab patients and when the list price for nivolumab was reduced by [redacted] to [redacted]%

Finally, and importantly, an updated survival analysis of the METEOR trial became available during the ACD consultation period and we provide this more mature data to address the concerns of the Committee regarding the uncertainty of the survival estimates for cabozantinib. The updated METEOR trial data cut at 2nd October 2016 is based on an additional nine months of follow-up and an additional [redacted] events. These results show that at [redacted] months [redacted] per cent of cabozantinib patients are still alive, compared with [redacted] per cent on everolimus. Also of note is that the Kaplan-Meier curves based on this latest data-cut continue to separate rather than converge. We incorporated these data into the economic model as a scenario analysis. With the revised PAS, cabozantinib remained dominant over nivolumab in all scenarios. Compared with axitinib and everolimus, with the updated survival data the with-PAS cost per QALYs increased and ranged from £30,954 to £62,419 and £59,650 to £74,440 respectively, depending on the survival function and comparator list price discount.

Cabozantinib meets the end of life criteria in its comparison with axitinib and everolimus. Of these two comparators, everolimus is most likely to be used later in the RCC treatment pathway, as suggested by the clinical experts at the Committee meeting for this appraisal (see 4.2 of the ACD) and has only recently been approved by NICE (February 2017). Cabozantinib is a cost-effective use of NHS resources with most cost per QALYs versus axitinib and including

the revised PAS, at or below £50,000. Compared with nivolumab, cabozantinib is dominant and this finding remains consistent regardless of the approach used to estimate survival.

1. Revised Indirect Treatment Comparison (ITC) / Network meta-analysis (NMA)

Background to revised ITC

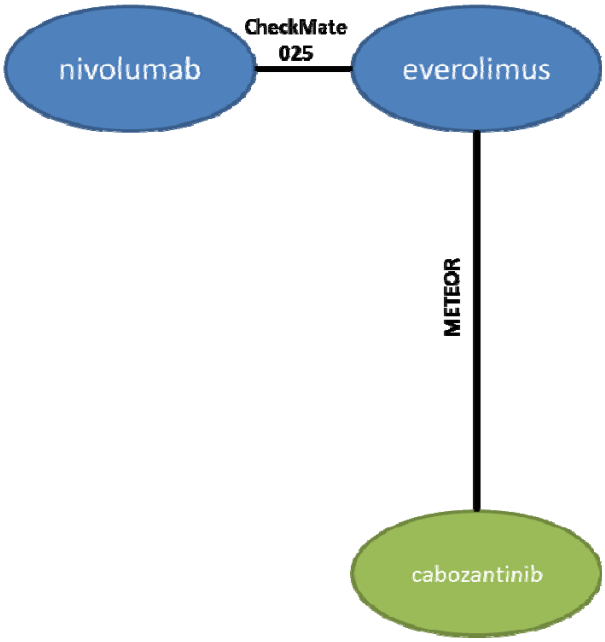
In the original company submission a NMA comparison of parametric survival curves described by Ouwens et al. (2010)[2] was used to compare cabozantinib with axitinib, nivolumab and BSC. METEOR study was used to inform cabozantinib versus everolimus comparison.

The ERG considered the results of the network meta-analysis to be unreliable due to differences in the trials in the evidence network and due to the distributions not fitting well enough to the original Kaplan-Meier (KM) data. Instead of the parametric survival curve NMA, the ERG estimated the relative effect of axitinib by assuming that it is as effective as everolimus. Despite this different method, the ERG's NMA results were largely similar to the original submission results. The Committee preferred the ERG's approach because it simplified the evidence network and reduced the potential bias associated with using TARGET in the network, but the Committee remained concerned about the methodology underpinning the network meta-analysis and the fits to the original KM data.

As a response to these concerns, we have revised the analyses informing the economic model:

- We assumed that axitinib is equivalent to everolimus in terms of OS and PFS. We have used this assumption for both endpoints, not only for OS, to avoid the network relying on the TARGET study. Figure 1 displays the new evidence network.
- For the cabozantinib versus nivolumab comparison we have used an alternative ITC method described by Jansen 2011[1]. The statistical fit to KM data in METEOR and CheckMate025 studies, as well as to real-world data, are examined and discussed.

Figure 1: New pair-wise ITC evidence network



ITC Methods

Based on the results of the proportional hazard (PH) test (see original submission section 4.10.3 for more details), instead of using a fixed HR-based ITC (such as the Bucher method) to compare the efficacy of cabozantinib and nivolumab, we have used an alternative method described by Jansen (2011)[1]. As an extension to the method laid out by Ouwens et al (2010)[2], Jansen proposed a NMA model using parametric survival functions which includes not only common survival distributions such as Weibull or Gompertz but more flexible fractional polynomials.

The first order fractional polynomial is written as:

$$\log(h_{jkt}) = \beta_{0jk} + \beta_{1jk}t^{P}, \text{ with } t^{0} = \log(t)$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\end{pmatrix} = \begin{cases} \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}, & \text{if } k = b, b = \{everolimus\} \\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} + \begin{pmatrix}d_{0Ak} - d_{0Ab}\\ d_{1Ak} - d_{1Ab}\end{pmatrix}, & \text{if } k \text{ different from } b \end{cases}$$

where h_{jkt} reflects the underlying hazard rate in trial j for intervention k, at time point t, and is now described as a function of time t with the power P chosen from the following set {-2, -1, -0.5, 0, 0.5, 1, 2, 3} with $t^0 = \log(t)$.The vector $\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}$ reflects the parameters β_{0jk} and β_{1jk} of the baseline treatment b, whereas d_{0Ak} corresponds to the treatment effect of k relative to overall reference treatment A and the vector $\begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\end{pmatrix}$ reflects the difference inβ_{0jk} and β_1 of the log hazard curve for treatment b relative to k. Note that if β_{1jk}≠ 0 and P = 1, a linear hazard function is obtained which corresponds to a Gompertz survival function, and if β_{1jk} ≠ 0 and P = 0, a Weibull hazard function is obtained. As such, the log-hazard function of the Weibull and Gompertz survival distributions are special cases of the fractional polynomial models.

For additional flexibility, this first-order fractional polynomial model can be generalized to a 2nd order fractional polynomial.

$$\log(h_{jkt}) = \begin{cases}\beta_{0jk} + \beta_{1jk}t^{p_1} + \beta_{1jk}t^{p_2}, & p_1 \neq p_2\\ \beta_{0jk} + \beta_{1jk}t^{p} + \beta_{1jk}t^{p}(\log t), & p_1 = p_2 = p\end{cases} \quad with\ t^0 = \log(t)$$

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\\ \beta_{2jk}\end{pmatrix} = \begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix}, & \text{if } k = b, b = \{everolimus\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\\ \mu_{2jb}\end{pmatrix} + \begin{pmatrix}d_{0Ak}-d_{0Ab}\\ d_{1Ak}-d_{1Ab}\\ d_{2Ak}-d_{2Ab}\end{pmatrix}, & \text{if } k \text{ different from } b\end{cases}$$

The order of the polynomial and the parameters p, or p1 and p2 can be determined via model selection criteria such as the Deviance information criterion (DIC).

Programming code

Appendix 1 includes the codes used in the programming of the fractional polynomial ITC.

ITC Results

In the original submission, we tested both random- and fixed-effects models. We found that fixed-effects models provided as good estimates as random-effects models, but were more stable and faster to run (see section 4.10.5 of the original submission). Given the limited time for this new analysis, we focused on testing fixed-effects models only, assuming that the finding holds with the Jansen 2011[1] method also. The model fit statistics to the previous models (re-run for narrower network to allow comparison) and the new models are provided in Table 1 and Table 2.

Table 1: Model fit statistics from the previous NMA method (parametric curves, Ouwens et al. 2010) – OS Dec 2015

Model fit statistics	Weibull		Gompertz		Log-logistic		Log-normal		Exponential	
	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS
Residual deviance (*Dbar*)	2137.6	3476.4	2159.9	3481.8	2133.7	3329.1	2131.2	3291.0	2181.0	3513.5
Effective number of parameters (*pD*)	7.2	7.6	7.4	7.6	7.7	7.8	7.7	7.8	4.1	4.1
Deviance information criteria (*DIC*)	2130.4	3468.8	2152.5	3474.2	2126.0	3321.3	2123.5	3283.2	2176.9	3509.4

Note: The previous NMA method was re-run as a pair-wise comparison of METEOR and CheckMate025 studies in order to compare the fit statistics.

Table 2: Model fit statistics from the new NMA method (fractional polynomials, Jansen 2011) – OS Dec 2015

Model fit statistics	First order with P=0		First order with P=1		First order with P=-1		Second order with P1=-1, P2=0		Second order with P1=-1, P2=-1	
	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS
Residual deviance (*Dbar*)	2137.6	3476.4	2159.9	3481.8	2127.8	3409.4	2137.8	3209.1	2137.2	3176.8
Effective number of parameters (*pD*)	7.2	7.6	7.4	7.6	7.8	8.1	11.4	11.8	11.1	11.6
Deviance information criteria (*DIC*)	2130.4	3468.8	2152.5	3474.2	2120.0	3401.3	2126.4	3197.3	2126.1	3165.2

Model fit statistics indicate that, for OS, first order fractional polynomial with P = -1 provided the best statistical fit for trial data. For PFS, second order polynomial with P1 = -1 and P2 = -1 provided the best fit. For OS, only the first order fractional polynomial with P = -1 improved the statistical fit compared with the best-fitting model originally submitted (log-normal). For PFS, second order polynomials with P1 = -1 and P2 = -1 or P1 = -1 and P2 = 0 improved the best-fitting model originally submitted (log-normal). First order fractional polynomial where P=0 is equivalent to Weibull, and where P=1 is equivalent to Gompertz. We tested that the results were, indeed, consistent with the results from the previous NMA method (see Table 1 and Table 2). Additional models were tested for statistical fit of the ITC development, and statistical fitness results for these further models are listed Table 47 in Appendix 2.

The fitted PFS and OS curves were superimposed on the extracted Kaplan-Meier data to observe the visual fit of extracted data versus modelled data (Figure 2 and Figure 3). Visually, the best fitting fractional polynomial models provided a good fit for PFS and OS data for cabozantinib, everolimus and nivolumab for the trial duration. For the best fitting model, PFS under cabozantinib was predicted to be always superior to everolimus, and superior to nivolumab prior to the end of the 22nd month. OS under cabozantinib is always superior to its comparators during the 3 years. The estimated hazard ratios for cabozantinib versus other treatments were more favorable to cabozantinib for OS. For PFS, the estimated hazard ratios became more favorable to nivolumab after 9 months. Further results from the ITC are shown in Appendix 2.

Figure 2. Fitted PFS based on the best fitting fixed-effects second order fractional polynomial model (p1= -1, P2=0) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.

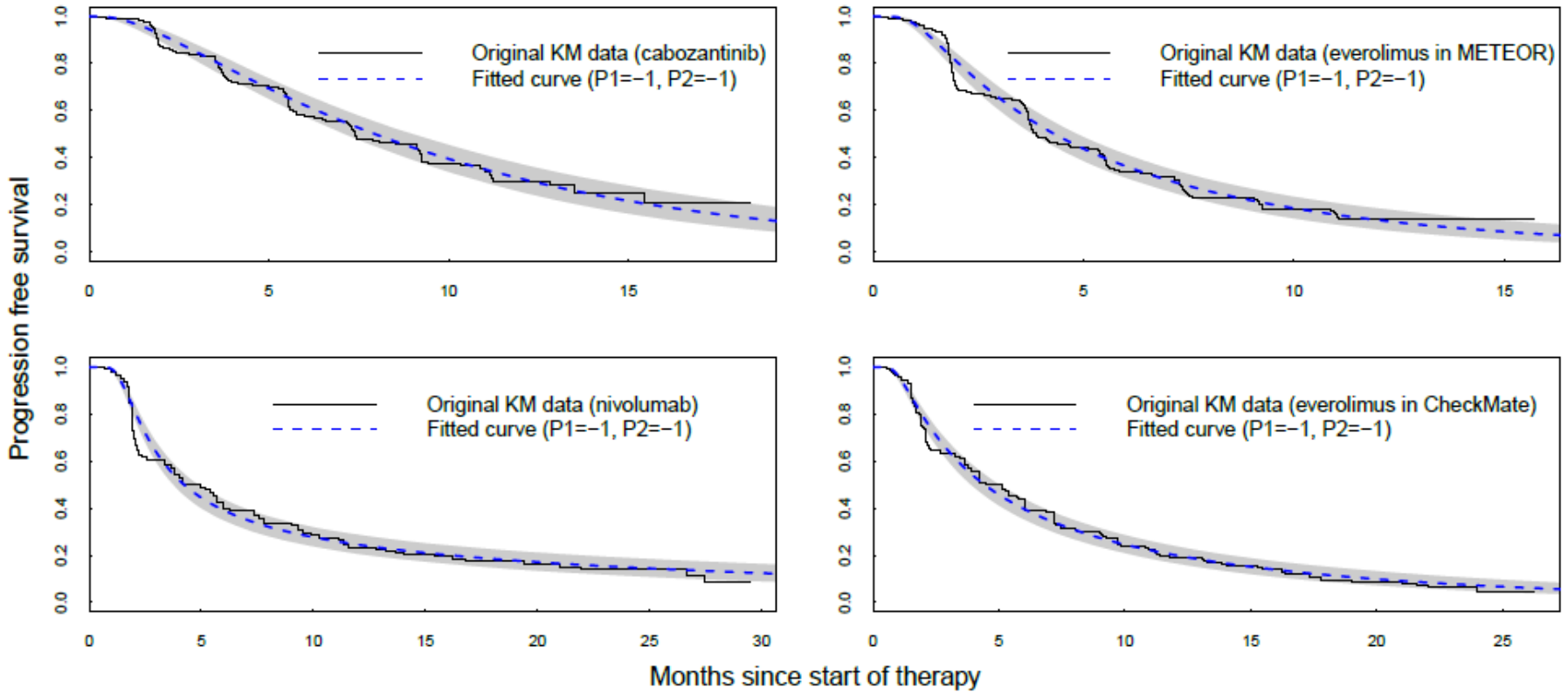
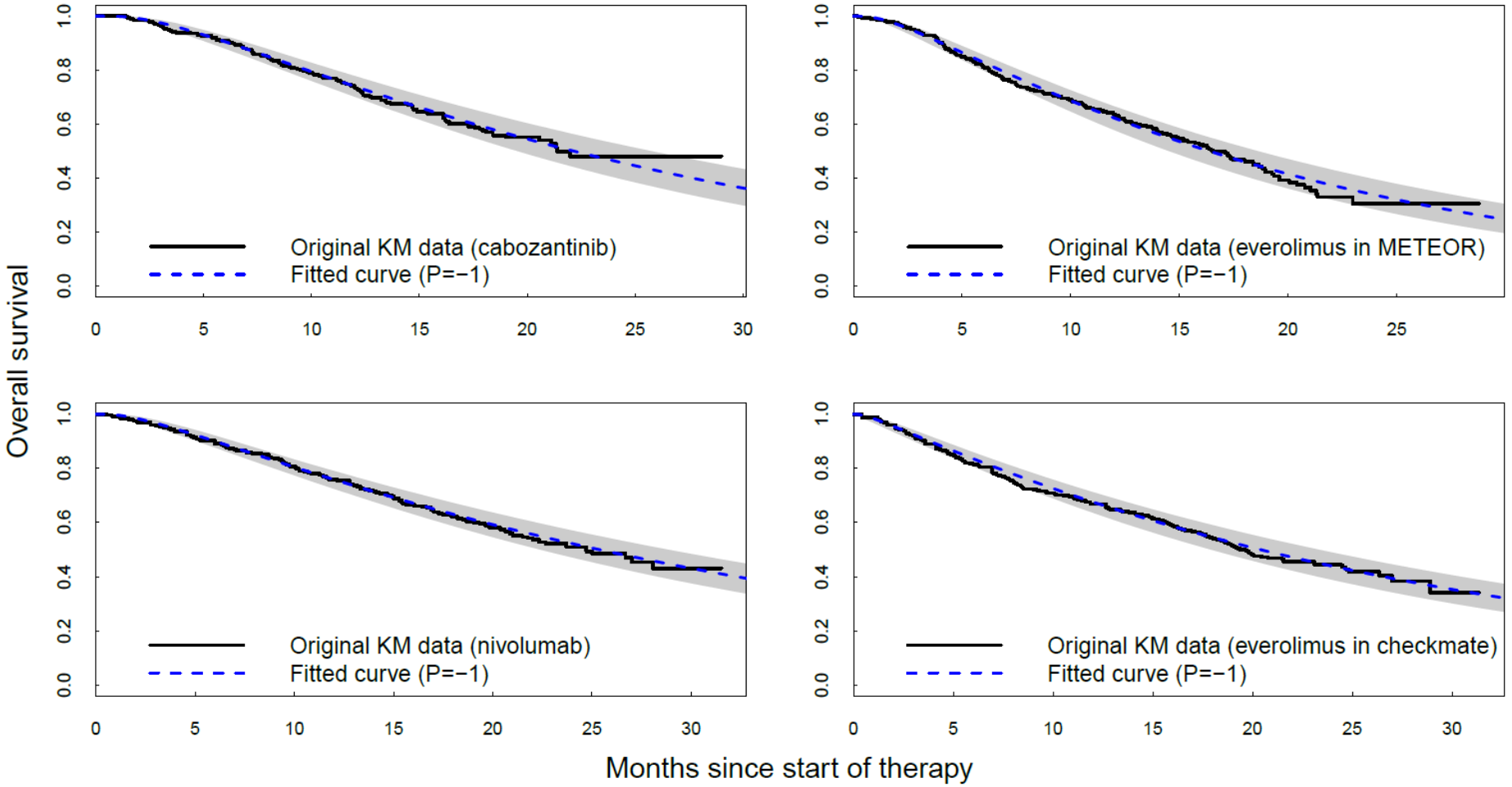


Figure 3. Fitted OS based on the best fitting fixed-effects first-order fractional polynomial model (p= -1) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.



Real-world evidence compared to fitted PFS and OS

The Appraisal Committee agreed that, when modelling overall survival, it was important to choose the parametric distribution based on reliable evidence on the natural history of the disease in current UK clinical practice, and invited submission of any such evidence, accounting for differences in population and disease characteristics that may increase or decrease the risk of death. A search of datasets was conducted, with a focus on survival information from UK patients only, or with significant UK patient cohorts. On analysis of these data it was found that they were not useful in the context we required because length of follow up was too short, patient numbers were too small, quality of the data presented made it impossible to extract the particular survival data we required, data was only available for the first line setting, outdated prior treatments were used, or survival data was not available for the whole population of the study (i.e. it had been separated into different prognostic criteria groups). We then broadened our search to global, relevant datasets, most of which had the same problems as outlined above. In total 14 publications were identified from both searches[3-16].The most appropriate dataset found was in the Ruiz-Morales et al 2016 publication[15]. This contained a large enough number of patients for robust analysis, a long enough period of survival data, and an analysis for survival in the whole second line population specifically. Although no UK patients were in the study it was conducted in countries with many similarities in respect to population baseline characteristics, socio-economic characteristics, and health systems

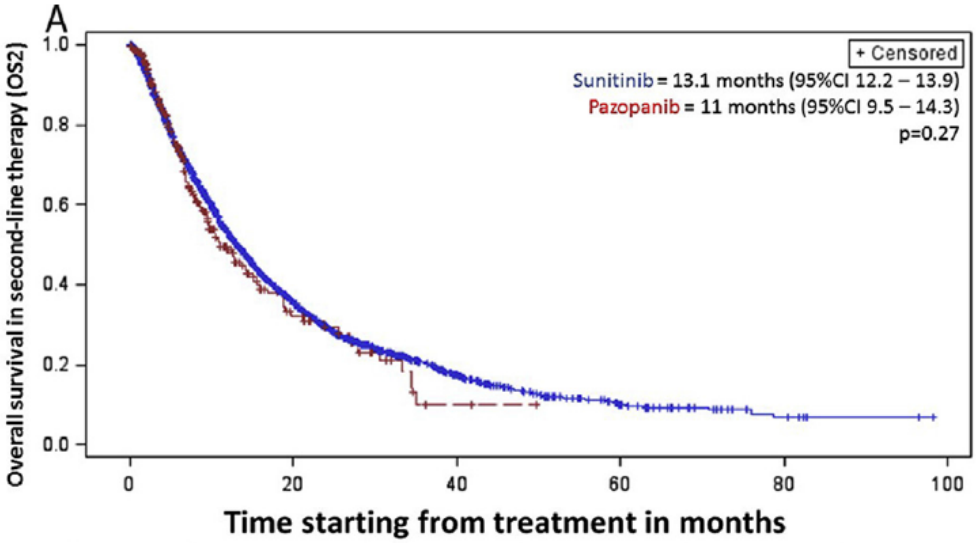
This study by Ruiz-Morales et al. 2016 obtained data from 7,438 patients from the International mRCC Database Consortium (IMDC) with metastatic RCC with either first-line sunitinib (n = 6,519) or pazopanib (n = 919)[15]. Of these two groups, 41 per cent of patients treated first-line with sunitinib (n=2,667) and 32 per cent of the first-line pazopanib group (n=290) also received second-line therapy. The study found that OS from start of second line therapy was 13.1 months and PFS was 3.7 months with prior sunitinib exposure (see

Figure **4**). At five years, the percentage of patients still alive was approximately 10 per cent. Whilst baseline characteristics were reported for the whole study cohort only, there were similarities with the METEOR trial in the proportion of females, nephrectomy and prior sunitinib use.

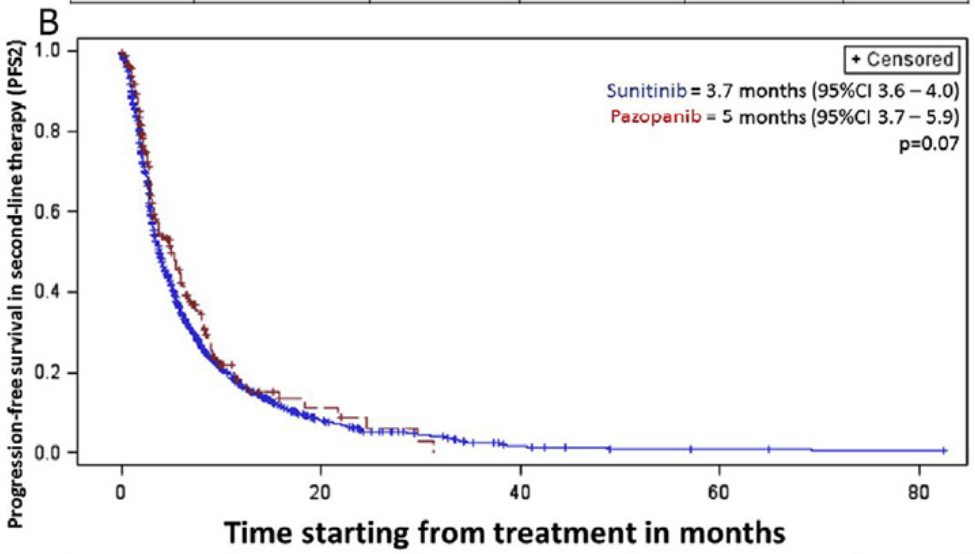
In Figure 4, it can be seen that, while the statistical fits were improved by employing the alternative ITC method described by Jansen (2011)[1] compared to those observed from the method described by Ouwens et al. (2010)[2], the proportion of patients that remain alive after 7-15 years may be too low with the best fitting fractional polynomial model when compared with the real-world evidence. The five-year survival rates for the fractional polynomial model were 4.9 per cent, whereas in the Ruiz-Morales study 10 per cent of second-line patients were alive at five years. Moreover the clinical experts predicted five-year survival rates of between 10 and 12 per cent in the nivolumab NICE appraisal (see section 4.14 of the FAD). For this reason, we have provided an option in the model for testing a scenario where the best fitting fractional polynomial model is used for the trial duration, and for extrapolation it is possible to either keep the fractional polynomial approach or to use the lognormal model fit after a specified time period (suggested 2.5 years, i.e., end of trial follow-up).

A further issue with the fractional polynomial model was observed for the best fitting PFS model (second order where P1=-1 and P2=-1) in the nivolumab comparison. The PFS and OS curves cross at around 5.5 years (see Figure 6). For this reason we provide a scenario that uses the lognormal model for PFS since this provides a good statistical fit and the long-term prediction is more aligned with clinical expectations (see Figure 7). Median and mean survival estimates (in months) are shown from Table 3 to Table 8.

Figure 4. OS and PFS data from publication by Ruis-Morales et al. 2016[15]



2633	620	146	37	7	0
289	27	2	0	0	0



2595	117	12	3	1
284	5	0	0	0

Fig. 3. (A) Overall survival in second-line therapy after either sunitinib (SU) or pazopanib (PZ). (B) Progression-free survival in second-line therapy after either SU or PZ.

Figure 5. Comparison of everolimus lognormal, Weibull and best fitting fractional polynomial models with second line OS, PFS from Ruiz-Morales et al. 2016[15]

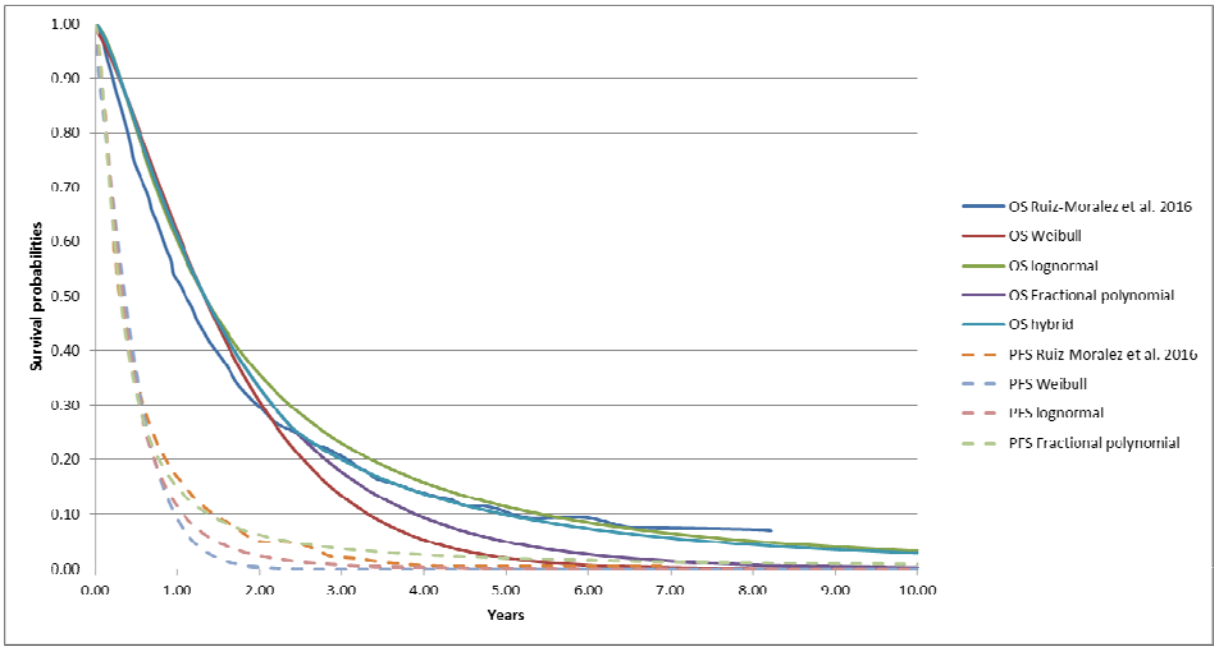


Figure 6. Nivolumab PFS and OS with best fitting fractional polynomial models

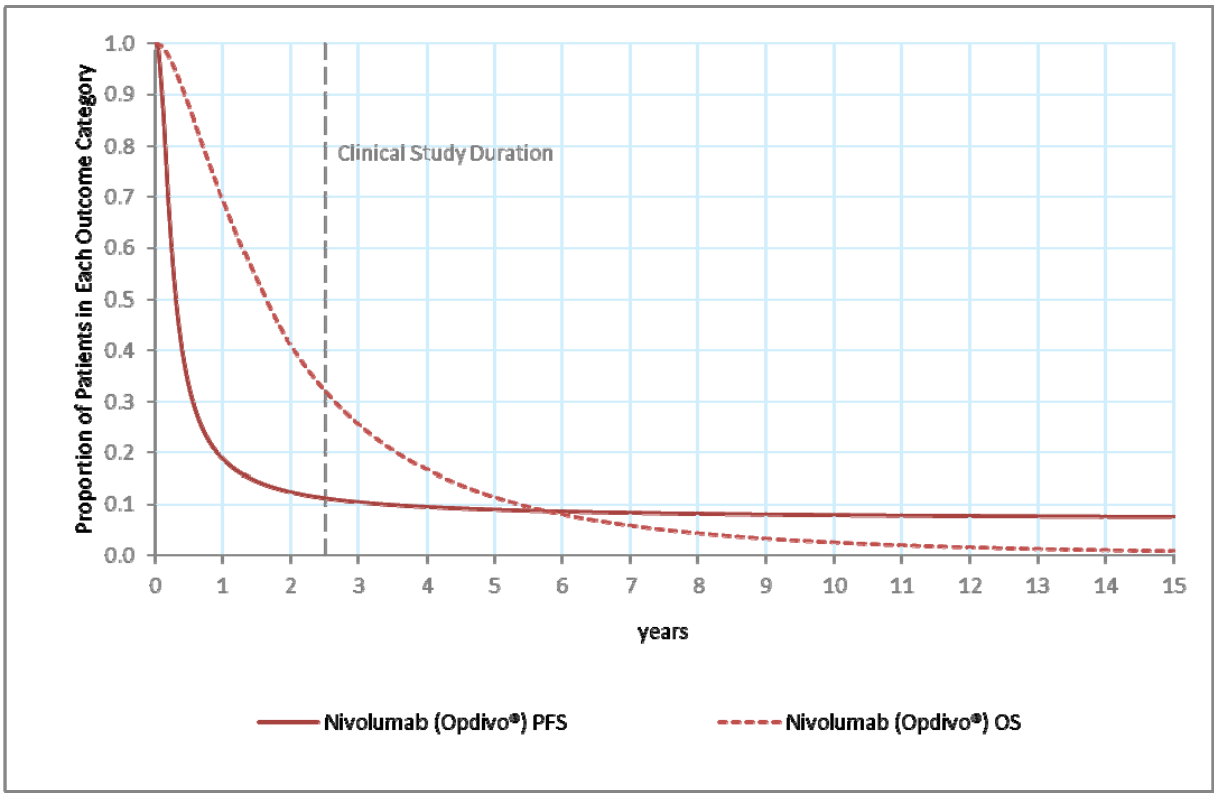


Figure 7. Nivolumab PFS with lognormal model and OS with best fitting fractional polynomial model

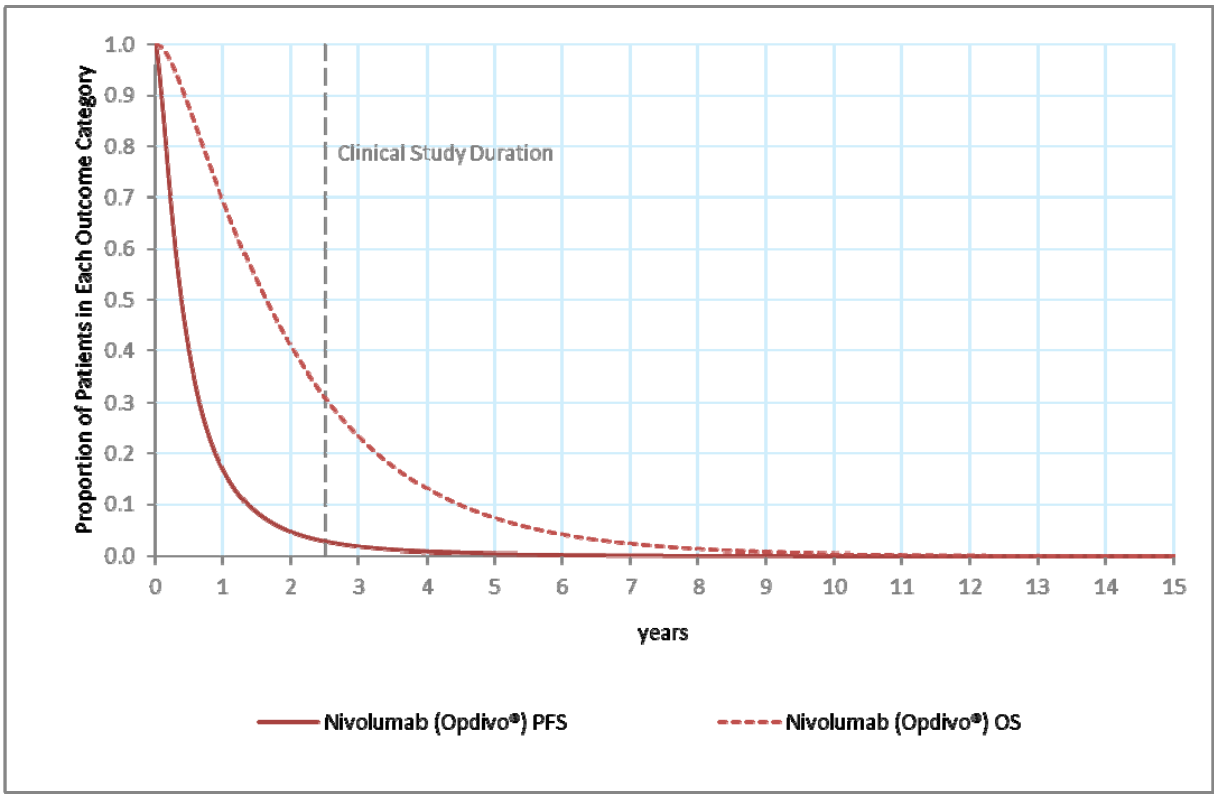


Figure 8. Nivolumab PFS with lognormal model, and OS with best fitting fractional polynomial model and applying general population mortality to 50% of nivolumab patients

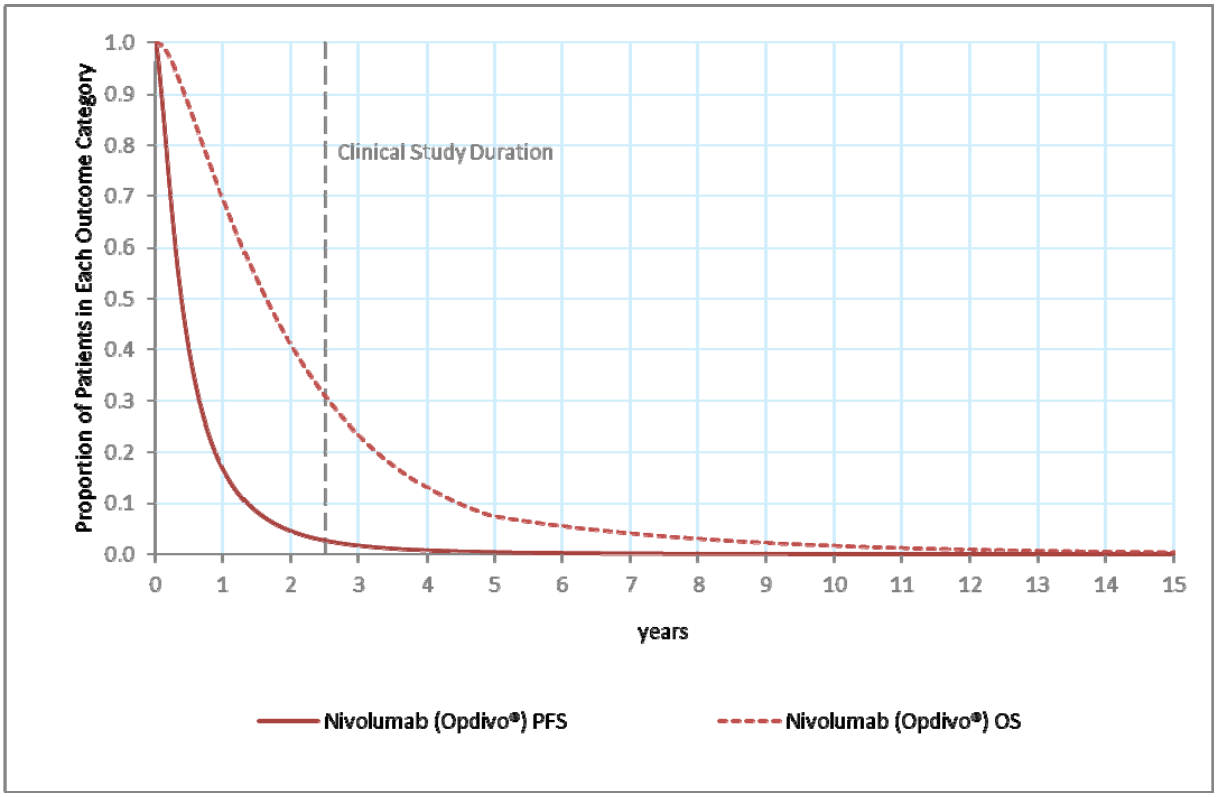


Table 3: Survival estimates (months): Lognormal model

Drug	Median OS	Mean OS	Median PFS	Mean PFS
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

Table 4: Survival estimates (months): Weibull model

Drug	Median OS	Mean OS	Median PFS	Mean PFS
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

Table 5: Survival estimates (months): Best fitting fractional polynomial model

Drug	Median OS	Mean OS	Median PFS	Mean PFS
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

Table 6: Survival estimates (months): Best fitting fractional polynomial model trial duration, lognormal extrapolation

Drug	Median OS	Mean OS	Median PFS	Mean PFS
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

Table 7: Survival estimates (months): Best fitting fractional polynomial model OS, lognormal PFS

Drug	Median OS	Mean OS	Median PFS	Mean PFS
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

Table 8: Survival estimates (months): Best fitting fractional polynomial model, lognormal PFS, 50% general mortality for nivolumab after 5 years

Drug	Median OS	Mean OS	Median PFS	Mean PFS
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

2. Revised cost-effectiveness model

Overview of adjustments made to the model

Model adjustment	Details
Comparators	BSC has been excluded as a comparator option. We have not removed the engines and formulas associated with BSC, merely the option to choose BSC and hence populate the results.
Relative efficacy comparison	• Axitinib is assumed to be as effective as everolimus in terms of OS and PFS. • Inclusion of best fitting fractional polynomials (FP) curves. • Parametric Survival curve method - updated: o We have re-run the originally submitted network meta-analysis including only METEOR and CheckMate025 studies. • Allow extrapolation with lognormal distribution after specified time period to provide a visual match to real-world data.
Mortality	The model allows general population mortality to be used for one or more treatments for those patients who survival 5 years or more. • A scenario analysis is run where 50% of those patients who are alive at 5 years and receiving nivolumab are assumed to have general population mortality. This assumption is in line with the nivolumab appraisal (Page 10 in Company response to the nivolumab ACD).
Utilities	• Apply age-adjustment to model utility values. o The formula applied was EQ-5D = 0.9454933 + 0.0256466*male - 0.0002213*age - 0.0000294*age^{2}[17] o We used the mean age and proportion male from the METEOR study (62.5 years and 75.1% male). • No changes to utility decrements as extreme values were shown to have limited impact on results. o For the original submission we conducted a systematic literature review on utilities, which included search terms for utility decrements (see Figure 5). o Limited information was identified. o Publication by Swinburn included utility and utility decrement information for selected adverse events[18]. We took the lowest adverse event utility decrement reported, which was 0.469 for palmar-plantar erythrodysesthesia (PPE) i.e. hand-foot syndrome. Compared to stable RCC without adverse events

	that had utility of 0.795, the difference was 0.3260. o We ran a model scenario where this value was applied to all adverse events and found that the ICER did not change significantly (see Table 30). o Based on the modest change in the results, utility decrement from METEOR is continued to be applied in the base case.
Subsequent treatments	• Exclusion of sorafenib from subsequent treatments. o We have assumed that patients receive axitinib instead of sorafenib. o It is assumed that sorafenib has approximately equal efficacy to axitinib (AXIS OS HR 0.969, 95% CI 0.800-1.174). Axitinib, in turn, is assumed to have equal efficacy to everolimus. o Hence, only the cost of subsequent treatments is modified by this change.
Reporting of results	• QALY and LY results are provided for pre- and post-disease progression • - Fully incremental analysis of the cost effectiveness results are presented • - Probabilistic sensitivity analyses are also presented
Cost and resource use	• Inclusion of nivolumab wastage in the base case. • Assume patients are monitored by consultant oncologists once every 4 weeks. o Previously we assumed that the patients have 1 GP visit every 4 weeks and 1 consultant oncologist visit every 6 weeks. o Instead, we now assume that patients are monitored by consultant oncologists once every 4 weeks and do not visit their GP.
Final OS data cut METEOR (October 2016)	See Appendix 1 – programming code and Appendix 3 CE model

Results

Results are provided for:

1. Lognormal (as in the original submission) but in a reduced network of METEOR and CheckMate025 studies only, and assuming equal efficacy for axitinib and everolimus.

2. Best fitting fractional polynomial models: OS P=-1 and PFS P1=-1, P2=-1.

Additionally, results are provided for scenario analyses:

a) Best fitting fractional polynomial models for trial duration and lognormal for extrapolation – "Hybrid".

b) Best fitting fractional polynomial model for OS, but using lognormal model for PFS.

c) Best fitting fractional polynomial models for OS, lognormal for PFS, but applying general mortality to 50% of those patients who are alive at 5 years and receiving nivolumab.

Results with list prices for the survival assumptions described above are provided from Table 9 to Table 13. Table 14 to Table 16 provide the results for drug prices including cabozantinib PAS of [redacted] discount and [redacted], [redacted] and [redacted] discounts for comparators using the lognormal models (item 1 on the above list). The PAS discount scenarios for best fitting fractional polynomial model are provided from Table 17 to Table 19 (item 2 on the above list).

Table 9: Lognormal model; pair-wise and incremental analysis of cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Analysis							**ICER vs baseline**
Everolimus	[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]

Key:ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 10: Fractional Polynomial model; pair-wise and incremental analysis of cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Analysis							**ICER vs baseline**
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]
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 11: Hybrid model; pair-wise and incremental analysis of cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Analysis							**ICER vs baseline**
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]
Key:ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 12: FP OS & Lognormal PFS; pair-wise and incremental analysis of cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Analysis							**ICER vs baseline**
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]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 13: Nivo 50% general pop mortality; pair-wise and incremental analysis of cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental Analysis							**ICER vs baseline**
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]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 14: Lognormal model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,740
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,474
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	38,740
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 15: Lognormal model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,031
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,177
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,031
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 16: Lognormal model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,323
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57,880
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,323
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 17: Fractional polynomial model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,010
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	59,600
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	35,010
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 18: Fractional polynomial model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,926
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	64,071
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	42,926
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 19: Fractional polynomial model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,842
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,542
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,842
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 20: Hybrid model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,759
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,072
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	25,759
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 21: Hybrid model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,638
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52,675
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	32,638
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 22: Hybrid model; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,516
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,278
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,516
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 23: FP OS & Lognormal PFS; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,394
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,198
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,394
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 24: FP OS & Lognormal PFS; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,621
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,563
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,621
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 25: FP OS & Lognormal PFS; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,848
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66,928
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,848
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 26: Nivolumab 50% general pop mortality; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,394
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	58,198
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,394
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year

Table 27: Nivolumab 50% general pop mortality; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,621
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,563
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50,621
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 28: Nivolumab 50% general pop mortality; pair-wise and incremental analysis of cabozantinib versus comparator - with cabozantinib PAS ([redacted]) & [redacted] discount comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,848
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	66,928
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Incremental Analysis							**ICER vs baseline**
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	56,848
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year							

Table 29: QALY and LY accrual by health state (best fitting fractional polynomial model)

Drug	QALY			LY		
	Pre-progression	Post-progression	Total	Pre-progression	Post-progression	Total
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 30: Comparison of (without PAS) model results with METEOR utility decrement and extreme utility decrement (Best fitting fractional polynomial model)

Drug	Total costs	Total QALYs	Total life-years	Incremental versus cabozantinib			ICER versus cabozantinib (QALYs)
				Costs	QALYs	Life years	
METEOR study utility decrement (							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPE utility decrement							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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							

Sensitivity analyses

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 of the original submission. Uncertainties for distributions derived from the ITC were tested by drawing random samplings from the multivariate-normal distribution derived from the variance-covariance matrix.

The mean probabilistic results are reported in Table 31 for list prices. Results for PAS scenarios are shown from Table 32 to Table 34. The scatterplots and cost acceptability curves are provided in Appendix 6.

Table 31: Fractional Polynomial model PSA; without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 32: Fractional Polynomial model PSA; with [redacted] PAS cabozantinib, [redacted] PAS comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	34,822
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	57,325
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 33: Fractional Polynomial model; with [redacted] PAS cabozantinib, [redacted] PAS comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,101
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	63,838
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 34: Fractional Polynomial model; with [redacted] PAS cabozantinib, [redacted] PAS comparators

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	51,766
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,551
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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 of the original submission.

Figures 9 – 11 show tornado diagrams depicting the top 10 most influential model parameters using list prices and best fitting fractional polynomial models. The results with the PAS scenarios are shown from Figure 12 to Figure 20. Results are robust to isolated parameter changes to the vast majority of variables in the model.

Figure 9: [redacted]

Figure 10: [redacted]

Figure 11: [redacted]

Figure 12: [redacted]

Figure 13: [redacted]

Figure 14: [redacted]

Figure 15: [redacted]

Figure 16: [redacted]

Figure 17: [redacted]

Figure 18: [redacted]

Figure 19: [redacted]

Figure 20: [redacted]

Scenario analysis (SA)

The scenarios tested are shown from Table 35 to Table 46.

Table 35: Scenario analyses fractional polynomial model cabozantinib versus axitinib without PAS

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
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=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PFS=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	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	During PFS patients managed by GP	[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]
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 36: Scenario analyses fractional polynomial model cabozantinib versus everolimus without PAS

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
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=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PFS=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	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	During PFS patients managed by GP	[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]
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 37: Scenario analyses fractional polynomial model cabozantinib versus nivolumab without PAS

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
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=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	PFS=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	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	During PFS patients managed by GP	[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]
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38: Scenario analyses fractional polynomial model cabozantinib versus axitinib with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	35,010
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	36,110
	0%	[redacted]	[redacted]	[redacted]	[redacted]	33,411
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	34,994
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	35,009
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	44,248
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	46,696
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	42,734
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	44,394
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	47,758
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	29,503
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	23,909
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	38,970
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	25,166
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	35,904
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	35,028
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	34,478
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	35,010
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	36,857
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	35,014
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	37,717
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	38,329
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	36,121
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	35,266

Table 39: Scenario analyses fractional polynomial model cabozantinib versus everolimus with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	59,600
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	61,369
	0%	[redacted]	[redacted]	[redacted]	[redacted]	57,068
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	59,601
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	59,600
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	58,397
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	59,200
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	58,205
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	58,198
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	59,028
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	54,818
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	48,861
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	62,582
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	50,562
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	61,127
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	60,610
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	58,691
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	59,600
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	61,452
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	59,604
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	69,276
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	64,477
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	60,305
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	59,857

Table 40: Scenario analyses fractional polynomial model cabozantinib versus nivolumab with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	(105,008)
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	(111,507)
	0%	[redacted]	[redacted]	[redacted]	[redacted]	(95,795)
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	(105,234)
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	(105,024)
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	(95,449)
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	(98,604)
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	(94,829)
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	(94,996)
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	(97,388)
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	(94,817)
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	(121,168)
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	(107,422)
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	(99,386)
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	(111,907)
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	(113,507)
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	(103,171)
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	(79,901)
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	(100,421)
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	(105,014)
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	(95,209)
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	(94,923)
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	(104,000)
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	(104,731)

Table 41: Scenario analyses fractional polynomial model cabozantinib versus axitinib with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	42,926
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	44,364
	0%	[redacted]	[redacted]	[redacted]	[redacted]	40,848
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	42,916
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	42,925
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	50,542
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	52,805
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	49,207
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	50,621
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	53,673
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	37,365
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	31,703
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	46,933
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	32,969
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	44,023
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	42,947
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	42,273
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	42,926
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	44,773
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	42,930
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	45,469
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	45,994
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	43,469
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	43,182

Table 42: Scenario analyses fractional polynomial model cabozantinib versus everolimus with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	64,071
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	66,091
	0%	[redacted]	[redacted]	[redacted]	[redacted]	61,182
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	64,076
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	64,071
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	62,776
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	63,641
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	62,571
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	62,563
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	63,456
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	59,126
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	53,152
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	67,251
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	54,795
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	65,713
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	65,158
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	63,094
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	64,071
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	65,924
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	64,075
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	72,606
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	68,492
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	64,413
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	64,328

Table 43: Scenario analyses fractional polynomial model cabozantinib versus nivolumab with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	(61,603)
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	(65,730)
	0%	[redacted]	[redacted]	[redacted]	[redacted]	(55,751)
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	(61,769)
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	(61,614)
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	(55,964)
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	(57,825)
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	(55,598)
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	(55,697)
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	(57,107)
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	(54,713)
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	(79,542)
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	(62,276)
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	(60,242)
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	(65,650)
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	(66,589)
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	(60,525)
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	(40,083)
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	(57,015)
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	(61,608)
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	(52,773)
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	(52,527)
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	(61,099)
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	(61,326)

Table 44: Scenario analyses fractional polynomial model cabozantinib versus axitinib with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	50,842
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	52,618
	0%	[redacted]	[redacted]	[redacted]	[redacted]	48,285
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	50,837
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	50,841
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	56,835
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	58,915
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	55,680
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	56,848
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	59,587
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	45,227
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	39,497
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	54,895
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	40,771
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	52,141
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	50,867
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	50,069
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	50,842
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	52,688
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	50,846
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	53,221
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	53,658
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	50,816
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	51,098

Table 45: Scenario analyses fractional polynomial model cabozantinib versus everolimus with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	68,542
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	70,813
	0%	[redacted]	[redacted]	[redacted]	[redacted]	65,297
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	68,551
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	68,543
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	67,156
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	68,082
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	66,936
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	66,928
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	67,884
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	63,433
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	57,444
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	71,920
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	59,027
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	70,299
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	69,705
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	67,497
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	68,542
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	70,395
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	68,547
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	75,936
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	72,508
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	68,522
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	68,800

Table 46: Scenario analyses fractional polynomial model cabozantinib versus nivolumab with PAS (cabozantinib [redacted], comparator [redacted])

		Total costs		Total QALYs		ICER
		Cabo.	Comparator	Cabo.	Comparator	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	(18,197)
Discount: 3.5%	6%	[redacted]	[redacted]	[redacted]	[redacted]	(19,952)
	0%	[redacted]	[redacted]	[redacted]	[redacted]	(15,707)
Time horizon: 30years	15 years	[redacted]	[redacted]	[redacted]	[redacted]	(18,303)
	20 years	[redacted]	[redacted]	[redacted]	[redacted]	(18,204)
PFS curves	PFS=exponential	[redacted]	[redacted]	[redacted]	[redacted]	(16,478)
	PFS=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	(17,045)
	PFS=loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	(16,367)
	PFS=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	(16,397)
	PFS=weibull	[redacted]	[redacted]	[redacted]	[redacted]	(16,827)
Time on treatment curves	TTD=exponential	[redacted]	[redacted]	[redacted]	[redacted]	(14,609)
	TTD=gompertz	[redacted]	[redacted]	[redacted]	[redacted]	(37,915)
	TTD=lognormal	[redacted]	[redacted]	[redacted]	[redacted]	(17,131)
	TTD=weibull	[redacted]	[redacted]	[redacted]	[redacted]	(21,098)
Utility	Decrement due to progression (average decrement)	[redacted]	[redacted]	[redacted]	[redacted]	(19,393)
	Decrement due to AEs (worst scenario: Swinburn)	[redacted]	[redacted]	[redacted]	[redacted]	(19,670)
	Exclude the age-adjusted utility	[redacted]	[redacted]	[redacted]	[redacted]	(17,879)
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	(264)
	Disease manament cost (Nivolumab TA)	[redacted]	[redacted]	[redacted]	[redacted]	(13,610)
	During PFS patients managed by GP	[redacted]	[redacted]	[redacted]	[redacted]	(18,203)
	Subsequent treatment cost (UK clinicians' opinion)	[redacted]	[redacted]	[redacted]	[redacted]	(10,337)
	Subsequent treatment cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	(10,132)
	Sorafenib included in the subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]	(18,199)
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	(17,920)

3.Factual inaccuracies

Section, page	Factual inaccuracy	Correction
Section 1.1, page 3 Recommendations	Indication needs to be amended to include the word 'prior'	The text should be amended as follows: 'Cabozantinib is indicated for the treatment of advanced renal cell carcinoma in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.'
Section 2, page 4, Price	The list of available doses is incorrect.The correct doses are 20 mg, 40 mg and 60 mg.	The text should be amended as follows: 'The list price is £5,143.00 per 30-tab pack applicable to all dosages (20 mg, ~~30~~ 40 mg and 60 mg)'.
Section 4.6, page 7, Clinical effectiveness	Typographical error	The text should be amended as follows: 'The intention-to-treat analysis: all patients randomised at baseline (n= 658)'.
Section 4.18, page 15, Cost and effects of subsequent treatments	Typographical error	The text should be amended as follows: 'The company included the cost of sorafenib as a subsequent treatment in the model, whereas the ERG excluded it because sorafenib ~~it~~ is not available in the NHS'.
Summary of appraisal Committee's key conclusions, page 24, Availability, nature and quality of evidence	Typographical error	The text should be amended as follows: 'The intention-to-treat analysis: all patients randomised at baseline (n= 658)'.
Summary of appraisal Committee's key conclusions, page 28, Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	Typographical error	The text should be amended as follows: 'The Committee did not identify a benefit to utility that was not otherwise ~~accounting~~ accounted for in the modelling'.

References

1. Jansen JP.Network meta-analysis of survival data for fractional polynomials. BMC Medical Research Metholodolofy 2011. 11: 61

2. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods 2010; 1: 258-71.

3. Chan K, Chow S, Galvis G, et al. Sequential everolimus in metastatic Renal Cell Carcinoma (mRCC): A Single-institution experience in clinical practice. European Supplements 2013; 123-180

4. Elson PJ, Witte RS, Trump DL. Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Research 1988; 48: 7310-7313

5. Gore ME, Szcylik C, Porta C, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. British Journal of Cancer 2015; 113: 12-19

6. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study.Lancet Oncology 2013; 14:141-148

7. Heng DY, Signorovitch J, Swallow E, et al. Comparative effectiveness of second-line targeted therapies for metastatic renal cell carcinoma: A systematic review and meta-analysis of real-world observational studies. PLoS ONE 2014 doi: 10:1371/jounal.pone.0114264

8. Iacovelli R, Carteni G, Sternberg CN, et al. Clinical outcomes in patients receiving three lines of targeted therapy for metastatic renal cell carcinoma: Results from a large patient cohort. European Journal of Cancer 2013; 49: 2134-2142

9. National Cancer Intelligence Network. Kidney Cancer: Survival Report. Urological Cancers SSCRG.

10. Manola J, Royston p, Elson P, et al. Prognostic model for survival in patients with metastatic renal cell carcinoma: Results from the International Kidney Cancer Working Group. Clinical Cancer Research 2011: 17 (16): 5443-5450

11. Motzer R, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. Journal of Clinical Oncology 1999; 17 (8): 2530-2540

12. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. Journal of Clinical Oncology 2002; 20 (1): 289-296

13. Motzer RJ, Bacik B, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. Journal of Clinical Oncology 2004; 22: 454-463

14. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology 2014. Doi 10.1200/JCO.201354.6911

15. Ruiz-Morales et al. 2016. First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur J Cancer. 2016 Sep;65:102-108

16. Wagstaff J, Jones R, Hawkins R, et al. Treatment patterns and clinical outcomes in patients with renal cell carcinoma in the UK: insights from the RECORD registry. Annals of Oncology 2016; 27: 159-165

17. Ara R, Brazier JE. Populating an economic model with health state utility values: moving towards better practice. Value in Health 2010. 13:5

18. Swinburn P, Lloyd A, Nathan P, et al Elicitation of health state utilities in metastatic renal cell carcinoma, Current Medical Research and Opinion 2010; 26 (5): 1091-1096.

4. Appendices

Appendix 1 – programming code

```
#########################################################################
######### Bayesian network meta-analysisvia FP
#########################################################################
library(R2WinBUGS)
library(ggplot2)
library(survival)

#########################################################################
###       PREPARING INPUT DATA AND INITIAL VALUES FOR WINBUGS
#########################################################################
ns_convert <- function(input, t, b, s) {
                input$time <- c(input[-1,"V1"], 1000)
                input$dt <- input$time - c(0, input[-nrow(input),"time"])
                input$n <- input$V2# number of patients at risk in the interval
                input$r <- input$V3# number of deaths in the interval
                input$t <- t # treatment
                input$b <- b # baseline treatment
                input$s <- s # study
                return(input[-nrow(input),c("time", "dt", "n", "r", "t", "b", "s")])
}


winbugsi_new <- rbind(ns_convert(read.table("OS2_cabo.txt", header=T), 2, 1, 1),
ns_convert(read.table("OS2_ever.txt", header=T), 1, 1, 1),
ns_convert(read.table("checkmate_OS_nivolumab_KMdata.txt", header=T), 3, 1, 2),
ns_convert(read.table("checkmate_OS_everolimus_KMdata.txt", header=T), 1, 1, 2))

winbugsi <- winbugsi_new[winbugsi_new$n > 0,]

#################################################

##### Fixed effects model

#################################################
```

```
##### Second order fractional polynomial

#######################################################

bugs_inits_fixed_2nd <- list(

                list("mu"=matrix(-c(1,1,.1,.1,.1,.1),2,3),                "d"=matrix(c(NA,    2,    -
2,NA,.1, -.1,NA,.1, .1),3,3)),

                list("mu"=matrix(-c(1,1,.1,.1,.1,.1),2,3),                "d"=matrix(c(NA,-2,  2,NA,
-.1, .1,NA,.1, -.1),3,3)),

                list("mu"=matrix( c(-1,-1,-.1,-.1,.1,.1),2,3),    "d"=matrix(c(NA,  2,  2,NA,  .1,
.1,NA,.1, -.1 ),3,3))

          )

####### P1 = -1, P2 = 0

bugs_input_2nd_Pm10 <- list("N"=nrow(winbugsi), "NS"=2, "NT"=3, "mean"=c(0,0,0),
"prec2"=diag(rep(0.0001,3)), "R"=diag(rep(0.01,3)), "time"=winbugsi[,1], "dt"=winbugsi[,2],
"n"=winbugsi[,3], "r"=winbugsi[,4], "t"=winbugsi[,5], "b"=winbugsi[,6], "s"=winbugsi[,7],
"ts"=c(2,3), "bs"=c(1,1), P1=-1, P2=0)

 bugs_input_fixed_2nd_Pm10 <- bugs_input_2nd_Pm10

bugs_input_fixed_2nd_Pm10$R <- NULL


FP.fixed.2nd.Pm10 <- bugs(data = bugs_input_fixed_2nd_Pm10, inits=bugs_inits_fixed_2nd,
"BUGS                run",                model.file="bugs_model_FP_fixed_2nd.txt",
bugs.directory="C:/Users/shuaifu/Documents/WinBUGS14",    parameters=c("mu",    "d"),
n.chains=3, n.iter=500000, n.burnin=250000, n.thin=10, debug=F)

#######################################################

##### First order fractional polynomial

#####################################################

bugs_inits_fixed_1st <- list(

                list("mu"=matrix(-c(1,1,.1,.1),2,2),              "d"=matrix(c(NA,   2,   -2,NA,.1,   -
.1),3,2)),

                list("mu"=matrix(-c(1,1,.1,.1),2,2),              "d"=matrix(c(NA,-2,    2,NA,    -.1,
.1),3,2)),

                list("mu"=matrix( c(-1,-1,-.1,-.1),2,2),  "d"=matrix(c(NA, 2, 2,NA, .1, .1 ),3,2))

          )
```

```
####### P = 1

#inputs:

bugs_input_1st_P1 <- list("N"=nrow(winbugsi), "NS"=2, "NT"=3, "mean"=c(0,0), "prec2"=diag(rep(0.0001,2)), "R"=diag(rep(0.01,2)), "time"=winbugsi[,1], "dt"=winbugsi[,2], "n"=winbugsi[,3], "r"=winbugsi[,4], "t"=winbugsi[,5], "b"=winbugsi[,6], "s"=winbugsi[,7], "ts"=c(2,3), "bs"=c(1,1), P1=1)

 bugs_input_fixed_1st_P1 <- bugs_input_1st_P1

bugs_input_fixed_1st_P1$R <- NULL


FP.fixed.1st.P1 <- bugs(data = bugs_input_fixed_1st_P1, inits=bugs_inits_fixed_1st, "BUGS run", model.file="bugs_model_FP_fixed_1st.txt", bugs.directory="C:/Users/shuaifu/Documents/WinBUGS14", parameters=c("mu", "d"), n.chains=3, n.iter=500000, n.burnin=250000, n.thin=10, debug=F)

#############################################################################
###      WINBUGS MODELS
#############################################################################
#####################################################

##### First order fractional polynomial

 ##################################################

#Winbugs code for second order fractional polynomial

#random effects network meta-analysis model

Model{

for (i in 1:N){ # N number of datapoints in dataset

# time is expressed in months and transformed

#according powers of fractional polynomial P1 and P2

time_transf1[i]<-(equals(P1,0)*log(time[i]) + (1-equals(P1,0))*pow(time[i],P1))

# likelihood

# hazard over interval [t,t+dt] expressed as deaths per person-month

# r is deaths in interval, n is number at risk, h is hazard

r[i]~ dbin(p[i],n[i])
```

```
p[i]<-1-exp(-h[i]*dt[i]) # cumulative hazard over interval [t,t+dt] expressed as deaths per person-month

# random effects model

# loop over datapoints

# s refers to study, t is intervention t, b is comparator

log(h[i])<-Beta[i,1]+ Beta[i,2]*time_transf1[i]

Beta[i,1]<-mu[s[i],1]+delta[s[i],1]*(1-equals(t[i],b[i]))

Beta[i,2]<-mu[s[i],2]+delta[s[i],2]*(1-equals(t[i],b[i]))

}

# loop over studies

# NS is number of studies

# ts is intervention k, bs is comparator

for(m in 1:NS){

#delta[m,1:3]~dmnorm(md[m,1:3],omega[1:3,1:3])

delta[m,1]<-md[m,1]

delta[m,2]<-md[m,2]

md[m,1]<-d[ts[m],1]-d[bs[m],1]

md[m,2]<-d[ts[m],2]-d[bs[m],2]

}

# priors

# NT is number of treatments

d[1,1]<-0

d[1,2]<-0

for(j in 2:NT){

d[j,1:2] ~ dmnorm(mean[1:2],prec2[,])

}

for(k in 1:NS){

mu[k,1:2] ~ dmnorm(mean[1:2],prec2[,])
```

```
}

#omega[1:3, 1:3] ~ dwish(R[1:3,1:3],3)

# output SD and correlation based on estimated covariance matrix

#sigma.theta[1:3,1:3] <- inverse(omega[1:3,1:3])

#rho[1,2] <-sigma.theta[1,2]/sqrt(sigma.theta[1,1]*sigma.theta[2,2])

#rho[1,3] <-sigma.theta[1,3]/sqrt(sigma.theta[1,1]*sigma.theta[3,3])

#rho[2,3] <-sigma.theta[2,3]/sqrt(sigma.theta[2,2]*sigma.theta[3,3])

#sd[1]<-sqrt(sigma.theta[1,1])

#sd[2]<-sqrt(sigma.theta[2,2])

#sd[3]<-sqrt(sigma.theta[3,3])

# output hazard ratio for month 1 to 60

# NT is number of treatments, c is reference treatment, k is treatment of interest, l is month

#for (c in 1:(NT-1)) {

#for (j in (c+1):NT) {

#for (l in 1:60) {

#t1[c,j,l]<-(equals(P1,0)*log(l) + (1-equals(P1,0))*pow(l,P1))

#t2[c,j,l]<-((1-equals(P2,P1))*(equals(P2,0)*log(l) + (1-equals(P2,0))*pow(l,P2)) +
equals(P2,P1)*(equals(P2,0)*log(l)*log(l) + (1-equals(P2,0))*pow(l,P2) *log(l)))

#log(hazard_ratio[c,j,l])<-d[j,1]-d[c,1]+(d[j,2]-d[c,2])*t1[c,j,l]+(d[j,3]-d[c,3])*t2[c,j,l]

#}}}

}

#########################################################

##### Second order fractional polynomial

 ##################################################

#Winbugs code for second order fractional polynomial

#random effects network meta-analysis model

Model{

for (i in 1:N){ # N number of datapoints in dataset
```

```
# time is expressed in months and transformed

#according powers of fractional polynomial P1 and P2

time_transf1[i]<-(equals(P1,0)*log(time[i]) + (1-equals(P1,0))*pow(time[i],P1))

time_transf2[i]<-((1-equals(P2,P1))*(equals(P2,0)*log(time[i]) + (1-equals(P2,0))*pow(time[i],P2)) + equals(P2,P1)*(equals(P2,0)*log(time[i])*log(time[i]) + (1-equals(P2,0))*pow(time[i],P2) *log(time[i])))

# likelihood

# hazard over interval [t,t+dt] expressed as deaths per person-month

# r is deaths in interval, n is number at risk, h is hazard

r[i]~ dbin(p[i],n[i])

p[i]<-1-exp(-h[i]*dt[i]) # cumulative hazard over interval [t,t+dt] expressed as deaths per person-month

# random effects model

# loop over datapoints

# s refers to study, t is intervention t, b is comparator

log(h[i])<-Beta[i,1]+ Beta[i,2]*time_transf1[i]+ Beta[i,3]* time_transf2[i]

Beta[i,1]<-mu[s[i],1]+delta[s[i],1]*(1-equals(t[i],b[i]))

Beta[i,2]<-mu[s[i],2]+delta[s[i],2]*(1-equals(t[i],b[i]))

Beta[i,3]<-mu[s[i],3]+delta[s[i],3]*(1-equals(t[i],b[i]))

}

# loop over studies

# NS is number of studies

# ts is intervention k, bs is comparator

for(m in 1:NS){

#delta[m,1:3]~dmnorm(md[m,1:3],omega[1:3,1:3])

delta[m,1]<-md[m,1]

delta[m,2]<-md[m,2]

delta[m,3]<-md[m,3]
```

```
md[m,1]<-d[ts[m],1]-d[bs[m],1]

md[m,2]<-d[ts[m],2]-d[bs[m],2]

md[m,3]<-d[ts[m],3]-d[bs[m],3]

}

# priors

# NT is number of treatments

d[1,1]<-0

d[1,2]<-0

d[1,3]<-0

for(j in 2:NT){

d[j,1:3] ~ dmnorm(mean[1:3],prec2[,])

}

for(k in 1:NS){

mu[k,1:3] ~ dmnorm(mean[1:3],prec2[,])

}

#omega[1:3, 1:3] ~ dwish(R[1:3,1:3],3)

# output SD and correlation based on estimated covariance matrix

#sigma.theta[1:3,1:3] <- inverse(omega[1:3,1:3])

#rho[1,2] <-sigma.theta[1,2]/sqrt(sigma.theta[1,1]*sigma.theta[2,2])

#rho[1,3] <-sigma.theta[1,3]/sqrt(sigma.theta[1,1]*sigma.theta[3,3])

#rho[2,3] <-sigma.theta[2,3]/sqrt(sigma.theta[2,2]*sigma.theta[3,3])

#sd[1]<-sqrt(sigma.theta[1,1])

#sd[2]<-sqrt(sigma.theta[2,2])

#sd[3]<-sqrt(sigma.theta[3,3])

# output hazard ratio for month 1 to 60

# NT is number of treatments, c is reference treatment, k is treatment of interest, l is month

#for (c in 1:(NT-1)) {
```

```
#for (j in (c+1):NT) {

#for (l in 1:60) {

#t1[c,j,l]<-(equals(P1,0)*log(l) + (1-equals(P1,0))*pow(l,P1))

#t2[c,j,l]<-((1-equals(P2,P1))*(equals(P2,0)*log(l) + (1-equals(P2,0))*pow(l,P2)) + equals(P2,P1)*(equals(P2,0)*log(l)*log(l) + (1-equals(P2,0))*pow(l,P2) *log(l)))

#log(hazard_ratio[c,j,l])<-d[j,1]-d[c,1]+(d[j,2]-d[c,2])*t1[c,j,l]+(d[j,3]-d[c,3])*t2[c,j,l]

#}}}

}
```

Appendix 2 – Additional model results for new ITC

Table 47: Additional models tested

	pD	**DIC**
P=0	8.2	2131.9
P=1	8.0	2153.6
P=0.5	8.1	2143.6
P=-0.5	7.9	2122.1
P=-1	7.8	2120.0
P=-2	7.5	2128.8
P1=0, P2=0	11.8	2128.0
P1=0.5, P2=0	12.0	2129.6
P1=1, P2=0	11.8	2130.6
P1=-0.5, P2=0	10.9	2126.4
P1=-1, P2=0	11.4	2126.4
P1=-1, P2=-1	11.1	2126.1

Figure 21. Fitted PFS based on the fractional polynomial model (P=0) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.

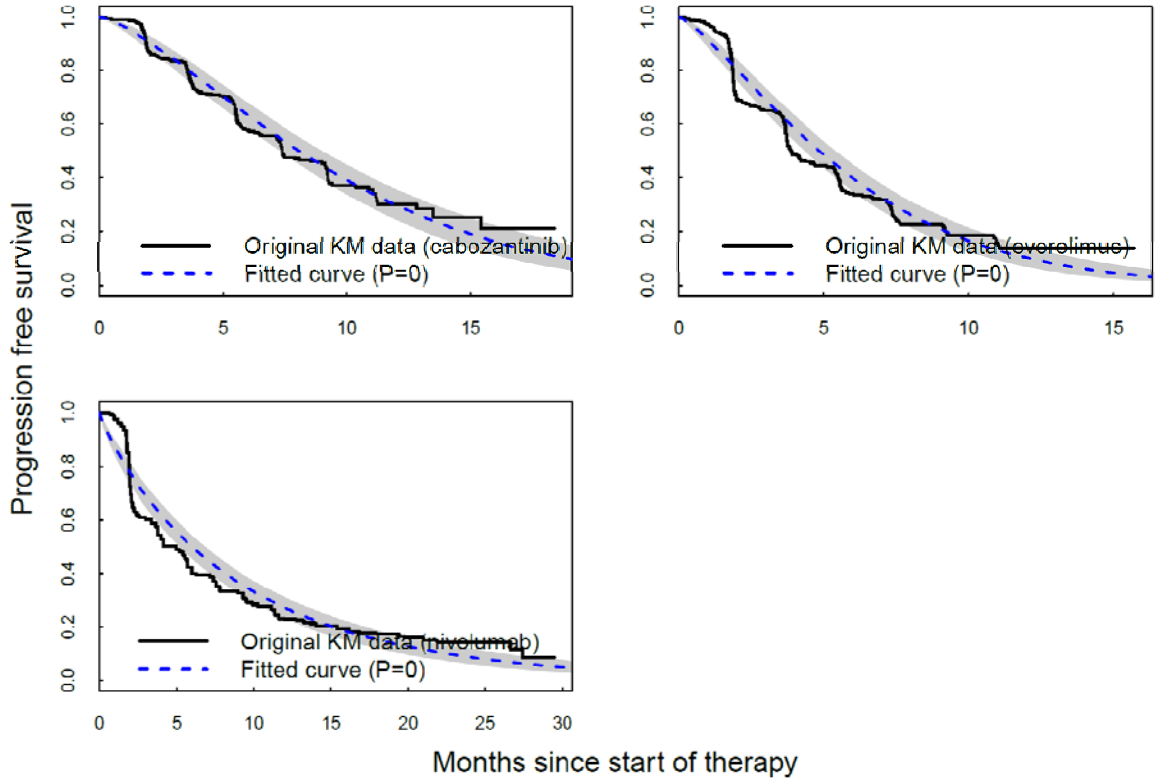


Figure 22. Fitted PFS based on the fractional polynomial model (P=1) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.

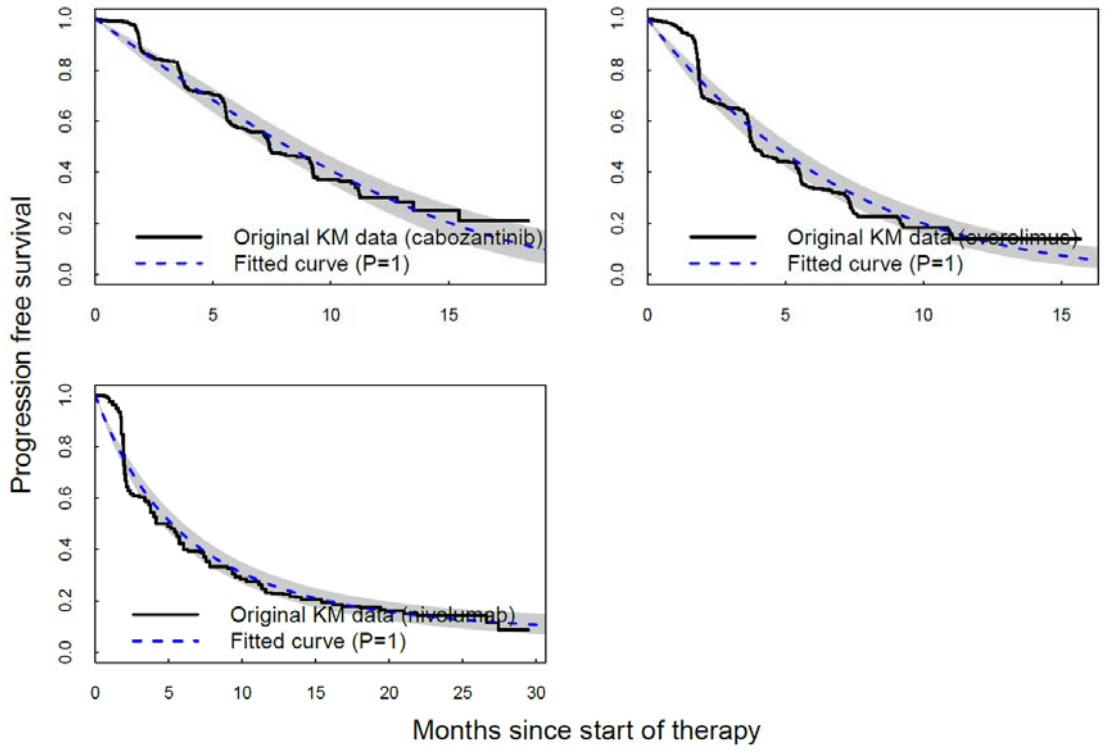


Figure 23. Fitted PFS based on the fractional polynomial model (P=-1) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.

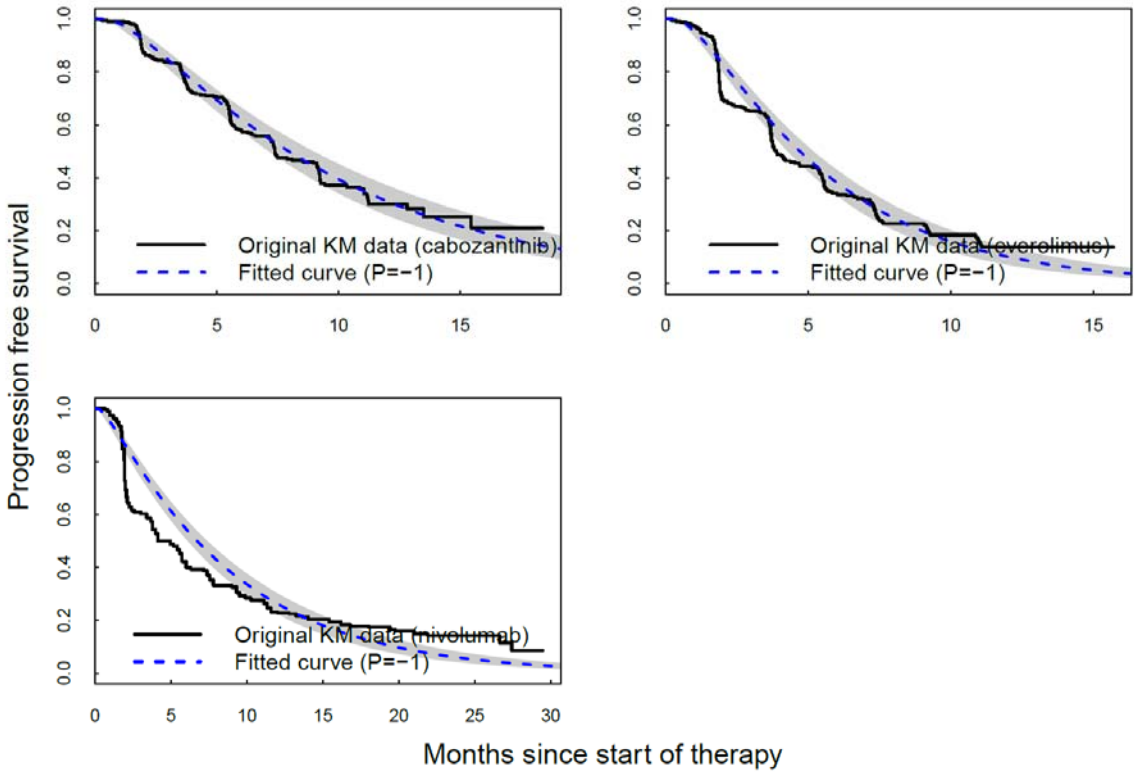


Figure 24. Averaged PFS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P=0).

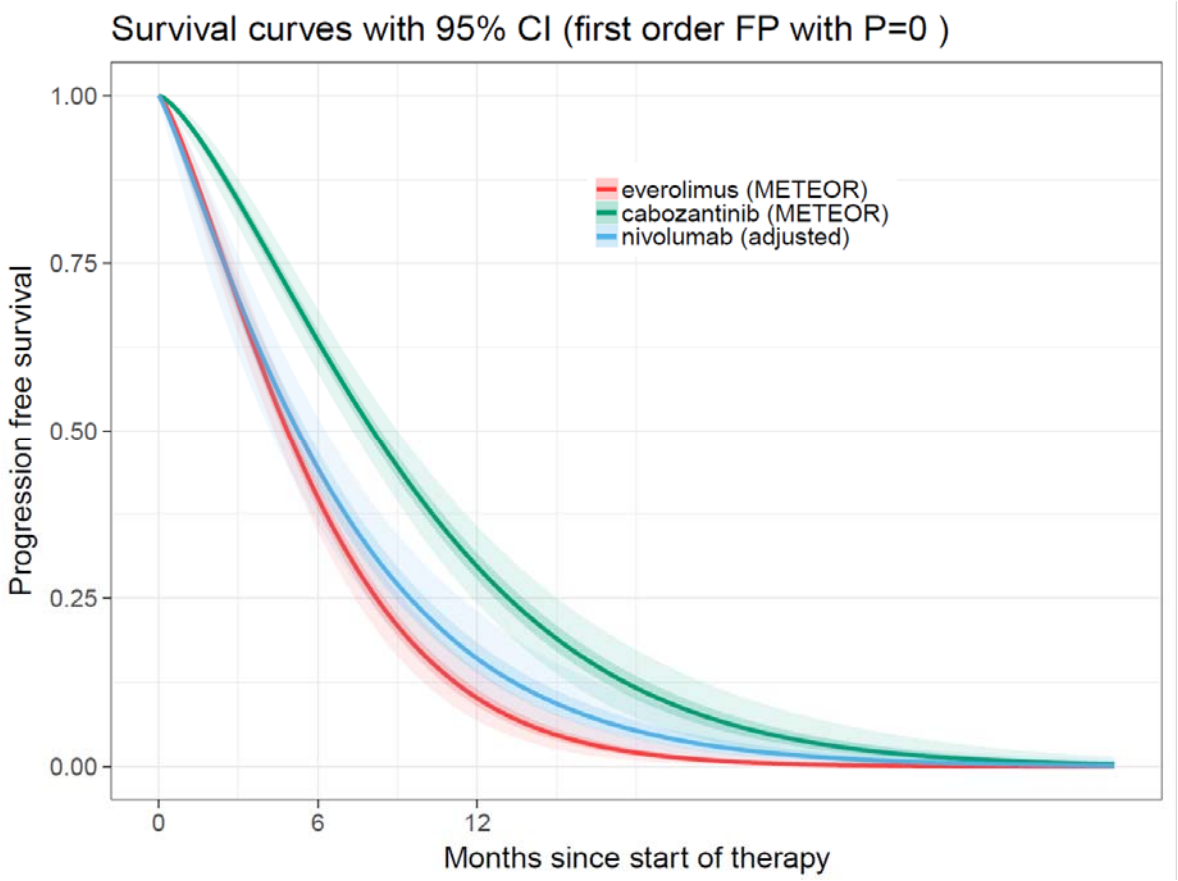


Figure 25. Averaged PFS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P=1).

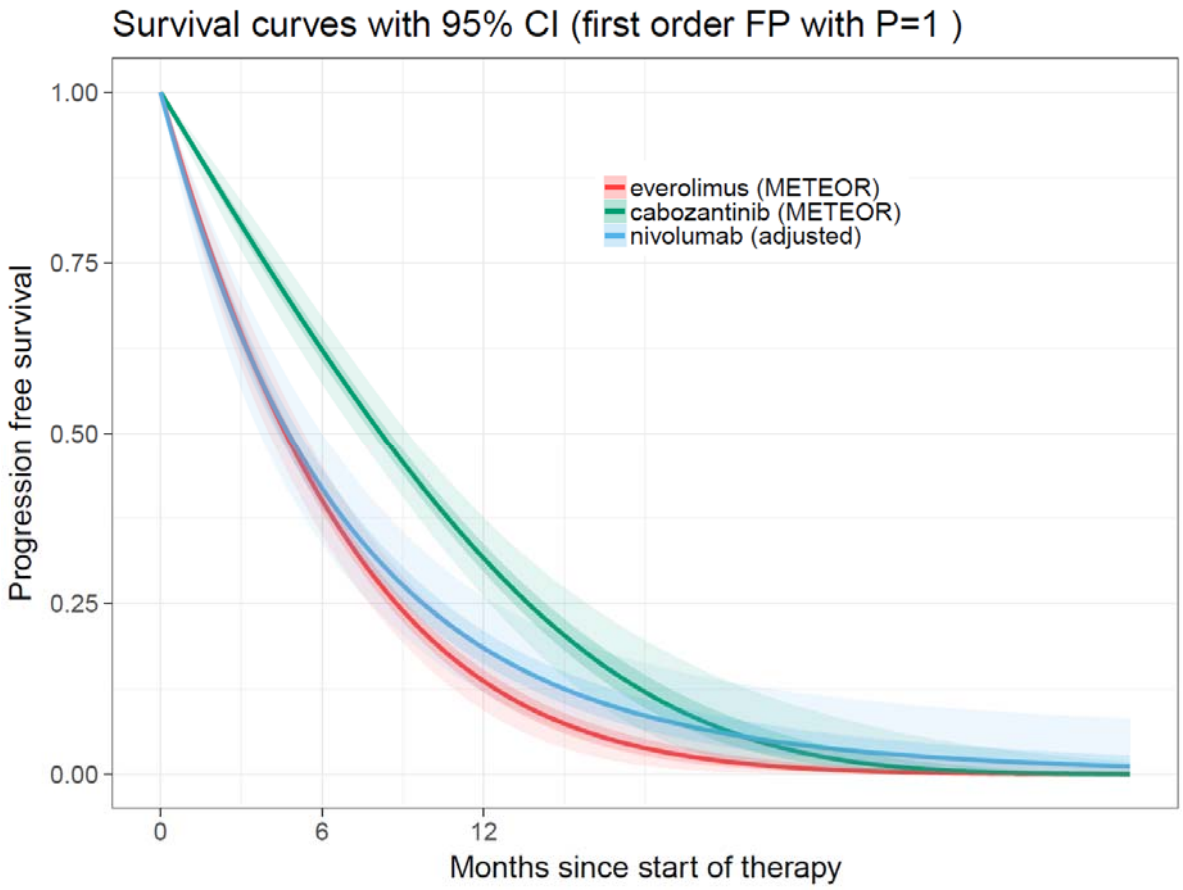


Figure 26. Averaged PFS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P=-1).

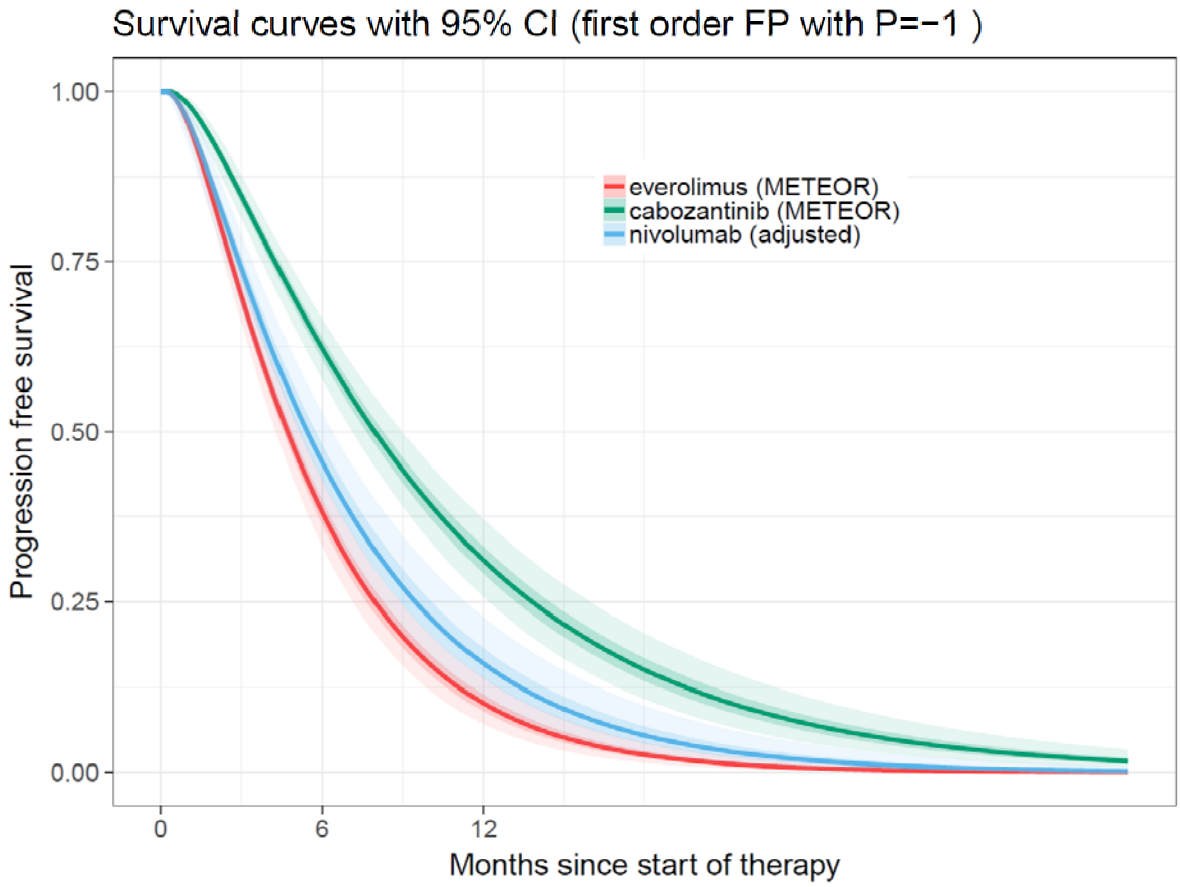


Figure 27. Averaged PFS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P1=-1, P2=-1).

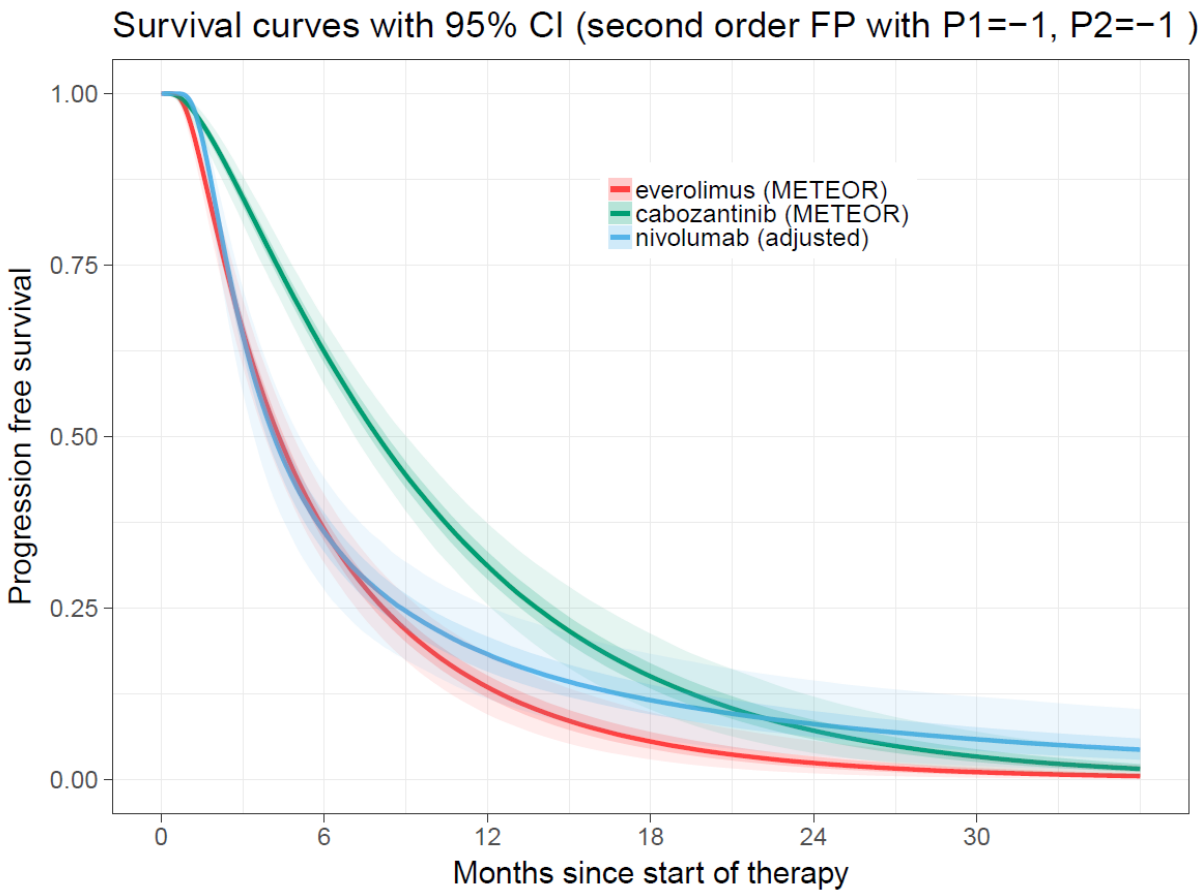


Figure 28. Estimated PFS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P=0).

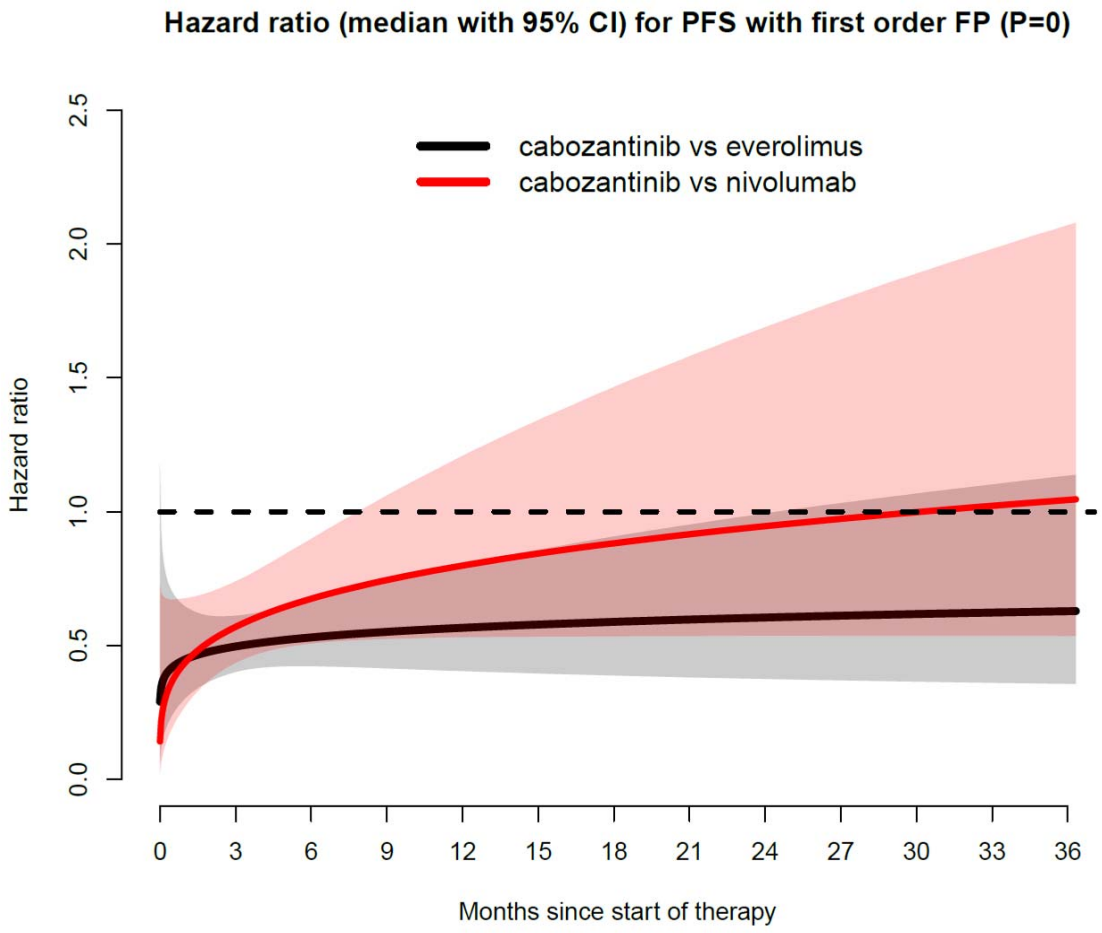


Figure 29. Estimated PFS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P=1).

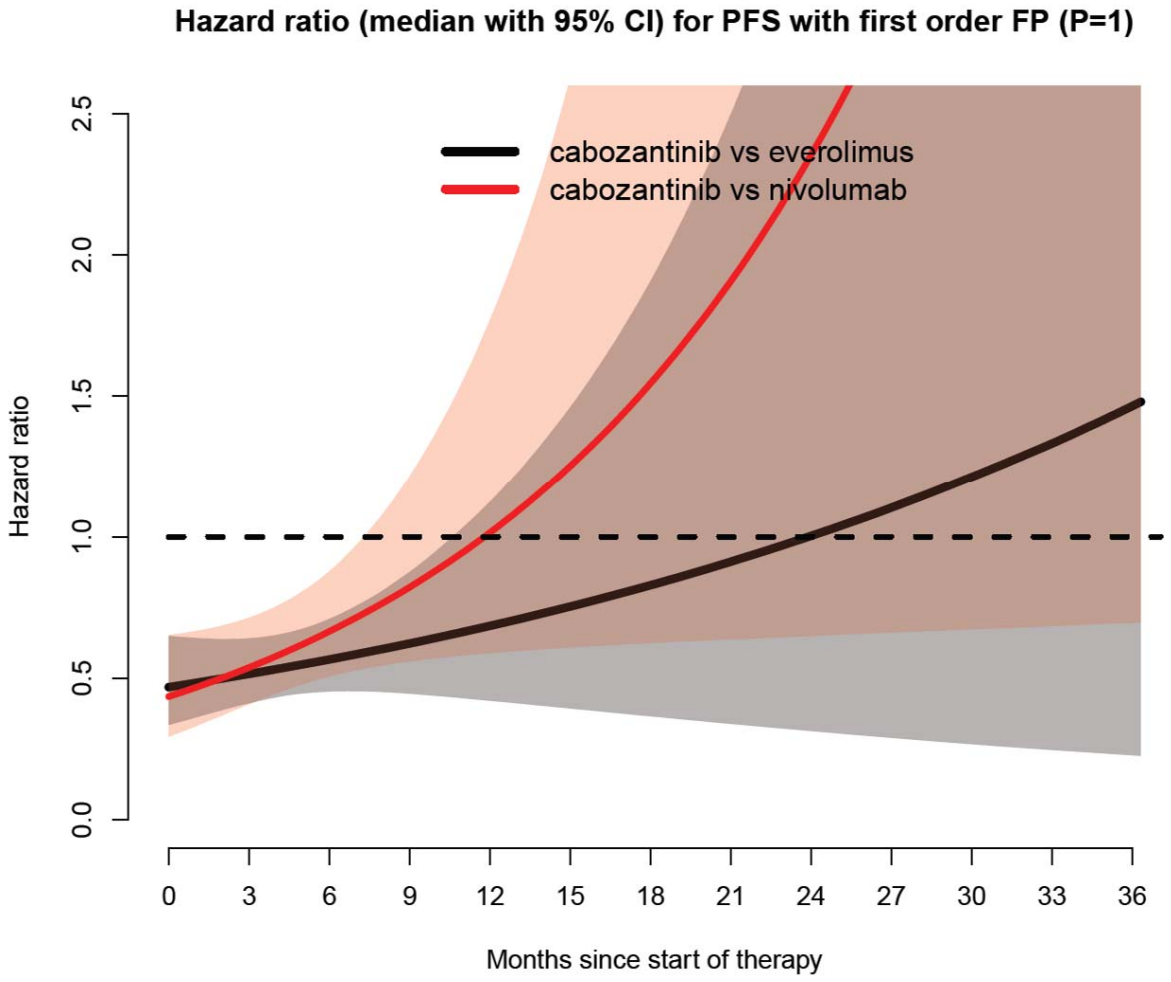


Figure 30. Estimated PFS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P=-1).

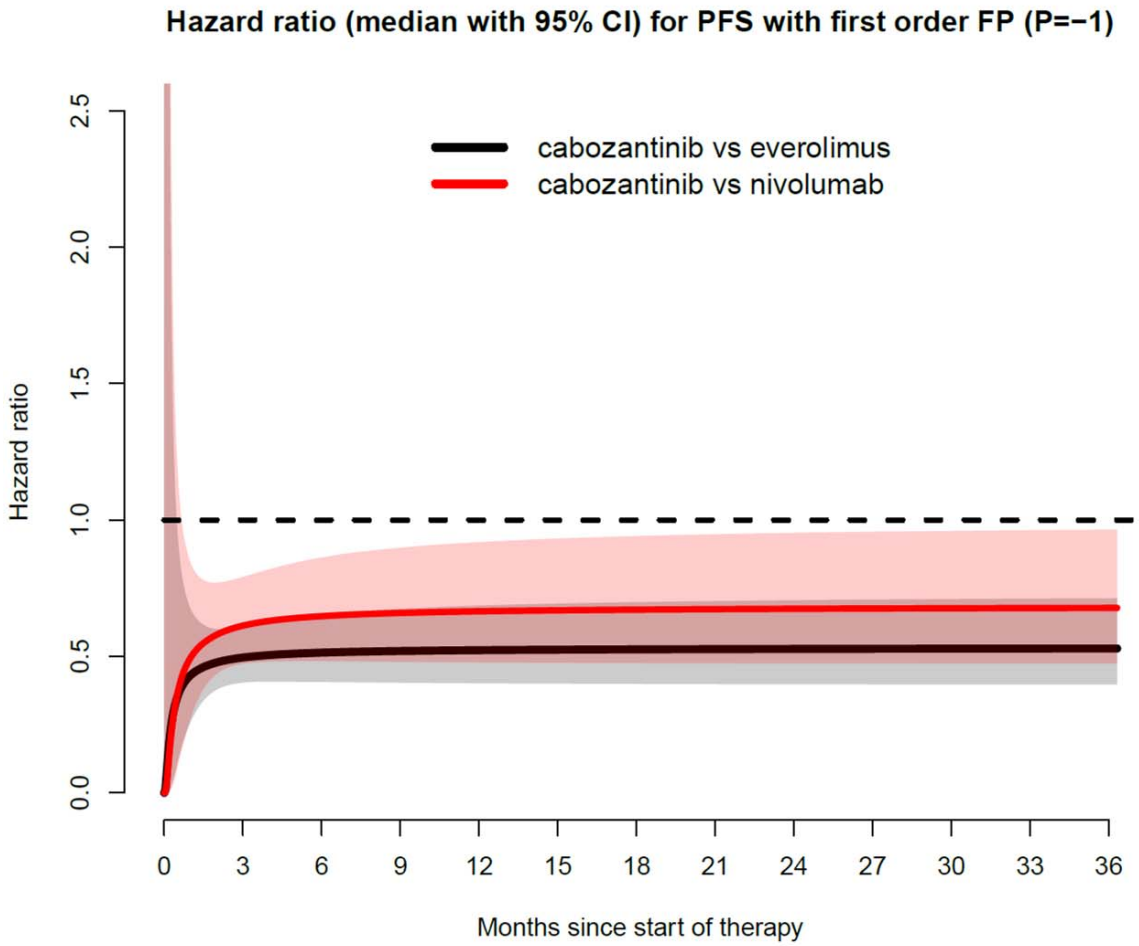


Figure 31. Estimated PFS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P1=-1, P2=-1).

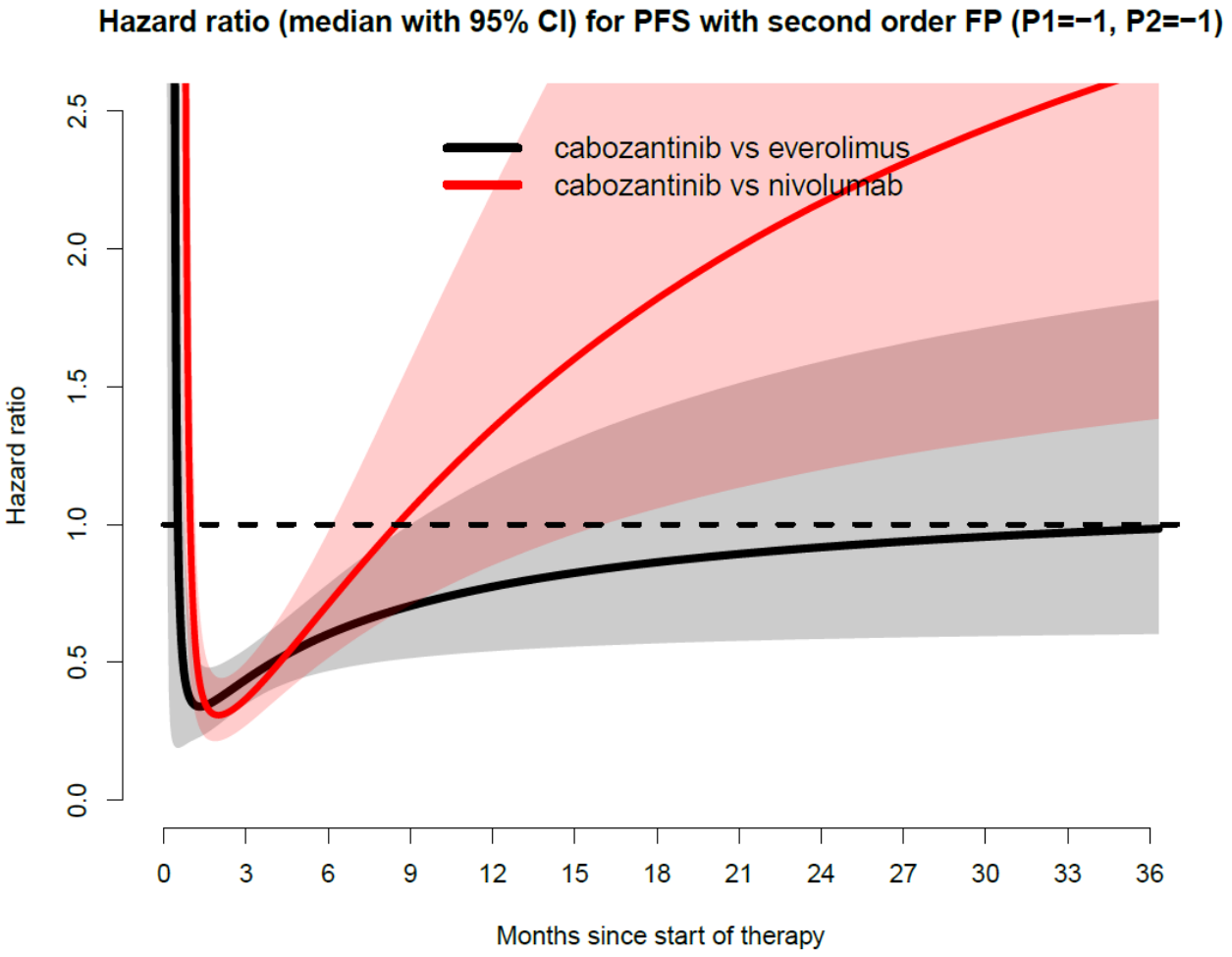


Figure 32. Fitted OS based on the fractional polynomial model (P=0) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.

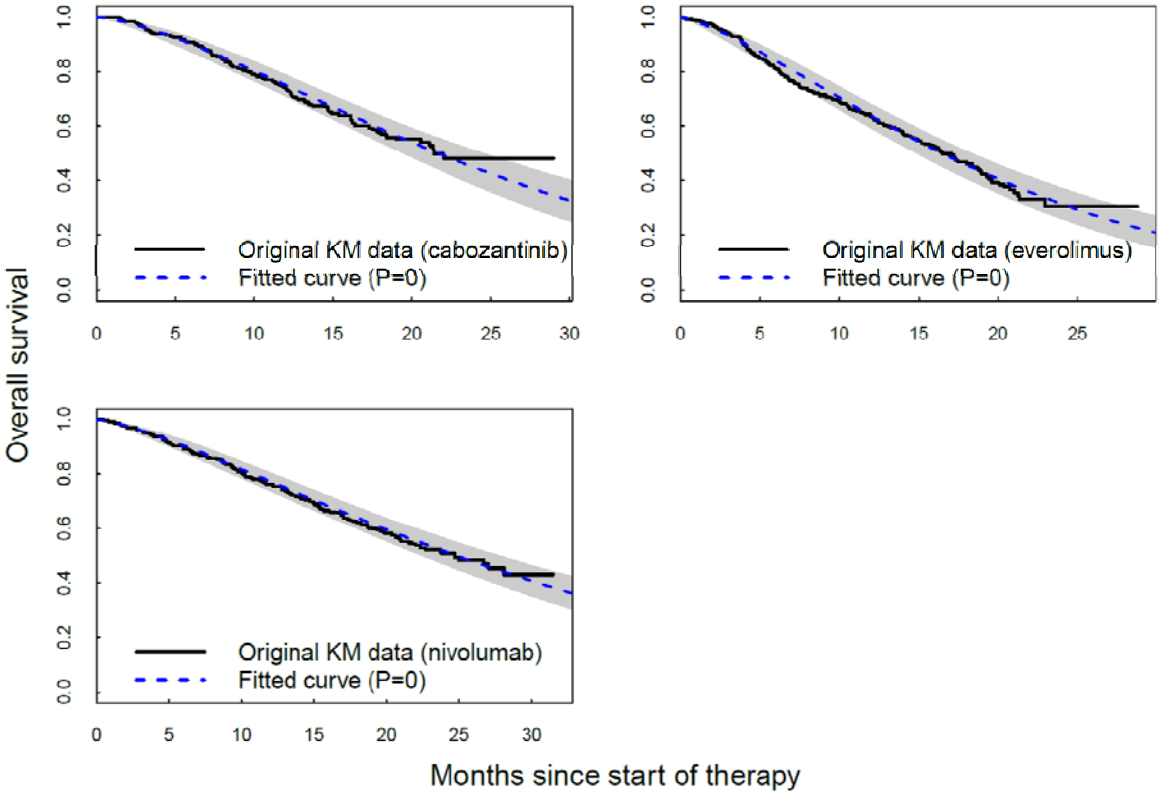


Figure 33. Fitted OS based on the fractional polynomial model (P=1) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.

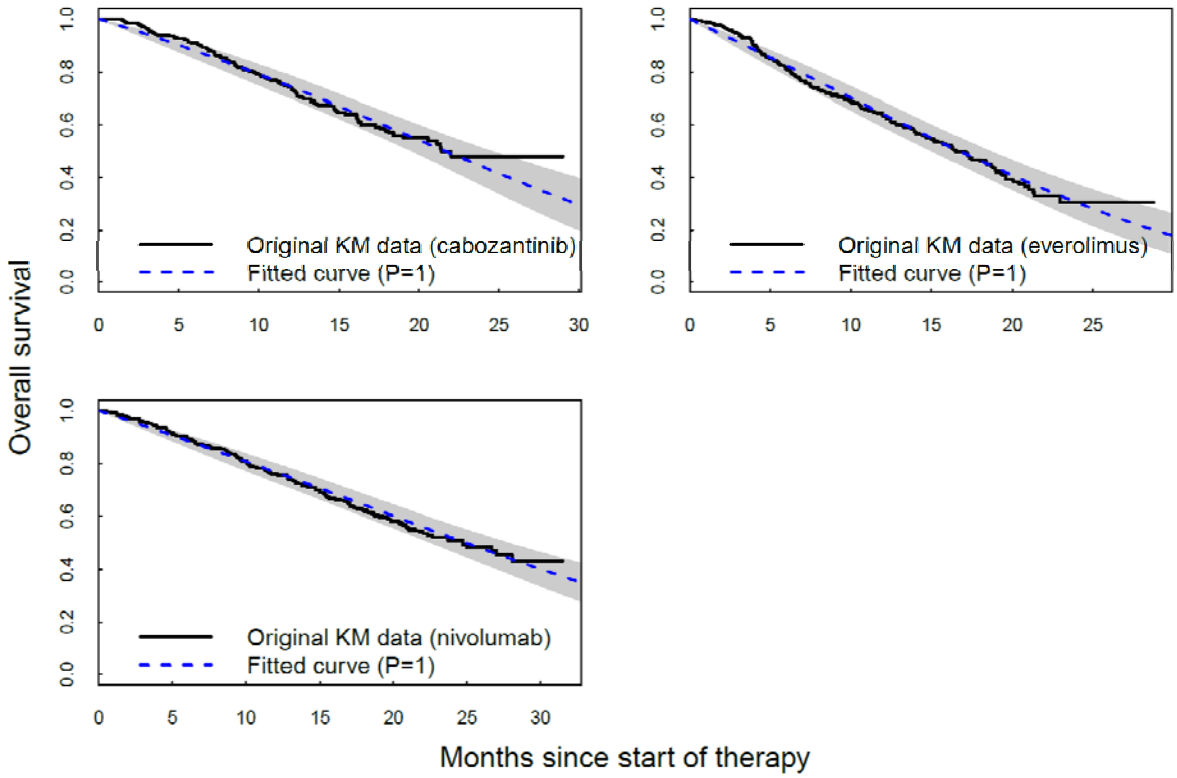


Figure 34. Fitted OS based on the fractional polynomial model (P=-1) overlaid on extracted Kaplan-Meier (KM) data, with shaded areas representing 95% credible intervals.

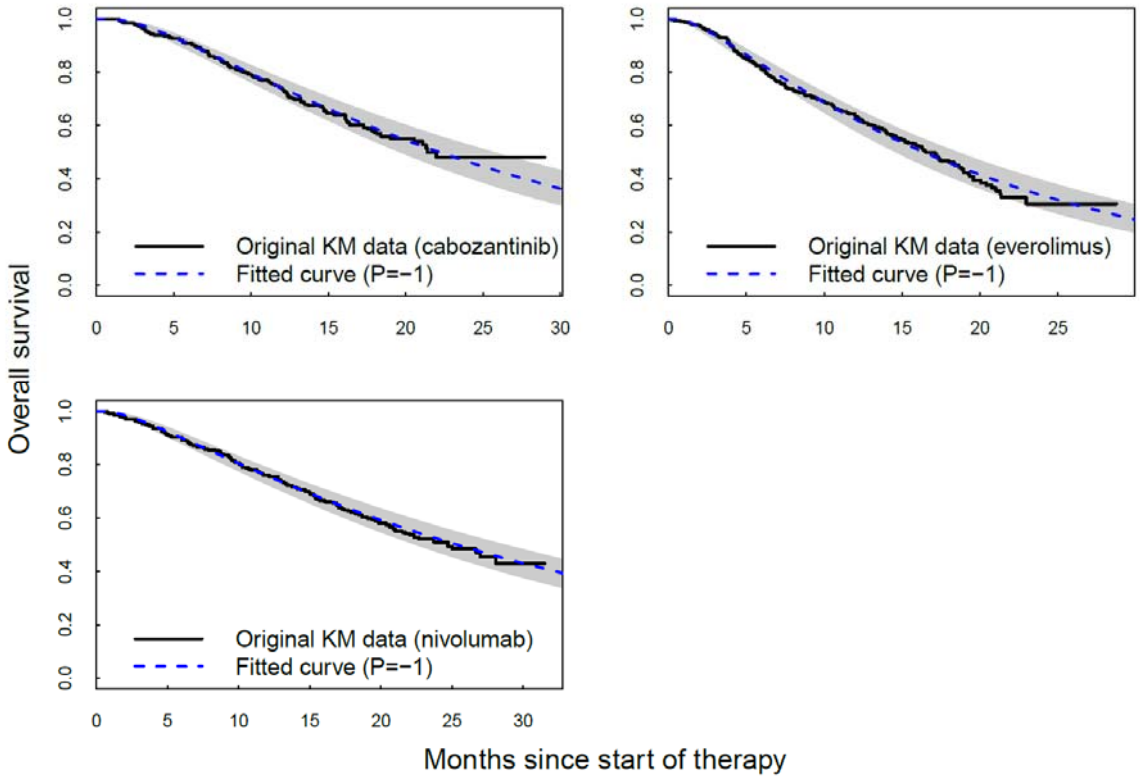


Figure 35. Averaged OS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P=0).

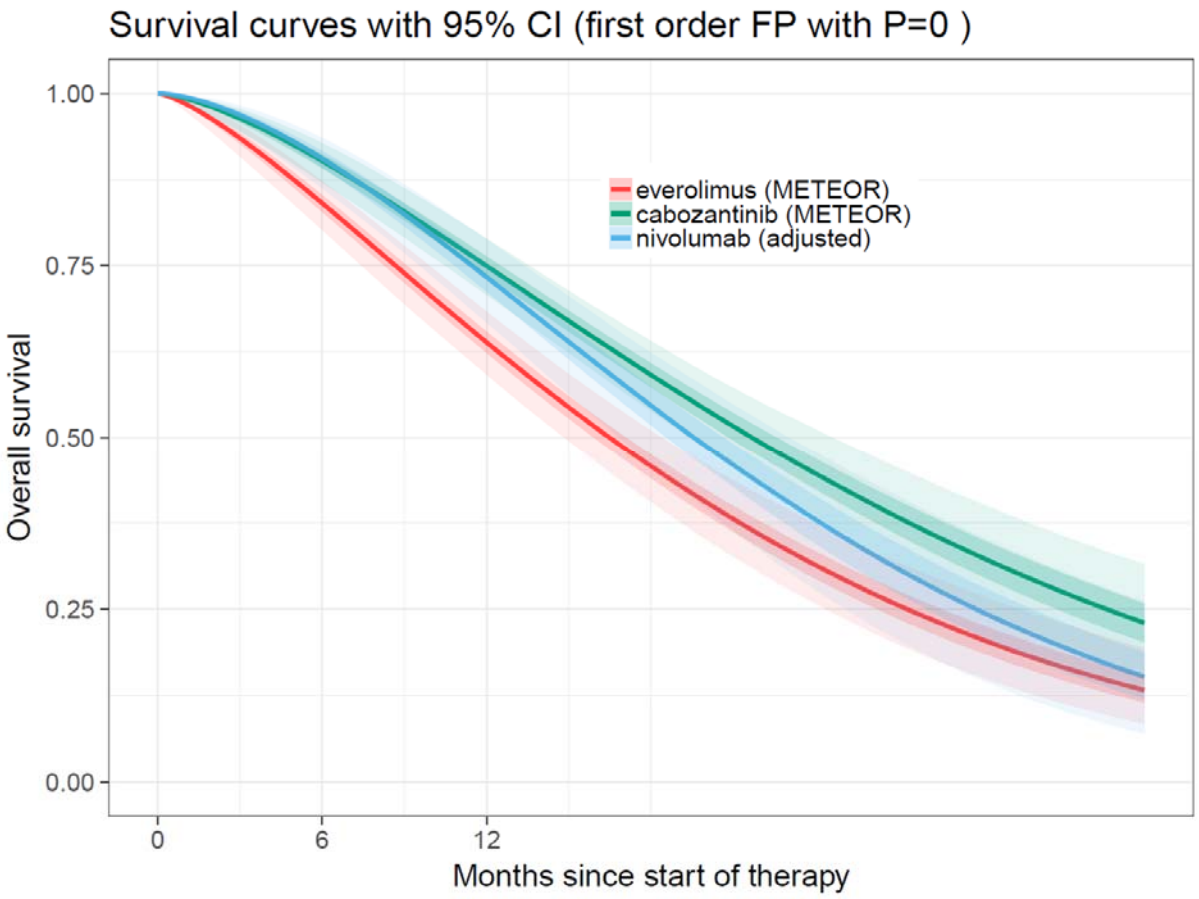


Figure 36. Averaged OS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P=1).

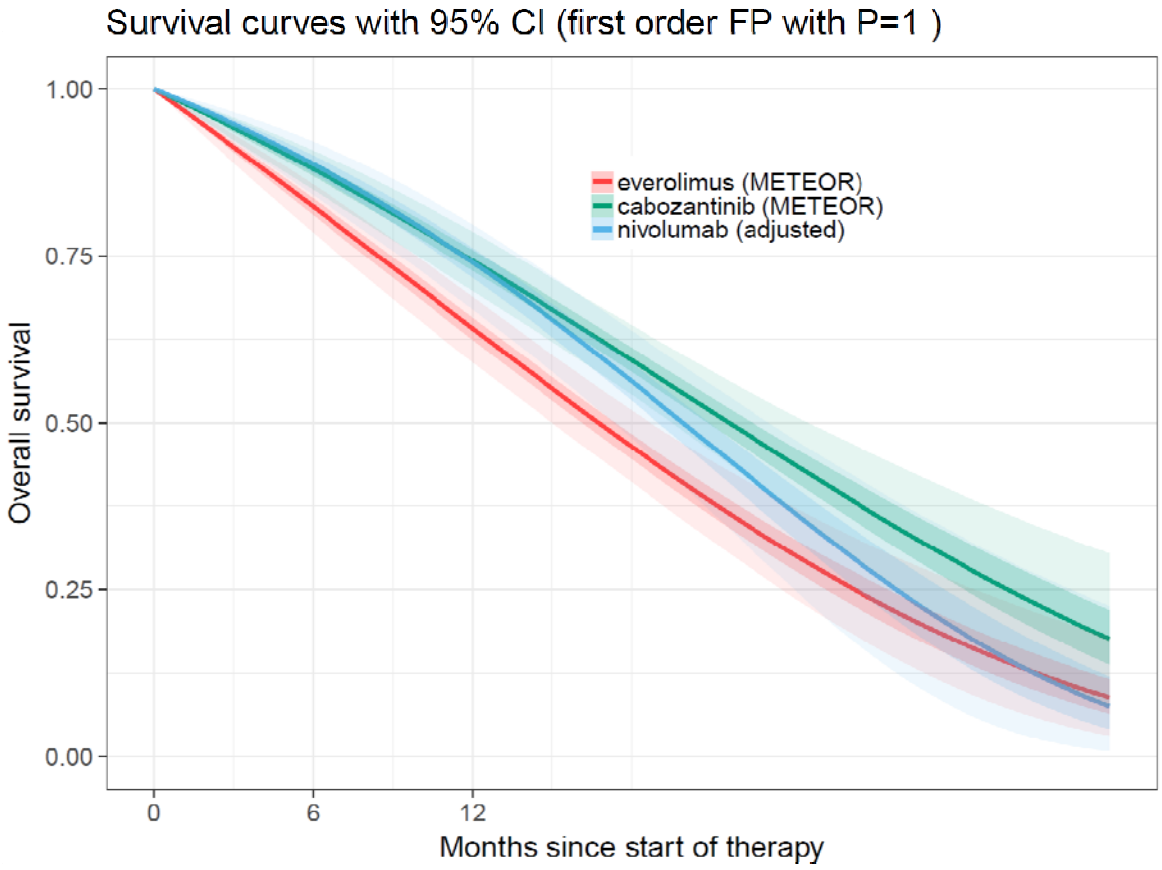


Figure 37. Averaged OS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P=-1).

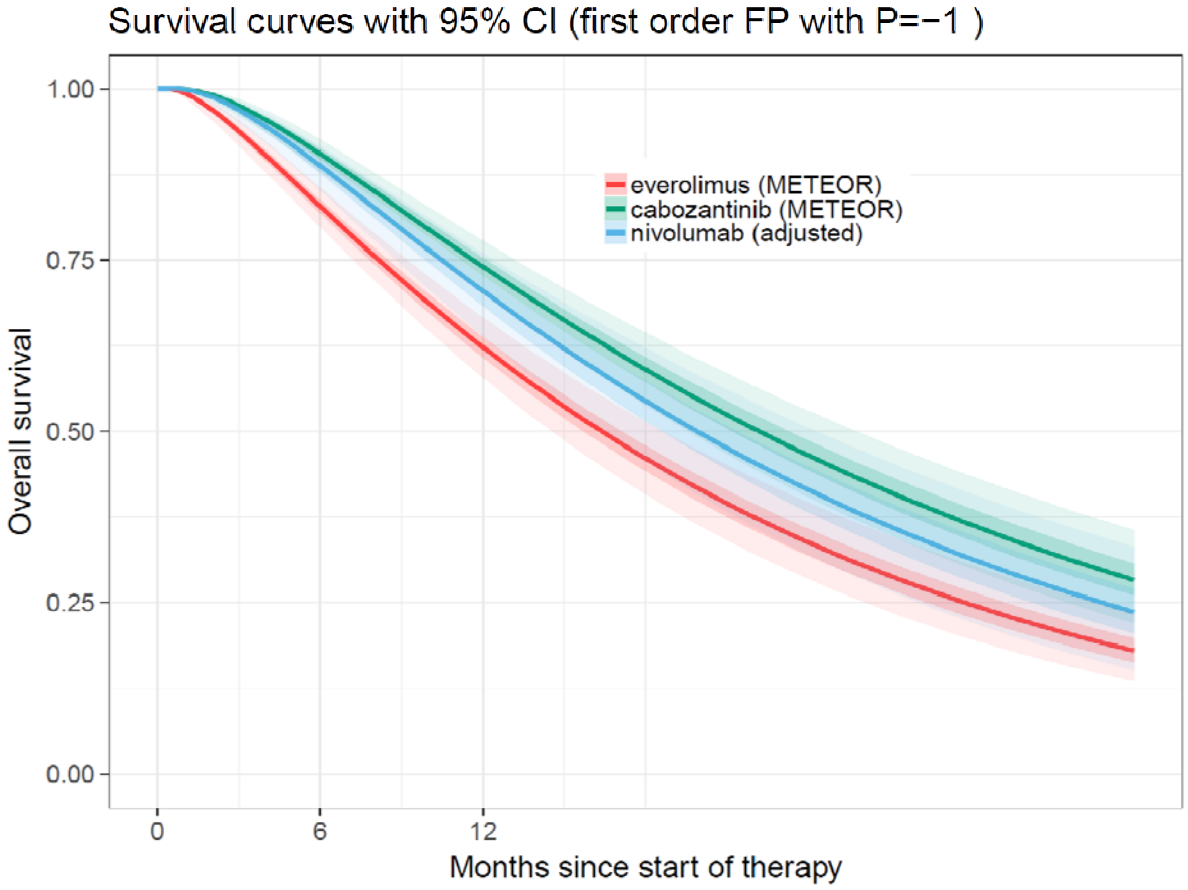


Figure 38. Averaged OS over time, adjusted to the baseline from METEOR study, with shaded areas representing 95% credible intervals (P1=-1, P2=0).

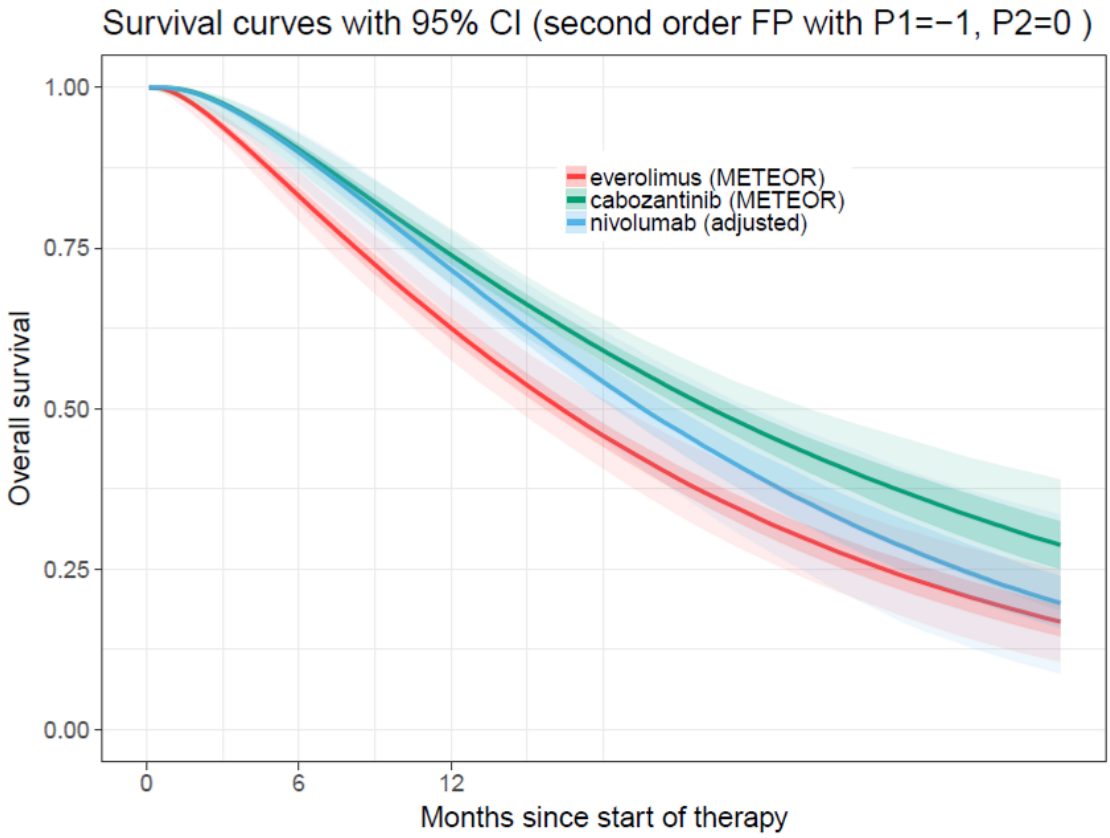


Figure 39. Estimated OS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P=0).

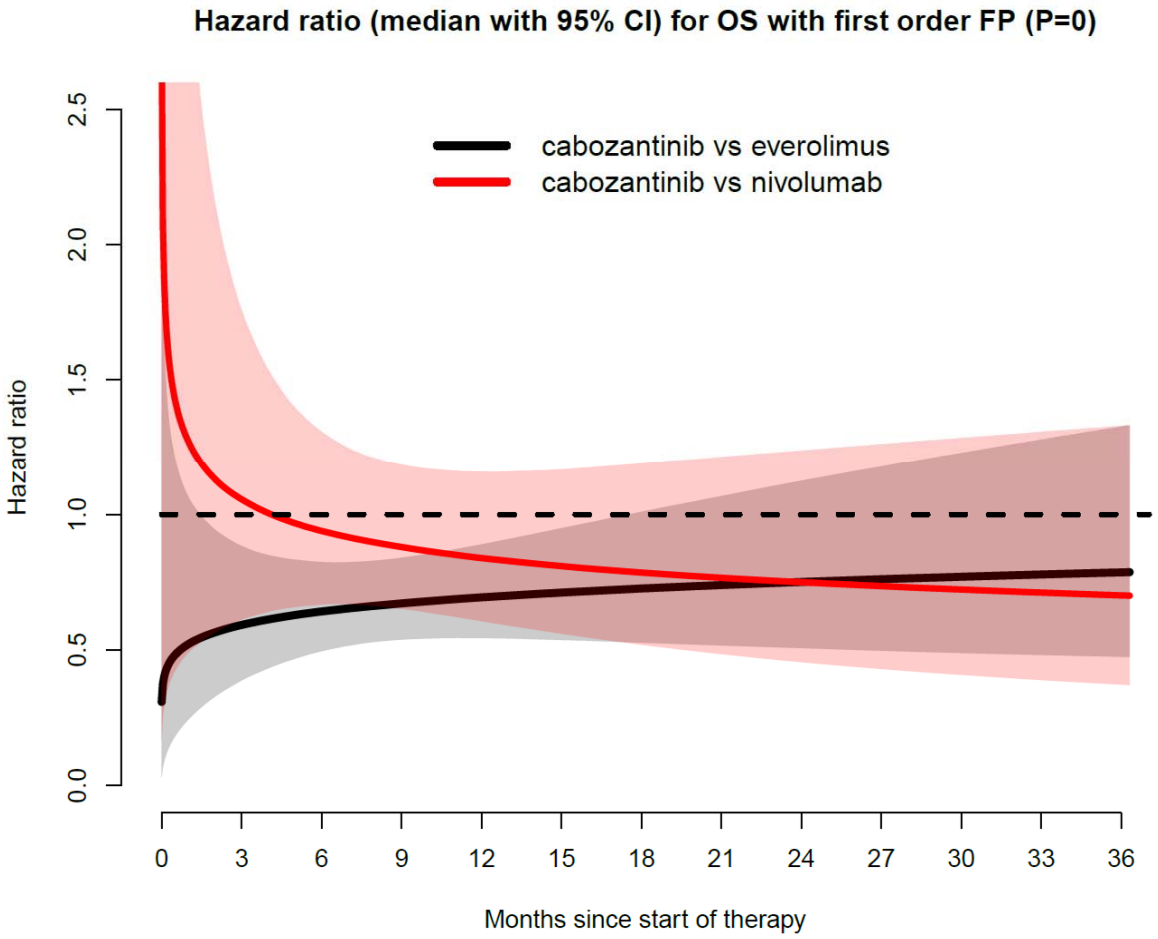


Figure 40. Estimated OS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P=1).

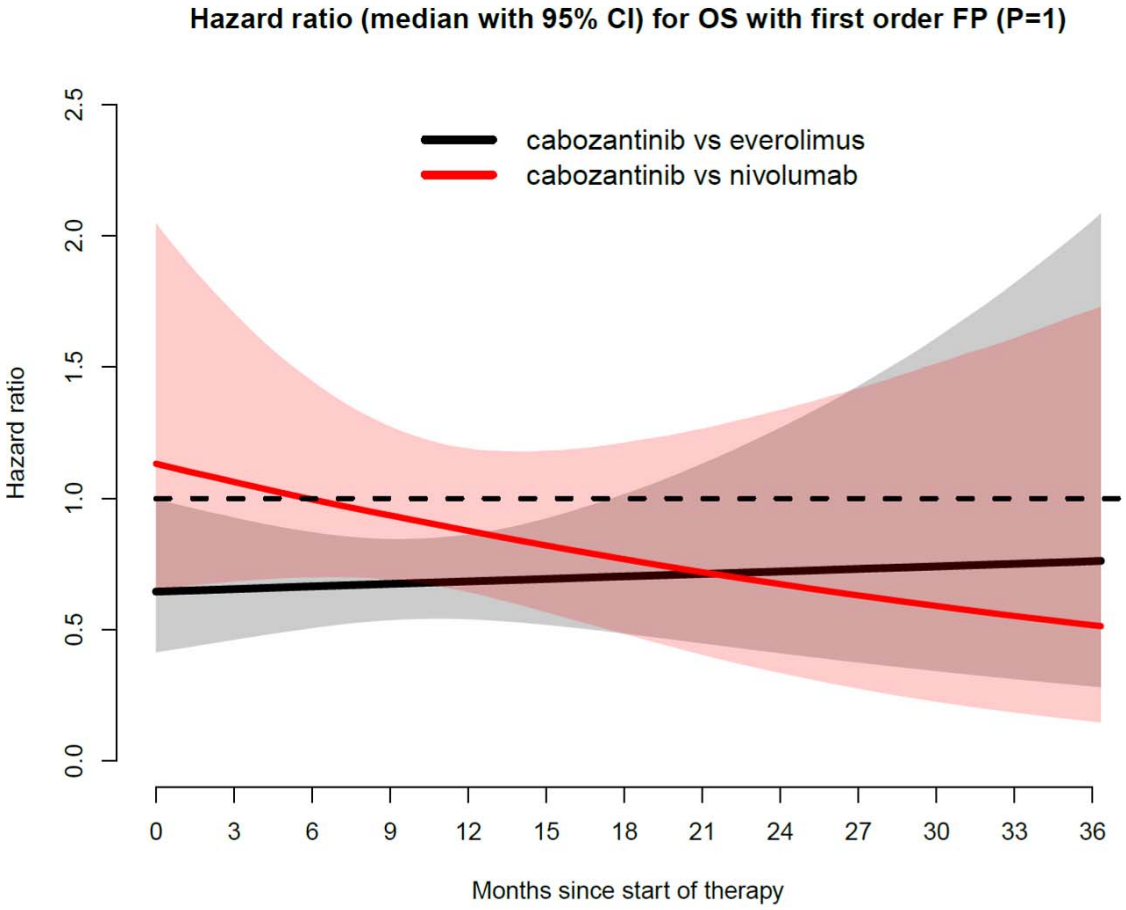


Figure 41. Estimated OS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P=-1).

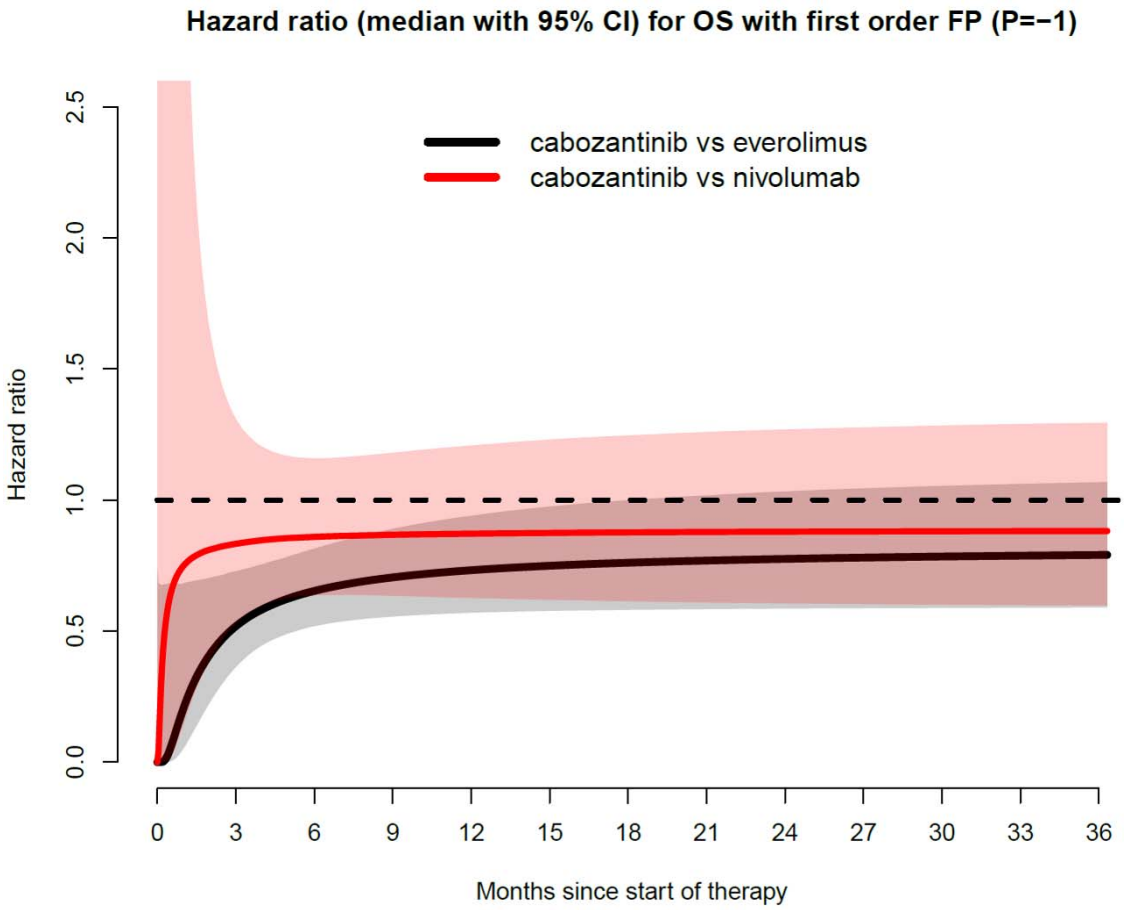
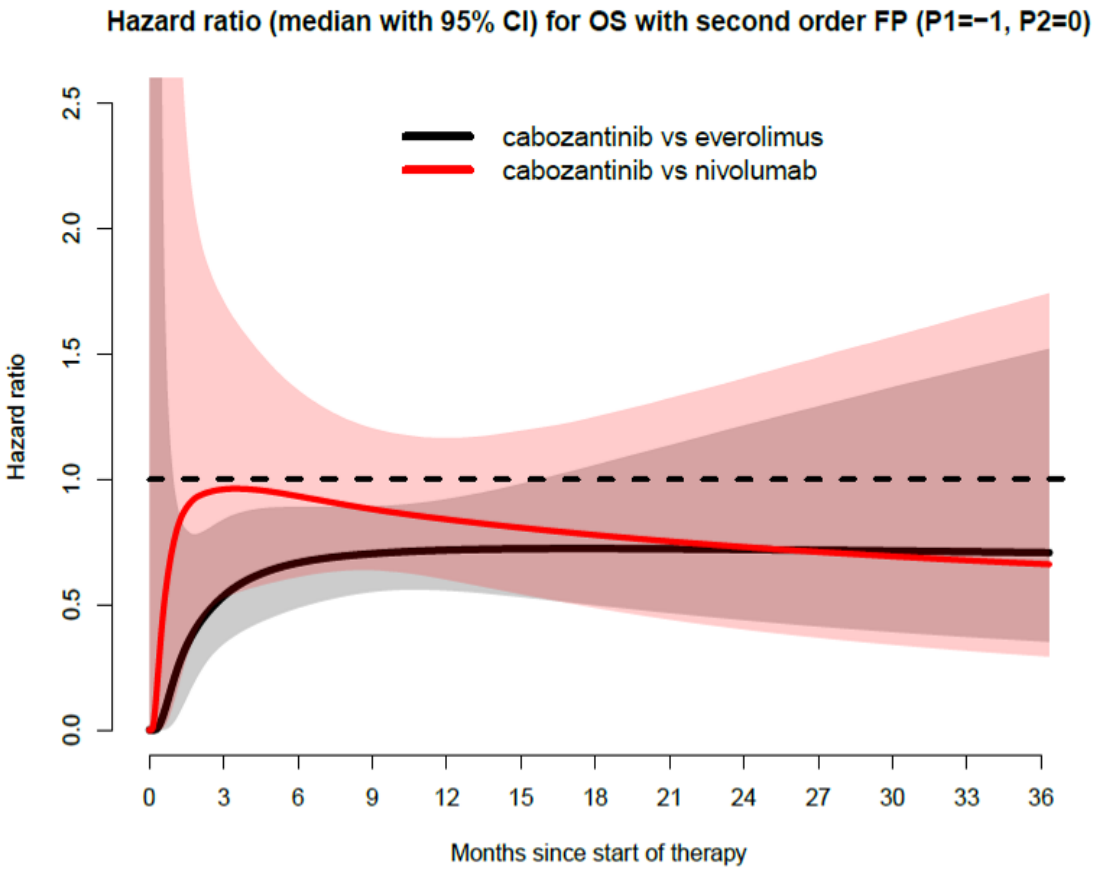


Figure 42. Estimated OS hazard ratios over time, with solid line representing median and shaded areas representing 95% credible intervals (P1=-1, P2=0).



Appendix 3 – new OS data: ITC results

Out of Weibull, Gompertz, loglogistic, lognormal and exponential models, the loglogistic provides the best statistical fit. Of the fractional polynomial models tested, the best fit continues to be P=-1.

Table 48: Model fit statistics from previously (Ouwens et al. 2010) – OS Oct 2016

Model fit statistics	Weibull	Gompertz	Log-logistic	Log-normal	Exponential
Residual deviance (*Dbar*)	2389.4	2414.1	2378.9	2383.2	2434.1
Effective number of parameters (*pD*)	8.2	8.0	7.7	7.7	4.1
Deviance information criteria (*DIC*)	2381.2	2406.1	2371.2	2375.5	2430.0

Note: The previous NMA method was re-run as a pair-wise comparison of METEOR and CheckMate025 studies in order to make the fit statistics comparable.

Table 49: Model fit statistics from fractional polynomial (Jansen 2011) – OS Oct 2016

Model fit statistics	First order with P=0	First order with P=1	First order with P=-1	Second order with P1=-1, P2=0	Second order with P1=-1, P2=-1
Residual deviance (*Dbar*)	2389.4	2414.1	2374.3	2382.8	2381.5
Effective number of parameters (*pD*)	8.2	8.0	7.8	10.9	10.3
Deviance information criteria (*DIC*)	2381.2	2406.1	2366.5	2371.9	2371.2

Figure 43. [redacted]

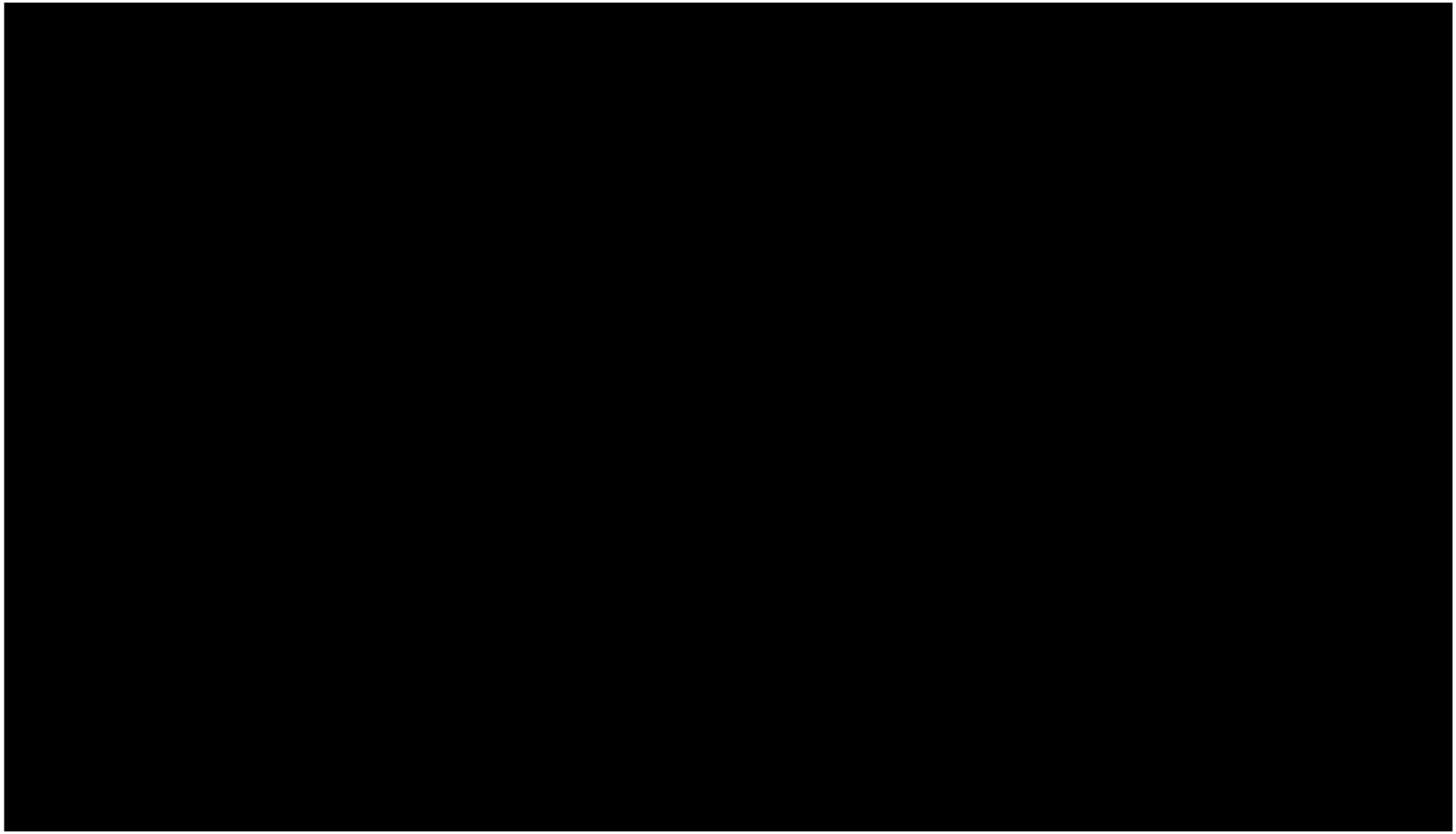


Figure 44. [redacted]

Figure 45. [redacted]

Figure 46. [redacted]

Figure 47. [redacted]

Figure 48. [redacted]

Figure 49. [redacted]

Figure 50. [redacted]

Figure 51. [redacted]

Figure 52. [redacted]

Figure 53. [redacted]

Figure 54. [redacted]

Figure 55. [redacted]

Figure 56. [redacted]

Figure 57. [redacted]

Figure 58. [redacted]

Figure 59. [redacted]

Figure 60. [redacted]

Figure 61. [redacted]

Figure 62. [redacted]

Figure 63. [redacted]

Figure 64. [redacted]

Figure 65. [redacted]

Figure 66. [redacted]

Figure 67. [redacted]

Figure 68. [redacted]

Figure 69. [redacted]

Figure 70. [redacted]

Figure 71. [redacted]

Figure 72. [redacted]

Appendix 4 –new OS data: CE model results

Table 50: Fractional polynomial model; cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 51: Fractional polynomial model; cabozantinib versus comparator – with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	37,768
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	64,652
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 52: Fractional polynomial model; cabozantinib versus comparator – with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,424
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	69,546
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 53: Fractional polynomial model; cabozantinib versus comparator – with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,080
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	74,440
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 54: OS Loglogistic, PFS lognormal model; cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: For the new OS data loglogistic (not lognormal) provided the best statistical fit

Table 55: : OS Loglogistic, PFS lognormal model; cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48,742
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	63,862
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 56: : OS Loglogistic, PFS lognormal model; cabozantinib versus comparator – with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,581
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,664
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 57: : OS Loglogistic, PFS lognormal model; cabozantinib versus comparator – with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,419
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73,466
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 58: Hybrid model (best fitting FP for trial duration, loglogistic for extrapolation); cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 59: Hybrid model (best fitting FP for trial duration, loglogistic for extrapolation); cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	30,954
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	59,650
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 60: Hybrid model (best fitting FP for trial duration, loglogistic for extrapolation); cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	39,425
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	64,097
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 61: Hybrid model (best fitting FP for trial duration, loglogistic for extrapolation); cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,896
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	68,545
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 62: FP OS & lognormal PFS; cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 63: FP OS & lognormal PFS; cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,975
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,991
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 64: FP OS & lognormal PFS; cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,764
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67,758
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 65: FP OS & lognormal PFS; cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,553
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	72,525
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 66: Nivolumab 50% general pop mortality, lognormal for PFS, best fitting fractional polynomial model for OS; cabozantinib versus comparator - without PAS

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]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 67: Nivolumab 50% general pop mortality, lognormal for PFS, best fitting fractional polynomial model for OS; cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,975
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	62,991
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 68: Nivolumab 50% general pop mortality, lognormal for PFS, best fitting fractional polynomial model for OS; cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	54,764
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	67,758
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 69: Nivolumab 50% general pop mortality, lognormal for PFS, best fitting fractional polynomial model for OS; cabozantinib versus comparator - with [redacted] cabozantinib PAS, [redacted] comparator PAS

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]	-
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61,553
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	72,525
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Appendix 5 – Search protocol for systematic literature review on utility decrements

Objectives

A systematic literature search was conducted to identify health state utility values in respect of advanced RCC.

Methods

Score of review

An overview of the scope of the review is shown in Table 70formulated in accordance with PICOS scheme which includes population (P), intervention (I), comparator (C), outcomes (O), study design (S) and further details.

Table 70: Scope of literature review for health state utility values

Category	Details
Population	Renal cell cancer (advanced / metastatic, previously treated)
Interventions	No restriction
Comparators	No restriction
Outcomes	EQ-5D utilities, utilities derived from generic preference-based instruments such as the SF-36, SF-12, SF-6D, HUI2 or HUI3, health related quality of life instruments
Study Design	No restriction

Table 71: Further parameters and restrictions

Timeframe of Search	2006-2016[1]

[1] The timeframe of the search was restricted from 2006-2016, because in the HTA report published by the Peninsula Technology Assessment Group (PenTAG) in 2008, they did not identify publications with relevant information before 2006:

(→ see respective PenTAG report:

- *Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K, Moxham T, Stein K, Peninsula Technology Assessment Group (PenTAG). Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: A systematic review and economic evaluation [Internet]. 2008 May [cited 2016 Jun 28]. Available from: https://www.nice.org.uk/guidance/TA178/documents/renal-cell-carcinoma-sunitinib-assessment-report2*

Language	No language restriction
Other restrictions	Exclusion of mere animal studies

Table 72: Bibliografic database searched

Databases	Date of Search
Medline (includes Medline in Process and other non-indexed citations with status: publisher, in-data review or Pubmed-not-Medline)	Jul 6, 2016
Embase	Jul 6, 2016
NHS Economic Evaluation Database, HTA Database	Jul 6, 2016

Literature search

A search protocol has been developed documenting search strategy, search parametars such as search terms and data sources and results per database.

Search strategy per database

Database	Medline (includes Medline in Process and other non-indexed citations (with status: publisher, in-data review or Pubmed-not-Medline)	
Search platform: DIMDI Classic SearchDate of search: July 6, 2016 [Last Database Update:July 6, 2016] **Date range searched: 1966-2016, restricted to 2006-2016 in the last step**		
Search Strategies guided by the named search filters:	• Papaioannou, D., Brazier, J.E., Paisley, S. (2011) NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. Available from http://www.nicedsu.org.uk • Paisley, S., Booth, A., Mensinkai, S.. Health-related quality of life studies. Etext on Health Technology Assessment (HTA) Information Resources. US National Library of Medicine (NLM) National Information Center on Health Services Research and Healthcare Technology (NICHSR); Bethesda: 2005.	
#	**Search Terms**	**Hits**
1	ME66	23833954

- *Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K, Moxham T, et al.Bevacizumab, sorafenib tosylate and sunitinib for renal cell carcinoma: a systematic review and economic evaluation. Health Technol Assess 2010;14(2) Available from: http://www.journalslibrary.nihr.ac.uk/hta/volume-14/issue-2)*

2	CT=CARCINOMA, RENAL CELL	25533
3	CT=KIDNEY NEOPLASMS	56468
4	RENAL # # (CARCINOMA#; ADENOCARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)/(TI; AB; UT)	43595
5	(CARCINOMA#; ADENOCARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###) # RENAL/(TI; AB; UT)	4012
6	KIDNEY # # (CARCINOMA#; ADENOCARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###)/(TI; AB; UT)	7520
7	(CARCINOMA#; ADENOCARCINOMA#; CANCER#; NEOPLASM#; TUMO#R#; MALIGNANC###) # # KIDNEY/(TI; AB; UT)	5103
8	(HYPERNEPHROMA# OR NEPHROID CARCINOMA# OR HYPERNEPHROID CARCINOMA# OR GRAWITZ TUMO#R)/(TI; AB; UT)	1108
9	RCC/(TI; AB; UT) OR MRCC/(TI; AB; UT)	11421
10	2 TO 9	75393
11	CT=QUALITY OF LIFE	137226
12	CT=VALUE OF LIFE	5493
13	CT D HEALTH STATUS	118425
14	CT D HEALTH STATUS INDICATORS	221370
15	CT=QUALITY-ADJUSTED LIFE YEARS	8320
16	CT=ACTIVITIES OF DAILY LIVING	54077
17	CT=SURVEYS AND QUESTIONNAIRES	342916
18	CT=HEALTH SURVEYS	50940
19	CT=SELF REPORT	14313
20	CT=PSYCHOMETRICS	59420
21	CT=KIDNEY NEOPLASMS/QF=PSYCHOLOGY OR CT=RENAL CELL CARCINOMA NEOPLASMS/QF=PSYCHOLOGY	102
22	QUALITY OF LIFE/(TI; AB; UT)	189486
23	LIFE QUALITY/(TI; AB; UT)	4611

24	QUALITY ADJUSTED LIFE/(TI; AB; UT)	8320
25	(QOL OR HRQOL OR HRQL OR HQL OR QALY# OR QALE)/(TI; AB; UT)	43839
26	DISABILITY ADJUSTED LIFE/(TI; AB; UT)	1885
27	DALY#/(TI; AB; UT)	1750
28	(HEALTH# YEAR# EQUIVALENT# OR HYE#)/(TI; AB; UT)	82
29	HEALTH # STAT##/(TI; AB; UT)	49587
30	UTILIT### # # #, (HEALTH; VALU?; MEASUR?; LIFE; ESTIMAT?; ELICIT?; DISEASE?; SCORE?; WEIGHT?)./(TI; AB; UT)	10645
31	PREFERENCE # # #, (HEALTH; VALU?; MEASUR?; LIFE; ESTIMAT?; ELICIT?; DISEASE?; SCORE?; WEIGHT?; INSTRUMENT#)./(TI; AB; UT)	4514
32	(DISUTILIT### OR HSUV#)/(TI; AB; UT)	338
33	(INDEX # # WELLBEING OR INDEX # # WELL BEING OR QUALITY # # WELLBEING OR QUALITY # # WELL BEING OR QWB)/(TI; AB)	710
34	ROSSER/(TI; AB; UT)	79
35	(SF36 OR SF 36 OR SHORT FORM 36 OR SHORTFORM 36 OR SF THIRTYSIX OR SF THIRTY SIX OR SHORTFORM THIRSTYSIX OR SHORTFORM THIRTY SIX OR SHORT FORM THIRTY SIX OR SHORT FORM THIRTYSIX OR SHORT FORM THIRTY SIX)/(TI; AB; UT)	19587
36	(SF6 OR SF 6 OR SHORT FORM 6 OR SHORTFORM 6 OR SF SIX OR SFSIX OR SHORTFORM SIX OR SHORT FORM SIX)/(TI; AB; UT)	1654
37	(SF12 OR SF 12 OR SHORT FORM 12 OR SHORTFORM 12 OR SF TWELVE OR SFTWELVE OR SHORTFORM TWELVE OR SHORT FORM TWELVE)/(TI; AB; UT)	3832
38	(SF16 OR SF 16 OR SHORT FORM 16 OR SHORTFORM 16 OR SF SIXTEEN OR SFSIXTEEN OR SHORTFORM SIXTEEN OR SHORT FORM SIXTEEN)/(TI; AB; UT)	25
39	(SF20 OR SF 20 OR SHORT FORM 20 OR SHORTFORM 20 OR SF TWENTY OF SFTWENTY OR SHORTFORM TWENTY OR SHORT FORM TWENTY)/(TI; AB; UT)	348
40	(EUROQOL OR EQ-5D OR EQ5D)/(TI; AB; UT)	6043
41	(HEALTH UTILITIES INDEX OR HUI OR HUI1 OR HUI2 OR HUI3)/(TI; AB; UT)	1855
42	MEDICAL OUTCOMES SURVEY#/(TI; AB; UT)	244
43	(TIME TRADE OFF OR TIME TRADEOFF OR TTO)/(TI; AB; UT)	1432

44	STANDARD GAMBLE/(TI; AB; UT)	730
45	(WILLINGNESS T% PAY OR WTP)/(TI; AB; UT)	3506
46	(RATING SCALE# OR LINEAR ANALOG? OR VISUAL ANALOG? OR CATEGOR? # SCALE?)/(CT; TI; AB; UT)	141622
47	(QLQ-C30 OR FKSI OR FACIT OR FACT-G OR FLIC)/(TI; AB; UT)	4327
48	FUNCTIONAL LIVING INDEX CANCER/(TI; AB; UT)	108
49	QUALITY OF LIFE CANCER SCALE#/(TI; AB; UT)	3
50	QUALITY OF LIFE QUESTIONNAIRE CORE 30 ITEMS/(TI; AB; UT)	10
51	FUNCTIONAL ASSESSMENT OF CANCER THERAPY/(TI; AB; UT)	1434
52	FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY/(TI; AB; UT)	420
53	FACT KIDNEY SYMPTOM INDEX/(TI; AB; UT)	7
54	11 TO 53	1043301
55	10 AND 54	1605
56	55 NOT (CT D ANIMALS NOT CT=HUMANS)	1595
57	56 AND PY> =2006	1085

Embase.com

Database	**Embase**
Search platform: DIMDI Classic Search ***Date of the search:*** **July 6, 2016 [Last Database Update: July 5, 2016** ***Data range searched:*** **1974-2016, restricted to 2006-2016 in the last step**	
Search Strategies guided by the named search filters:	• Papaioannou, D., Brazier, J.E., Paisley, S. (2011) NICE DSU Technical Support Document 9: The identification, review and synthesis of health state utility values from the literature. Available from http://www.nicedsu.org.uk • Paisley, S., Booth, A., Mensinkai, S.. Health-related quality of life studies. Etext on Health Technology Assessment (HTA) Information Resources. US National Library of Medicine (NLM) National Information Center on Health Services Research and Healthcare Technology (NICHSR); Bethesda: 2005.

#	Search Terms	Hits
#1	'kidney carcinoma'/exp	53423
#2	'kidney tumor'/de OR 'kidney cancer'/de	48046
#3	(renal NEAR/3 (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour*)):ab,ti	64659
#4	(kidney NEAR/3 (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour*)):ab,ti	15740
#5	mrcc:ab,ti OR rcc:ab,ti OR hypernephroma*:ab,ti OR (nephroid NEXT/1 carcinoma*):ab,ti OR (hypernephroid NEXT/1 carcinoma*):ab,ti OR (grawitz NEXT/1 tumor*):ab,ti OR (grawitz NEXT/1 tumour*):ab,ti	20658
#6	#1 OR #2 OR #3 OR #4 OR #5	109630
#7	'quality of life'/de	319857
#8	'quality adjusted life year'/exp	16387
#9	'health status'/de	98625
#10	'health status indicator'/exp	12407
#11	'health survey'/de	165961
#12	'scoring system'/exp	200241
#13	'rating scale'/exp	95816
#14	'functional assessment'/exp	53349
#15	'self report'/exp	82753
#16	'psychometry'/de	48635
#17	'quality of life':ab,ti	270843
#18	'life quality':ab,ti	8395
#19	'quality adjusted life':ab,ti	12078

#20	qol:ab,ti OR hrqol:ab,ti OR hrql:ab,ti OR hql:ab,ti OR qaly*:ab,ti OR qale:ab,ti	74427
#21	'disability adjusted life':ab,ti	2211
#22	daly*:ab,ti	2293
#23	(health* NEXT/1 year* NEXT/2 equivalent*):ab,ti OR hye*:ab,ti	1247
#24	(health NEXT/2 status):ab,ti OR (health NEXT/2 state):ab,ti	58967
#25	disutilit*:ab,ti OR hsuv:ab,ti OR hsuvs:ab,ti	574
#26	(utilit* NEAR/3 health):ab,ti OR (utilit* NEAR/3 valu*):ab,ti OR (utilit* NEAR/3 measur*):ab,ti OR (utilit* NEAR/3 life):ab,ti OR (utilit* NEAR/3 estimat*):ab,ti OR (utilit* NEAR/3 elicit*):ab,ti OR (utilit* NEAR/3 disease*):ab,ti OR (utilit* NEAR/3 score*):ab,ti OR (utilit* NEAR/3 weight*):ab,ti	13336
#27	(preference* NEAR/3 health):ab,ti OR (preference* NEAR/3 valu*):ab,ti OR (preference* NEAR/3 measur*):ab,ti OR (preference* NEAR/3 life*):ab,ti OR (preference* NEAR/3 estimat*):ab,ti OR (preference* NEAR/3 elicit*):ab,ti OR (preference* NEAR/3 disease*):ab,ti OR (preference* NEAR/3 score*):ab,ti OR (preference* NEAR/3 weight*):ab,ti OR (preference* NEAR/3 instrument*):ab,ti	9684
#28	(index NEAR/3 wellbeing):ab,ti OR (index NEAR/3 'well being'):ab,ti OR (quality NEAR/3 wellbeing):ab,ti OR (quality NEAR/3 'well being'):ab,ti OR qwb:ab,ti	3363
#29	rosser:ab,ti	96
#30	'short form 36'/exp	19166
#31	sf36:de,ab,ti OR 'sf 36':de,ab,ti OR 'short form 36':de,ab,ti OR 'shortform 36':de,ab,ti OR 'sf thirtysix':de,ab,ti OR 'sf thirty six':de,ab,ti OR 'shortform thirtysix':de,ab,ti OR 'shortform thirty six':de,ab,ti OR 'short form thirtysix':de,ab,ti OR 'short form thirty six':de,ab,ti	33317
#32	sf6:de,ab,ti OR 'sf 6':de,ab,ti OR 'short form 6':de,ab,ti OR 'shortform 6':de,ab,ti OR 'sf six':de,ab,ti OR 'sfsix':de,ab,ti OR 'shortform six':de,ab,ti OR 'short form six':de,ab,ti	1784

#33	sf12:de,ab,ti OR 'sf 12':de,ab,ti OR 'short form 12':de,ab,ti OR 'shortform 12':de,ab,ti OR 'sf twelve':de,ab,ti OR 'sftwelve':de,ab,ti OR 'shortform twelve':de,ab,ti OR 'short form twelve':de,ab,ti	6677
#34	sf16:de,ab,ti OR 'sf 16':de,ab,ti OR 'short form 16':de,ab,ti OR 'shortform 16':de,ab,ti OR 'sf sixteen':de,ab,ti OR 'sfsixteen':de,ab,ti OR 'shortform sixteen':de,ab,ti OR 'short form sixteen':de,ab,ti	47
#35	sf20:de,ab,ti OR 'sf 20':de,ab,ti OR 'short form 20':de,ab,ti OR 'shortform 20':de,ab,ti OR 'sf twenty':de,ab,ti OR 'sftwenty':de,ab,ti OR 'shortform twenty':de,ab,ti OR 'short form twenty':de,ab,ti	384
#36	euroqol:ab,ti OR 'eq-5d':ab,ti OR eq5d:ab,ti	10499
#37	'health utilities index':ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti	2707
#38	(medical NEXT/1 outcomes NEXT/1 survey*):ab,ti	315
#39	psychometr*:ab,ti	39424
#40	'time trade off':ab,ti OR 'time tradeoff':ab,ti OR tto:ab,ti	1948
#41	'standard gamble':ab,ti	887
#42	'willingness to pay':ab,ti OR wtp:ab,ti	5322
#43	(rating NEXT/1 scale*):ab,ti OR (linear NEXT/1 analog*):ab,ti OR (visual NEXT/1 analog*):ab,ti AND (categor* NEXT/2 scale*):ab,ti	317
#44	'qlq-c30':ab,ti OR fksi:ab,ti OR facit:ab,ti OR 'fact-g':ab,ti OR flic:ab,ti	7606
#45	'functional living index cancer':ab,ti	122
#46	('quality of life' NEXT/1 cancer NEXT/1 scale*):ab,ti	6
#47	'quality of life questionnaire core 30 items':ab,ti	11
#48	'functional assessment of chronic illness therapy':ab,ti	690
#49	'fact kidney symptom index':ab,ti	18
#50	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	105316

	OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49	3
#51	#6 AND #50	3628
#52	#51 NOT ('animal'/exp NOT 'human'/exp)	3607
#53	#52 AND [2006-2016]/py	3000

Cochrane Library (NHSEED, HTA Database)

Databases	**NHS Economic Evaluation Database (NHS EED), HTA Database**
Search Platform:	Cochrane Library (Wiley)
Date of Search:	July 6, 2016 [Last Database Update: NHS EED April 2015, HTA database April 2016]
Date Range Searched:	Restricted to 2006-2016 in the last step
Search Filters Used	none

#	Search Terms	Hits
#1	[mh ^"Carcinoma, Renal Cell"]	546
#2	[mh ^"kidney neoplasms"]	720
#3	(renal near/3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumor* or tumour*)):ab,ti,kw	1420
#4	(kidney near/3 (carcinoma* or adenocarcinoma* or cancer* or neoplasm* or tumor* or tumour*)):ab,ti,kw	1307
#5	mrcc:ab,ti,kw or rcc:ab,ti,kw or hypernephroma*:ab,ti,kw or (nephroid next/1 carcinoma*):ab,ti,kw or (hypernephroid next/1 carcinoma*):ab,ti,kw or (grawitz next/1 tumor*):ab,ti,kw or (grawitz next/1 tumour*):ab,ti,kw	554
#6	#1 or #2 or #3 or #4 or #5	1867
#7	#6 in Technology Assessments and Economic Evaluations	116
#8	#7 Publication Year from 2006 to 2016	93

In addition, NICE website was searched for evidence review group reports, manufacturer submissions and other relevant documents for second-line mRCC.

Results

Overview of the results

Database	Number of Findings
Medline	1085
Embase	3000
Cochrane Library	93
Total (including duplicates)	4178
Total (excluding 571 duplicates)	**3607**

Results per database

Medline (includes Medline in Process and other non-indexed citations (with status: publisher, in-data review or Pubmed-not-Medline)

Short description	Position in Search Protocol	No. of findings
RENAL CELL CANCER		75393
AND HEALTH STATE UTILITIES	55	1605
NOT (ANIMALS NOT HUMANS)	56	1595
AND PY>=2006	**57**	**1085**

Embase

Short description	Position in Search Protocol	No. of findings
RENAL CELL CANCER	#6	109630
AND HEALTH STATE UTILITIES	#51	3628
NOT (ANIMALS NOT HUMANS)	#52	3607
AND PY>=2006	**#53**	**3000**

Cochrane Library (NHSEED, HTA Database)

Short description	Position in Search Protocol	No. of findings
RENAL CELL CANCER	#6	1867
RESTRICTION OF HITS TO NHSEED, HTA-DATABASE	#7	116
AND PY>=2006	#8	93

Study selection

During the systematic review of abstracts and full-text articles following in- and exclusion criteria were applied in Table 73, Data was extracted into the summary tables by a single reviewer. Uncertainties were resolved following discussion with a second reviewer.

Table 73: In- and exclusion criteria

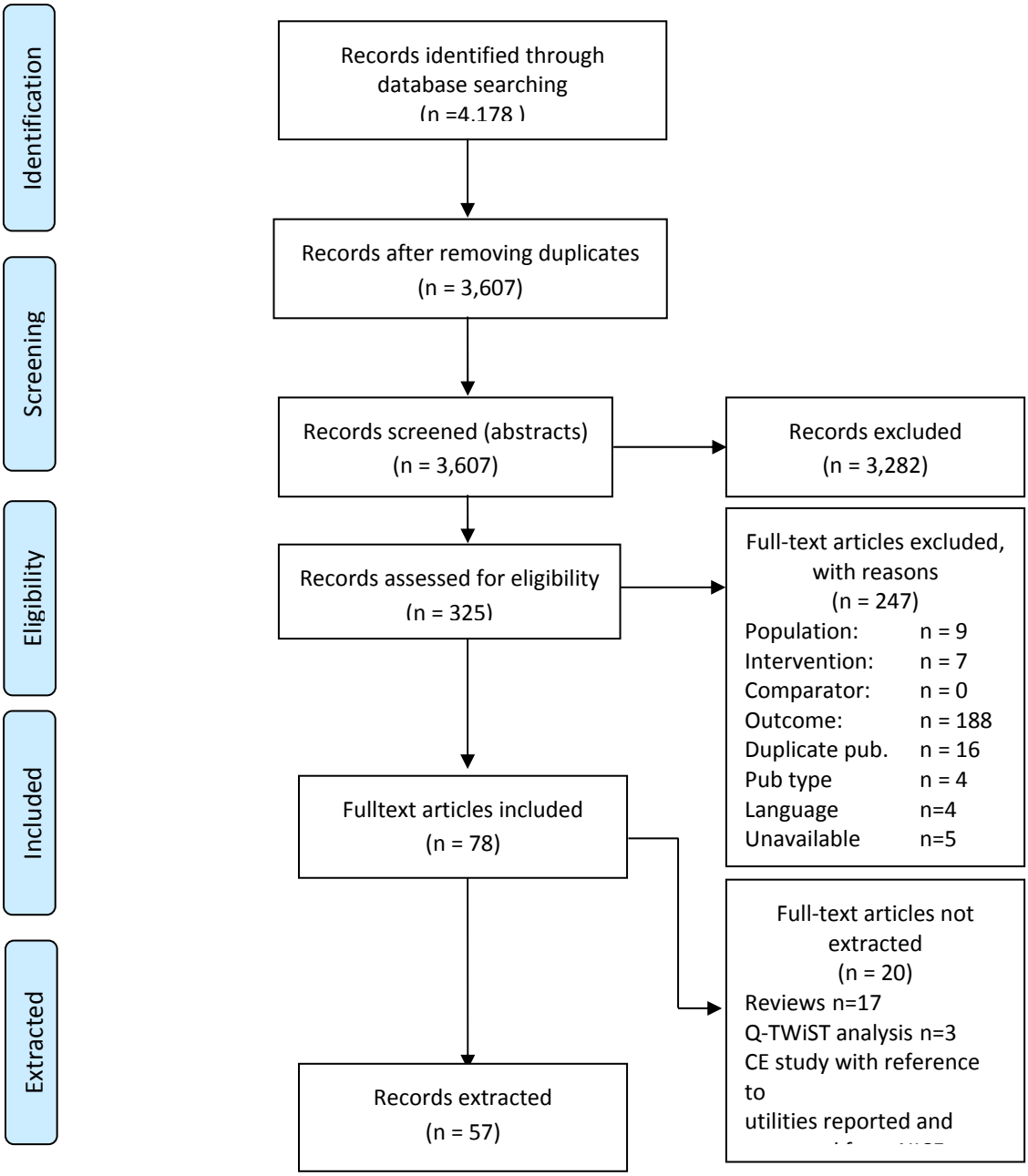
Criteria	Code	Include	Exclude
Population	I1	Adult patients with RCC	Paediatric population and other indications
Intervention	I2	Any (excluded interventions such as surgery, ablation and non - pharmacological therapy, included BSC treatment)	-
Comparator	I3	'Any (excluded interventions such as surgery, ablation and non - pharmacological therapy, included BSC treatment)	-
Outcomes	I4	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	I5	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	I6	No restrictions. English, German, French, Spanis and Italian (publications in other languages will be listed, and only abstracts in English included)	-

Publication type	I7	Full-text publications, conference proceedings	-
Duplicate	E1	Duplicate (including previouse cersions of updated Cohrane reviews; multiple conference abstract/publication on the same study with no additional results)	

Results

Study flow chart

In total, 4,178 papers were identified through the electronic searches. Upon removal of 613 duplicates, 3,607 abstracts were reviewed. Of these, 3,282 were excluded leaving 325 citations for the next screening stage. Out of the 325 full-text publications, there were 78 included in this review.



Identified studies

In total 78 studies were included.Evidence was extracted from N=57 publications (including HTA reports, cost-effectiveness/utility studies; clinical and observational trials). There were N=17 reviews , N=3 studies were Q-TWiST analysis (being more methodological papers and actually survival analysis). For the potential future use these studies were included and marked in comment cells in the sheet, however evidence was not extracted form them. One cost-effectiveness analysis was included, butas the utility information references data already extracted under NICE TA178, this cost-effectiveness anlaysis was only listed.

Data extraction

Relevant data from full-text articles and conference abstracts were extracted into an Excel spreadsheet. Three key technology assessment at NICE: everolimus, Axitinib and Nivolumab for advanced and/or metastatisc RCC were extracted in a separate Excel sheet.

Appendix 6 – Cost acceptability

Figure 73. [redacted]

Figure 74: [redacted]

Figure 75: [redacted]

Figure 76: [redacted]

Figure 77: [redacted]

Figure 78: [redacted]

Figure 79: [redacted]

Figure 80: [redacted]

Figure 81: [redacted]

Figure 82: [redacted]

Figure 83: [redacted]

Figure 84: [redacted]

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Response to the Appraisal Consultation Document: Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Kidney Cancer Support Network Statement

The NICE technology appraisal committee have not recommended cabozantinib for use within its marketing authorisation for the treatment of advanced renal cell carcinoma (RCC) in adults after vascular endothelial growth factor (VEGF)-targeted therapy. This is despite cabozantinib's proven effectiveness at prolonging the life of kidney cancer patients by 4.9 months compared to everolimus in the METEOR trial, and impressive progression-free survival benefit in patients with spread to their bones, reducing the risk of death by 46% compared with everolimus in patients with bone metastases.

The Kidney Cancer Support Network's response to the cabozantinib ACD has been informed by the views of advanced kidney cancer patients who are taking cabozantinib as part of a clinical trial or through a Managed Access Programme in the UK.

1. Innovative, breakthrough therapy

Cabozantinib has been proven to be a clinically effective and well-tolerated drug, and **designated a 'promising innovative medicine' for advanced RCC by the Medicines and Healthcare products Regulatory Agency (MHRA)** last year. Also, cabozantinib was **designated a breakthrough therapy by the FDA for the treatment of advanced RCC** in 2015. As an innovative, breakthrough therapy, cabozantinib has been fast tracked for approval in a number of countries, and has been made available in the UK through a Managed Access Programme by the manufacturer.

Cabozantinib is the first tyrosine kinase inhibitor to act on multiple tyrosine kinase receptors, including c-MET, VEGF2, AXL and RET. Its c-MET activity may explain its effectiveness against bone metastases, since MET appears to be an important growth factor in the bone microenvironment. The following statement from the husband of a patient highlights the importance to patients of cabozantinib's efficacy against bone metastases:

> *"…..CT and MRI results …… yesterday gave excellent news confirming her 10-off* [sic] *spinal bone Mets being reported stable. This is a great result having halted the disease given she only recently commenced her Cabozantinib treatment on 23/11/16; at a time when the bone progression appeared aggressive, i.e. with 3 lytic bone Mets being reported by CT scan on 21/10/16 increasing to 10 Mets reported from an MRI scan on 19/12/16.*
>
> *"……. the immediate issue was rapidly developing bone mets (i.e. crocodiles nearest the boat, so to speak). Since Cabo was the only 'available' agent that has a pathway able to specially target bone Mets, then this became OUR first choice …... Note: we had overturned the originally advised preference ranking order for Axitinib, Nivolumab and lastly Cabozantinib."*

It seems that cabozantinib may be particularly effective for treating patients with bone metastases. Bearing this in mind, if the committee is minded not to approve cabozantinib, the **Kidney Cancer Support Network urge NICE to reconsider cabozantinib for the Cancer Drugs Fund (CDF) while further survival data are collected from the cohort of patients with bone metastases** to provide further evidence to support this effect in advanced RCC patients. With around 5,000 patients diagnosed with advanced RCC per year, this disease is designated a rare cancer. This should be considered when setting time limits for the collection of survival data, and the 24-

month period, as specified in the CDF SOP for collection of addition evidence to support this observation, should to be extended for the small population of patients who have spread to their bones.

Cabozantinib is already available in North America and Europe for advanced RCC. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that innovative new drugs are made available to patients in order that they have the best possible care. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. A contributory factor to poor survival rates in the UK is possibly due to the restrictions in clinical choice brought about by UK regulatory authorities.

The committee's decision to not recommend cabozantinib for advanced RCC patients after failure of prior systemic therapy denies terminally ill kidney cancer patients access to innovative and effective treatment within NHS England, despite the drug being available for kidney cancer patients living in other European countries. This is confusing for the patient community because the committee has acknowledged the fact that cabozantinib is effective, but recommends the drug as not a good use of NHS England resources. The committee does not attempt to explain how they reconcile these two positions to those affected by their decision.

Nowadays, kidney cancer patients do not exist in silos. They communicate widely; international discussion forums exist where patients talk to one another daily. An international coalition of patient organisations (www.ikcc.org) currently has 23 member countries. Patients and clinicians are right to expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so they have the same choices as patients in other countries. The following statements are from a patient and the wife of a patient with a bone metastasis, and demonstrates how well informed advanced RCC patients are:

> *"Three years after a nephrectomy for RCC, I became aware of bone pain in my femur, which subsequently broke due to a single site metastasis that had become so large there was very little bone remaining. Following surgery, in December 2014 I was started on Sunitinib. At that time I had no other mets, and that is still the case, so Sunitinib has been successful in preventing spread, however, it has had no measurable impact in reducing the bone met, over 2 years later. Sunitinib, like the other currently approved drugs is not greatly effective on bone mets. However Cabozantinib has clear data demonstrating that it can be highly effective in shrinking and removing altogether bone metastases. For me, that could mean achieving NED, which result in a big saving in no requiring further expensive treatment* [sic].
>
> *"This is the only drug currently available that is so effective on bone mets and therefore for patients like myself it is essential that this drug is approved for use at least in the second line setting to offer real hope to patients with bone metastases. I would therefore urge NICE to approve this new drug as soon as possible"*
>
> *"My husband has run out of options for surgery on his maxilla area without it compromising his eye. His other secondaries are kept under control and after nearly 7 years he is stable. He needs a drug, which works on bone metastases as none of the current drugs appear to have any measurable success and sadly kidney cancer often goes to hips and spine as well as other areas."*

2. Safety, tolerability and quality of life

The METEOR trial confirms that adverse events with cabozantinib are as expected for a VEGF receptor inhibitor for the treatment of advanced RCC. The proportion of patients reporting an adverse event was similar for cabozantinib and everolimus, the most common adverse events for cabozantinib being diarrhoea, fatigue and nausea. Clinicians and patients have a number of years of experience dealing with VEGF receptor inhibitor adverse events, and consider the benefits of improved overall survival and effectiveness against bone metastases outweigh the inconvenience of adverse events. As for other VEGF receptor inhibitors, such as sunitinib and pazopanib, adverse events are managed by dose reductions or 'drug holidays', and patients are prepared to accept this inconvenience for the benefits the drug provides:

> *"Just been to see you* [sic] *oncologist, cabos not been very kind sore mouth peeling hands and high blood pressure decided to give me a two week break bit disappointed but it's a new drug I probably know more than they do they follow the drug advice and play it by ear starting again on January 1st on 40 mg down from 60 heres* [sic] *hoping the side effects wear off quickly and I can enjoy my turkey."*

"This is an update on cabozantnib [sic] *after the first month on 40mg the side effects are better with the reduced dose the worst seems to be the sore mouth and loss of taste although I have a number of cures nothing gets rid of it completely I also got unexplained muscle pain and a need to sleep at least twice a day I have not had full diarrhoea something in between. I am glad to say this is all wearing off for now and I am starting to feel good again so to sum up nothing terrible has happened and I have coped the real test will be when I have a scan and we find out how successful it has been".*

The following statement is from the husband of a patient taking cabozantinib, and highlights the proactivity of patients when managing side effects. This patient has been taking cabozantinib for nearly 3 months and now has stable disease:

" As regards side effects, these were getting too tough last week and coincidentally combined with a urinary tract infection, prompting antibiotics and an unscheduled intermission in her Cabo treatment. Planing [sic] *to resume Cabo this Saturday but shall need to keep the proactive drinking and exercise regime to alleviate toxicity effects and fatigue. Diarrhoea has been problem but treated with Imodium and codiene."*

From the evidence we have gathered from the advanced RCC patients from the Kidney Cancer Support Network currently taking cabozantinib through the Managed Access Programme, this drug offers hope and an alternative effective treatment to patients who have failed on previous VEGF receptor inhibitors, and who have spread to their bones:

"Just finished first week on cabo and to be honest I cant believe how well it has gone I started to feel better almost immediately and it has carried on the pain in my back has reduced and my mobility improved so far few problems very sore mouth slight blood pressure and diabetes variations but otherwise ok I can't believe it if this carries on it could be the wonder drug were all hoping for. 2nd week on cabo not as good as first side effects started Monday sore mouth is worst got gelclair difflam but there [sic] *not very effective at the moment and fatigue its messed my sleep patterns up ….. but I suppose side effects must mean its working just trying to keep positive.*

"I have now had the official report on my scan tumour in my lung which was 2cm is now 1cm and although it is difficult to see because of the metalwork on my spine it is stable this is great news. Because bone doesn't regenerate itself stability is something as far as cabozantnib [sic] *its self it has been challenging sore mouth peeling hands dioreaha* [sic] *and muscle pain and fatigue my oncologist had been to a presentation by the drug company at which they made light of the side effects but she stated that all patients …. taking the drug were finding it challenging however when you find it is working then it is all worthwhile. I am on a 2 week break which may be necessary to tolerate as with sutent and also further reduction to 20mg as you can imagine I am delighted and it is another weapon in the armoury something to give hope to all."*

"I [am] on Cabozantinib but have only had 4 weeks on it (with a week's gap in between as I had some radiotherapy)…….. the doctor I saw noticed that a visible lump on my jaw (on the muscle) which I had been told, after a biopsy, was down to the kidney cancer, had gone down quite a bit. Obviously this doesn't mean much overall but he did say that they've found when the Cabozantinib works, it works quite quickly so it looks like a positive sign at least…. So far the side-effects have been quite manageable but ……. I don't know how it will be after a few weeks without a break. …… I have some bone mets…… I previously had 18 months on Everolimus, which suddenly stopped working, then a few weeks on Nivolumab, which the doctors felt was enough to show it wouldn't work for me so I'm not sure what the alternative would have been."

3. Choice of treatment and unmet need at third line

In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available, and **without cabozantinib, the clinician's choice of treatment is seriously compromised**. Without treatment alternatives in the second- and third-line, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life:

"Whilst I have not had direct experience of taking Cabozantinib as I am still responding to Pazopanib, I have read both the clinical trial reports and real world patient experience. I believe that this would form a

useful addition to the portfolio of drugs available to clinicians and will be especially useful for those patients with bone metastasis. The addition of more potential drugs would introduce more competitive pricing between suppliers."

Current second-line treatment options are not effective for everyone, and can be difficult to access. Undue restrictions in accessing cabozantinib would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the second- and third-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient. Cabozantinib will also address the massive unmet need for treatment options in the third-line.

The following statements are from a patient carer and two patients talking about the importance of having choice of treatment in the second- and third-line setting:

"Another important consideration to factor is that some drugs can work better later in the cycle of this disease, what I mean is - research supports Nivo tends to be more effective when your cancer is more mutated, so had we chose [sic] *this option now (possibly too early) then it may have not worked and we could have lost a valuable treatment option needed later."*

"I have used sutent, pazopanib and now axitinib for almost five years. When Axitinib is done, I want to be able to turn to Cabozantinib as I have a bone met. Please give me the choice."

"In response to cazantinib [sic] *not being approved by NICE, this is a drug that had been mentioned to me as a next step to help keep my kidney cancer at bay, it could give me valuable extra time with my two young daughters aged 4 & 2 years old. Without this medication my girls could lose their mummy too soon & they don't deserve that. This could help so many people live longer, everybody is worthy of that chance. Please think again."*

Choice of treatment is also important when it comes to drug combinations. Cabozantinib is already being tested in combination with immunotherapy in the USA, and could prove to be a formidable treatment regimen, if successful. The following are some thoughts of a patient carer on the subject of drug combinations:

"…….. it could open opportunities to be within the mix of combination, e.g. it could be beneficially combined with Nivolumab and Iplimumab [sic] *to improve the chance of a complete response. I believe this specific combination is being trialled in USA now."*

4. Cost effectiveness

We are disappointed that **yet again another drug for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare cancer):** Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life-prolonging treatments during a desperately difficult time for both themselves and their families.

We understand that cabozantinib is expensive, and we appreciate the budgetary implications, but nonetheless NICE and the manufacturers must negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as failure of professional competence. NICE and the manufacturer need to think outside the box to agree an alternative funding scheme, and work collaboratively to negotiate an acceptable patient access scheme to ensure kidney cancer patients who need it can have access to this latest clinically effective drug.

"My dad's consultant has suggested that should nivolumab stop working then this would be the next step. He specifically mentioned that Cabozantinib was more effective on bone mets than other lines of treatment, which we took as a positive since dad has mets on his spine. If this wasn't an option I think we'd be at the end of the line as dad has had IL2, sutent and axitinib prior to nivolumab. It really would be a matter of life and death and to know that there is something there that could extend life but wasn't available would be heart breaking. I know there has to be assessments around cost versus impact, but given dad's history it might have been felt that nivolumab wouldn't work when it has - he's been on it for

almost a year now. Some weren't as lucky as dad and missed nivolumab. I'd hate to see this happen again."

5. Effect of NICE's decision on UK clinical research

We are concerned that NICE's decision not to recommend cabozantinib may negatively impact the clinical research environment in the UK. Patients who participated in UK clinical trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of cabozantinib on the NHS in England, we must question whether patients will continue to support future research by taking part in clinical trials.

Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if NICE fail to allow these drugs to get to the patients who need them. A rejection of cabozantinib will mean that a substantial number of late stage kidney cancer patients will be denied the opportunity to benefit from a new, innovative and clinically effective drug.

Thank you for allowing the Kidney Cancer Support Network to take part in this single technology appraisal. We welcome the opportunity to put forward the views of our Kidney Cancer Support Network patient community for this important health technology appraisal of cabozantinib in advanced renal cell carcinoma.

Best regards

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Kidney Cancer UK response to the cabozantinib ACD

Kidney Cancer UK are currently very disappointed that it appears NICE are unlikely to recommend cabozantinib as an alternate second line treatment for kidney cancer. The clinical trial METEOR appeared very successful with a significant extension on the overall survival and progression free survival over everolimus. This extension of life can be invaluable for people spending precious time with their loved ones. For some people the extension of life can continue long term and the cancer can be classed as a chronic rather than a life limiting disease.

Kidney cancer UK have direct contact with people who have received cabozantinib as a treatment for advanced kidney cancer. Dave Chessum a kidney cancer patient kindly shared his experience with cabozantinib with Kidney Cancer UK in order to help others going through similar experiences. A copy of this video can be viewed on our YouTube channel.
https://www.youtube.com/watch?v=9asTUb1CZRU

His experience describes his kidney cancer returning 4 years after his original nephrectomy. The past 4 years he has been receiving systemic drug treatments to reduce the growth of his tumour. Initially he was on everolimus and then axitinib. Both of which gave him fairly severe side effects such as sore mouth and feet, lack of taste and uncontrollable diarrhoea. He describes the diarrhoea as being very antisocial and that he had to change his whole lifestyle. However, he has a positive outlook and explains how he was still happy to take the drug to control the cancer.

His second line drug axitinib also increased his blood pressure and unfortunately he had a stroke which hospitalised him for 3 weeks. At this stage he stopped all medication for 13 weeks. Axitinib cessed working for him and he felt that the gap in treatment has set him back in the fight against the tumour growth.

He was then approached by Addenbrookes hospital and asked to try cabozantinib. He describes the change to cabozantinib as providing him with “a complete change in my social outlook and wellbeing” due to the diarrhoea side effects being almost eradicated. “All of a sudden my life wasn’t being dictated to by where the nearest toilet was”. Dave Chessum says he feels much more positive and relaxed and although he is trying to catch up after stopping medication for a while he is hoping that the next scan will show less growth.

Dave Chessum’s experience illustrates that different drugs can have varying side effect profiles for different people and that alternate options can provide a great deal of hope. So a variety of options is vital for the treatment of advanced kidney cancer. Cabozantinib has proved to have a favourable side effect profile for Dave Chessum and at this stage has provided him and his family an alternative option and positivity for the future.

Currently the number of recommended drug options for patients with kidney cancer is limited, especially compared to America and the rest of Europe. We urge you to consider this when deciding whether to recommend cabozantinib or not.

Dear NICE Committee B members,

Thank you for the opportunity to comment on the February 2017 draft Appraisal Consultation Document (ACD) for cabozantinib for previously treated advanced renal cell carcinoma.

It is with the importance of allocating scarce NHS resources both equitably and efficiently in mind that we make three observations about this ACD, which seem to be crucial for fair decision making.

The different survival implications of immunotherapies and tyrosine kinase inhibitors (TKIs)

Noting that both the company's preferred approach and the preferred approach of the Evidence Review Group (ERG) impose similar survival assumptions upon cabozantinib, nivolumab, axitinib and everolimus, we are grateful to the Committee for (i) highlighting the need for evidence on the natural history of disease to guide overall survival modelling (Section 4.15) and (ii) for acknowledging the clinical expectation of immunotherapeutic survival benefit for nivolumab in the recently completed TA417 (Section 4.16), which has crucial implications for decision making for cabozantinib.

During TA417, different Consultant NHS Oncologists independently reported that it was "likely" and "very likely" that an immunotherapeutic tail would be seen for patients in the key trial for nivolumab in RCC (CheckMate 025), and that patients who experienced this effect would be expected to have survival similar to age-matched general population values. In exploratory analyses for TA417, we presented results assuming 50% of nivolumab patients who survive to 5 years would then have the same risk of death after 5 years as the age-matched general population, and this had a profound effect upon results.

We hope, in light of the evidence the Committee has in its hands from TA417, that the different survival extrapolation implications of immunotherapies and TKIs will be considered in the decision for this appraisal.

The importance of robust EQ-5D data analysis

Patient-reported EQ-5D data are the NICE Reference Case gold standard utility data source, and it is a strength of the company's submission that the METEOR study collected such data. As such, it is appropriate that in Section 4.20 the Committee expressed a preference for these data to inform utility assumptions in the economic model. However, we would like to raise two issues relating to the analysis and incorporation of the utility data in the company analysis:

1. It is crucial that such data are analysed in a way that attempts to address bias, or appraisals will be subject to unnecessary bias, as we fear may be the case here.
2. Analyses of the data collected within CHECKMATE 025 demonstrated an independent impact of both progression status and treatment allocation on utility.

Both of these points are discussed, in brief, below.

As the ERG has observed, the company's EQ-5D utility estimates (0.817 for progression-free survival, 0.777 for post-progression survival) are very high. The median patient age at baseline in the METEOR study was 63 years old; the average EQ-5D utility for general population 63-year-olds from the Health Survey for England data analysis published by Brazier and Ara is 0.813.[1] In this context, the post-progression estimate of 0.777 is even harder to believe.

The most likely reasons for these unlikely results are autocorrelation (repeated estimates from the same patient being correlated but assumed independent in the analysis) and sample attrition biasing

results. Fitter patients are more likely to complete the EQ-5D questionnaire, and more likely to continue to respond to questionnaires if they continue to be healthy. If this is the case, it is important that the company, as a minimum:

- presents evidence on completion rates over time for the EQ-5D questionnaire, and
- analyses the data in a way that is suitable in the presence of autocorrelation, such as using a generalised estimating equation.

It is extremely difficult to fully account for autocorrelation and attrition bias when they are present. However, we advise that the steps taken in TA417 contributed to what was as fair an appraisal as was possible. If the company has not shown evidence for completion over time or has not considered measures to address the potential problems we highlight here, we encourage the Committee to ensure that this is done before a decision is made.

In Section 4.20, the ACD states that the METEOR utility values should be adjusted for aging. That is fair, and could be done using general population utility data if utility is expected to diminish with age in a similar way for renal cell carcinoma patients, with acceptable assumptions. However, we stress that this does not address the bias we suspect is present from incorrect analysis of the METEOR EQ-5D data.

In addition, analyses of utility data from CheckMate 025 demonstrated that the treatment received had a significant impact on utility both pre- and post-progression. The rationale behind this observed effect is sound; nivolumab has a more favourable toxicity profile than everolimus, nivolumab treatment can continue beyond progression, nivolumab's immunotherapeutic benefit can continue beyond discontinuation, and there is a benefit for utility of the hope of potential long-term survival because of the anticipated immune-oncology effect. The simple application of the METEOR utility data to all comparators in the company submission is inconsistent with this.

Life expectancy for previously treated renal cell carcinoma patients

Section 4.23 of the ACD discusses the life expectancy for previously treated renal cell carcinoma patients, and rightly expresses concern regarding the company's model's prediction of survival for nivolumab. We hope it may be helpful to summarise the evidence presented in TA417.

Median expected survival for renal cell carcinoma receiving second-line axitinib is less than 24 months (20.1 months in the AXIS trial; 15.2 months in the sunitinib-pre-treated subgroup), as is median expected survival for everolimus patients (19.6 months in CheckMate 025, 14.8 months in Record-1).

In TA417, the Committee concluded that CheckMate 025 results were generalisable to the NHS (TA417 ACD, July 2016). Median survival for nivolumab patients was 25.0 months. Median survival for nivolumab patients from the base case model extrapolations of CheckMate 025 data in TA417 was 26.0 months. It is important to note that these estimates are medians. Given the distribution of overall survival for these treatments, mean life expectancy based on extrapolations is typically greater than median life expectancy. In the final TA417 model, the mean life expectancy for nivolumab patients (without an assumed immunotherapeutic survival benefit) was over 40 months, and for axitinib and everolimus patients was over 30 months.

Yours,

[redacted]

References

1. Ara R and Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health*. 2010; 13(5):509-18.

Comment of NICE appraisal of Cabozantinib for previously treated Advanced Renal Cell Carcinoma

Observation – it would be a great shame if patients did not get access to a drug that has demonstrated clear benefits compared to Everolimus in a well conducted study. The demonstrated benefit in all 3 key endpoints (Response Rate, PFS and OS) is unprecedented in recent RCC trials. The recent approval of Everolimus makes this seem odd although obviously I recognize the key importance of the cost per QALY.

Detailed comments on appraisal

Section 4.1 – the line stating that the clinical experts consider Cabozantinib to be more effective than Axitinib and Everolimus is incorrect or a misunderstanding. In my view it should say:

….the clinical experts perceived Cabozantinib to be proven as more effective than Everolimus and probably more effective than Axitinib, although it is also associated with more adverse events.

I would leave it silent on Nivolumab although it could say: The clinical experts consider Cabozantinib to be of comparable efficacy to Nivolumab – there are however some patients for whom Cabozantinib would clearly be a preferred option (eg those with autoimmune disease) and those for whom Nivolumab may be preferable (eg intolerant of prior TKI therapy).

Section 4.14 – long-term survival of patients receiving second line data. At the meeting, we had some discussion about the long-term survivors and the companies assertion that 6% of patients would be alive at 7 years vs the NICE hypothesis that all would be dead by then. I suggested a few patients would be alive 5-10 years post second line therapy and based this on the experience with first line data. I could not quantify this but have since got our audit data for second line therapy.

I have since extracted relevant data from our database. For all patients treated with second line targeted therapy (Axitinib or Everolimus) the overall survival of our 282 patients audited is shown below (Figure 1). It does show a long-term survival of around 6% of patients.

Not surprisingly the outcome varies with over 10% of good prognosis patients alive 5-10 years and no poor prognosis patients (data not shown). Trials tend to be biased to better prognosis patients and I would therefore agree with the company's assumptions for modeling purposes – indeed 6% may well be a slight underestimate.

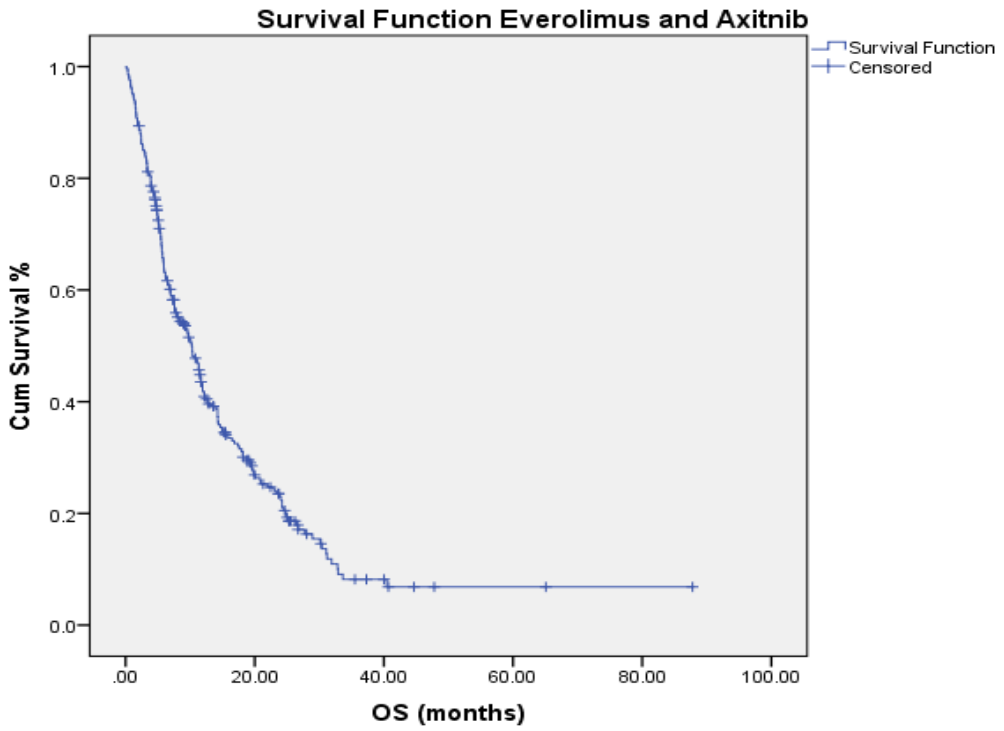


Figure 1: Overall survival of patients treated with Axitinib or Everolimus in the Christie Hospital (n=282).

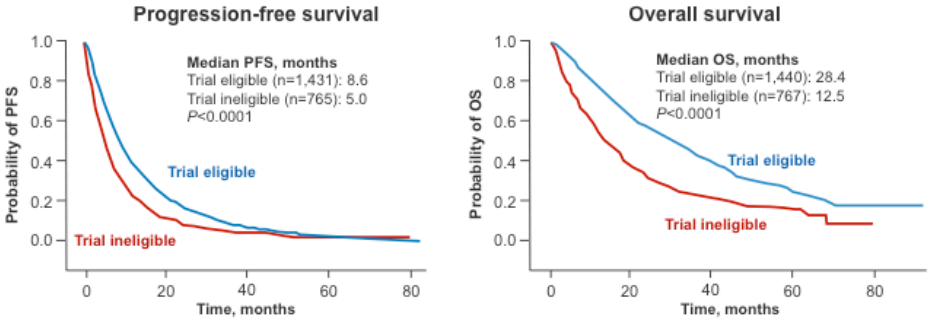
Section 4.23 – End of life considerations

It Is obviously pleasing to see that the overall survival of patients with advanced RCC is improving. At present, I do no think it is reasonable to assume it is >24 months in the second/third line setting. Certainly the Nivolumab Checkmate 025 study showed this but I suspect this will not be the case for the general UK (or elsewhere) data. Our audit data suggest current (pre-Nivolumab/Cabozantinib) overall survival of 18.0, 9.5 and 3.5 months respectively, for good intermediate and poor prognosis patients out of trial with the median out of trial being only 10.5 months because of a lot of poor prognosis patients in real life. Certainly, the good outcome of patients who are eligible for trials vs those who are not eligible for trials is well recognized and was recently quantified by Heng et al. (Heng DY et al*. Ann Oncol.* 2014;25:149–154) – see a slide from my recent ECCO 2017 presentation (Figure 2). This showed that in real life those meeting trial eligibility criteria had a survival of 28 months vs only 12 months for those not meeting the criteria and this was in the first line setting.

In addition, given the very recent approval of Everolimus, I think it is very important to maintain similar ground rules for both drugs.

Patients in everyday clinical practice perform differently than patients treated in clinical trials

IMDC: Retrospective analysis of outcomes among mRCC patients treated with targeted therapies who do not meet eligibility criteria for clinical trials



IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mRCC, metastatic renal cell carcinoma; OS, overall survival. PFS, progression-free survival.

Heng DY et al. *Ann Oncol.* 2014;25:149–154.

I hope this provides useful information – I would be happy to discuss / provide more data from our audit if it help.

Robert Hawkins
14 March 2017

Cabozantinib for previously treated advanced renal cell carcinoma

ERG's review of the Company response ACD

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 at the request of the NICE technical team for the following graphs:
    - Comparison of curve fits with raw data
    - OS: Kaplan-Meir (METEOR) vs old fit (log-normal) vs new fit (fractional polynomial) for cabozantinib over the trial follow-up period
    - OS: Kaplan-Meir (METEOR) vs old fit (log-normal) vs new fit (fractional polynomial) for everolimus over the trial follow-up period
    - PFS: Kaplan-Meir (METEOR) vs old fit (log-normal) vs new fit (fractional polynomial) for cabozantinib over the trial follow-up period
    - PFS: Kaplan-Meir (METEOR) vs old fit (log-normal) vs new fit (fractional polynomial) for everolimus over the trial follow-up period
- Comparison of modelled curves with natural history data
    - OS: Base-case survival curve (fractional polynomial) vs scenario survival curve (hybrid: fractional polynomial + log-normal) vs Ruiz-Morales curve for everolimus over 15 years
    - PFS: Base-case survival curve (fractional polynomial) vs scenario survival curve (log normal PFS) vs Ruiz-Morales curve for everolimus over 15 years

Figure 1. Comparison of KM data to Lognormal and Fractional Polynomial distribution for cabozantinib PFS

Figure 2. Comparison of KM data to Lognormal and Fractional Polynomial extrapolation for cabozantinib PFS

Figure 3. Comparison of KM data to Lognormal and Fractional Polynomial distribution for cabozantinib OS

Figure 4. Comparison of KM data to Lognormal and Fractional Polynomial extrapolation for cabozantinib OS

Figure 5. Comparison of KM data to Lognormal and Fractional Polynomial distribution for everolimus PFS

Figure 6. Comparison of KM data to Lognormal and Fractional Polynomial extrapolation for everolimus PFS

Figure 7. Comparison of KM data to Lognormal and Fractional Polynomial distribution for everolimus OS

Figure 8. Comparison of KM data to Lognormal and Fractional Polynomial extrapolation for cabozantinib OS

Figure 9. Comparison of Fractional Polynomial and Hybrid extrapolation to Ruiz-Morales 2016 for cabozantinib OS

Figure 10. Comparison of Fractional Polynomial and Hybrid extrapolation to Ruiz-Morales 2016 for everolimus OS

Figure 11. Comparison of Fractional Polynomial and Hybrid extrapolation to Ruiz-Morales 2016 for nivolumab OS

Figure 12. Comparison of Fractional Polynomial and Lognormal extrapolation to Ruiz-Morales 2016 for cabozantinib PFS

Figure 13. Comparison of Fractional Polynomial and Lognormal extrapolation to Ruiz-Morales 2016 for everolimus PFS

Figure 14. Comparison of Fractional Polynomial and Lognormal extrapolation to Ruiz-Morales 2016 for nivolumab PFS

Cabozantinib for previously treated advanced renal cell carcinoma

ERG's review of the Company response ACD

This report was commissioned by the NIHR HTA Programme as project number 16/10/09

BMJ Technology Assessment Group

1 SUMMARY OF THE COMPANY'S MODIFIED ANALYSIS

In response to the Appraisal Consultation Document, the Company provided NICE with an updated cost effectiveness analysis which incorporated the following changes to the original base case:

- Use of the fractional polynomial (FP) method for the indirect treatment comparison (ITC) to estimate overall survival (OS) and progression free survival (PFS);
- Simplification of the network meta-analysis (NMA) by assuming axitinib is clinically equivalent to everolimus for both OS and PFS, thus removing the TARGET study from the network;
- Application of age-adjusted health state utilities values (HSUVs) based on data from the METEOR trial;
- Inclusion of drug wastage costs for nivolumab;
- Removal of GP costs for the PFS health state;
- Exclusion of sorafenib from subsequent treatments; and
- Exclusion of best supportive care from the comparison with cabozantinib.

In addition to the revised base case, the Company have increased the PAS discount from [redacted] to [redacted] and have also provided separate analysis of the base case using an updated survival analysis of the METEOR trial based on an October 2016 trail data cut. For the purposes of this report, all presented analyses and results will be based on the new trial data cut, which the ERG considers more appropriate as it reflects more mature survival data.

The Company also explored a range of scenarios assessing the impact of different assumptions on the ICERs, of which the ERG deemed the following as key scenarios:

- Implementation of general population mortality for 50% of nivolumab patients who have survived 5 years or more, as requested by the Committee; and
- Hybrid model (best fitting FP model for trial duration and lognormal extrapolation) for OS.

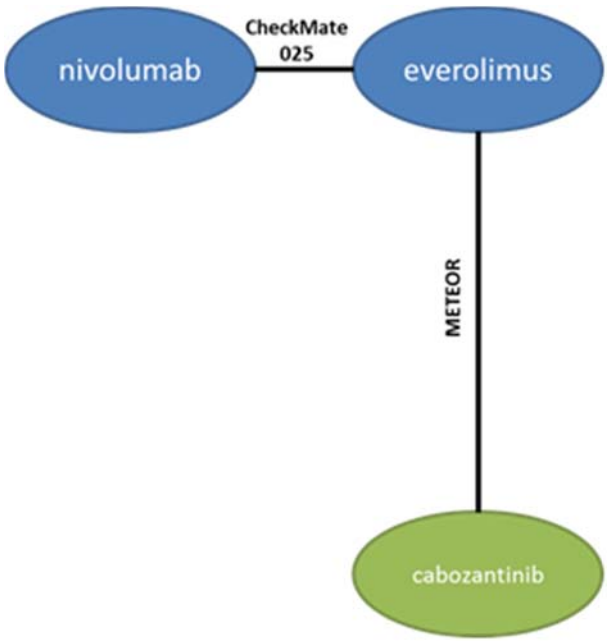
1.1 *Network Meta-analysis*

The Company has re-analysed its network meta-analysis (NMA) taking on board comments from the Committee and the critique by the ERG. Specifically, the company has:

- Assumed axitinib and everolimus have equal efficacy for PFS and OS. For TTD, the PFS curve was used for axitinib which is consistent with previous technology appraisals of interventions for second line RCC;
- Excluded best supportive care as a potential second line treatment option, and so excluded it from the network;
- Used a more flexible method based on fractional polynomials to allow for a better fit to the available data reported in the studies in the analysis.

This leads to a simplified network of studies depicted in Figure 1.

Figure 1. Network of studies used in the company's network meta-analysis (reproduced from Figure 1 in the company's response to the ACD)



The ERG has examined the programming code supplied by the Company and considers that the method proposed by Jansen 2011 has been implemented appropriately.[1] Similarly, the ERG accepts that the time available to the company has limited their opportunity to explore random effects models or additional values for power (i.e. p and, p_1 and p_2 taking values of -1.5, -0.5, 0.5, 1.5).

The Company used the Deviance Information Criteria (DIC) to assess model fit (where lower values signify a better fitting model, Table 1). The Company considered that, for OS, first order fractional polynomial (p = -1) provided the best statistical fit for trial data. For PFS, the second order polynomial (p_1 = -1 and p_2 = -1) provided the best fit. The ERG agrees with the Company's interpretation of the DIC but considers that the two second order fractional polynomial curves could also have been explored further for OS.

Table 1. Model fit statistic from the new NMA (adapted from Table 2 in the Company's response to the ACD)

Model fit statistic	First order with p=0		First order with p=1		First order with p=-1		Second order with p_1=-1, p_2=0		Second order with p_1=-1, p_2=-1	
	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS
Deviance information criteria	2130.4	3468.8	2152.5	3474.2	2120.0	3401.3	2126.4	3197.3	2126.1	3165.2

Abbreviations in table: OS, overall survival; p, power; PFS, progression-free survival.

The Company presented fitted PFS and OS curves superimposed on the extracted Kaplan-Meier data to allow visual assessment of the fit of Kaplan-Meier data to the modelled data (Figure 2 and Figure 3). The ERG agrees that the best fitting fractional polynomial models appear to be a good fit for PFS and OS for cabozantinib, everolimus and nivolumab for the duration of the trials. Table 2 presents the median OS and PFS estimates using the fractional polynomial method.

Table 2. Fractional polynomial median OS and PFS estimates (Oct 2016 METEOR trial data cut)

Treatment	Median OS	Median PFS
Cabozantinib	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]

The ERG would like to highlight (as with the Company's previous NMA), a limitation of the approach taken is that it produces a family of related survival curves for all treatments in the network. This simplification means that the model fit statistics refer to the "average fit" across the network. That is, the fractional polynomial chosen may not fit any individual treatment well but, on average, that family of curves fits the network of treatments best. However, based on a visual inspection of fitted PFS and OS curves superimposed on the extracted Kaplan-Meier data, this appears to be less of an issue with the fractional polynomial approach.

Figure 2. PFS produced by the company's network meta-analysis (second order fractional polynomial model, p_1= -1, p_1=-1) overlaid on extracted Kaplan-Meier data (shaded areas represent 95% credible intervals, reproduced from Figure 2 in the company's response to the ACD)

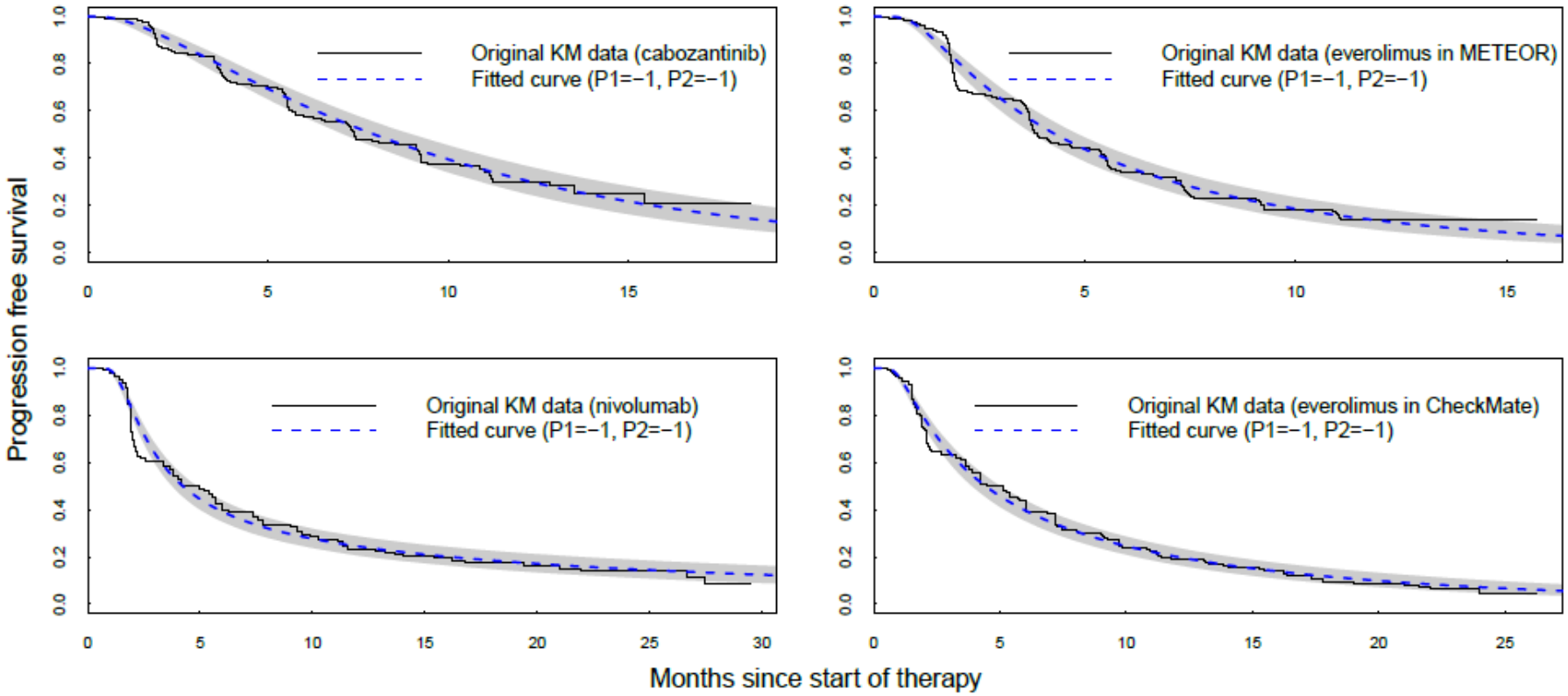


Figure 3. OS produced by the company's network meta-analysis (first order fractional polynomial model, p_1= -1) overlaid on extracted Kaplan-Meier data (shaded areas represent 95% credible intervals, reproduced from Figure 45 in the company's response to the ACD)

Comparison of PFS and OS for nivolumab

Use of the fractional polynomial approach for the extrapolation of PFS and OS for nivolumab resulted in curves that crossed (Figure 4) which the Company stated is clinically implausible. As such they ran a scenario whereby OS is extrapolated using the fractional polynomial method and PFS is extrapolated using the original lognormal method which does not result in crossing curves (Figure 5). The ERG's critique on the original NMA methodology for estimating PFS still holds, which is that the results need to be treated with caution as the lognormal distribution visually had a poor fit to the KM data resulting in a degree of uncertainty around the estimates produced by this method (Figure 6).

The ERG investigated how, in practice, the engine in economic model handles the issue of PFS greater than OS and at the point at which the curves cross (around year 5). Here patients can no longer progress (and therefore only accrue PFS utilities) and will die of causes other than RCC (as they now follow the OS curve). The ERG considers that given how the curves are implemented in the model (Figure 7), that the fractional polynomial approach for both PFS and OS for nivolumab could be reasonable if it is clinical plausible for nivolumab patients who survive past 5 years to remain progression free from RCC and die from other causes. It should be noted that given the time to review the Company's response to the ACD, the ERG were unable to verify the clinical plausibility of this assumption with its clinical experts.

Figure 4: Comparison of PFS and OS curves for nivolumab (fractional polynomial method)

Figure 5: Comparison of PFS and OS curves for nivolumab (fractional polynomial method for OS, lognormal for PFS)

Figure 6. Comparison of re-generated KM data and fitted curves – PFS nivolumab (Clarification response to B3)

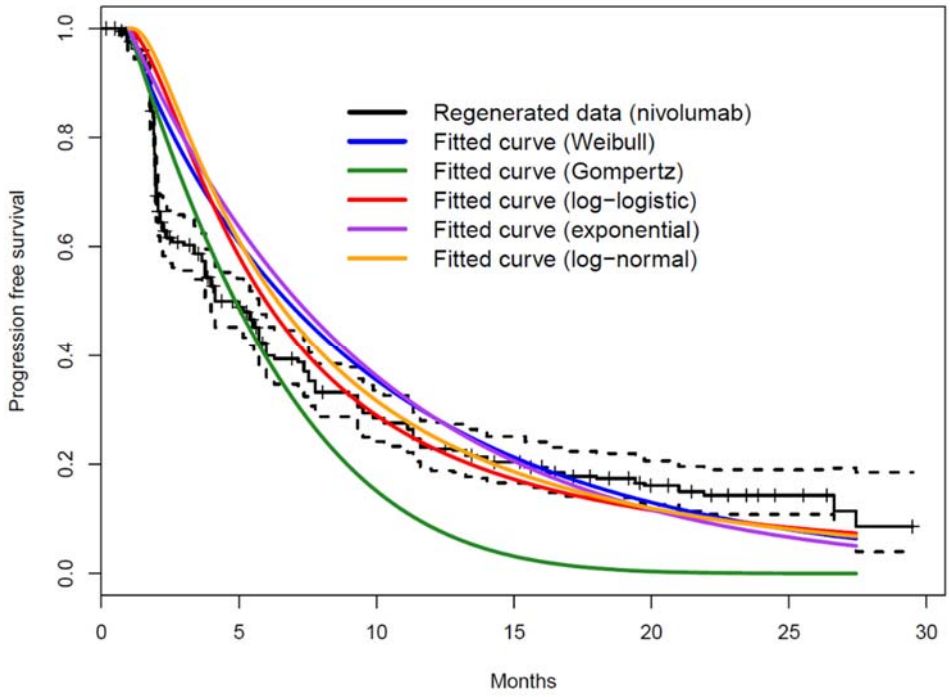


Figure 7: Comparison of PFS and OS curves for nivolumab taken from engine in the economic model (fractional polynomial)

1.2 *Real World Evidence*

As requested by the Committee, the Company performed a search of "real world" datasets to obtain evidence of the natural history of the disease in current UK clinical practice. From their search they identified a publication by Ruiz-Morales *et al.* 2016 that reported relevant data on second line patients in order to perform an analysis of long term survival.[(2)] Ruiz-Morales 2016 is a retrospective analysis of mRCC patients derived from the International mRCC Database Consortium (IMDC). The study did not include any patients from the UK, though the ERG agrees with the Company that the few baseline characteristics which are reported for both METEOR and Ruiz-Morales 2016 are similar. However, the ERG notes that the baseline characteristics of patients for the Ruiz-Morales 2016 data are reported at the beginning of 1st line therapy rather than 2nd line, and that the proportions of patients from countries with similar population baseline characteristics, socio-economic characteristics, and health systems as the UK, were not specified. Similar to METEOR the patients in Ruiz-Morales 2016 received sunitinib of pazopanib as first line therapy. Second line therapies included sorafenib, axitinib and everolimus.

A smaller proportion of patients in the Ruiz-Morales 2016 study had a favourable prognostic risk category (23%-24% Heng score) compared to the patient population in METEOR (45% MSKCC score). The proportion of patients with a poor prognostic risk category were higher in Ruiz-Morales 2016 compared with the population in METEOR (18-20% RWE Heng score, 12% METEOR MSKCC score). This indicates that the second and third line population in METEOR were healthier than the first line

population in the Ruiz-Morales 2016 study, which in this respect may be more representative of patients in UK clinical practice than the METEOR population, and more appropriate evidence of the natural history of the disease.

The Ruiz-Morales 2016 data indicates that at five years, 10% of patients were expected to be alive. The Company state results from the best fitting FP curve for everolimus estimated that at 5 years approximately 5% of patients would still be alive and as such produced a scenario that uses the FP curve for the within trial duration period (2.5 years) and then applies a lognormal distribution for the post trial extrapolation, bringing estimates of 5 year survival in line with that of the real world evidence. The ERG considers that there may be significant uncertainty around choosing an extrapolation method based purely on meeting a notional 5-year survival estimate – the shape of the extrapolated curve is likely to be at least as important as meeting a survival target at 5-years. As mentioned previously, the lognormal distribution was a poor fit to the KM data and as such may not produce reliable predictions of survival beyond the trial duration. For the RWE to provide any meaningful insight into the natural history of the disease and be used to inform the economic model, assessment of the curve fit of the best fitting fractional polynomial and lognormal distributions should have been compared to the KM data from Ruiz-Morales 2016.

Although the new evidence submitted by the Company for the fractional polynomial method does produce conservative estimates for 5 year survival compared to the real world data, it does improves the fit of the curve to the KM data. The ERG considers that ICER estimate produced using the fractional polynomial method is likely to be conservative. If in clinical practice 5-year survival rates are around 10% estimate, the impact would produce a more favourable ICER for cabozantinib compared to the comparators.

1.3 *Exclusion of sorafenib from subsequent treatments*

In the ACD, the Committee stated a preference for subsequent treatments not available in the NHS (such as sorafenib) to be excluded from the economic analysis. As such the Company reassigned the proportion of patients who received sorafenib as a subsequent treatment to receive axitinib instead. The ERG considers that the assumption made by the Company is reasonable and overall has little impact on the ICER, however there are 4 key issues with this adjustment that should be noted:

- This adjustment only affects the comparator treatments, as for cabozantinib no patients received sorafenib as a subsequent treatment;
- The list price of axitinib is more expensive than the list price of sorafenib (please see confidential appendix for more details on this issue);
- The model assumes that second line axitinib patients will receive third line axitinib; and

- Axitinib is not currently recommended as a third line treatment.

1.4 *Removal of GP costs*

In the revised base case analysis, the Company removed GP costs from the PFS health state as recommended by the Committee in the ACD. However, the ERG's clinical experts stated that second line RCC patients would be unlikely to be monitored in primary care and for the ERG's base case GP costs were removed altogether from the model. The ERG considers that removal of these costs from only the PFS health state is inappropriate and explores in a revised base case analysis the impact of removing GP costs from both PFS and PPS health states in Section 3.

1.5 *Age adjusted utilities based on the METEOR trial data*

In the ACD, the Committee recommended the use of age adjusted utilities based on the METEOR trial. The Company implemented this change by using the following algorithm obtained from a study by Ara and Brazier 2010:

$$EQ\text{-}5D = 0.9454933 + 0.0256466*male - 0.0002213*age - 0.0000294*age^2$$

The mean age (62.5 years) proportion of male patients (75.1%) were obtained from the METEOR trial. The adjustment was then applied to utility values obtained from the METEOR trial for PFS and PPS health states. The ERG considers that the method to adjust utilities for age is robust and has been applied correctly in the model. However, the ERG still considers the initial utility values from METEOR (PFS = 0.817, PPS = 0.777) high based on clinical expert opinion obtained by the ERG. In the ERG's original base case, utility values from the AXIS trial were used (PFS = 0.692, PPS = 0.610). The ERG acknowledges the Committee's preference for utility values based on the clinical trial, however, it still views the METEOR based values as high given that a widely reported utility study estimates that the average UK general population utility for people aged 55-64 is 0.80.[3] As such, the ERG explores the impact of using age adjusted AXIS based utility values on the ICER in Section 3.1.

1.6 *Other model adjustments explored in scenarios*

Adverse event utility values

In the ACD, the Committee recommended the Company use utility decrements for adverse events based on a well conducted systematic review of the literature. In response the ACD, the Company refer back to their original submission where they conducted a systematic review of the literature on utilities, which included search terms for utility decrements. The Company stated limited information was found and rely on a paper published by Swinburn *et al.* 2010, which contained information on utility decrements for selected adverse events.[4] The Company used the lowest adverse event utility reported in the paper (which was for palmar-plantar erythrodysesthesia) and compared it to the utility for stable RCC without adverse events to obtain a utility decrement of -0.33. The Company ran a scenario using

this decrement (Table 30 in Company Response to ACD) and found the adjustment had minimal impact on the ICER.

In the ERG's critique of the original CS, a weighted average utility decrement of -0.17 was calculated using the Swinburn *et al.* 2010 study, which also had minimal impact on the ICER. The ERG therefore considers that Company's analysis demonstrates that the ICER is robust to extreme changes to the adverse event utility decrement.

Predictions of better overall survival for nivolumab

As per the Committee's request, the Company explored a scenario whereby 50% of patients who survive beyond 5 years are assumed to have general population mortality rates. The Company state that this assumption is in line with nivolumab appraisal (TA417). The Company found that applying this assumption to the base case resulted in cabozantinib being dominant over nivolumab. The ERG explored a scenario whereby 100% of nivolumab 5 year survivors move to general population mortality rates and found that this extreme assumption generated an ICER of approximately £20,000 (see Section 3.1 for more details).

The ERG explored an additional scenario around OS for nivolumab based on it being clinical equivalent to cabozantinib for OS (Section 3.1). This scenario was explored based on interrogation of the hazard plot for the best fitting factional polynomial model for OS indication that the hazard ratio over time for nivolumab compared to cabozantinib was not significantly different (i.e. the 95% credible intervals crossed 1).

2 COMPANY'S BASE CASE

The Company's revised base case is based on the following assumptions:

- Use of the fractional polynomial method for the indirect treatment comparison (ITC) to estimate overall survival (OS) and progression free survival (PFS);
- Simplification of the network meta-analysis (NMA) by assuming axitinib is clinically equivalent to everolimus for both OS and PFS, thus removing the TARGET study from the network;
- Application of age-adjusted health state utilities values (HSUVs) based on data from the METEOR trial;
- Inclusion of drug wastage costs for nivolumab;
- Removal of GP costs for the PFS health state;
- Exclusion of sorafenib from subsequent treatments and;
- Exclusion of best supportive care from the comparison with cabozantinib.

As mentioned previously, the use of the FP method to estimate PFS and OS for nivolumab resulted in curves that cross which is clinically implausible, however as mentioned previously the implementation of that data in the model means that after the point in time the curves cross, PFS becomes equal to OS. It has not been verified whether this could be clinically plausible. However, in order to have a robust comparison of clinical effectiveness, to perform a meaningful incremental analysis, the method employed to estimate PFS should be consistent across treatments. Therefore, the ERG presents the two options for the Company's base case results, one using the fractional polynomial method for both PFS and OS and the other option using the fractional polynomial method for OS and the lognormal method for PFS.

Table 3 and Table 4 presents the revised Company base case results (see Appendix for results with cabozantinib PAS discount applied). Table 5 and Table 6 present the PSA results and Table 7 & 8 present the incremental analysis of pairwise cost-effectiveness results.

Table 3. Pairwise analysis cost-effectiveness results based on fractional polynomial indirect treatment comparison

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]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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

Table 4. Pairwise analysis cost-effectiveness results based on fractional polynomial for OS and lognormal for PFS

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]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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

Table 5. PSA cost-effectiveness results based on fractional polynomial indirect treatment comparison

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]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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

Table 6. PSA cost-effectiveness results based on fractional polynomial for OS and lognormal for PFS

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]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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

Table 7. Incremental analysis of pairwise analysis cost-effectiveness results based on fractional polynomial indirect treatment comparison

Treatment	Cost	LYs	QALYs	Incremental costs Cabozantinib versus comparator	Incremental LYs Cabozantinib Versus comparator	Incremental QALYs Cabozantinib Versus comparator	ICER Cabozantinib Versus comparator (£/QALY)
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

Table 8. Incremental analysis of pairwise analysis cost-effectiveness results based on fractional polynomial indirect treatment comparison

Treatment	Cost	LYs	QALYs	Incremental costs Cabozantinib versus comparator	Incremental LYs Cabozantinib Versus comparator	Incremental QALYs Cabozantinib Versus comparator	ICER Cabozantinib Versus comparator (£/QALY)
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

The cost-effectiveness analysis of the trial data are presented in Table 7 to provide a comparison to the ITC analysis.

Table 9. Cost-effectiveness results for METEOR

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.

3 ADDITIONAL ANALYSIS UNDERTAKEN BY THE ERG

The original ERG base case made the following assumptions:

- Using the Weibull distribution to extrapolate OS for the trial based analysis;
- 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;
- 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;
- 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 and;
- Exclusion of GP costs in line with the ERG's clinical expert opinion.

Overall the Company has reasonably addressed the concerns of the ERG and also adhered to the preferences of the Committee regarding the analysis of the base case. Based on the Committee's preferred approach and the new analysis submitted by the Company, the ERG has performed additional analysis on the Company's revised base case to produce a revised ERG base case based on the following assumptions:

- Use of the fractional polynomial method for the indirect treatment comparison (ITC) to estimate overall survival (OS) and progression free survival (PFS) for all interventions;
- Applying the weighted average adverse event utility decrement (-0.17) based on Swinburn *et al.* 2010.
- Exclusion of GP costs for both PFS and PPS in line with the ERG's clinical expert opinion

The ERG chose to focus on the fractional polynomial method for the ITC due to the way the engine in the economic model handles PFS and OS for nivolumab, but in addition the scenario of assuming 50% of nivolumab 5 year survivors moving to general mortality rates supports that after 5 years a proportion of patients will remain progression free until they die.

The ERG modified base case is presented in Table 10 (see Appendix for ERG base case ICERs with the incorporated cabozantinib PAS discount).

Table 10. ERG modified base case results

Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	Nivolumab (5)	Incremental value		
					(1-2)	(1-3)	(1-4)
Revised Company base case (fractional polynomial method)							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
Weighted average adverse event utility decrement							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)					[redacted]	[redacted]	[redacted]
Removal of GP costs for PFS and PPS							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)					[redacted]	[redacted]	[redacted]

3.1 *ERG scenario analysis*

The ERG ran a number of different scenarios in addition to the ERG modified base case, to explore the impact of the following changes, which have been mentioned previously in the report:

- Using age adjusted AXIS utilities (Table 11);
- Assuming 100% of nivolumab 5 year survivors move on to general population mortality rates (Table 12); and
- Assuming clinical equivalency for OS between nivolumab and cabozantinib (Table 13).

All scenarios are run using the fractional polynomial method for extrapolating PFS and OS. Please refer to the Appendix for results with cabozantinib PAS discount applied.

It can be seen in Table 9, changing the source of age adjusted utilities has a large impact on the ICER (approximately £20,000-£30,000 difference). As mentioned previously, the Committee stated a preference for trial based utilities, however this scenario highlights if utilities for second line RCC patients are lower in practice than the cost-effectiveness of cabozantinib may be less favourable.

The assumption of 100% of nivolumab 5 year survivors moving on to general population mortality, while could be considered an extreme assumption, generated an ICER of approximately £20,000 (approximately [redacted] with cabozantinib PAS discount applied). The ICER differences for this scenario are driven by a relatively large QALY difference in favour of nivolumab, yet this can be considered a "worst case scenario" as it effectively assumes all patients are cured after surviving 5 years. As mentioned previously in the discussion around PFS extrapolation for nivolumab, the assumption of patients being cured after 5 years may be clinical plausible, but only for a certain percentage of the population, therefore the 50% assumption may not be unreasonable and the results shown for this assumption demonstrates that there is minimal difference between the two treatments.

The results of the scenario assuming nivolumab is clinically equivalent to cabozantinib demonstrates that there is a minimal difference between costs and benefits between the two treatments. There is a small QALY decrement that is being driven by PFS, which causes the ICER to be largely inflated. It should be noted that when the distribution is changed to lognormal for PFS, the QALY difference changes to a positive value (0.01), reversing the ICER to become dominant in favour of cabozantinib. As with the previous scenario, depending on which assumption is deemed plausible, it can be seen that there is no meaningful difference for costs and QALYs between treatments.

Table 11. Scenario analysis of using age adjusted AXIS utility rates

Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	Nivolumab (5)	Incremental value		
					(1-2)	(1-3)	(1-4)
Revised Company base case (fractional polynomial method)							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
Age adjusted AXIS utilities							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]

Table 12. Scenario analysis of 50% and 100% nivolumab 5 year survivors moving to general population mortality rates

Results per patient	Cabozantinib	Nivolumab	Incremental value
Revised Company base case			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
Nivolumab 50% 5 year survivor general population mortality			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
Nivolumab 100% 5 year survivor general population mortality			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[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 13. Scenario analysis of equal OS for nivolumab and cabozantinib

Results per patient	Cabozantinib	Nivolumab	Incremental value
Revised Company base case (fractional polynomial method)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
Equal OS for nivolumab and cabozantinib			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[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.

4 REFERENCES

1. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.

2. Ruiz-Morales JM, Swierkowski M, Wells JC, Fraccon AP, Pasini F, Donskov F, et al. First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. European journal of cancer (Oxford, England : 1990). 2016;65:102-8.

3. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. York: The University of York, Economics CfH; 1999 Discussion paper 172.

4. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Current Medical Research & Opinion. 2010;26(5):1091-6.

5 APPENDIX

5.1 *Revised Company base case results with cabozantinib PAS discount applied*

Table 14. Pairwise analysis cost-effectiveness results based on the fractional polynomial indirect treatment comparison (with cabozantinib PAS discount applied)

Treatment	Total Cost	Total LYs	Total QALYs	Incremental (vs cabozantinib)			ICER (£/QALY)
				Costs	QALYs	LYs	
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[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							

Table 15. Pairwise analysis cost-effectiveness results based on fractional polynomial indirect treatment comparison for OS and lognormal for PFS (with cabozantinib PAS discount applied)

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]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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							

Table 16. PSA cost-effectiveness results based on fractional polynomial indirect treatment comparison (with cabozantinib PAS discount applied)

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]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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							

Table 17. PSA cost-effectiveness results based on fractional polynomial indirect treatment comparison for OS and lognormal for PFS (with cabozantinib PAS discount applied)

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]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[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

Table 18. Incremental analysis of pairwise analysis cost-effectiveness results based on fractional polynomial indirect treatment comparison (with cabozantinib PAS discount applied)

Treatment	Cost	LYs	QALYs	Incremental costs Cabozantinib versus comparator	Incremental LYs Cabozantinib Versus comparator	Incremental QALYs Cabozantinib Versus comparator	ICER Cabozantinib Versus comparator (£/QALY)
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

Table 19. Incremental analysis of pairwise analysis cost-effectiveness results based on fractional polynomial indirect treatment comparison (with cabozantinib PAS discount applied)

Treatment	Cost	LYs	QALYs	Incremental costs Cabozantinib versus comparator	Incremental LYs Cabozantinib Versus comparator	Incremental QALYs Cabozantinib Versus comparator	ICER Cabozantinib Versus comparator (£/QALY)
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

Table 20. Cost-effectiveness results for METEOR (with cabozantinib PAS discount applied)

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.							

5.2 *ERG modified base case results with cabozantinib PAS discount applied*

Table 21. ERG modified base case results

Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	Nivolumab (5)	Incremental value		
					(1-2)	(1-3)	(1-4)
Revised Company base case (fractional polynomial method)							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
Weighted average adverse event utility decrement							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)					[redacted]	[redacted]	[redacted]
Removal of GP costs for PFS and PPS							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
ICER (with all changes incorporated)					[redacted]	[redacted]	[redacted]

5.3 *ERG scenario analysis with cabozantinib PAS discount applied*

Table 22. Scenario analysis of using age adjusted AXIS utility rates

Results per patient	Cabozantinib (1)	Axitinib (2)	Everolimus (3)	Nivolumab (5)	Incremental value		
					(1-2)	(1-3)	(1-4)
Revised Company base case (fractional polynomial method)							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]
Age adjusted AXIS utilities							
Total costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER					[redacted]	[redacted]	[redacted]

Table 23. Scenario analysis of 50% and 100% nivolumab 5 year survivors moving to general population mortality rates (with cabozantinib PAS discount)

Results per patient	Cabozantinib	Nivolumab	Incremental value
Revised Company base case			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
Nivolumab 50% 5 year survivor general population mortality			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[redacted]
Nivolumab 100% 5 year survivor general population mortality			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[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 24. Scenario analysis of equal OS for nivolumab and cabozantinib (with cabozantinib PAS discount)

Results per patient	Cabozantinib	Nivolumab	Incremental value
Revised Company base case			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER			[redacted]
Equal OS for nivolumab and cabozantinib			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
ICER (compared with base case)			[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.			