NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabozantinib for untreated advanced renal cell carcinoma [ID1208]

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

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Ipsen – comments on the ACD
   - Ipsen – additional evidence
   - Kidney Cancer Support Network
     The Department of Health and Social Care stated that they had no comments on the ACD

3. **Evidence Review Group critique of additional information submitted by the company**

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

Cabozantinib for untreated advanced renal cell carcinoma

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Ipsen	We appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for the above appraisal. We have, via a separate document, and with the agreement of NICE, submitted additional analyses to address the uncertainties and questions raised by the Appraisal Committee. Our responses to the questions specified above are provided below:	Thank you for your comments. The additional analyses, including an updated patient access scheme were considered by committee. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the final appraisal document (FAD).
2	Company	Ipsen	**Has all of the relevant evidence been taken into account?** We agree that all the relevant information has been taken into account.	
3	Company	Ipsen	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries are reasonable interpretations, and as stated above, we have submitted additional analyses to address the points raised by the Appraisal Committee.	
4	Company	Ipsen	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS**? We are disappointed that the provisional recommendations do not recommend cabozantinib, particulary as there is a recognised need (as per ACD Section 3.1) for an additional treatment option. We believe that the additional analysis provided will reassure the Committee that cabozantinib is cost-effective and can be recommended for use following the second Appraisal Committee meeting.	
5	Patient group	Kidney Cancer Support Network (KCSN)	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	Thank you for your comments. The committee concluded that there were no additional benefits of cabozantinib which were not captured in the company's economic model. Please see section 3.19 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			approval in a number of countries, and has been made available in the UK through a **Managed Access Programme** by the manufacturer.	Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
6	Patient group	KCSN	Cabozantinib is a tyrosine kinase inhibitor, which acts 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. Anecdotal evidence suggests 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 (KCSN) 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 evidence to support this unmet need in advanced RCC patients.	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
7	Patient group	KCSN	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.	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
8	Patient group	KCSN	The committee's decision not to recommend fist-line cabozantinib was based upon the fact that cabozantinib did not meet the end-of-life criteria for a combined population of intermediate- and poor-risk patients. However, this model is based upon data from clinical trials, which do not necessarily reflect routine clinical practice. KCSN urge NICE to consider funding for cabozantinib through the CDF to enable collection of real world survival data for intermediate- and poor-risk patients, which could potentially impact the final recommendation.	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
9	Patient group	KCSN	The committee's decision to not recommend cabozantinib for untreated advanced RCC patients 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	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			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 directly affected by their decision.	
10	Patient group	KCSN	The committee's decision to not recommend cabozantinib for untreated advanced RCC patients 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 directly affected by their decision.	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
11	Patient group	KCSN	Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
12	Patient group	KCSN	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 in the first-line. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
13	Patient group	KCSN	Current first-line treatment options are not effective for everyone. Undue restrictions in accessing cabozantinib would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.	Comment noted. Cabozantinib is now recommended for adults with untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.
14	Patient group	KCSN	Clinical trials have been conducted in untreated advanced/metastatic RCC patients with cabozantinib in the UK. The patients who participated in these trials did so in the expectation that their data would enable other	Comment noted. Cabozantinib is now recommended for adults with

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			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 first-line cabozantinib on the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.	untreated advanced renal cell carcinoma Please see section 1.1 of the FAD.

Cabozantinib for untreated advanced renal cell carcinoma [ID1208]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 June 2018 email: TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Ipsen Ltd UK**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Not applicable**]
Name of commentator person completing form:	[**Eleonora Skentzou**]

Comment number	**Comments** Insert each comment in a new row.

Please return using NICE Docs

Cabozantinib for untreated advanced renal cell carcinoma [ID1208]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 June 2018 email: TACommB@nice.org.uk/NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	We appreciate the opportunity to respond to the Appraisal Consultation Document (ACD) for the above appraisal. We have, via a separate document, and with the agreement of NICE, submitted additional analyses to address the uncertainties and questions raised by the Appraisal Committee. Our responses to the questions specified above are provided below:
2	**Has all of the relevant evidence been taken into account?** We agree that all the relevant information has been taken into account.
3	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** The summaries are reasonable interpretations, and as stated above, we have submitted additional analyses to address the points raised by the Appraisal Committee.
4	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS**? We are disappointed that the provisional recommendations do not recommend cabozantinib, particulary as there is a recognised need (as per ACD Section 3.1) for an additional treatment option. We believe that the additional analysis provided will reassure the Committee that cabozantinib is cost-effective and can be recommended for use following the second Appraisal Committee meeting.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 June 2018 email: TACommB@nice.org.uk/NICE DOCS

send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Ipsen Ltd – Response to ACD consultation – 22 June 2018

ID1208 – Cabozantinib for untreated 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 that this additional evidence will reassure the Committee that cabozantinib is cost-effective and can be recommended for use following the second Appraisal Committee meeting.

Executive summary

In summary, in addressing the points raised by the Appraisal Committee, we have:

- Removed the Indirect Treatment Comparison (ITC) following the Committee's conclusion that it is not needed.
- Incorporated the Committee's preferred assumptions and implemented these throughout our revised analyses.
- Included the latest July 2017 overall survival (OS) data from the CABOSUN trial.
- Applied a revised patient access scheme (PAS) of [redacted].

An overview of the adjustments made to the economic model are provided in Table 1.

Table 1: Overview of adjustments made to the model

Model adjustment	Details
Relative efficacy comparison	• Pazopanib is assumed to be as effective as sunitinib. • Given that the OS estimate for pazopanib is now based on the CABOSUN trial (sunitinib arm), the subsequent treatments for pazopanib have been assumed to be equal to those in the sunitinib arm.
Final OS data cut CABOSUN (July 2017)	• Patient level analyses conducted on July 2017 data for OS endpoint o Fitting: Separate ▪ Scenario: Joint fit o Parametric survival curve: Exponential ▪ Scenarios: Weibull and Gompertz
PFS	• Base case: Joint fit o Scenario analysis: Separate fit
Treatment persistence	• 5 years

The ICERs for the revised base case based on a separate fit of the OS July 2017 patient level data using the exponential model and assuming equal efficacy for sunitinib and pazopanib, demonstrate that cabozantinib is a cost-effective treatment when compared with sunitinib (£26,550) and pazopanib (£24,635).

In addition to the base case, the following scenario analyses were performed (holding everything else equal to the base case above), with cabozantinib demonstrating to be cost-effective in each scenario compared with sunitinib and pazopanib (Table 2).

Table 2: Scenario analyses results

Scenario	ICER (Cost/QALY) Cabozantinib vs. sunitinib	ICER (Cost/QALY) Cabozantinib vs. pazopanib
OS scenario parametric survival curve distribution: Weibull	£29,857	£27,637
OS scenario parametric survival curve distribution: Gompertz	£24,982	£23,120
PFS separately fitted	£26,062	£24,182
Updated ERG simple indirect comparison	£26,974	£24,953

The results of the revised analysis clearly demonstrate the cost-effectiveness of cabozantinib compared with sunitinib and pazopanib for the treatment of untreated locally advanced or metastatic renal cell carcinoma.

Section 1: Revised cost-effectiveness model

In summary, in addressing the points raised by the Appraisal Committee, and as stated above, we have:

- Removed the Indirect Treatment Comparison (ITC) following the Committee's conclusion that it is not needed (ACD Section 3.9).
- Incorporated the Committee's preferred assumptions (ACD Section 3.17) and implemented these throughout our revised analyses.
- Included the latest July 2017 overall survival (OS) data from the CABOSUN trial (ACD Sections 3.7 and 3.17)
    - Applied a revised patient access scheme (PAS) of [redacted]. This revised PAS will also improve the cost-effectiveness of cabozantinib in the second line indication (TA463: Cabozantinib for previously treated advanced renal cell carcinoma. August 2017).

The results are provided below in Section 1.1. The base case results are provided for separately fitted OS July 2017 patient level data using the exponential model (see statistical fits in Table 15), and assuming equal efficacy for sunitinib and pazopanib. For PFS, jointly fitted lognormal distribution is used. As per the original Ipsen submission, PFS as assessed by an independent review committee (IRC) is used. Use of independently assessed PFS was deemed acceptable by the Committee on the basis that, due to the size of the CABOSUN study, it would minimise bias and reduce the uncertainty resulting from small patient numbers (ACD Section 3.12). In addition, the joint fit was used for PFS because the proportional hazard (PH) assumption was deemed to hold in CABOSUN by the ERG and was preferred by the Committee. Furthermore, a treatment persistence effect of 5 years is assumed in line with the Committee's preferred assumption (ACD Section 3.14).

Additionally, results are provided for scenario analyses (holding everything else equal to the base case above):

- July 2017 OS data jointly fitted
- OS scenario parametric survival curve distributions:
    - Weibull
    - Gompertz

- o PFS separately fitted
- o Updated ERG simple indirect comparison

Section 1.1 Results

Results for the base case described above are provided in Table 3. The scenarios for the base case are provided from Table 4 to Table 7. The ERG and the clinical expert present at the Appraisal Committee meeting preferred the exponential distribution for OS. The Committee, however, concluded that chosen distributions fit the data poorly, and that the OS extrapolation is a source of uncertainty in the model. Hence, we have included two other curves as scenario analyses that were considered clinically plausible: Weibull and Gompertz. The ERG expressed an opinion favouring jointly fitted PFS, and in response to this we have provided the separately fitted PFS as a scenario analysis. In addition, the ERG simple ITC has been updated with the new data cut (July 2017), and is included as a scenario analysis.

Table 3: Revised base case with July 2017 OS data exponential distribution; pair-wise and incremental analysis of cabozantinib versus comparator

Drug	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (vs cabozantinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	9,072	0.342	0.472	26,550
Pazopanib	[redacted]	[redacted]	[redacted]	8,362	0.339	0.472	24,635
Incremental Analysis (vs baseline)							
Sunitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	710	0.002	0.000	314,238
Cabozantinib	[redacted]	[redacted]	[redacted]	8,362	0.339	0.472	24,635
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; LY, life-year							

Table 4: Scenario with July 2017 OS data Weibull distribution; pair-wise and incremental analysis of cabozantinib versus comparator

Drug	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (vs cabozantinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	8,711	0.292	0.392	29,857
Pazopanib	[redacted]	[redacted]	[redacted]	8,001	0.290	0.392	27,637
Incremental Analysis (vs baseline)							
Sunitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	710	0.002	0.000	314,394
Cabozantinib	[redacted]	[redacted]	[redacted]	8,001	0.290	0.392	27,637
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; LY, life-year							

Table 5: Scenario with July 2017 OS data Gompertz distribution; pair-wise and incremental analysis of cabozantinib versus comparator

	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (vs cabozantinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	8,827	0.353	0.491	24,982
Pazopanib	[redacted]	[redacted]	[redacted]	8,117	0.351	0.491	23,120
Incremental Analysis (vs baseline)							
Sunitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	710	0.002	0.000	314,332
Cabozantinib	[redacted]	[redacted]	[redacted]	8,117	0.351	0.491	23,120
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; LY, life-year							

Table 6: Scenario with PFS separately fitted; pair-wise and incremental analysis of cabozantinib versus comparator

	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (vs cabozantinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	9,258	0.355	0.472	26,062
Pazopanib	[redacted]	[redacted]	[redacted]	8,536	0.353	0.472	24,182
Incremental Analysis (vs baseline)							
Sunitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	723	0.002	0.000	319,858
Cabozantinib	[redacted]	[redacted]	[redacted]	8,536	0.353	0.472	24,182
Key: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; LY, life-year							

Table 7: Scenario with updated ERG simple indirect comparison; pair-wise and incremental analysis of cabozantinib versus comparator

	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (vs cabozantinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	8,721	0.323	0.445	26,974
Pazopanib	[redacted]	[redacted]	[redacted]	8,011	0.321	0.445	24,953
Incremental Analysis (vs baseline)							
Sunitinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	710	0.002	0.000	314,238
Cabozantinib	[redacted]	[redacted]	[redacted]	8,011	0.321	0.445	24,953
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life-year; LY, life-year NOTE: Scenario includes the PFS joint fit.							

Sensitivity analyses

Probabilistic sensitivity analysis (PSA)

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 59 of the original Ipsen submission. The updated efficacy variables are shown in Table 8 and Table 9 of this document. Uncertainties for survival distributions were tested by drawing random samplings from the multivariate-normal distribution derived from the variance-covariance matrix.

Table 8: Summary of the updated efficacy variables applied in the economic model – OS July 2017 data cut separate fit

OS July 2017 - Separate fit		Cabozantinib					Sunitinib				
Curve	Parameters	Estimate	SE	Intercept	Scale	Shape	Estimate	SE	Intercept	Scale	Shape
Exponential	Intercept	3.6713	0.1525	0.0233			3.4347	0.1459	0.0213		
	Scale	1.0000					1.0000				
Weibull	Intercept	3.6128	0.1394	0.0194	0.0054		3.4176	0.1384	0.0192	0.0033	
	Scale	0.8611	0.1164	0.0054	0.0135		0.9297	0.1190	0.0033	0.0142	
Gompertz	Shape	-0.0006	0.0157	0.0002	-0.0034		0.0035	0.0153	0.0002	-0.0032	
	Rate	-3.6633	0.2645	-0.0034	0.0700		-3.4819	0.2547	-0.0032	0.0649	
Loglogistic	Intercept	3.2492	0.1488	0.0221	0.0036		3.0349	0.1588	0.0252	0.0022	
	Scale	0.6930	0.0907	0.0036	0.0082		0.7562	0.0938	0.0022	0.0088	
Lognormal	Intercept	3.2722	0.1602	0.0257	0.0086		3.0169	0.1699	0.0288	0.0070	
	Scale	1.2076	0.1433	0.0086	0.0205		1.3209	0.1458	0.0070	0.0213	
Generalized gamma	Intercept	3.2444	0.2897	0.0839	-0.0317	0.1419	3.2150	0.2974	0.0884	-0.0570	0.1560
	Scale	1.2277	0.2223	-0.0317	0.0494	-0.0997	1.1607	0.2801	-0.0570	0.0785	-0.1510
	Shape	-0.0689	0.5902	0.1419	-0.0997	0.3483	0.4457	0.6166	0.1560	-0.1510	0.3802

Table 9: Summary of the updated efficacy variables applied in the economic model – PFS joint fit and OS July 2017 joint fit

Curve	Parameters	Estimate	SE	Intercept	Treatment	Scale	Shape
PFS - Joint fit (IRC)							
Exponential	Intercept	2.0514	0.1429	0.0204	-0.0204	0.0000	
	Treatment	0.6847	0.2090	-0.0204	0.0437	0.0000	
	Scale	1.0000					
Weibull	Intercept	2.0696	0.1218	0.0148	-0.0150	-0.0008	
	Treatment	0.6375	0.1787	-0.0150	0.0319	0.0015	
	Scale	0.8483	0.0684	-0.0008	0.0015	0.0047	
Gompertz	Shape	0.0002	0.0189	0.0007	0.0004	-0.0033	
	Treatment	-0.6847	0.2121	0.0450	0.0007	-0.0733	
	Rate	-2.0524	0.3794	-0.0733	-0.0033	0.1439	
Loglogistic	Intercept	1.6250	0.1324	0.0175	-0.0173	0.0006	
	Treatment	0.6343	0.1875	-0.0173	0.0352	0.0003	
	Scale	0.5868	0.0496	0.0006	0.0003	0.0025	
Lognormal	Intercept	1.6507	0.1309	0.0171	-0.0168	0.0010	
	Treatment	0.6159	0.1829	-0.0168	0.0335	0.0008	
	Scale	0.9892	0.0749	0.0010	0.0008	0.0056	
Generalized gamma	Intercept	1.4651	0.1927	0.0371	-0.0105	0.0016	0.0511
	Treatment	0.5682	0.1853	-0.0105	0.0343	0.0008	0.0156
	Scale	1.0071	0.0763	0.0016	0.0008	0.0058	-0.0005
	Shape	-0.4737	0.3634	0.0511	0.0156	-0.0005	0.1321
OS July 2017 - Joint fit							
Exponential	Intercept	3.4347	0.1459	0.0213	-0.0213		
	Treatment	0.2366	0.2110	-0.0213	0.0445		
	Scale	1.0000					
Weibull	Intercept	3.4102	0.1322	0.0175	-0.0168	0.0015	

	Treatment	0.2173	0.1900	-0.0168	0.0361	0.0013	
	Scale	0.8974	0.0834	0.0015	0.0013	0.0070	
Gompertz	Shape	0.0015	0.0110	0.0001	-0.0001	-0.0016	
	Treatment	-0.2371	0.2111	-0.0001	0.0446	-0.0204	
	Rate	-3.4546	0.2073	-0.0016	-0.0204	0.0430	
Loglogistic	Intercept	3.0277	0.1526	0.0233	-0.0228	0.0010	
	Treatment	0.2361	0.2136	-0.0228	0.0456	0.0009	
	Scale	0.7265	0.0655	0.0010	0.0009	0.0043	
Lognormal	Intercept	3.0000	0.1600	0.0256	-0.0242	0.0034	
	Treatment	0.2982	0.2214	-0.0242	0.0490	0.0010	
	Scale	1.2694	0.1025	0.0034	0.0010	0.0105	
Generalized gamma	Intercept	3.0811	0.2490	0.0620	-0.0308	-0.0245	0.0814
	Treatment	0.2816	0.2205	-0.0308	0.0486	0.0068	-0.0168
	Scale	1.2146	0.1733	-0.0245	0.0068	0.0300	-0.0592
	Shape	0.1701	0.4189	0.0814	-0.0168	-0.0592	0.1755

The mean probabilistic results for the revised base case are reported in Table 10. Results for scenarios are shown in Table 11 and Table 12. The scatterplots and cost acceptability curves are provided from Figure 1 to

Figure **6**.

Table 10: Revised base case with July 2017 OS data exponential distribution

	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (cabozantinib vs sunitinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	8,761	0.338	0.465	25,937
Pair-wise Analysis (cabozantinib vs pazopanib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	7,882	0.334	0.463	23,611

Figure 1: Revised base case with July 2017 OS data exponential distribution - PSA scatter plot and cost acceptability curve, cabozantinib versus sunitinib

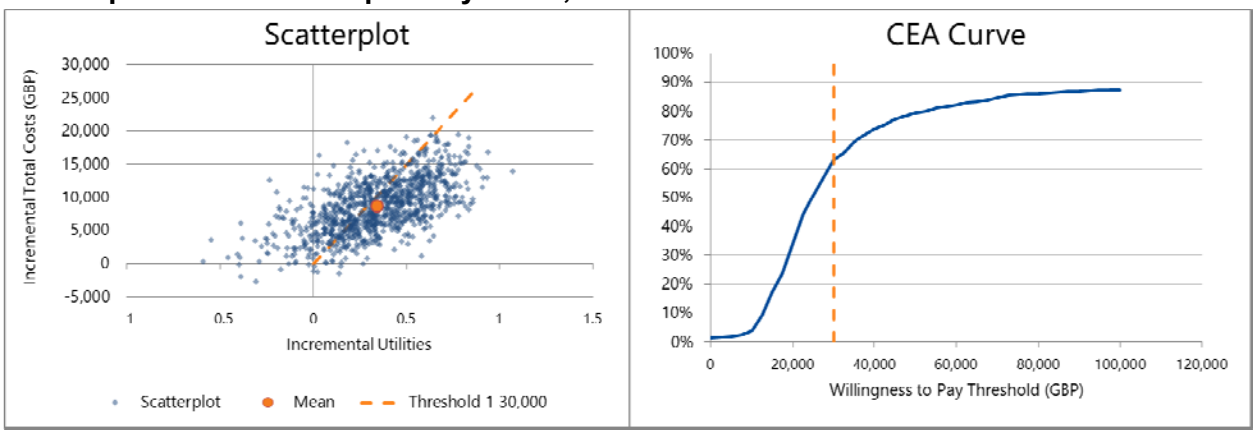


Figure 2: Revised base case with July 2017 OS data exponential distribution - PSA scatter plot and cost acceptability curve, cabozantinib versus pazopanib

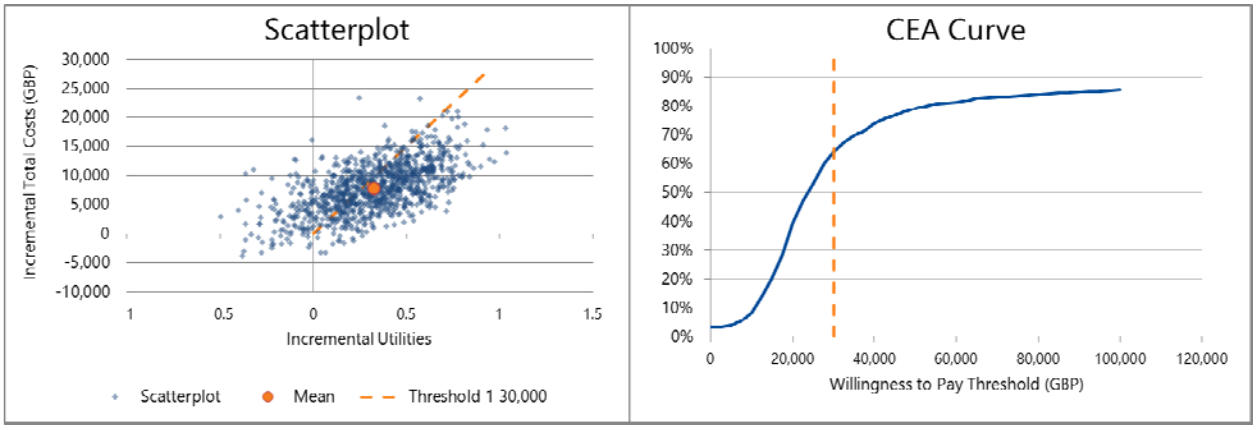


Table 11: Scenario with July 2017 OS data Weibull distribution

	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (cabozantinib vs sunitinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	8,067	0.281	0.374	28,743
Pair-wise Analysis (cabozantinib vs pazopanib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	7,277	0.276	0.371	26,404

Figure 3: Scenario with July 2017 OS data Weibull distribution - PSA scatter plot and cost acceptability curve, cabozantinib vs sunitinib

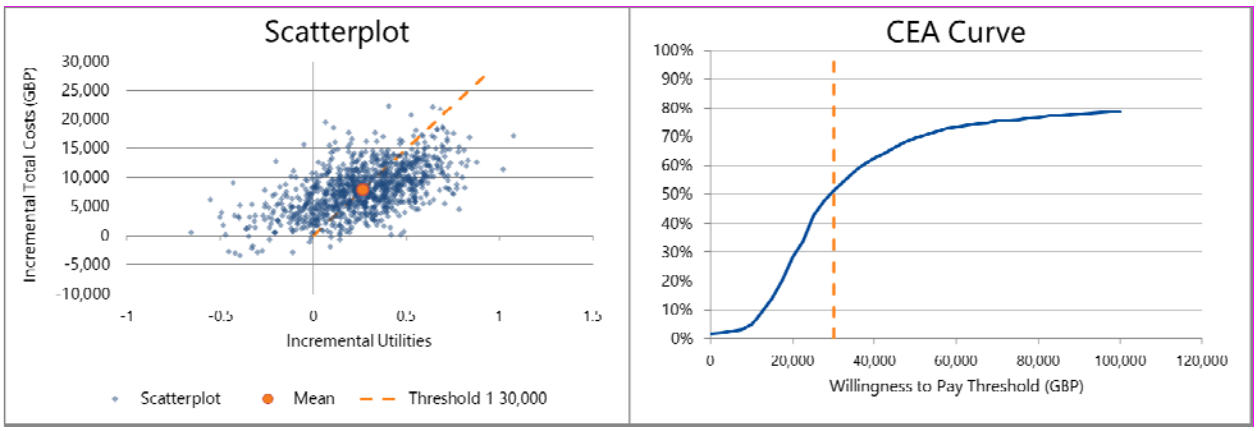


Figure 4: Scenario with July 2017 OS data Weibull distribution - PSA scatter plot and cost acceptability curve, cabozantinib vs pazopanib

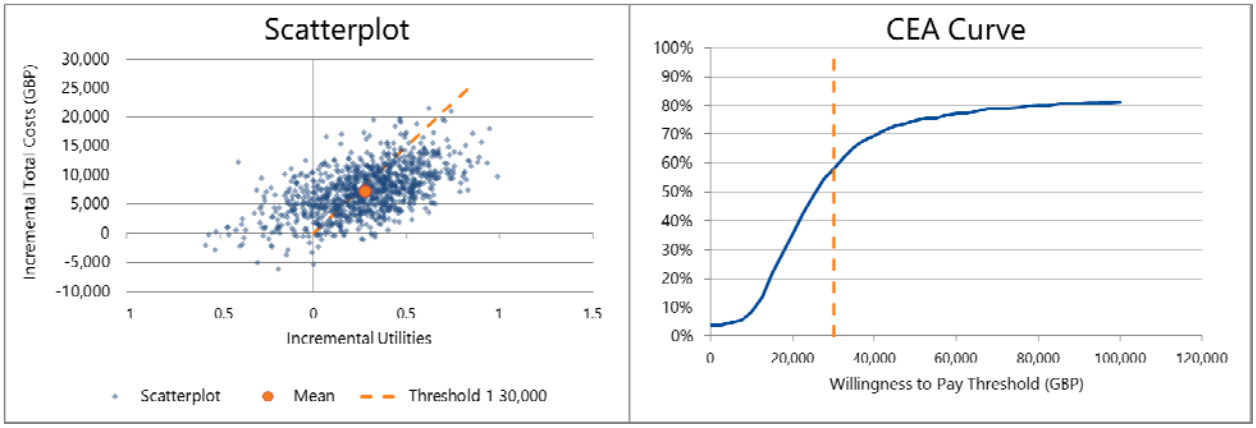


Table 12: Scenario with July 2017 OS data Gompertz distribution

	Total costs	Total QALYs	Total LYs	Incremental			ICER (cost/QALY)
				Costs	QALYs	LYs	
Pair-wise Analysis (cabozantinib vs sunitinib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	8,073	0.296	0.400	27,251
Pair-wise Analysis (cabozantinib vs pazopanib)							
Cabozantinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Pazopanib	[redacted]	[redacted]	[redacted]	7,369	0.313	0.433	23,507

Figure 5: Scenario with July 2017 OS data Gompertz distribution - PSA scatter plot and cost acceptability curve, cabozantinib versus sunitinib

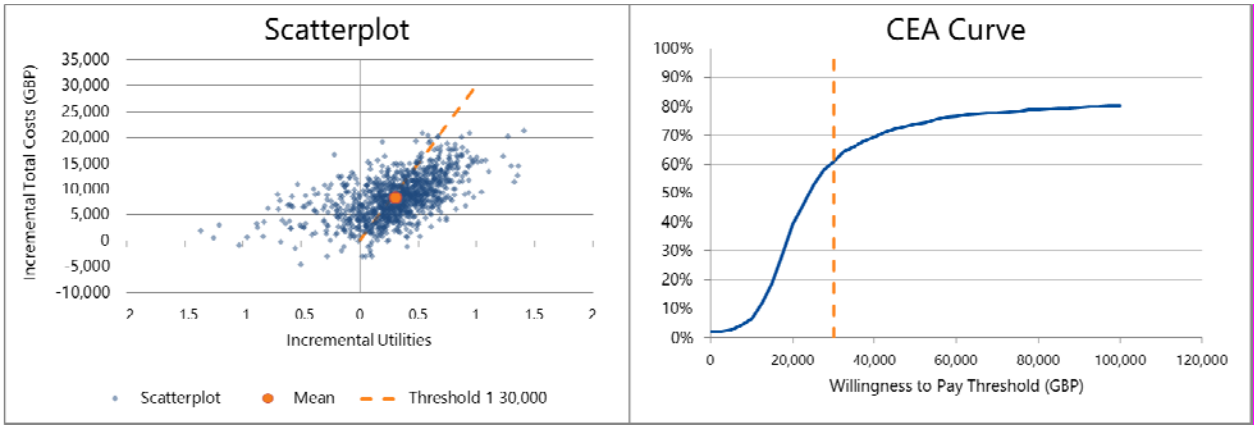
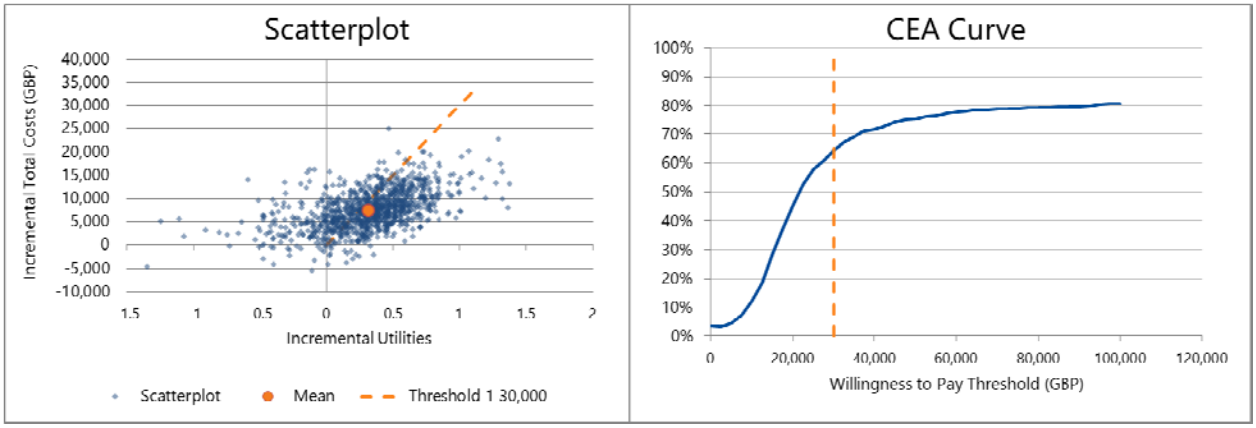


Figure 6: Scenario with July 2017 OS data Gompertz distribution - PSA scatter plot and cost acceptability curve, cabozantinib versus pazopanib



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 65 of the original Ipsen submission.

Figure 7 and Figure 8

Figure 8 show tornado diagrams depicting those variables that increase or decrease the ICERs by more than £500 per QALY. Results are robust to isolated parameter changes to the vast majority of variables in the model.

Figure 7: Revised base case with July 2017 OS data exponential distribution; tornado graph, cabozantinib versus sunitinib

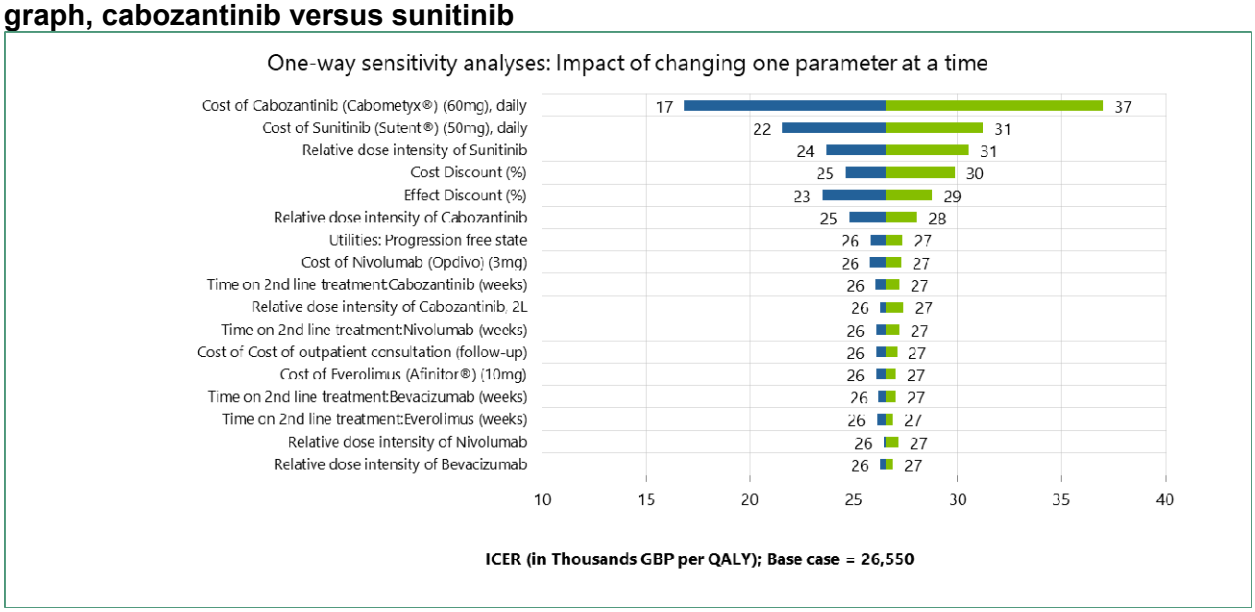
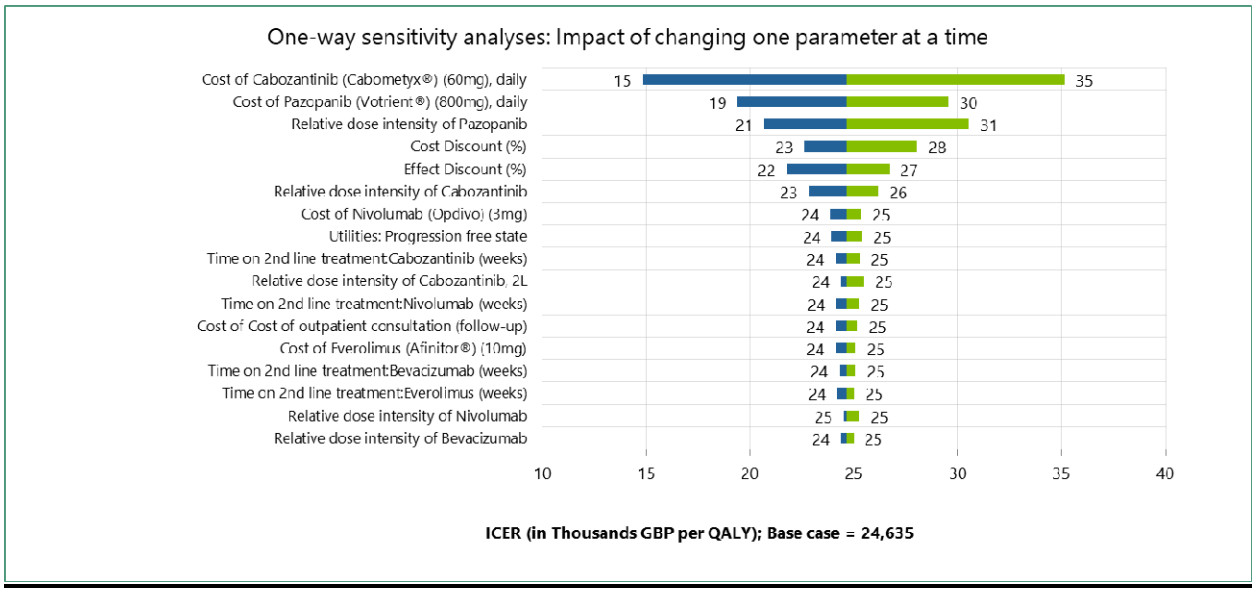


Figure 8: Revised base case with July 2017 OS data exponential distribution; tornado graph, cabozantinib versus pazopanib



Scenario analysis (SA)
The scenarios tested are shown from Table 13 to Table 14.

Table 13: Revised base case with July 2017 OS data exponential distribution cabozantinib versus sunitinib

Scenario		Total costs		Total QALYs		ICER (cost/QALY)
		Cabo	Suni	Cabo	Suni	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	26,550
Discount	0%	[redacted]	[redacted]	[redacted]	[redacted]	26,417
	6%	[redacted]	[redacted]	[redacted]	[redacted]	26,635
Time horizon	10 years	[redacted]	[redacted]	[redacted]	[redacted]	26,505
CABOSUN data						
PFS curves	PFS = exponential	[redacted]	[redacted]	[redacted]	[redacted]	24,940
	PFS = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	23,781
	PFS = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	24,919
OS curves	OS = exponential	[redacted]	[redacted]	[redacted]	[redacted]	26,550
	OS = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	29,857
	OS = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	24,982
TTD curves	TTD = exponential	[redacted]	[redacted]	[redacted]	[redacted]	22,108
	TTD = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	22,147
	TTD = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	24,397
	TTD = Gamma	[redacted]	[redacted]	[redacted]	[redacted]	25,336
Utility values	Swinburn	[redacted]	[redacted]	[redacted]	[redacted]	22,308
	Pazo NICE STA	[redacted]	[redacted]	[redacted]	[redacted]	27,271
	Suni NICE STA	[redacted]	[redacted]	[redacted]	[redacted]	24,753
Age-adjusted utilities	Exclude	[redacted]	[redacted]	[redacted]	[redacted]	26,034
AE disutility source	METEOR AE disutilities	[redacted]	[redacted]	[redacted]	[redacted]	26,478
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	26,783
	Subsequent treatment- ERG scenario 2[a]	[redacted]	[redacted]	[redacted]	[redacted]	31,533
	Blood test (comprehensive test)	[redacted]	[redacted]	[redacted]	[redacted]	26,857
	Health resource (UK clinicians)	[redacted]	[redacted]	[redacted]	[redacted]	25,240
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	26,928

Cabo, cabozantinib; Pazo, pazopanib; PFS, progression-free survival; OS, overall survival; Suni, sunitinib; TTD, time to discontinuation

[a] In the NICE Appraisal Committee meeting, the ERG scenario 2 was preferred by the clinical expert present for the scenario analyses, and hence it is included as a scenario. In the base case, CABOSUN subsequent treatments are used, as these include both the costs and benefits of the subsequent treatments.

Table 14: Revised base case with July 2017 OS data exponential distribution cabozantinib versus pazopanib

Scenario		Total costs		Total QALYs		ICER (cost/QALY)
		Cabo	Pazo	Cabo	Pazo	
Base case		[redacted]	[redacted]	[redacted]	[redacted]	24,635
Discount	0%	[redacted]	[redacted]	[redacted]	[redacted]	24,796
	6%	[redacted]	[redacted]	[redacted]	[redacted]	24,505
Time horizon	10 years	[redacted]	[redacted]	[redacted]	[redacted]	24,510
CABOSUN data						
PFS curves	PFS = exponential	[redacted]	[redacted]	[redacted]	[redacted]	22,920
	PFS = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	21,455
	PFS = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	22,896
OS curves	OS = exponential	[redacted]	[redacted]	[redacted]	[redacted]	24,635
	OS = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	27,637
	OS = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	23,120
TTD curves	TTD = exponential	[redacted]	[redacted]	[redacted]	[redacted]	20,056
	TTD = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	20,003
	TTD = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	22,449
	TTD = Gamma	[redacted]	[redacted]	[redacted]	[redacted]	23,158
Utility values	Swinburn	[redacted]	[redacted]	[redacted]	[redacted]	20,678
	Pazo NICE STA	[redacted]	[redacted]	[redacted]	[redacted]	25,309
	Suni NICE STA	[redacted]	[redacted]	[redacted]	[redacted]	22,958
Age-adjusted utilities	Exclude	[redacted]	[redacted]	[redacted]	[redacted]	24,153
AE disutility source	METEOR AE disutilities	[redacted]	[redacted]	[redacted]	[redacted]	24,449
Cost	Wastage excluded	[redacted]	[redacted]	[redacted]	[redacted]	24,870
	Subsequent treatment- ERG scenario 2[a]	[redacted]	[redacted]	[redacted]	[redacted]	29,651
	Blood test (comprehensive test)	[redacted]	[redacted]	[redacted]	[redacted]	24,944
	Health resource (UK clinicians)	[redacted]	[redacted]	[redacted]	[redacted]	23,316
	End-of-life cost excluded	[redacted]	[redacted]	[redacted]	[redacted]	25,015

Cabo, cabozantinib; Pazo, pazopanib; PFS, progression-free survival; OS, overall survival; Suni, sunitinib; TTD, time to discontinuation

Appendix 1 – new OS data: July 2017 data cut-off

The statistical fits are shown in Table 15.

Table 15: Model fit statistics – OS July 2017

Distribution	AIC	AICC	BIC
Cabozantinib (separate fit)			
Lognormal	**401.084**	**401.242**	**405.823**
Loglogistic	401.670	401.828	406.409
Gamma	403.070	403.390	410.178
Exponential	403.733	403.785	406.103
Weibull	404.580	404.738	409.319
Gompertz	405.732	405.890	410.471
Sunitinib (separate fit)			
Exponential	**418.862**	**418.915**	**421.205**
Gamma	421.859	422.188	428.890
Gompertz	420.809	420.969	425.522
Loglogistic	420.599	420.761	425.286
Lognormal	420.380	420.542	425.068
Weibull	420.547	420.709	425.234
Joint fit			
Lognormal	**819.769**	**819.927**	**828.919**
Loglogistic	820.502	820.660	829.651
Gamma	821.606	821.871	833.806
Exponential	822.595	822.673	828.695
Weibull	823.296	823.454	832.446
Gompertz	824.576	824.733	833.745

Cabozantinib for untreated advanced renal cell carcinoma [ID1208]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 June 2018 email: TACommB@nice.org.uk/NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Cancer Support Network
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Please return using NICE Docs

Cabozantinib for untreated advanced renal cell carcinoma [ID1208]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 26 June 2018 email: TACommB@nice.org.uk/NICE DOCS

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	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.
2	Cabozantinib is a tyrosine kinase inhibitor, which acts 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. Anecdotal evidence suggests 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 (KCSN) 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 evidence to support this unmet need in advanced RCC patients.
3	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.
4	The committee's decision not to recommend fist-line cabozantinib was based upon the fact that cabozantinib did not meet the end-of-life criteria for a combined population of intermediate- and poor-risk patients. However, this model is based upon data from clinical trials, which do not necessarily reflect routine clinical practice. KCSN urge NICE to consider funding for cabozantinib through the CDF to enable collection of real world survival data for intermediate- and poor-risk patients, which could potentially impact the final recommendation.
4	The committee's decision to not recommend cabozantinib for untreated advanced RCC patients 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 directly affected by their decision.
5	Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.
6	In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which

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	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 in the first-line. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.
7	Current first-line treatment options are not effective for everyone. Undue restrictions in accessing cabozantinib would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the first-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.
8	Clinical trials have been conducted in untreated advanced/metastatic RCC patients with cabozantinib in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of first-line cabozantinib on the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

Cabozantinib for untreated advanced renal cell carcinoma [ID1208]

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Consultation on the appraisal consultation document – deadline for comments 5pm on 26 June 2018 email: TACommB@nice.org.uk/NICE DOCS

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Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Cabozantinib for untreated locally advanced or metastatic renal cell carcinoma - ERG critique of additional company analysis

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Date 5 July 2018

Commercial in confidence information is redacted.

Introduction

This document is a critique by the ERG of additional analyses submitted by Ipsen Ltd (on 25 June 2018) as their response to NICE's ACD consultation (June 2018). Following the first committee meeting for this appraisal (10th May 2018) an ACD was issued with the provisional recommendation not to recommend cabozantinib for untreated locally advanced or metastatic renal cell carcinoma. The company's response to the ACD is intended to address the key issues raised by the appraisal committee in support of their recommendation.

The company submitted a 19 page response document and an update of their economic model. The revised model includes 4 key changes to align with the Committee's preferred assumptions (ACD Section 3.17):

1. Equal clinical effects for pazopanib and sunitinib, based on progression free survival (PFS), overall survival (OS) and time to treatment discontinuation (TTD) in the sunitinib arm of the CABOSUN trial;
2. OS results based on the most recent data cut from the CABOSUN trial (July 2017);
3. Duration of relative treatment effects for cabozantinib compared with sunitinib only persist up to 5 years;
4. Distribution of subsequent treatments based on that observed in CABOSUN, with distribution for pazopanib assumed equal to that of sunitinib.

In addition to the above changes, the model includes parameters for new OS and PFS survival curves using CABOSUN individual patient data (July 2017 for OS) for models fitting the curves separately and jointly to the two treatment arms.

The company applied an increased confidential Patient Access Scheme (PAS) discount for first line (but not second line) cabozantinib in their model. The model also includes a publicly available PAS discount for one of the comparators, pazopanib, and includes provision of the first cycle of sunitinib free to the NHS (this is in common with the previous version of the model). The model does not include (confidential) PAS discounts for treatments used in subsequent lines. The results of analyses incorporating these discounts plus the confidential PAS discounts for drugs used in subsequent lines of treatment are available in a separate confidential ERG addendum.

Summary of the company's revisions to their model

1. Clinical equivalence for pazopanib and sunitinib

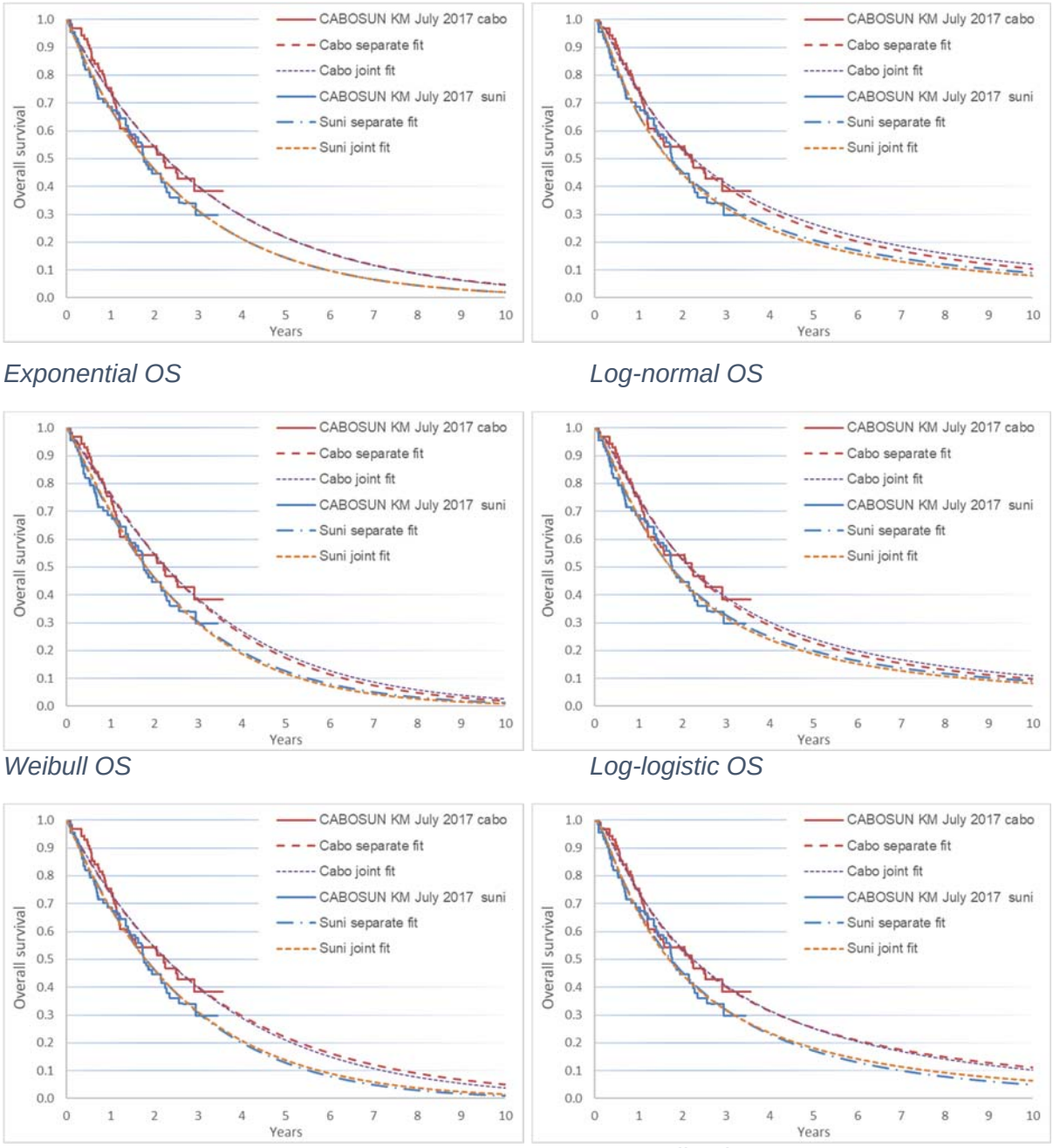
The economic model no longer uses the company's indirect treatment comparisons (ITC) to compare cabozantinib with pazopanib. The ERG had previously concluded that the statistical methods used to conduct the ITC are appropriate, but noted that there is uncertainty in the results due to differences between the trials in patient prognostic characteristics. The appraisal committee acknowledged that pazopanib and sunitinib can be considered equally clinically effective and therefore the ITC was not necessary (ACD Section 3.9). The company's updated analyses are therefore only based on OS, PFS and TTD estimates from the CABOSUN trial.

2. OS curves based on July 2017 CABOSUN data

The company's previous analysis used OS data from the January 2017 data cut of the CABOSUN trial, which the ERG noted was less mature and more favourable to cabozantinib, than the most recent data cut of July 2017. At their meeting, the appraisal committee meeting expressed a preference for the July 2017 data cut. The company's revised base case analysis uses this data cut.

In response to the ACD, the company has fitted parametric curves to the CABOSUN July 2017 OS data (see Figure 1 of this document). They estimated six parametric survival functions (exponential, Weibull, Gompertz, log-logistic, log-normal and generalised gamma), using separate and joint fitting for the intervention and control arms of the trial. The resulting parameter estimates are shown in Tables 8 and 9 of the company's ACD response, and model fit statistics are shown in Table 15. Based purely on AIC, AICC and BIC statistics, the best-fitting curve appears to be the log-normal (cabozantinib separate fit and joint fit for both treatment arms) or exponential (sunitinib separate fit). However, as noted in the ACD, as the Kaplan-Meier curves crossed, no parametric curve fitted the data well. In their original submission, the company had attempted to get a better fit using a fractional polynomial approach, but the visual fit of the resulting curves was still poor.

In addition to the fit of the estimated survival curves to the trial data, it is important to consider the plausibility of the extrapolations. The company and ERG had previously preferred the exponential fit, and the clinical experts at the committee meeting agreed that these curves produced plausible predictions at 5 and 10 years after starting treatment. The committee concluded that whether the proportional hazards assumption holds was unclear, and that the OS extrapolation was a source of uncertainty.



Exponential OS *Log-normal OS*

Weibull OS *Log-logistic OS*

Gompertz OS *Generalised gamma OS*

Figure 1 Overall survival curve estimates from CABOSUN trial (July 2017 data cut)

The company chose exponential OS curves for their revised base case analysis and separately-fitted Weibull and Gompertz OS curves in scenario analyses. We present additional scenario analyses using the other available distributions: log-logistic, log-normal and generalised gamma), below. We also provide results using the 6 jointly-fitted survival functions as scenario analyses.

3. Duration of relative treatment benefit limited to 5 years

The company adjusted the OS curve for cabozantinib to set the relative risk for cabozantinib compared with sunitinib equal to 1 from a fixed time point: 5 years in the base case. This reflects the committee's preferred assumptions stated in the ACD. To illustrate the effect of uncertainty around this assumed duration of relative effect, we also present scenario analyses assuming a duration of 3.5 years (currently-available trial follow up) and 7 years.

4. Equal use of subsequent treatments for pazopanib and sunitinib

Both the company and ERG base cases assumed that following progression, patients would receive subsequent therapy in the same proportions as in the clinical trials: cabozantinib and sunitinib arms of the CABOSUN trial and the pazopanib arm of the COMPARZ trial. The company and ERG conducted scenario analyses to explore uncertainty over subsequent treatment, based on clinical advice usage in practice:

- **ERG scenario 1**: For patients who progress after cabozantinib, 10% have axitinib, 30% nivolumab; 20% everolimus; 30% lenvatinb plus everolimus and 10% usual care. After pazopanib or sunitinb, 10% have axitinib, 20% nivolumab; 20% everolimus; 20% cabozantinib, 20% lenvatinb plus everolimus and 10% usual care.
- **ERG scenario 2**: After cabozantinib, 45% of patients have nivolumab, 45% have lenvatinb plus everolimus and 10% usual care: after pazopanib or sunitinb, 30% have nivolumab, 30% cabozantinib, 30% lenvatinb plus everolimus and 10% usual care.
- **Company scenario**: After cabozantinib, 50% of patients have axitinib; 30% nivolumab, 10% everoliumus; and 10% usual care. After pazopanib or sunitinib, 40% have axitinib, 30% nivolumab, 10% everolimus; 10% cabozantinib and 10% usual care.

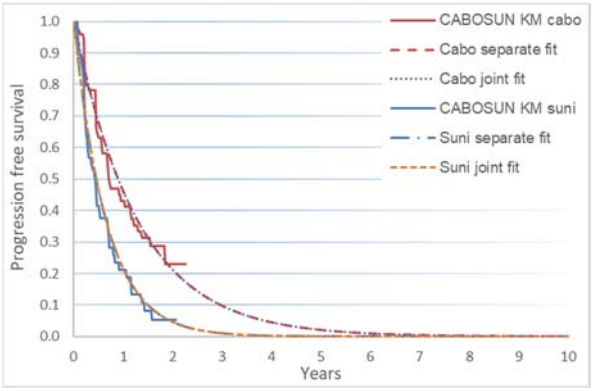
The committee concluded that proportions of subsequent treatments in the model should be based on observed usage in the CABOSUN trial. This is a compromise, as although it ensures that both costs and benefits of subsequent therapy are incorporated in the cost-effectiveness estimates, it does not fully reflect NHS practice. The committee further concluded that although the use of clinical trial data to inform assumptions about the distribution of subsequent therapies was acceptable, the same distribution should be used for pazopanib and sunitinib. It also concluded that it was appropriate to use the ERG's scenario analyses about the proportions of subsequent therapies to estimate costs. We present scenario analysis below based on all of the above scenarios.

5. Addition of jointly-fitted PFS curves

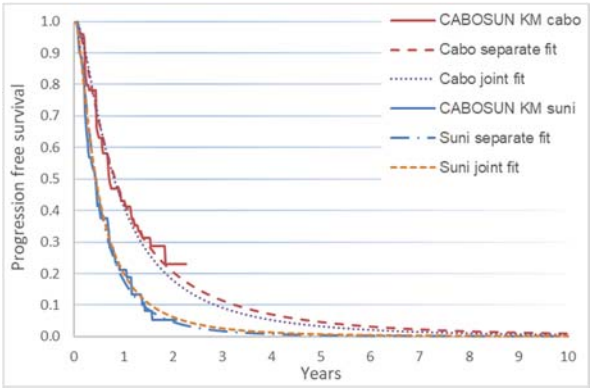
The company presented further parametric survival analysis for PFS in their ACD response and model. In addition to the PFS curves separately fitted to the CABOSUN trial data (as used in the original submission), the company estimated jointly-fitted curves. The same six functions were estimated as for OS: exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma. For their base case, the company chose jointly-fitted log-normal curves. The rationale for changing from separately fitted to jointly fitted PFS curves was that the ERG had argued that the proportional hazards assumption was appropriate for PFS, and that joint curve fitting would reduce uncertainty. The company has not presented model fit statistics for the new jointly-fitted PFS curves. We illustrate the model fit and extrapolation in Figure 2 below. We also present scenarios with all jointly and separately fitted PFS curves.

6. Revised PAS discount

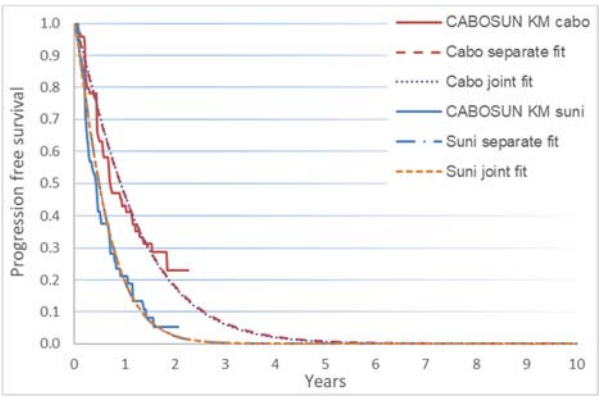
The results presented in the company's ACD response and in this report are based on an increased PAS discount for cabozantinib. The company did not incorporate this new PAS discount for second-line use of cabozantinib in the model. Non-confidential PAS agreements are in place for pazopanib and sunitinib. These are included in the cost calculations for the company base case and in this report for first-line use of these drugs, but not for second-line use. In addition, there are confidential PAS discounts not included for other second line treatments. We present results including all available PAS discounts for first and second-line treatment in a separate confidential addendum to this report.



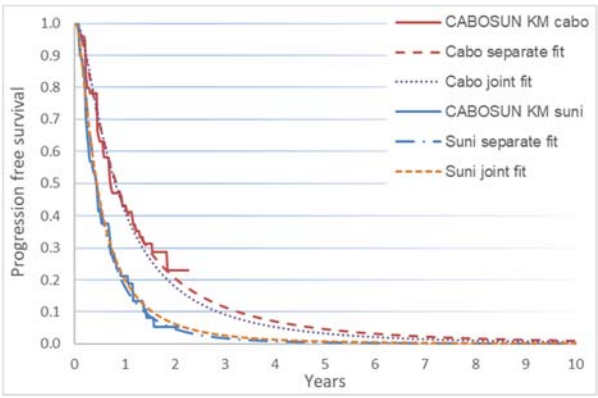
Exponential PFS



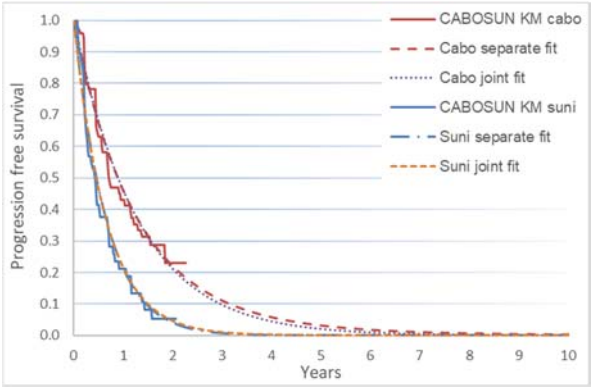
Log-normal PFS



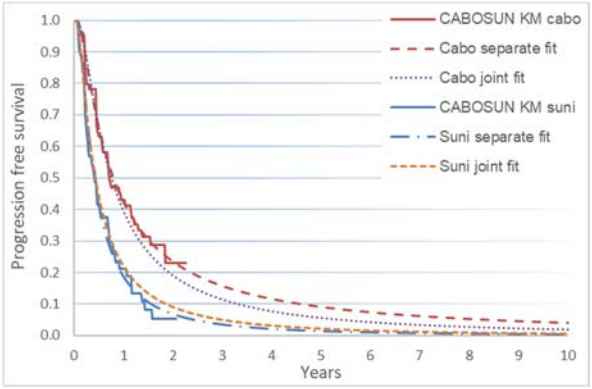
Weibull PFS



Log-logistic PFS



Gompertz PFS



Generalised gamma PFS

Figure 2 Progression-free survival curves estimated from CABOSUN trial

7. ERG 'simple comparison'

The ERG had previously conducted a simple comparison by estimating the PFS and OS effects of cabozantinib relative to the sunitinib survival directly from the CABOSUN trial, and assuming the pazopanib survival curves to be equal to those for sunitinib. (NB. Although we refer to this as an indirect treatment comparison, which would imply that more than one trial was involved, it should be acknowledged that it is based upon a single trial (CABOSUN), with the assumption that pazopanib is of equal efficacy to sunitinib). The motivation for this approach was to avoid the use of an indirect comparison using the CABOSUN and COMPARZ trials, because of differences between their the included patient populations, and also to enable use of the most recent relative survival estimates for cabozantinib compared with sunitinib in the CABOSUN trial (the July 2017 data cut). A key difference between our simple comparison and the company's new base case analysis, is that the latter is based on OS curves fitted to the July 2017 data, whereas our simple approach used an OS curve for sunitinib based on the January 2017 data cut, adjusted for cabozantinib using the July 2017 hazard ratio in comparison with sunitinib.

The company have incorporated the ERG simple comparison into their updated model. The results of this are reported as a scenario analysis.

ERG validation of the revised company model

We conducted a series of checks to assess whether the above changes had been correctly implemented. These included:

- Replicating all of the company analyses presented in the ACD response document by running the analyses in the revised submitted model.
- Comparing the OS and PFS parameters from Tables 8 and 9 in the company ACD response document against the selected parameters defining the survival curves on the TPs_CABOSUN_sep and TPs_CABOSUN_joint sheets.
- Checking that the relative risks of OS and PFS for pazopanib compared with sunitinib equal 1 throughout time horizon on TPs_CABOSUN_sep, TPs_CABOSUN_joint and TPs_ERG sheets. This also provided a cross-check that the estimated OS and PFS hazard ratios reflected reported results (CS Figure 5 and Figure 7, pages 37 and 40).
- Checking that the relative risks of OS and PFS for cabozantinib compared with sunitinib equal 1 after the assumed duration of relative effects (5 years) on TPs_CABOSUN_sep, TPs_CABOSUN_joint and TPs_ERG sheets.

- Checking that the model is using the same mix of subsequent treatments for pazopanib as for sunitinib (User-Inputs rows 222 to 225).

We identified two potential issues:

- There are discrepancies between the Gompertz rate parameter estimates for separately fitted PFS and OS (January 2017) as entered in the original version of the model submitted with the CS and the updated post-ACD version of the company model. These differences do not affect the company's base case analysis, which does not use the Gompertz distribution, but they do introduce uncertainty about the validity of the Gompertz extrapolations.
- The company applied the limitation on the duration of relative treatment benefit (5 years) to OS only, whereas the ERG preferred analysis included this constraint for both PFS and OS. This difference should have a relatively modest impact on results, as few patients have not progressed by 5 years: 3.3% in the cabozantinib arm and 0.7% in the sunitinib arm in the company's new base case model. However, due to the assumption that treatment stops on disease progression, changes to the PFS curve can also affect TTD and hence costs. We test the effect of adding the 5-year limit on PFS effects in scenario analysis.

We also noted a transcription error in the company's response document. In tables 11 and 12 the company have transposed the table rows containing costs, QALYs and life years for cabozantinib and sunitinib/pazopanib. However, this does not affect the incremental costs, QALYs and life years, or the ICERs.

Otherwise, the ERG view is that the company have correctly implemented the committee's preferred assumptions as expressed in ACD paragraph 3.17.

Company new base case results

The company present their deterministic base case results in Table 3 (page 4) of their ACD response. We note that the company incremental analyses presented in their response document do not recognise that pazopanib is subject to extended dominance in the revised model. Thus the correct comparator for cabozantinib for fully incremental analysis is sunitinib not pazopanib. This means that the incremental ICER for cabozantinib is £26,550 per QALY gained. We show the company new base case results, including the correct incremental analysis in Table 1.

Table 1 Revised company base case results: deterministic

	Total cost (£)	***Total QALYs***	***Fully incremental analysis***			***Pairwise ICER (£ per QALY)***
			Incremental cost	*Incremental QALYs*	*ICER (£/QALY*	*(cabo vs. comparator*
Sunitinib	[redacted]	[redacted]	-	-	-	26,550
Pazopanib	[redacted]	[redacted]	710	0.002	Ext. dom.	24,635
Cabozantinib	[redacted]	[redacted]	9,072	0.342	26,550	-

Ext. dom, extended dominance

Probabilistic sensitivity analysis

The company characterised the impact of uncertainty over model input parameters through probabilistic sensitivity analysis (PSA). See Table 2 for probabilistic results for the company's new base case analysis (2,000 PSA iterations). The results are similar to the deterministic results in Table 1 above.

Table 2 Revised company base case results: probabilistic

	Total cost (£)	***Total QALYs***	***Incremental cost***	***Incremental QALYs***	***ICER (£ per QALY)***
Pairwise comparison (cabozantinib vs. sunitinib)					
Sunitinib	[redacted]	[redacted]	-	-	-
Cabozantinib	[redacted]	[redacted]	8,737	0.338	25,856
Pairwise comparison (cabozantinib vs. pazopanib)					
Pazopanib	[redacted]	[redacted]	-	-	-
Cabozantinib	[redacted]	[redacted]	7,644	0.318	24,068

The extent of uncertainty around these probabilistic estimates is illustrated in the cost-effectiveness scatterplots and cost-effectiveness acceptability curves (CEACs) in Figure 3 and Figure 4 for cabozantinib compared with sunitinib and pazopanib respectively. The CEACs suggest a probability of approximately 60% that cabozantinib falls with a £30,000 per QALY ICER threshold.

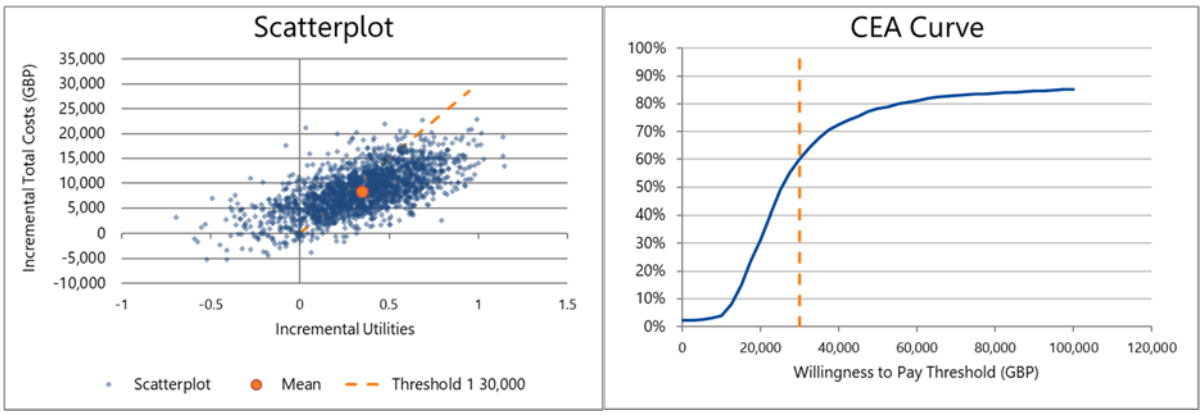


Figure 3 Cost-effectiveness scatterplot and acceptability curves: cabozantinib vs. sunitinib: company base case

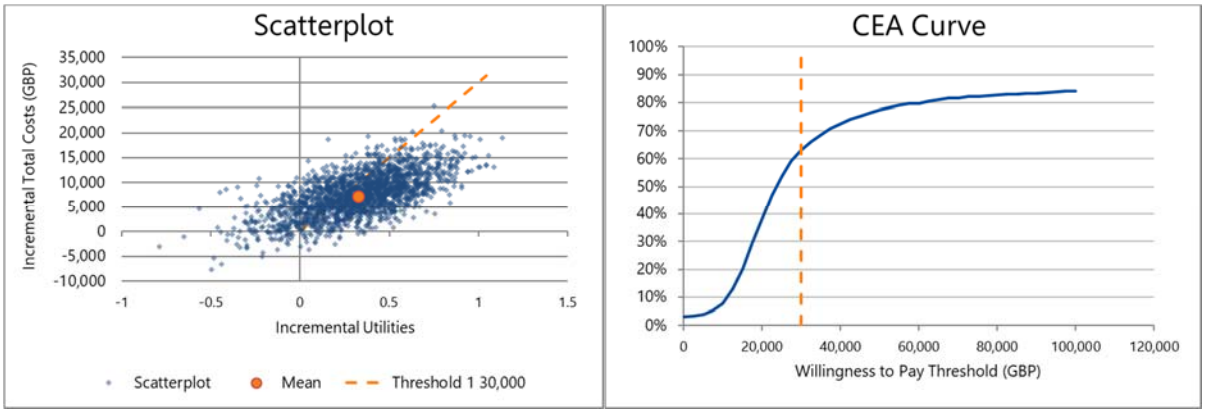


Figure 4 Cost-effectiveness scatterplot and acceptability curves: cabozantinib vs. pazopanib: company base case

One-way sensitivity analysis

Sensitivity of the ICER estimates to individual input parameters is illustrated in the tornado diagrams in Figure 5 and Figure 6. The results are most sensitive to the cost and relative dose intensity of cabozantinib, sunitinib and pazopanib, and the discount rates for costs and health effects.

Note however that this analysis does not include uncertainty around the clinical effectiveness parameters parameters, which is incorporated in the above PSA analyses and the scenario analyses below (through the choice of OS and PFS distribution).

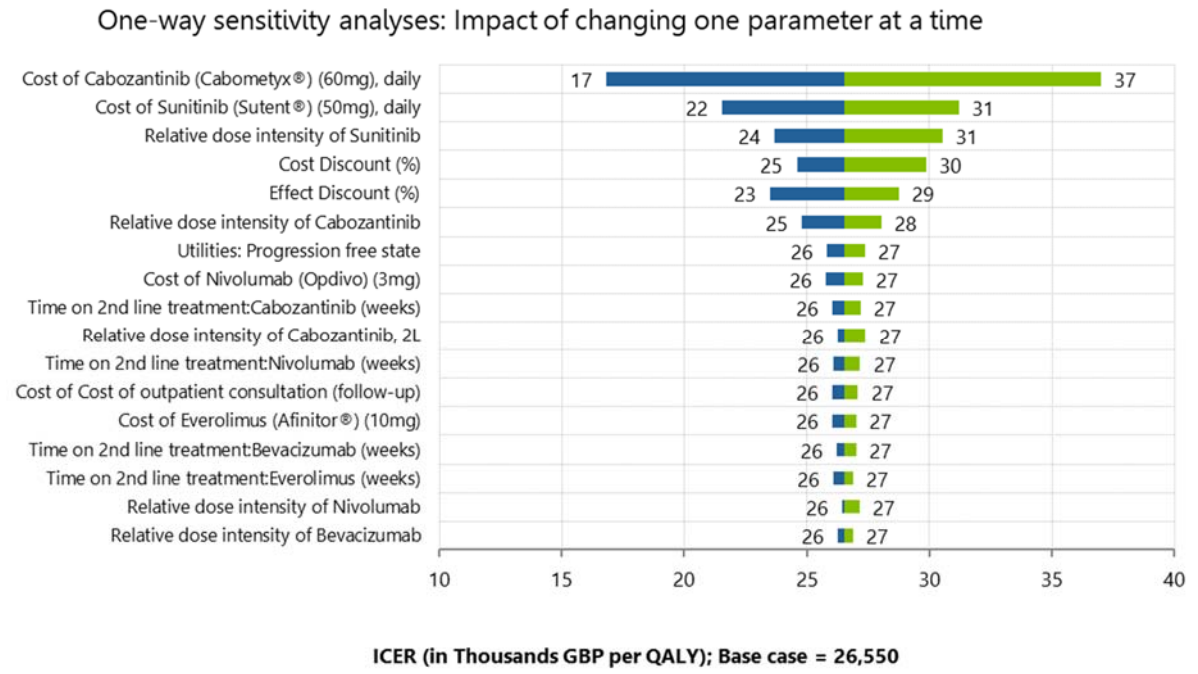


Figure 5 Tornado diagram for cabozantinib compared with sunitinib

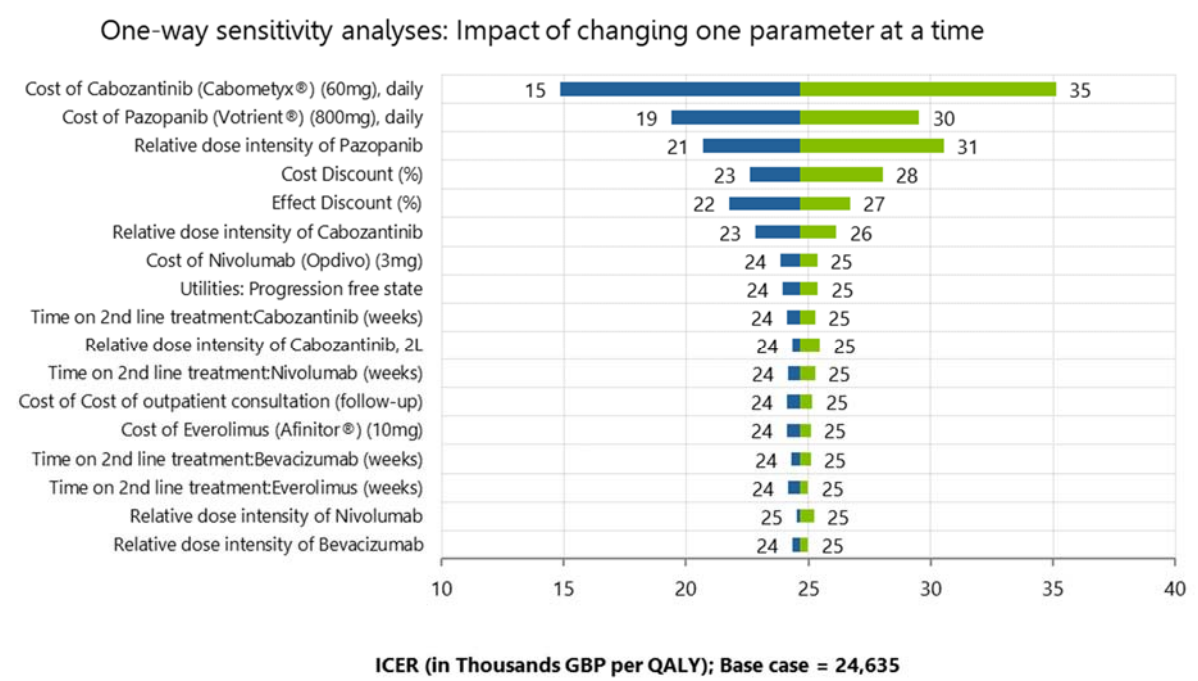


Figure 6 Tornado diagram for cabozantinib compared with pazopanib

Scenario analysis

The company present four key scenario analyses in Tables 4 to 7 of their ACD response document: OS Weibull (separate); OS Gompertz (separate); PFS log-normal (joint); ERG simple comparison. They also repeat a set of other scenario analyses from additional analyses in the ERG report (Table 13, page 17 ACD response). We summarise the results of these scenarios, along with additional ERG scenarios in the tables below.

Table 3 Deterministic scenario around new company base case: OS and PFS curves

Scenario	Pairwise (cabo vs comparator)					
	Inc. cost (£)		Inc. QALYs		ICER *(£ per QALY)*	
	Suni	Pazo	Suni	Pazo	Suni	Pazo
Revised company base case	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
ERG simple comparison	[redacted]	[redacted]	[redacted]	[redacted]	26,974	24,953
OS curve scenarios (July 2017)						
Separate exponential	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
Separate Weibull	[redacted]	[redacted]	[redacted]	[redacted]	29,857	27,637
Separate Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	24,982	23,120
Separate log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	31,881	29,660
Separate log-normal	[redacted]	[redacted]	[redacted]	[redacted]	29,119	27,202
Separate generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	23,708	22,109
Joint exponential	[redacted]	[redacted]	[redacted]	[redacted]	26,550	24,635
Joint Weibull	[redacted]	[redacted]	[redacted]	[redacted]	26,827	24,768
Joint Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	26,930	24,958
Joint log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	25,089	23,341
Joint log-normal	[redacted]	[redacted]	[redacted]	[redacted]	22,938	21,463
Joint generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	23,610	22,050
PFS curve scenarios						
Separate exponential	[redacted]	[redacted]	[redacted]	[redacted]	24,940	22,919
Separate Weibull	[redacted]	[redacted]	[redacted]	[redacted]	24,095	21,757
Separate Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	26,041	23,993
Separate log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	25,879	24,035
Separate log-normal	[redacted]	[redacted]	[redacted]	[redacted]	26,062	24,182
Separate generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	24,860	23,083
Joint exponential	[redacted]	[redacted]	[redacted]	[redacted]	24,940	22,920
Joint Weibull	[redacted]	[redacted]	[redacted]	[redacted]	23,781	21,455
Joint Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	24,919	22,896
Joint log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	26,830	24,925
Joint log-normal	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
Joint generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	27,002	25,085

Scenario	Pairwise (cabo vs comparator)					
	Inc. cost (£)		Inc. QALYs		ICER *(£ per QALY)*	
	Suni	Pazo	Suni	Pazo	Suni	Pazo
Revised company base case	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
Persistence of relative benefits						
OS only: 3.5 years	[redacted]	[redacted]	[redacted]	[redacted]	29,591	27,413
OS only: 5 years	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
OS only: 7 years	[redacted]	[redacted]	[redacted]	[redacted]	24,735	22,977
OS and PFS: 3.5 years	[redacted]	[redacted]	[redacted]	[redacted]	28,682	26,480
OS and PFS: 5 years	[redacted]	[redacted]	[redacted]	[redacted]	26,105	24,182
OS and PFS: 7 years	[redacted]	[redacted]	[redacted]	[redacted]	24,562	22,802
Subsequent treatment use						
CABOSUN /COMPARZ	[redacted]	[redacted]	[redacted]	[redacted]	26,550	50,352
CABOSUN, pazo same as suni	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
Company clinical scenario	[redacted]	[redacted]	[redacted]	[redacted]	29,202	27,305
ERG 1 (all NICE approved)	[redacted]	[redacted]	[redacted]	[redacted]	32,943	31,071
ERG 2 (no axitinib/ everolimus)	[redacted]	[redacted]	[redacted]	[redacted]	31,533	29,651
Utilities						
Health state – Tivozanib STA	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
Health state – Swinburn	[redacted]	[redacted]	[redacted]	[redacted]	22,308	20,678
Health state - Pazo NICE STA	[redacted]	[redacted]	[redacted]	[redacted]	27,271	25,309
Health state - Suni NICE STA	[redacted]	[redacted]	[redacted]	[redacted]	24,753	22,958
AE disutility – Amdahl 2016	[redacted]	[redacted]	[redacted]	[redacted]	**26,550**	**24,635**
AE disutility - METEOR	[redacted]	[redacted]	[redacted]	[redacted]	26,478	24,449

Abbreviations: Cabo, cabozantinib; Suni, sunitinib; Pazo, pazopanib; OS, overall survival; QALY, Quality Adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio

End of life criteria

Based on the revised company model, the mean life expectation for the included patient population treated with sunitinib or pazopanib is estimated at [redacted] (95% CI: [redacted]) years. The expected life extension with cabozantinib compared with sunitinib or pazopanib is estimated at [redacted] years (95% CI: [redacted]) years.

Summary

- The ERG believes that the company have implemented the committee's preferred assumptions and the increased PAS discount correctly, with a couple of minor exceptions (these do not significantly alter the base case results).
- The introduction of an increased PAS discount and the adoption of the committee's preferred assumptions has reduced the base case ICER to less than £30,000 per QALY, when PAS discounts for cabozantinib and other treatments used after disease progression are not taken into consideration.
- Uncertainty in the extrapolation of immature OS data remains, with ICERs varying between approximately £22,000 and £32,000 depending on which parametric survival distribution is used.
- Probabilistic sensitivity analyses suggest a probability of approximately 60% that cabozantinib falls with a £30,000 per QALY ICER threshold for the analyses presented above.
- We present a confidential addendum to this report, which takes account of all available PAS discounts for this patient population at first and second line treatment.