Single Technology Appraisal

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

Contents:

The following documents are made available to stakeholders:

1. **Response to consultee, commentator and public comments on the Draft Guidance**

2. **Comments on the Draft Guidance from** the company, Ipsen**:**
   a. Main response
   b. Appendix

3. **Consultee and commentator comments on the Draft Guidance Document** from:
   a. NCRI-ACP-RCP-RCR

There were no comments on the Draft Guidance Document received through the NICE website.

4. **External Academic Group critique of company response to the DG**

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

Cabozantinib for previously treated advanced differentiated thyroid cancer unsuitable for or refractory to radioactive iodine

Single Technology Appraisal

Response to consultee, commentator and public comments on the Draft Guidance (DG)

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 Social Care 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 document (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 and Social Care, 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	Consultee - company	Ipsen Ltd	**Executive summary** The company would like to thank the committee for the opportunity to respond to the draft guidance consultation. We disagree with the draft negative recommendation for the use of cabozantinib within its marketing authorisation, despite the cost-effectiveness estimate generated by the NICE committee's preferred assumptions being £28,200 per QALY gained for treating locally advanced or metastatic differentiated thyroid cancer (DTC) that is unsuitable for or refractory to radioactive iodine (RAI), and that has progressed after systemic treatment, in adults. This represents a very small population with a clear unmet need currently in England and Wales. We are concerned that despite the statistically significant progression free survival (PFS) benefit (HR 96% confidence interval [CI] unstratified [redacted] and substantial overall survival (OS) benefit (at year 2, cabozantinib OS = [redacted]% compared with BSC OS = [redacted]%) demonstrated for the pure second-line population, the negative recommendation fails to address the needs of this important patient group and their unmet need. As recognised by the EMA[1], cabozantinib can help patients who have poor outcomes and a high unmet medical need by delaying disease progression and increasing OS. As such, we are committed to providing a comprehensive response that will enable NICE to recommend access to cabozantinib at second line as a life-prolonging therapy for radioiodine refractory (RAI-R) DTC patients. **As noted by the committee, there remains a significant unmet need for patients with DTC who are RAI refractory/ineligible that require second-line therapy.** As per Section 3.1 of the draft guidance consultation, Page 5: *"The committee noted that there are no NICE-recommended second-line treatments for people with advanced DTC that is unsuitable for or refractory to radioactive iodine and concluded that there is an unmet need in this population."*	Thank you for your comment. The committee considered the consultation responses from the company. Please see responses to individual issues below.

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			The committee's preferred assumptions which generate an ICER of £28,200 include: • Weibull model to extrapolate Time to Treatment Discontinuation (TTD) for cabozantinib (Section 3.9 of the draft guidance consultation) • Adherence approach for adjusting drug acquisition costs for cabozantinib (Section 3.10 of the draft guidance consultation) • COSMIC-311 utility value for the progression-free survival (PFS) health state utility and unadjusted utility values from Fordham et al. 2015 for the progressed disease (PD) health state utility (Section 3.8 of the draft guidance consultation) The company present a new base case in this response with the following changes from the committee's preferred assumptions with the rationale described herein: • OS blended survival analysis based on the second-line population to reduce OS uncertainty (see Comment 3) • Drug acquisition costs adjusted based on relative dose intensity (RDI) offering consistency with previous TAs (see Comment 4) • COSMIC-311 utilities aligned with the NICE manual preferred utilities (see Comment 5)	
2	Consultee - company	Ipsen Ltd	**COSMIC-311 second-line population is a subgroup and generalisable to England and Wales.** In the draft guidance consultation, (Section 3.4, Page 8) *"the EAG was concerned that, because the second-line population was a subgroup of COSMIC-311 [the intention to treat (ITT) population], the sample size was smaller and there was greater uncertainty in the trial results."* To confirm, the second-line population represents approximately 75% of the ITT population in the COSMIC-311 trial. Furthermore, the company confirmed during the committee meeting the power of the study for the second-line patient population and it was more than 100% powered to detect a difference in the co-primary endpoint of PFS with a hazard ratio (HR) of [redacted] (95% CI [redacted]). Note: the ITT population in the trial was not powered for the exploratory endpoint of OS. The company also confirmed during the committee meeting that the second-line population was representative of the patients likely to be treated in England and Wales. A comparison of the baseline characteristics in the second-line and ITT population from COSMIC-311 is shown in Table 6 of Appendix B and addresses any concerns regarding this due to the two populations being broadly comparable. In addition, given the ITT population was clinically validated to be generalisable to	Thank you for your comment. The committee concluded that the positioning of cabozantinib as a second-line treatment option was appropriate. Discussion around the second-line population can be seen in section 3.3 of the FDG.

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			England and Wales,[2,3] due to the comparable baseline characteristics, in turn the subgroup of second-line only patients is also deemed generalisable to England and Wales. It should be noted that the second-line population had a greater proportion of prior lenvatinib use compared to the ITT population, which considering that lenvatinib is the predominant first-line treatment in England and Wales makes the second-line population even more applicable for decision making. Overall, we understand from the draft guidance consultation that the committee is satisfied that the 2L population is suitable for decision making as per Section 3.3, Page 7: *"The committee was also aware that there are no treatments recommended by NICE for after first-line systemic treatment of radioactive iodine-refractory DTC. The committee concluded that the company's positioning of cabozantinib as a second-line treatment option was appropriate."*	
3	Consultee - company	Ipsen Ltd	**A blended analysis focusing on second-line patients reduces OS uncertainty.** We note in their report following the Technical Engagement (TE) phase the EAG queried why we did not do blended survival analysis for OS based on the pure second-line population. The company did present a blended survival analysis for the ITT population as part of the TE response and slides were available at the committee meeting but not presented or discussed. The reason the company did not present a blended survival analysis for the second-line population was due to the novelty of the approach which has not to our knowledge been presented to a NICE committee previously and therefore as we were uncertain that the second-line population positioning would be accepted we decided to only conduct the blended survival analysis for the ITT population. Whilst this methodology is novel, we do however believe this methodology has a lot of merit and potential to enable NICE committee decision making in real time when clinical expert validation assumptions for survival at different time points are available. An outline of the methodology is presented in Appendix A. We recognise limitations of the data in terms of longer term follow up. However, there is a consistent PFS response seen irrespective of duration of follow up. Longer term outcomes are heavily confounded by crossover and termination of the study. The committee expressed a desire for longer term follow-up of the pivotal COSMIC-311 trial, but this is not available and was not planned beyond the 10.1-month follow-up point. In addition, the PFS benefit of cabozantinib is robust with a HR of 0.22 (95% CI 0.15-0.32, p<0.0001) seen at the initial cut-off at 6.2 months (Clinical Cut-Off 1 – CCO1) and later at 10.1 months (Clinical Cut-Off 2 – CCO2) for the full ITT population and also for the pure second-line population HR [redacted] which is the optimised population that the company has requested. This reduction of [redacted] in progression free survival demonstrates a clear	Thank you for your comment. At the second committee meeting, the committee acknowledged that the blended survival analysis based on the second-line-only population was helpful to consider as an alternative approach to modelling OS, but noted the resulting OS models did not fit the observed data well in this case. The committee was also unclear what function had been used to fit the observed data in the blended survival analysis. The committee noted the lack of transparency around the blended survival analysis. Because of this, the committee concluded that the exponential function used by the EAG for modelling OS in both treatment arms was preferable for its decision making. Discussion around the modelling of overall survival can be seen in section 3.7 of the FDG.

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			clinical benefit for cabozantinib which is not confused and diluted by the crossover of patients in the trial which makes conclusions on the OS benefit uncertain. As noted in the draft guidance consultation large proportions of people in the placebo group switched treatment within a relatively short period from the start of the trial (31% at CCO1 and 45% at CCO2), in the ITT population. This highlights that *"there is otherwise a very poor prognosis of this patient population"*, as stated by the clinical experts in the draft consultation guidance (Section 3.4, Page 8), and the high unmet need in this RAI-R DTC population of patients who have failed first-line systemic treatment who currently have no second-line NICE recommended options in England and Wales. In the draft guidance consultation (Section 3.4 Page 8) the *"EAG noted that a large proportion of patients had censored data (64% in the cabozantinib group and 22% in the placebo group at CCO2). So, there was a large quantity of incomplete information for PFS and OS in the CCO2 follow up"*. This large degree of censoring is not unusual in oncology trials and NICE committees are or should be familiar with making positive recommendations in appraisals where this is often the norm e.g. (TA858 where 70.4% of the patients in the lenvatinib/pembrolizumab arm and 65.8% in the sunitinib arm were censored)[4]. In response to this draft guidance consultation the company has conducted the blended survival analysis for OS based on the second-line population and included it within the new base case analysis. This has the benefit of: • Addressing the remaining overestimation of survival in the second-line population from the model extrapolations (Table 4 and Table 5, Appendix A). This blended survival analysis for OS based on the second-line population provides the closest estimates to the expert estimates, (Table 1, Appendix A), for both cabozantinib and BSC, than the previously blended analysis using the whole ITT population and modelling overall survival using the exponential parametric curve for the second-line population (no blended analysis). • Including the blended survival analysis for both the cabozantinib and placebo/Best Supportive Care (BSC) arms. Only the BSC arm had the blended survival analysis conducted for the ITT population in the TE response prior to the first committee meeting as it was felt the cabozantinib arm was already close to the expert estimates. However, for consistency both arms have had the blended survival analysis performed for the second-line population. Note: To align with the original approach for treatment crossover, OS for the BSC arm adjusted according to the	

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			Rank-Preserving Structural Failure Time (RPFST) method was used. This new base case analysis, with the methodology and results presented in Appendix A and C, was performed to show the impact of clinical opinion data surrounding cabozantinib's impact on OS and highlight cabozantinib's efficacy in the second-line population. The analysis resulted in a probabilistic ICER of £20,126 with PAS at [redacted] resulting in [redacted] incremental costs and [redacted] incremental QALYs (Table 7, Appendix C). Note: This base case ICER also includes the use of RDI (see Comment 4) and COSMIC-311 utilities (see Comment 5). In addition, all ICERs based on the blended survival analysis are probabilistic. A scenario analysis using the exponential parametric curve for OS for the second-line population to show the impact on results leads to a deterministic ICER of £23,154, with [redacted] incremental costs and [redacted] incremental QALYs (Table 15, Appendix C).	
4	Consultee - company	Ipsen Ltd	**Using RDI as a dosing method offers consistency with previous TAs.** The company maintains that using RDI instead of compliance is the most appropriate way of deriving the true cost per cycle of cabozantinib due to uncertainty around the validity of the compliance figure and methods in past NICE appraisals. The analysis of compliance used to inform the economic model is not stated in the clinical study report or any of its addendums and was calculated based on CCO1 patient level data, however RDI was analysed and included in the clinical study report for CCO2. In addition, previous NICE appraisals have generally been consistent in the inclusion of RDI in the economic model regardless of whether the medicine was linear pricing per mg or flat price per mg. The most relevant example is TA535 for lenvatinib and sorafenib[5] in first line RAI-R DTC. Lenvatinib is flat priced with both the 4 mg and 10 mg priced the same. No issues were raised in this appraisal on the use of RDI to calculate the "true cost" of lenvatinib. Therefore, it would be unreasonable and inconsistent to apply a different method in this appraisal. In past appraisals of cabozantinib, RDI has also been used to adjust for the true cost per cycle of treatment such as the recent TA849[6], cabozantinib for previously treated advanced hepatocellular carcinoma. In a real world study in renal cell cancer, it was found that the RDI of cabozantinib was lower compared to the RDI in the clinical trial due to additional comorbidities seen in clinical practice that requires adjusted dosing schedules to manage any side effects.[7] Therefore, the compliance in the COSMIC-311 trial could be overestimating the true cost of cabozantinib in clinical practice. The company believes a consistent approach should be adopted in applying the	Thank you for your comment. The EAG commented that the real-world study referred to the overestimation of relative dose intensity rather than compliance. It also cautioned that the real-world study did not consider the potential consequence that taking less cabozantinib in practice may also lead to lower comparative effectiveness compared with what has been observed in a clinical trial setting. The committee acknowledged that the relative dose intensity approach aligned with methods used in previous technology appraisals. But it concluded that the EAG's adjustment based on adherence was more appropriate for decision making, because it reflected the true drug acquisition cost of cabozantinib to the NHS. Discussion around the modelling of drug cost adjustments can be seen in section 3.11 of the FDG.

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			RDI, as done previously and accepted, for the treatment intervention in this appraisal. The base case resulted in an ICER of £20,126, with [redacted] incremental costs, and [redacted] incremental QALYS when using RDI as a dosing method (Table 7, Appendix C) however a scenario has been ran using compliance resulting in an ICER of £22,592, with [redacted] incremental costs and [redacted] incremental QALYs (Table12, Appendix C).	
5	Consultee - company	Ipsen Ltd	**COSMIC-311 utilities align with NICE manual preferred utilities.** In the NICE committee meeting, the committee considered it would be more appropriate to use utility values from COSMIC-311 instead of Fordham et al. 2015[8] as per the NICE manual: In the draft guidance consultation (Section 3.8, Page 13) *"The committee considered that it would be more appropriate to use the utility estimate from COSMIC-311 than Fordham et al. (2015)[8]. It noted that the NICE health technology evaluations manual says that health-related quality of life should be measured directly by patients. The manual also advises using the EQ-5D measurement method to measure health-related quality of life in adults. The EQ-5D-5L data from the COSMIC-311 trial was mapped to the EQ-5D-3L using the crosswalk approach by Hernandez-Alava and Pudney (2017)."* The EAG explained that Fordham et al. 2015[8] values were only accepted in previous submissions due to the lack of EQ-5D data in pivotal trials. Due to greater inconsistency and thus uncertainty in using a mixture of sources for PFS and PD utilities, the company believes it to be appropriate to use the same source for both PFS and PD utilities. Therefore, the company has presented a new base case including COSMIC-311 values for both PFS and PD values ([redacted] and [redacted], respectively), which closely aligns with the NICE reference case rather than using Fordham et al. 2015[8] for PD only. The new base case resulted in an ICER of £20,126, with [redacted] incremental costs and [redacted] incremental QALYs (Table 7, Appendix C). Scenario analyses included testing the DECISION utility values for PFS (PFS tyrosine kinase inhibitor [TKI] utility: 0.72, and PFS BSC utility: 0.80) and PD (PD utility [both treatment arms]: 0.64) with no disutilities applied (aligned with the EAG approach in the EAG report). DECISION utilities were calculated using the EQ-5D and is relevant to sorafenib.[9] This population does not provide utility values for second-line patients but provides another scale for NICE to assess based on EQ-5D data. This scenario resulted in an ICER of £20,516, with [redacted] incremental costs and [redacted] incremental QALYs (Table 13, Appendix C). Combining TTO vignette study data (Fordham et al. 2015)[8] and EQ-5D data would	Thank you for your comment. The committee concluded that it preferred using the COSMIC-311 utility value for the progression-free state because it was based on the population being appraised and because it used the same source as that used for the model's clinical efficacy inputs. The committee also recognised that the EQ-5D-5L data available from COSMIC-311 for informing the progressed-disease utility was limited. So, it concluded that the unadjusted post-progression utility value from Fordham et al. (2015) was preferred for decision making. Discussion around the health state utility values can be seen in section 3.9 of the FDG.

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			not present a clinically accurate reflection of the impact of cabozantinib, when two alternative options are already available which use the same source (COSMIC-311 and DECISION[9]), population and methodology for both progressed and progression-free values of EQ-5D data. A scenario provided by the EAG in their report, preferred by the committee, used a combination of EQ-5D data from one source (COSMIC-311), and TTO vignette data (Fordham et al. 2015)[8]. Additionally, as the EAG committee and NICE have remained consistent in their dissatisfaction over Fordham et al. 2015[8] as a valid utility source, for reasons previously mentioned and with unadjusted values above general population utility values, the company believe that EQ-5D data from the pivotal trial should be used as a consistent source for the base case.	
6	Consultee - company	Ipsen Ltd	**The impact of continued lenvatinib post-progression has been explored.** In the draft guidance consultation (Section 3.2, Page 6) *"The EAG noted that some clinicians may continue to offer lenvatinib after progression. The EAG also recognized lenvatinib that there was unlikely to be enough evidence for a reliable comparison between cabozantinib and continued lenvatinib used post-progression. [As the clinical experts have acknowledged that in very specific situations lenvatinib may be continued after progression in clinical practice]"*, the company has modelled such a situation to explore the impact on results. A final scenario has been included using the base case inputs with the addition of continued lenvatinib (methodology described in the Appendix C). This resulted in an ICER of £11,499, with [redacted] incremental costs and [redacted] incremental QALYs (Table 14, Appendix C).	Thank you for your comment. The committee considered the company's additional analysis exploring the continued use of lenvatinib post-progression. It recalled that continued lenvatinib after progression would only be used in specific situations in clinical practice. Given that the extra cost of continued lenvatinib after progression was included in the best supportive care arm but the potential health gains were not, the committee concluded that the results for this analysis were uncertain, and susceptible to bias. So, this analysis was not considered in the committee's decision making. Discussion around the continued use of lenvatinib post-progression can be seen in section 3.8 of the FDG.
7	Consultee - company	Ipsen Ltd	**NICE Committee decision making and consideration of all factors under 3.2.7 of the NICE Methods Guide for the clinical evidence raises concerns for transparency.** The NICE Methods Guide[10], Section 6.2.7. states the committee's decisions on clinical effectiveness take account of the following factors: • The nature and quality of the evidence derived from: o the written evidence submissions o the analysis of the external assessment group o the views expressed by the clinical experts and, if relevant, specialist committee members, particularly their experience of the condition and the technology in clinical practice o the experience of the patient experts, carers and specialist lay committee members of living with the condition and using the	The committee considered all of the evidence submitted, including evidence from clinical trials, clinical experts, the External Assessment Group's economic analysis and the company's submissions. It also carefully considered the comments received from consultees and commentators during consultation. Discussion around the lack of alternatives to cabozantinib that are established in clinical practice can be seen in section 3.1 and section 3.2 of the FDG. The committee noted that there are no NICE-recommended second-line treatments for people with locally advanced or metastatic differentiated thyroid cancer that is unsuitable for or refractory to radioactive iodine. So, committee concluded that there is an unmet need in this population. This was considered in the committee's discussions of what incremental cost effectiveness ratio would be considered a cost-effective use of NHS resources in this appraisal (see section

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			technology being considered. • Uncertainty generated by the evidence and differences between the evidence submitted for regulatory approval and that relating to effectiveness in clinical practice. • The possible differential benefits or adverse outcomes in different groups of patients • The impact of benefits and adverse outcomes associated with the technology as seen from the patient's perspective. • The position of the technology in the overall care pathway and the alternatives to the technology that are established in clinical practice. Section 6.2.8 states the extent to which these factors are taken into account in making decisions about the clinical-effectiveness evidence is at the committee's discretion. The company is unclear from the draft guidance to what extent the lack of alternatives was taken into account into the committee decision making. The company is also concerned why there have been no patient submissions made and no patient organisation representation at the committee meeting and how the company's Summary of Patient Information (SIP) has been deployed during this appraisal. Neither do we know if or how patient organisations or clinicians were engaged during the TE phase. We also only received the EAG's critique on the company's TE response less than 48 hours before the committee meeting and their updated health economic model until after the committee meeting giving us little or no time to prepare. Whilst there is some uncertainty regarding the longer-term benefit of cabozantinib this is not unusual for oncology medicines that NICE committees review. A recent ABPI analysis[11] of medicines that have gone into the Cancer Drugs Fund (CDF) showed that most technology appraisals that entered the CDF (78%) went on to receive a positive recommendation for their full CDF indication. Despite the primary purpose of the CDF to allow time for companies to resolve data uncertainties, in the majority of resubmissions (63%) NICE still cited substantial remaining uncertainty in the data or that data collected within the CDF were limited, but nevertheless NICE committees still made positive recommendations despite recognising this remaining uncertainty at CDF exit. The analysis concluded that if a more pragmatic view was taken as to whether managed access was likely to resolve the clinical uncertainty rather than simply delaying the same questions by several years, it may be possible for more medicines to be recommended for use in routine commissioning at the time of the initial appraisal. The company	3.13 of the FDG). Stakeholders were invited to participate in this appraisal and to nominate clinical and patient experts to advise the appraisal committee. When no patient expert nominations were received, NICE made an additional request to stakeholders for participation and patient expert nominations but none were received. Additionally, the NICE Public Involvement Programme (PIP) team reached out specifically to all of the thyroid and thyroid cancer patient organisations identified as part of this appraisal but none were able to participate. A public consultation was conducted on the draft guidance document which provided further opportunity for patient experts to submit comments. NICE is eager to have patient organisations involvement during the appraisal process, and was disappointed that they were unable to submit consultation responses or attend the committee meetings for this topic. Experts were invited to participate in technical engagement before the committee meeting, including completing and returning an expert response form. The committee considers the expert response forms during the appraisal. For this appraisal, NICE received expert response forms from 2 clinical experts and 1 professional group. The completed expert response forms were made available to company within the committee papers circulated before the first committee meeting. Committee papers, including the external assessment group's comments on the company's response to technical engagement, are usually circulated to all attendees (except members of the public) 2 weeks before the first committee meeting. In this case, the external assessment group's comments on the company's technical engagement response was sent to the company on 14 March 2023, in advance of the first appraisal committee meeting on 16th March 2023. This was due to a procedural error for which NICE apologises. Given its conclusion that there is an unmet need in this

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			believes a more pragmatic approach should be taken by NICE committees especially in the context of the unmet need and the very small patient population in this appraisal. The company has performed a blended analysis on second-line data to account for a more pragmatic approach in showing the impact of clinical opinion data surrounding cabozantinib's impact on OS and demonstrate cabozantinib's efficacy.	population (see section 3.1 of the FDG) but that there was uncertainty in the cost-effectiveness estimates, the committee considered the maximum acceptable ICER would be in the lower half of the £20,000 to £30,000 range normally considered a cost-effective use of NHS resources (see section 3.13 of the FDG). The committee considered that when its preferred assumptions were incorporated, the cost-effectiveness estimates for cabozantinib plus best supportive care were towards the higher end of the range considered to be a cost-effective use of NHS resources. So, cabozantinib is not recommended for treating locally advanced or metastatic DTC that is unsuitable for or refractory to radioactive iodine, and that has progressed after systemic treatment. The committee concluded that cabozantinib could also not be recommended with managed access because the company are not planning further data collection from COSMIC-311 and did not submit an application for managed access. Discussion around the consideration of managed access can be seen in section 3.16 of the FDG.
8	Consultee - company	Ipsen Ltd	**Lack of transparency in the new severity quality-adjusted life year (QALY) weighting concept limits discussion from those without health economics and outcomes research (HEOR) training and/or backgrounds.** The company is concerned that the new severity QALY weighting concept compared to the previously adopted end-of-life (EoL) criteria is difficult to understand if you are not a health economist. We noted the clinical expert found this new concept challenging and unsurprisingly could not offer any insight to the committee which devalues the process. We also noted some committee members struggled to interpret the data during the meeting which is worrying in terms of enabling effective decision making. The company believes that cabozantinib would have met the previously adopted EoL criteria and thus qualified for a threshold of £50,000 per QALY. We note on slide three of the Committee Meeting slides the clinical expert statement: *"I cannot think of a single patient who has survived more than 2 years beyond progression on lenvatinib, unless further therapy has been available"* This is an example of how the new severity QALY weighting is causing issues for oncology medicines. Cabozantinib qualified for a multiplier of 1.2 but not 1.7, for which the latter would have been equivalent to the £50,000 per QALY threshold based on the previous EoL criteria as such the current decision making is based	Thank you for your comment. The new methods including consideration of a severity modifier came into effect from 1 February 2022, as per NICE's combined methods and processes manual and topic selection manual. At the first committee meeting, the committee concluded that a severity weight of 1.2 applied to the QALYs was appropriate in this appraisal. Discussion around the severity modifier can be seen in section 3.12 of the FDG. No action needed.

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			on a £36,000 per QALY threshold.	
9	Consultee – professional group	NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.	Thank you for your comment. The committee considered the consultation responses from the NCRI-ACP-RCP-RCR. Please see responses to individual issues below.
10	Consultee – professional group	NCRI-ACP-RCP-RCR	Radioiodine refractory differentiated thyroid cancer is associated with significant symptoms. The COSMIC-311 study demonstrated significant progression free survival, importantly in the second line setting. Patients who have progressed on first line treatment are more likely to develop symptoms that will require courses of radiotherapy, admission to hospital, and input from supportive care clinics. Treatment with cabozantinib after first line treatment may therefore alleviate these symptoms and in turn reduce the burden on other healthcare services.	Thank you for your comment. The committee recognised that cabozantinib plus best supportive care showed a significant improvement in progression-free survival compared with placebo plus best supportive care (see section 3.4 in the FDG). The committee also considered the symptom burden to people with previously treated locally advanced or metastatic DTC unsuitable for or refractory to radioactive iodine (see section 3.1 of the FDG). The economic model submitted by the company included the consideration of monitoring costs and healthcare resource use over a lifetime horizon. Given its conclusion that there is an unmet need in this population (see section 3.1 of the FDG) but that there was uncertainty in the cost-effectiveness estimates generated from the economic model, the committee considered the maximum acceptable ICER would be in the lower half of the £20,000 to £30,000 range normally considered a cost-effective use of NHS resources. The committee considered that when its preferred assumptions were incorporated, the cost-effectiveness estimates for cabozantinib plus best supportive care were towards the higher end of the range considered to be a cost-effective use of NHS resources. So, cabozantinib is not recommended for treating locally advanced or metastatic DTC that is unsuitable for or refractory to radioactive iodine, and that has progressed after systemic treatment.
11	Consultee – professional group	NCRI-ACP-RCP-RCR	We understand that the discontinuation of follow up of patients in the COSMIC-311 study has meant it is very difficult to comment on any benefit in overall survival for patients treated with cabozantinib, and consequently, cost effectiveness. If NICE were to approve use of cabozantinib in the Cancer Drug Fund for a time limited period this would allow more data to be collected which could help address this uncertainty.	Thank you for your comment. The committee concluded that cabozantinib could not be recommended with managed access because the company are not planning further data collection from COSMIC-311 and did not submit an application for managed access. Discussion around the consideration of managed access can be seen in section 3.16 of the FDG.

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	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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	None
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]

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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	**Executive summary** The company would like to thank the committee for the opportunity to respond to the draft guidance consultation. We disagree with the draft negative recommendation for the use of cabozantinib within its marketing authorisation, despite the cost-effectiveness estimate generated by the NICE committee's preferred assumptions being £28,200 per QALY gained for treating locally advanced or metastatic differentiated thyroid cancer (DTC) that is unsuitable for or refractory to radioactive iodine (RAI), and that has progressed after systemic treatment, in adults. This represents a very small population with a clear unmet need currently in England and Wales. We are concerned that despite the statistically significant progression free survival (PFS) benefit (HR 96% CI unstratified [redacted] and substantial overall survival (OS) benefit (at year 2, cabozantinib OS = [redacted]% compared with BSC OS = [redacted]%) demonstrated for the pure second-line population, the negative recommendation fails to address the needs of this important patient group and their unmet need. As recognised by the EMA[1], cabozantinib can help patients who have poor outcomes and a high unmet medical need by delaying disease progression and increasing OS. As such, we are committed to providing a comprehensive response that will enable NICE to recommend access to cabozantinib at second line as a life-prolonging therapy for radioiodine refractory (RAI-R) DTC patients. **As noted by the committee, there remains a significant unmet need for patients with DTC who are RAI refractory/ineligible that require second-line therapy.** As per Section 3.1 of the draft guidance consultation, Page 5: *"The committee noted that there are no NICE-recommended second-line treatments for people with advanced DTC that is unsuitable for or refractory to radioactive iodine and concluded that there is an unmet need in this population."* The committee's preferred assumptions which generate an ICER of £28,200 include: • Weibull model to extrapolate Time to Treatment Discontinuation (TTD) for cabozantinib (Section 3.9 of the draft guidance consultation) • Adherence approach for adjusting drug acquisition costs for cabozantinib (Section 3.10 of the draft guidance consultation) • COSMIC-311 utility value for the progression-free survival (PFS) health state utility and unadjusted utility values from Fordham et al. 2015 for the progressed disease (PD) health state utility (Section 3.8 of the draft guidance consultation) The company present a new base case in this response with the following changes from the committee's preferred assumptions with the rationale described herein:

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	• OS blended survival analysis based on the second-line population to reduce OS uncertainty (see Comment 3) • Drug acquisition costs adjusted based on relative dose intensity (RDI) offering consistency with previous TAs (see Comment 4) • COSMIC-311 utilities aligned with the NICE manual preferred utilities (see Comment 5)
2	**COSMIC-311 second-line population is a subgroup and generalisable to England and Wales.** In the draft guidance consultation, (Section 3.4, Page 8) *"the EAG was concerned that, because the second-line population was a subgroup of COSMIC-311 [the intention to treat (ITT) population], the sample size was smaller and there was greater uncertainty in the trial results."* To confirm, the second-line population represents approximately 75% of the ITT population in the COSMIC-311 trial. Furthermore, the company confirmed during the committee meeting the power of the study for the second-line patient population and it was more than 100% powered to detect a difference in the co-primary endpoint of PFS with a hazard ratio (HR) of [redacted] (95% confidence interval [CI] [redacted]). Note: the ITT population in the trial was not powered for the exploratory endpoint of OS. The company also confirmed during the committee meeting that the second-line population was representative of the patients likely to be treated in England and Wales. A comparison of the baseline characteristics in the second-line and ITT population from COSMIC-311 is shown in Table 6 of Appendix B and addresses any concerns regarding this due to the two populations being broadly comparable. In addition, given the ITT population was clinically validated to be generalisable to England and Wales,[2,3] due to the comparable baseline characteristics, in turn the subgroup of second-line only patients is also deemed generalisable to England and Wales. It should be noted that the second-line population had a greater proportion of prior lenvatinib use compared to the ITT population, which considering that lenvatinib is the predominant first-line treatment in England and Wales makes the second-line population even more applicable for decision making. Overall, we understand from the draft guidance consultation that the committee is satisfied that the 2L population is suitable for decision making as per Section 3.3, Page 7: *"The committee was also aware that there are no treatments recommended by NICE for after first-line systemic treatment of radioactive iodine-refractory DTC. The committee concluded that the company's positioning of cabozantinib as a second-line treatment option was appropriate."*
3	**A blended analysis focusing on second-line patients reduces OS uncertainty.** We note in their report following the Technical Engagement (TE) phase the EAG queried why we did not do blended survival analysis for OS based on the pure second-line population. The company did present a blended survival analysis for the ITT population as part of the TE response and slides were available at the committee meeting but not presented or discussed. The reason the company did not present a blended survival analysis for the second-line population was due to the novelty of the approach which has not to our knowledge been presented to a NICE committee previously and therefore as we were uncertain that the second-line population positioning would be accepted we decided to only conduct the blended survival analysis for the ITT population. Whilst this methodology is novel, we do however believe this methodology has a lot of merit and potential to enable NICE committee decision making in real time when clinical expert validation

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

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	assumptions for survival at different time points are available. An outline of the methodology is presented in Appendix A. We recognise limitations of the data in terms of longer term follow up. However, there is a consistent PFS response seen irrespective of duration of follow up. Longer term outcomes are heavily confounded by crossover and termination of the study. The committee expressed a desire for longer term follow-up of the pivotal COSMIC-311 trial, but this is not available and was not planned beyond the 10.1-month follow-up point. In addition, the PFS benefit of cabozantinib is robust with a HR of 0.22 (95% CI 0.15-0.32, p<0.0001) seen at the initial cut-off at 6.2 months (Clinical Cut-Off 1 – CCO1) and later at 10.1 months (Clinical Cut-Off 2 – CCO2) for the full ITT population and also for the pure second-line population HR [redacted] which is the optimised population that the company has requested. This reduction of [redacted] in progression free survival demonstrates a clear clinical benefit for cabozantinib which is not confused and diluted by the crossover of patients in the trial which makes conclusions on the OS benefit uncertain. As noted in the draft guidance consultation large proportions of people in the placebo group switched treatment within a relatively short period from the start of the trial (31% at CCO1 and 45% at CCO2), in the ITT population. This highlights that *"there is otherwise a very poor prognosis of this patient population"*, as stated by the clinical experts in the draft consultation guidance (Section 3.4, Page 8), and the high unmet need in this RAI-R DTC population of patients who have failed first-line systemic treatment who currently have no second-line NICE recommended options in England and Wales. In the draft guidance consultation (Section 3.4 Page 8) the *"EAG noted that a large proportion of patients had censored data (64% in the cabozantinib group and 22% in the placebo group at CCO2). So, there was a large quantity of incomplete information for PFS and OS in the CCO2 follow up"*. This large degree of censoring is not unusual in oncology trials and NICE committees are or should be familiar with making positive recommendations in appraisals where this is often the norm e.g. (TA858 where 70.4% of the patients in the lenvatinib/pembrolizumab arm and 65.8% in the sunitinib arm were censored)[4]. In response to this draft guidance consultation the company has conducted the blended survival analysis for OS based on the second-line population and included it within the new base case analysis. This has the benefit of: • Addressing the remaining overestimation of survival in the second-line population from the model extrapolations (Table 4 and Table 5, Appendix A). This blended survival analysis for OS based on the second-line population provides the closest estimates to the expert estimates, (Table 1, Appendix A), for both cabozantinib and BSC, than the previously blended analysis using the whole ITT population and modelling overall survival using the exponential parametric curve for the second-line population (no blended analysis). • Including the blended survival analysis for both the cabozantinib and placebo/Best Supportive Care (BSC) arms. Only the BSC arm had the blended survival analysis conducted for the ITT population in the TE response prior to the first committee meeting as it was felt the cabozantinib arm was already close to the expert estimates. However, for consistency both arms have had the blended survival analysis performed for the second-line population. Note: To align with the original approach for treatment crossover, OS for the BSC arm adjusted according to the Rank-Preserving Structural Failure Time (RPFST) method was used.

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

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	This new base case analysis, with the methodology and results presented in Appendix A and C, was performed to show the impact of clinical opinion data surrounding cabozantinib's impact on OS and highlight cabozantinib's efficacy in the second-line population. The analysis resulted in a probabilistic ICER of £20,126 with PAS at [redacted] resulting in [redacted] incremental costs and [redacted] incremental QALYs (Table 7, Appendix C). Note: This base case ICER also includes the use of RDI (see Comment 4) and COSMIC-311 utilities (see Comment 5). In addition, all ICERs based on the blended survival analysis are probabilistic. A scenario analysis using the exponential parametric curve for OS for the second-line population to show the impact on results leads to a deterministic ICER of £23,154, with [redacted] incremental costs and [redacted] incremental QALYs (Table 15, Appendix C).
4	**Using RDI as a dosing method offers consistency with previous TAs.** The company maintains that using RDI instead of compliance is the most appropriate way of deriving the true cost per cycle of cabozantinib due to uncertainty around the validity of the compliance figure and methods in past NICE appraisals. The analysis of compliance used to inform the economic model is not stated in the clinical study report or any of its addendums and was calculated based on CCO1 patient level data, however RDI was analysed and included in the clinical study report for CCO2. In addition, previous NICE appraisals have generally been consistent in the inclusion of RDI in the economic model regardless of whether the medicine was linear pricing per mg or flat price per mg. The most relevant example is TA535 for lenvatinib and sorafenib[5] in first line RAI-R DTC. Lenvatinib is flat priced with both the 4 mg and 10 mg priced the same. No issues were raised in this appraisal on the use of RDI to calculate the "true cost" of lenvatinib. Therefore, it would be unreasonable and inconsistent to apply a different method in this appraisal. In past appraisals of cabozantinib, RDI has also been used to adjust for the true cost per cycle of treatment such as the recent TA849[6], cabozantinib for previously treated advanced hepatocellular carcinoma. In a real world study in renal cell cancer, it was found that the RDI of cabozantinib was lower compared to the RDI in the clinical trial due to additional comorbidities seen in clinical practice that requires adjusted dosing schedules to manage any side effects.[7] Therefore, the compliance in the COSMIC-311 trial could be overestimating the true cost of cabozantinib in clinical practice. The company believes a consistent approach should be adopted in applying the RDI, as done previously and accepted, for the treatment intervention in this appraisal. The base case resulted in an ICER of £20,126, with [redacted] incremental costs, and [redacted] incremental QALYS when using RDI as a dosing method (Table 7, Appendix C) however a scenario has been ran using compliance resulting in an ICER of £22,592, with [redacted] incremental costs and [redacted] incremental QALYs (Table12, Appendix C).
5	**COSMIC-311 utilities align with NICE manual preferred utilities.** In the NICE committee meeting, the committee considered it would be more appropriate to use utility values from COSMIC-311 instead of Fordham et al. 2015[8] as per the NICE manual: In the draft guidance consultation (Section 3.8, Page 13) *"The committee considered that it would be more appropriate to use the utility estimate from COSMIC-311 than Fordham et al. (2015)[8]. It noted that the NICE health technology evaluations manual says that health-related quality of life*

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 28 April 2023. Please submit via NICE Docs.

	should be measured directly by patients. The manual also advises using the EQ-5D measurement method to measure health-related quality of life in adults. The EQ-5D-5L data from the COSMIC-311 trial was mapped to the EQ-5D-3L using the crosswalk approach by Hernandez-Alava and Pudney (2017).” The EAG explained that Fordham et al. 2015[8] values were only accepted in previous submissions due to the lack of EQ-5D data in pivotal trials. Due to greater inconsistency and thus uncertainty in using a mixture of sources for PFS and PD utilities, the company believes it to be appropriate to use the same source for both PFS and PD utilities. Therefore, the company has presented a new base case including COSMIC-311 values for both PFS and PD values ([redacted] and [redacted], respectively), which closely aligns with the NICE reference case rather than using Fordham et al. 2015[8] for PD only. The new base case resulted in an ICER of £20,126, with [redacted] incremental costs and [redacted] incremental QALYs (Table 7, Appendix C). Scenario analyses included testing the DECISION utility values for PFS (PFS tyrosine kinase inhibitor [TKI] utility: 0.72, and PFS BSC utility: 0.80) and PD (PD utility [both treatment arms]: 0.64) with no disutilities applied (aligned with the EAG approach in the EAG report). DECISION utilities were calculated using the EQ-5D and is relevant to sorafenib.[9] This population does not provide utility values for second-line patients but provides another scale for NICE to assess based on EQ-5D data. This scenario resulted in an ICER of £20,516, with [redacted] incremental costs and [redacted] incremental QALYs (Table 13, Appendix C). Combining TTO vignette study data (Fordham et al. 2015)[8] and EQ-5D data would not present a clinically accurate reflection of the impact of cabozantinib, when two alternative options are already available which use the same source (COSMIC-311 and DECISION[9]), population and methodology for both progressed and progression-free values of EQ-5D data. A scenario provided by the EAG in their report, preferred by the committee, used a combination of EQ-5D data from one source (COSMIC-311), and TTO vignette data (Fordham et al. 2015)[8]. Additionally, as the EAG committee and NICE have remained consistent in their dissatisfaction over Fordham et al. 2015[8] as a valid utility source, for reasons previously mentioned and with unadjusted values above general population utility values, the company believe that EQ-5D data from the pivotal trial should be used as a consistent source for the base case.
	The impact of continued lenvatinib post-progression has been explored. In the draft guidance consultation (Section 3.2, Page 6) *“The EAG noted that some clinicians may continue to offer lenvatinib after progression. The EAG also recognized lenvatinib that there was unlikely to be enough evidence for a reliable comparison between cabozantinib and continued lenvatinib used post-progression. [As the clinical experts have acknowledged that in very specific situations lenvatinib may be continued after progression in clinical practice]”*, the company has modelled such a situation to explore the impact on results. A final scenario has been included using the base case inputs with the addition of continued lenvatinib (methodology described in the Appendix C). This resulted in an ICER of £11,499, with [redacted] incremental costs and [redacted] incremental QALYs (Table 14, Appendix C).
6	**NICE Committee decision making and consideration of all factors under 3.2.7 of the NICE Methods Guide for the clinical evidence raises concerns for transparency.**

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	The NICE Methods Guide[10], Section 6.2.7. states the committee's decisions on clinical effectiveness take account of the following factors:
	• The nature and quality of the evidence derived from:
	  ○ the written evidence submissions
	  ○ the analysis of the external assessment group
	  ○ the views expressed by the clinical experts and, if relevant, specialist committee members, particularly their experience of the condition and the technology in clinical practice
	  ○ the experience of the patient experts, carers and specialist lay committee members of living with the condition and using the technology being considered.
	• Uncertainty generated by the evidence and differences between the evidence submitted for regulatory approval and that relating to effectiveness in clinical practice.
	• The possible differential benefits or adverse outcomes in different groups of patients
	• The impact of benefits and adverse outcomes associated with the technology as seen from the patient's perspective.
	• The position of the technology in the overall care pathway and the alternatives to the technology that are established in clinical practice.
	
	Section 6.2.8 states the extent to which these factors are taken into account in making decisions about the clinical-effectiveness evidence is at the committee's discretion.
	
	The company is unclear from the draft guidance to what extent the lack of alternatives was taken into account into the committee decision making. The company is also concerned why there have been no patient submissions made and no patient organisation representation at the committee meeting and how the company's Summary of Patient Information (SIP) has been deployed during this appraisal. Neither do we know if or how patient organisations or clinicians were engaged during the TE phase. We also only received the EAG's critique on the company's TE response less than 48 hours before the committee meeting and their updated health economic model until after the committee meeting giving us little or no time to prepare.
	
	Whilst there is some uncertainty regarding the longer-term benefit of cabozantinib this is not unusual for oncology medicines that NICE committees review. A recent ABPI analysis[11] of medicines that have gone into the Cancer Drugs Fund (CDF) showed that most technology appraisals that entered the CDF (78%) went on to receive a positive recommendation for their full CDF indication. Despite the primary purpose of the CDF to allow time for companies to resolve data uncertainties, in the majority of resubmissions (63%) NICE still cited substantial remaining uncertainty in the data or that data collected within the CDF were limited, but nevertheless NICE committees still made positive recommendations despite recognising this remaining uncertainty at CDF exit. The analysis concluded that if a more pragmatic view was taken as to whether managed access was likely to resolve the clinical uncertainty rather than simply delaying the same questions by several years, it may be possible for more medicines to be recommended for use in routine commissioning at the time of the initial appraisal. The company believes a more pragmatic approach should be taken by NICE committees especially in the context of the unmet need and the very small patient population in this appraisal. The company has performed a blended analysis on second-line data to account for a more pragmatic approach in showing the impact of clinical opinion data surrounding cabozantinib's impact on OS and demonstrate cabozantinib's efficacy.

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Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

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7	**Lack of transparency in the new severity quality-adjusted life year (QALY) weighting concept limits discussion from those without health economics and outcomes research (HEOR) training and/or backgrounds.** The company is concerned that the new severity QALY weighting concept compared to the previously adopted end-of-life (EoL) criteria is difficult to understand if you are not a health economist. We noted the clinical expert found this new concept challenging and unsurprisingly could not offer any insight to the committee which devalues the process. We also noted some committee members struggled to interpret the data during the meeting which is worrying in terms of enabling effective decision making. The company believes that cabozantinib would have met the previously adopted EoL criteria and thus qualified for a threshold of £50,000 per QALY. We note on slide three of the Committee Meeting slides the clinical expert statement: *"I cannot think of a single patient who has survived more than 2 years beyond progression on lenvatinib, unless further therapy has been available"* This is an example of how the new severity QALY weighting is causing issues for oncology medicines. Cabozantinib qualified for a multiplier of 1.2 but not 1.7, for which the latter would have been equivalent to the £50,000 per QALY threshold based on the previous EoL criteria as such the current decision making is based on a £36,000 per QALY threshold.

Insert extra rows as needed

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- 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.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
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- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

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A.1. Appendix A Blended survival analysis second line population

To create the blended survival curves, the example code provided in the Che et al. 2022[1] paper was adapted (as per the methodology adopted during the Technical Engagement [TE]). To align with the original approach for treatment crossover, OS for the BSC arm adjusted according to the Rank-Preserving Structural Failure Time (RPFST) method was used. For the extrapolations using expert opinion, the mean average estimates for probability of survival for the cabozantinib and BSC arm at given times were used as presented in Table 1. To better fit the data estimates provided by the experts, an additional timepoint was added to the code, as such all three timepoints at 2, 5 and 10 years are included.

Table 1: Summary of the expert estimated survival for 2, 5 and 10 years; for the 2L CCO2 population (provided during TE)

	Cabozantinib			BSC		
	2 years	**5 years**	**10 years**	**2 years**	**5 years**	**10 years**
Mean average across EAG and company advisors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC – best supportive care; EAG – external assessment group

To explore the uncertainty around the estimations, the base case scenario utilised N=70 patients, for scenario analyses the number of patients was changed by ±20%. The blended survival curves were obtained by blending the survival curve extrapolated from observed data and survival curve informed by expert opinion between timepoints using a weighting function for each treatment arm, respectively. A number of different distributions were tested. The Weibull distribution provided a good fit among the models tested (standard parametric) and a conservative survival estimate over the long term (Figure 1 and Figure 2).

Figure 1: All models fitting for expert opinion survival curve (2L cabozantinib arm)

Abbreviations: AFT – accelerated failure time; 2L – second line

Figure 2: All models fitting for expert opinion survival curve (2L BSC arm)

Abbreviations: AFT – accelerated failure time; BSC – best supportive care; 2L – second line

As such the Weibull was chosen to be the base case scenario for the external data extrapolation (Figure 3 and Figure 4).

Figure 3: Weibull fitting for expert opinion survival curve (2L cabozantinib arm)

Abbreviations: AFT – accelerated failure time; 2L – second line

Figure 4: Weibull fitting for expert opinion survival curve (2L BSC arm)

Abbreviations: AFT – accelerated failure time; BSC – best supportive care; 2L – second line

Table 2 and Table 3 below present the base case and scenario values for cabozantinib and BSC, respectively.

In the base case, the Weibull marginally overestimated survival probabilities for both arms at 10 years and underestimated survival at 2 years and 5 years. For the cabozantinib arm, Weibull presented a conservative estimate, as the 5-year survival is underestimated. However these survival estimates provide a closer estimate to the expert elicitations (Table 1), for both cabozantinib and BSC, than the previously blended analysis using the whole ITT population and modelling overall survival using the exponential parametric curve for the second line population (no blended analysis). As displayed in Table 4 and Table 5 the companies new base case provides the closest modelling survival to the expert estimates of all scenarios presented. The graphical representation of the base case curves modelled are presented in Figure 5. Full results are presented in Appendix C.

Table 2: Median model survival estimates for 2-, 5- and 10-years scenario analysis (cabozantinib)

COSMIC-311 2L cabozantinib blended analysis	2 years	5 years	10 years
Base case	[redacted]	[redacted]	[redacted]
Lower uncertainty of external data	[redacted]	[redacted]	[redacted]
Higher uncertainty of external data	[redacted]	[redacted]	[redacted]
Blending interval	[redacted]	[redacted]	[redacted]
Parameter for weight function	[redacted]	[redacted]	[redacted]

Abbreviations: 2L – second line

Table 3: Median model survival estimates for 2-, 5- and 10-years scenario analysis (BSC)

COSMIC-311 2L BSC blended analysis	2 years	5 years	10 years
Base case	[redacted]	[redacted]	[redacted]
Lower uncertainty of external data	[redacted]	[redacted]	[redacted]
Higher uncertainty of external data	[redacted]	[redacted]	[redacted]
Blending interval	[redacted]	[redacted]	[redacted]
Parameter for weight function	[redacted]	[redacted]	[redacted]

Abbreviations: 2L – second line; BSC – best supportive care

Table 4: Median model survival estimates for 2-, 5- and 10-years per scenario (cabozantinib)

Scenario	2 years	5 years	10 years
Mean average across EAG and company advisors	[redacted]	[redacted]	[redacted]
Base case (2L blended analysis)	[redacted]	[redacted]	[redacted]
ITT blended analysis	[redacted]	[redacted]	[redacted]
2L population (exponential parametric curve [no blended analysis])	[redacted]	[redacted]	[redacted]

Table 5: Median model survival estimates for 2-, 5- and 10-years per scenario (BSC)

Scenario	2 years	5 years	10 years
Mean average across EAG and company advisors	[redacted]	[redacted]	[redacted]

Base case (2L blended analysis)	[redacted]	[redacted]	[redacted]
ITT blended analysis	[redacted]	[redacted]	[redacted]
2L population (exponential parametric curve [no blended analysis])	[redacted]	[redacted]	[redacted]

Figure 5: Mean blended survival curve for cabozantinib and BSC (Base case)

A.2. Appendix B Generalisability of second line population

Table 6: Comparison of COSMIC-311 overall trial population versus second-line population

COSMIC-311 Baseline characteristics	**Cabozantinib ITT**	**Placebo ITT**	**Cabozantinib 2L**	**Placebo 2L**
Population, n	n=170	N=88	[redacted]	[redacted]
Age, median years (range) [redacted]	65 (31-85) [redacted]	66 (37-83) [redacted]	[redacted]	[redacted]
Sex n (%) Male Female	 83 (49) 87 (51)	 39 (44) 49 (56)	[redacted]	[redacted]
Geographical Region n (%) Europe Asia North America (USA and Canada) Rest of the world	 82 (48) 24 (14) 15 (8.8) 49 (29)	 39 (44) 19 (22) 12 (14) 18 (20)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS, n (%) 0 (normal activity, asymptomatic) 1 (fully ambulatory, symptomatic)	 74 (44) 96 (56)	 43 (49) 45 (51)	[redacted]	[redacted]

[redacted]				
[redacted]				
[redacted]				
Previous sorafenib or lenvatinib n (%) Sorafenib but no lenvatinib Lenvatinib but no sorafenib Sorafenib and lenvatinib Other TKI therapy	 61 (36) 68 (40) 40 (23) 1	 33 (38) 34 (39) 21 (24) 0	[redacted]	[redacted]
Number of previous vascular endothelial growth factor receptor tyrosine kinase inhibitors n (%) 0 1 2	 1 126 (74) 43 (25)	 0 65 (74) 23 (26)	-	-
Histological subtype n (%) 1 Papillary Follicular	 96 (56) 78 (46)	 54 (61) 35 (43)	-	-
Metastatic lesions n (%) Bone Liver Lung Other	159 (94) 51 (30) 25 (15) 121 (71) 127 (75)	82 (93) 21 (24) 9 (10) 61 (69) 70 (80)	-	-
[redacted]			-	-
[redacted]			-	-

Source: Ipsen Data on File, April 2023[2]

Abbreviations: 2L – second line; BMI – body mass index; DTC – differentiated thyroid cancer; ITT – intention to treat; PD-1 – programmed cell death 1; PD-L1 – programmed cell death ligand 1; TKI – tyrosine kinase inhibitors.

A.3. Appendix C Cost-effectiveness model results

All results are probabilistic as the blended analysis produced 100 curves, the probabilistic method runs through the 100 curves multiple times to show the impact of the blended analysis. The exception is for the scenario analysis modelling overall survival using the exponential parametric curve for the second line population (no blended analysis); in this scenario both deterministic and probabilistic results are provided. All results presented included the PAS for cabozantinib at [redacted].

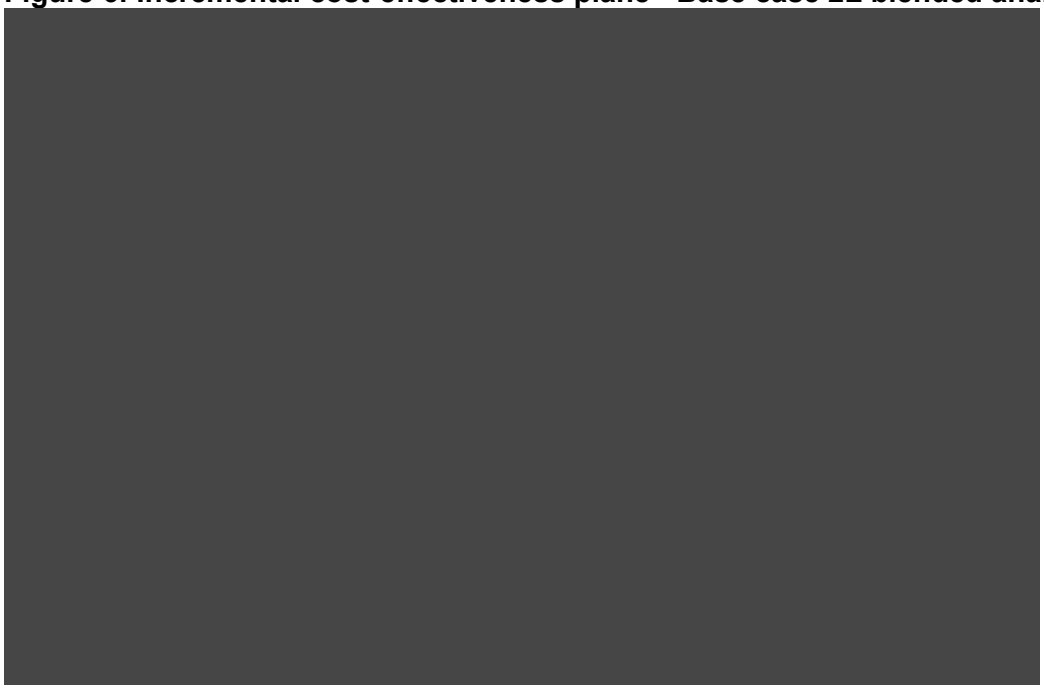
A.3.1. Base case – 2L blended analysis

Table 7: Probabilistic results – Base case 2L blended analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,126

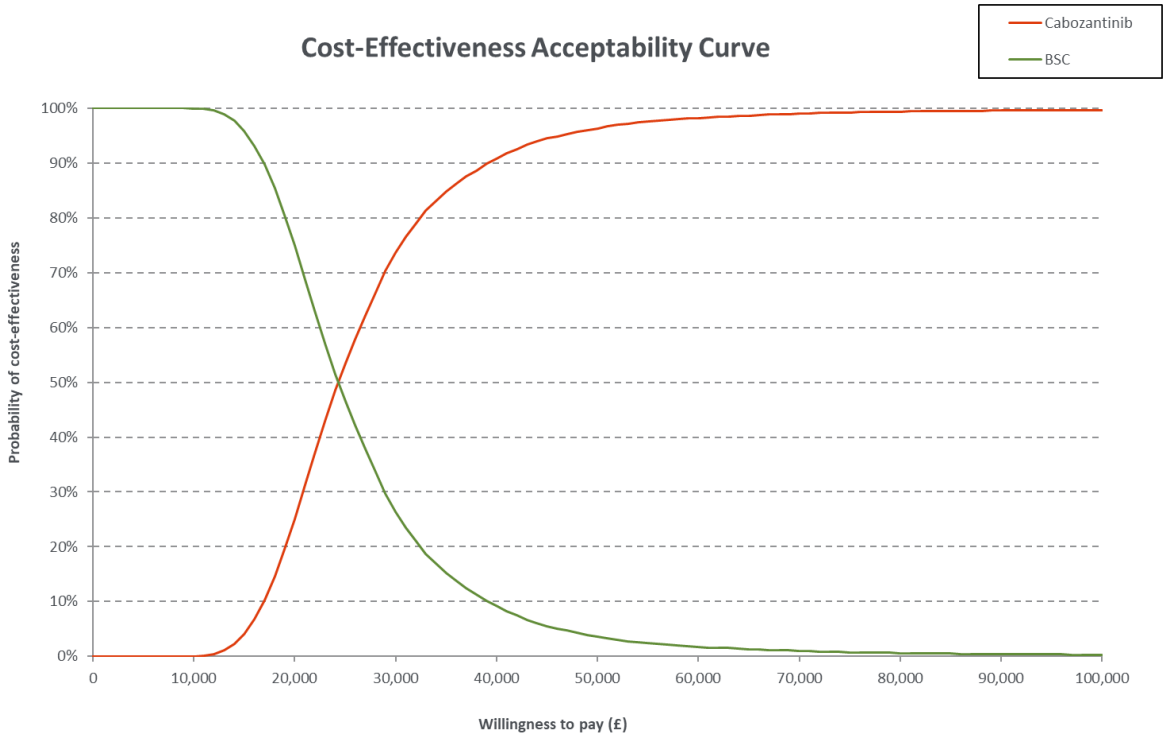
*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 6: Incremental cost-effectiveness plane - Base case 2L blended analysis



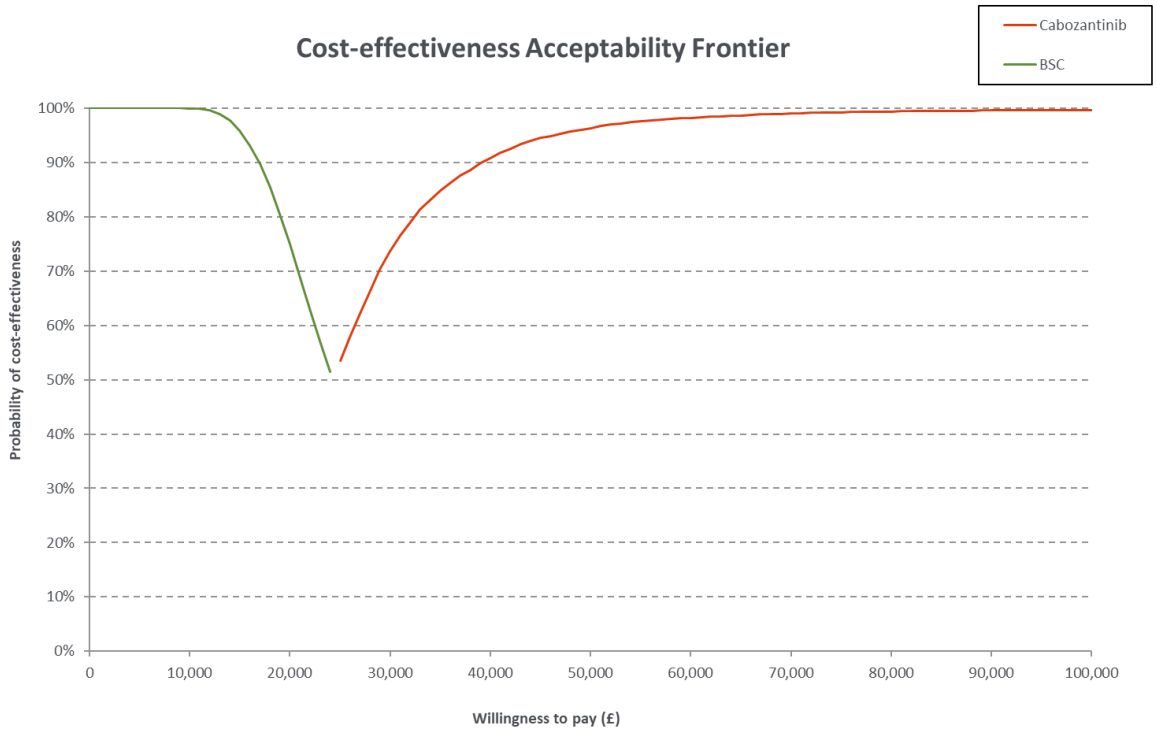
Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 7: Cost-effectiveness acceptability curve - Base case 2L blended analysis



Abbreviations: BSC – Best supportive care

Figure 8: Cost-effectiveness acceptability frontier - Base case 2L blended analysis



Abbreviations: BSC – Best supportive care

A.3.2. Blended survival blending interval (60 months) – Scenario analysis

Table 8: Probabilistic results – Blended survival blending interval (60 months) – Scenario analysis

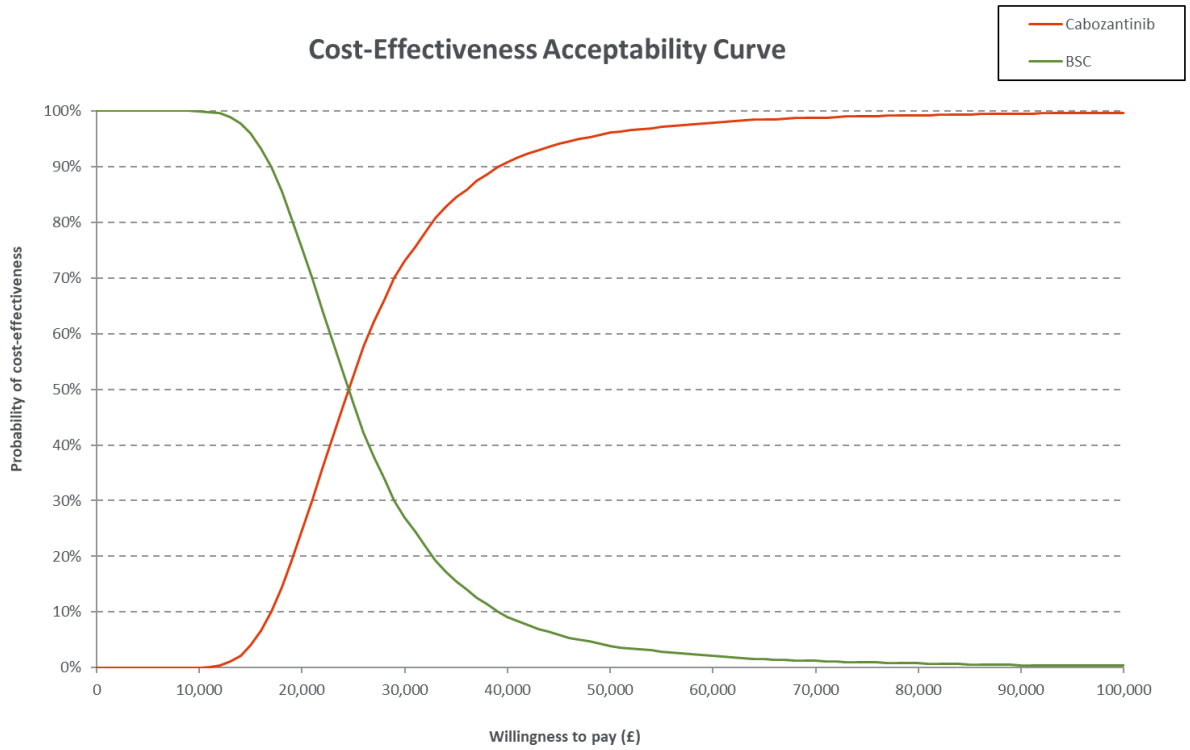
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,233

**Severity modifier of 1.2 has been applied to incremental QALYs*
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 9: Incremental cost-effectiveness plane - Blended survival blending interval (60 months) – Scenario analysis

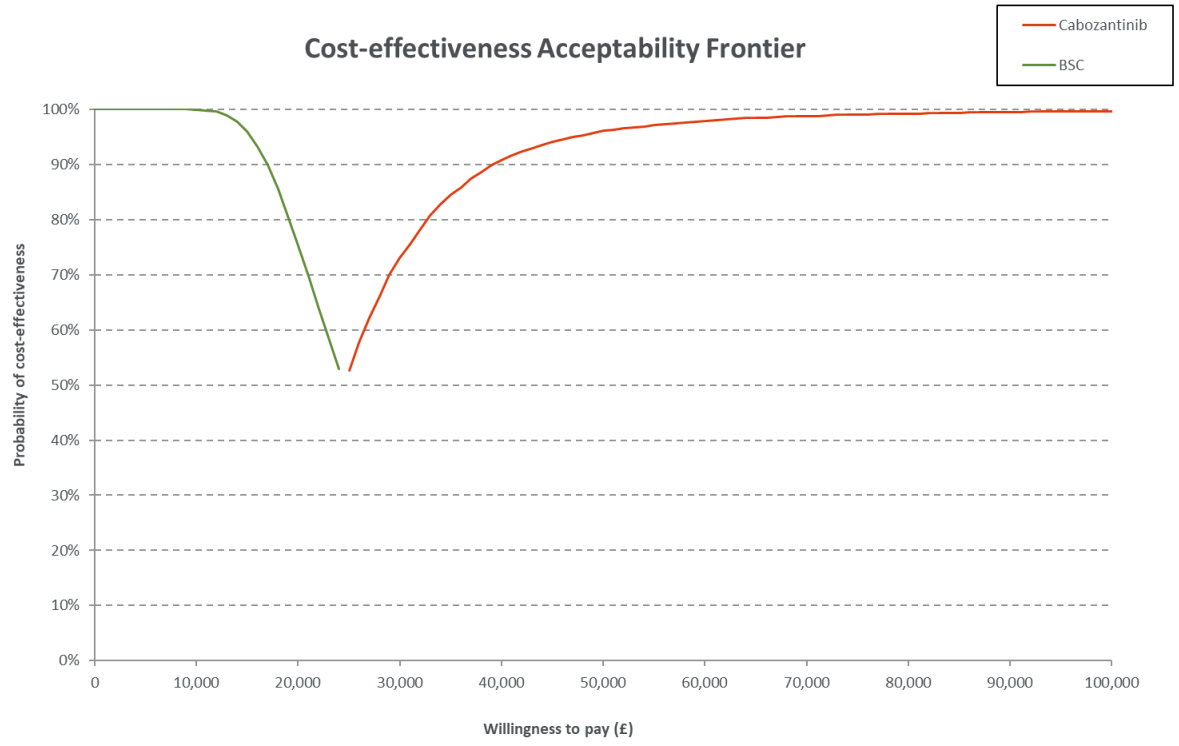
Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 10: Cost-effectiveness acceptability curve - Blended survival blending interval (60 months) – Scenario analysis



Abbreviations: BSC – Best supportive care

Figure 11: Cost-effectiveness acceptability frontier - Blended survival blending interval (60 months) – Scenario analysis



Abbreviations: BSC – Best supportive care

A.3.3. Blended survival parameter for weight function (Rate: Alpha=2, Beta=5) – Scenario analysis

Table 9: Probabilistic results – Blended survival parameter for weight function (Rate: Alpha=2, Beta=5) – Scenario analysis

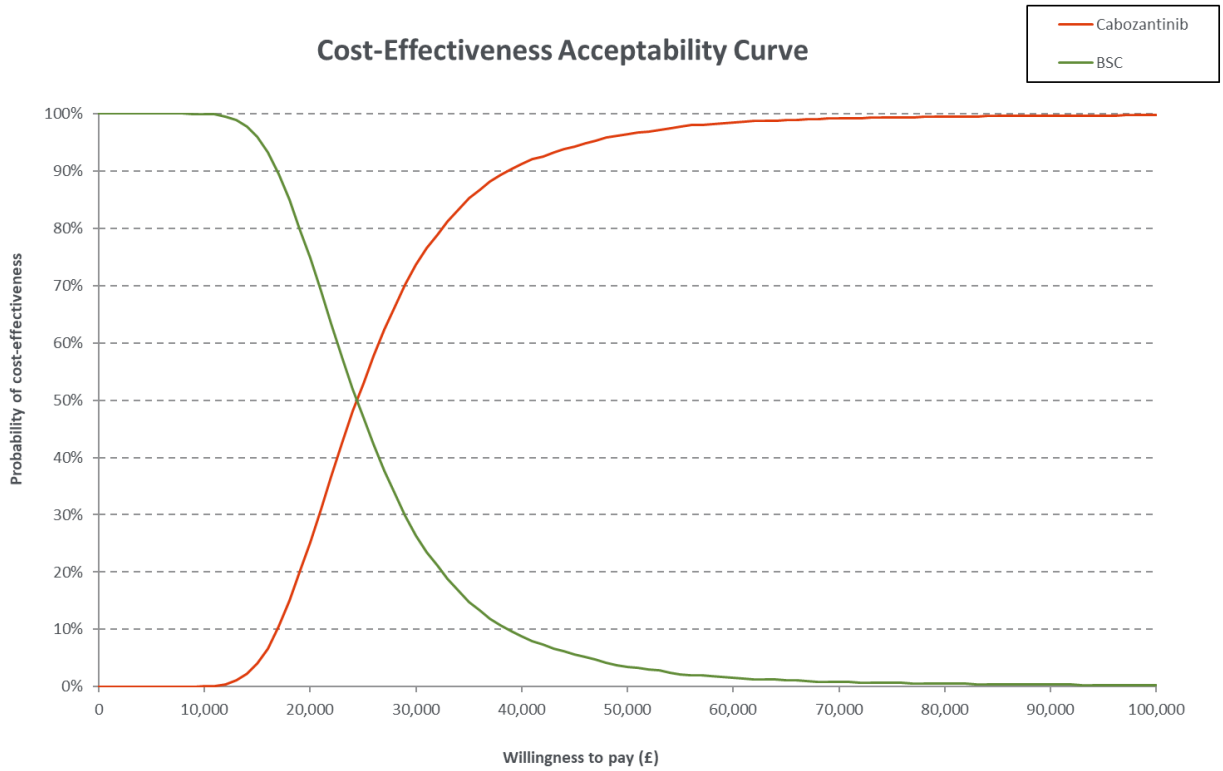
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,036

*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 12: Incremental cost-effectiveness plane - Blended survival parameter for weight function (Rate: Alpha=2, Beta=5) – Scenario analysis

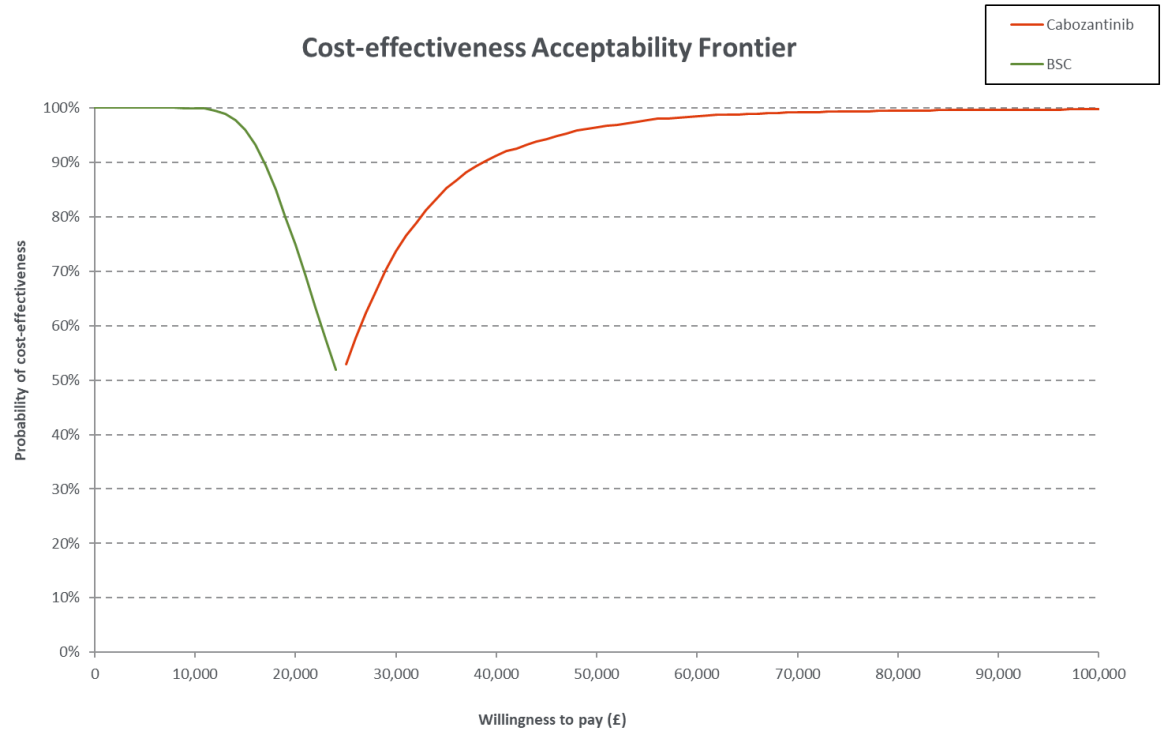
Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 13: Cost-effectiveness acceptability curve - Blended survival parameter for weight function (Rate: Alpha=2, Beta=5) – Scenario analysis



Abbreviations: BSC – Best supportive care

Figure 14: Cost-effectiveness acceptability frontier - Blended survival parameter for weight function (Rate: Alpha=2, Beta=5) – Scenario analysis



Abbreviations: BSC – Best supportive care

A.3.4. Blended survival high uncertainty – Scenario analysis

Table 10: Probabilistic results – Blended survival high uncertainty – Scenario analysis

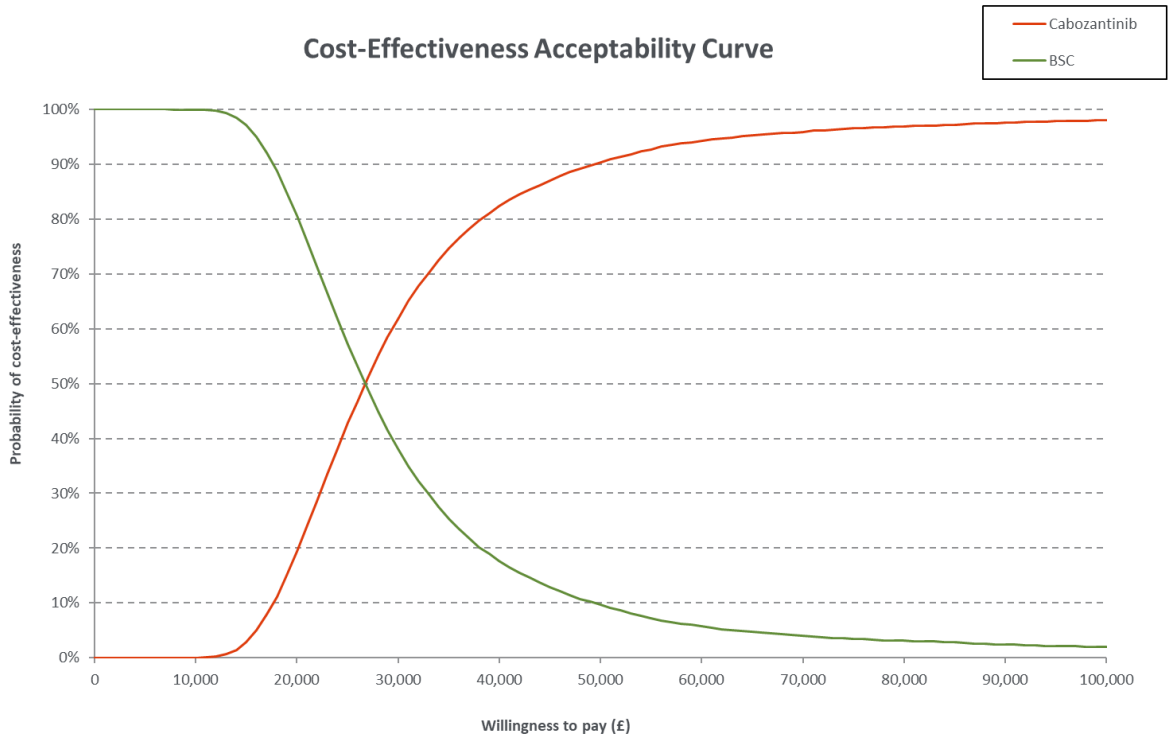
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,069

*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 15: Incremental cost-effectiveness plane - Blended survival high uncertainty – Scenario analysis

Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 16: Cost-effectiveness acceptability curve - Blended survival high uncertainty – Scenario analysis



Abbreviations: BSC – Best supportive care

Figure 17: Cost-effectiveness acceptability frontier - Blended survival high uncertainty – Scenario analysis

Abbreviations: BSC – Best supportive care

A.3.5. Blended survival low uncertainty – Scenario analysis

Table 11: Probabilistic results – Blended survival low uncertainty – Scenario analysis

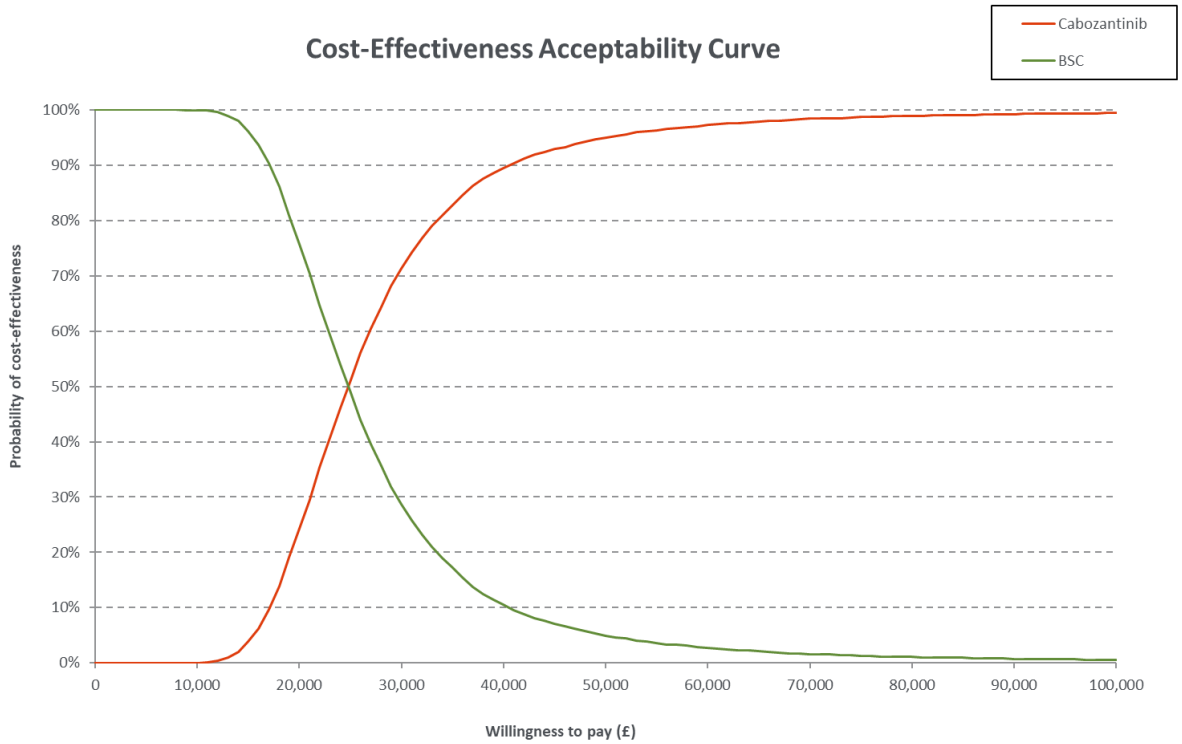
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,443

*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 18: Incremental cost-effectiveness plane - Blended survival low uncertainty – Scenario analysis

Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 19: Cost-effectiveness acceptability curve - Blended survival low uncertainty – Scenario analysis



Abbreviations: BSC – Best supportive care

Figure 20: Cost-effectiveness acceptability frontier - Blended survival low uncertainty – Scenario analysis

Abbreviations: BSC – Best supportive care

A.3.6. Compliance dosing method – Scenario analysis

Table 12: Probabilistic results - Compliance dosing method – Scenario analysis

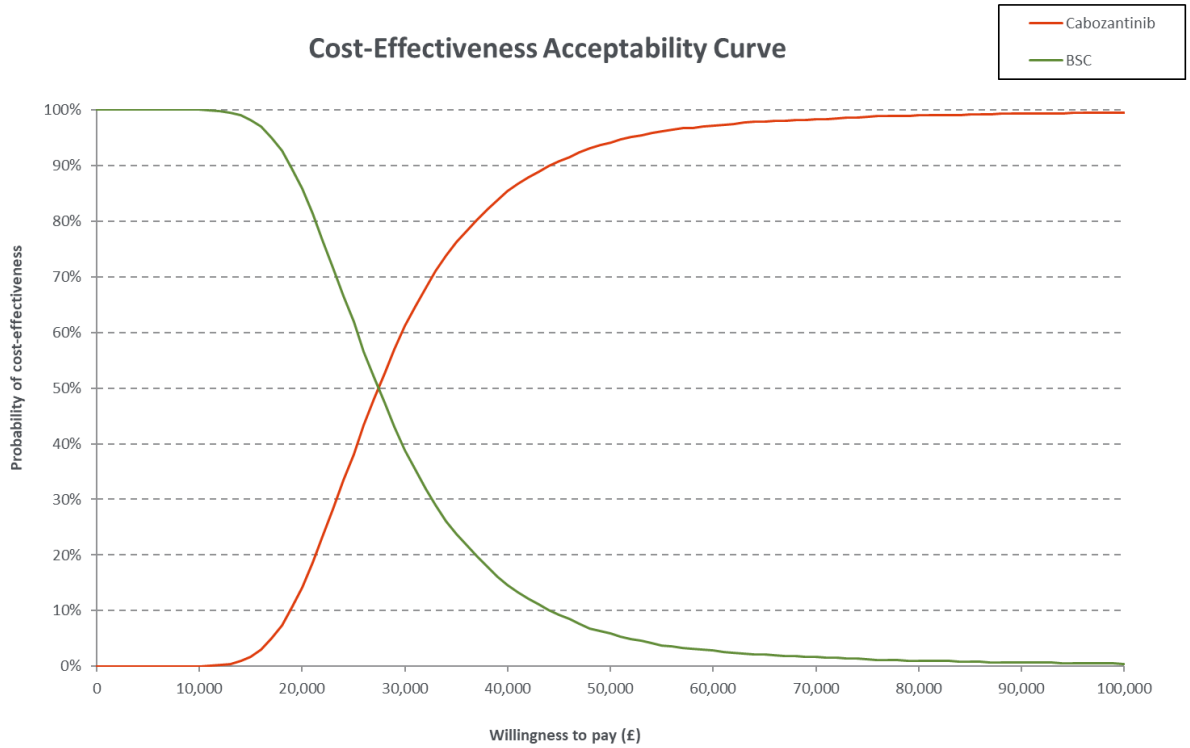
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,592

*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 21: Incremental cost-effectiveness plane – Compliance dosing method – Scenario analysis

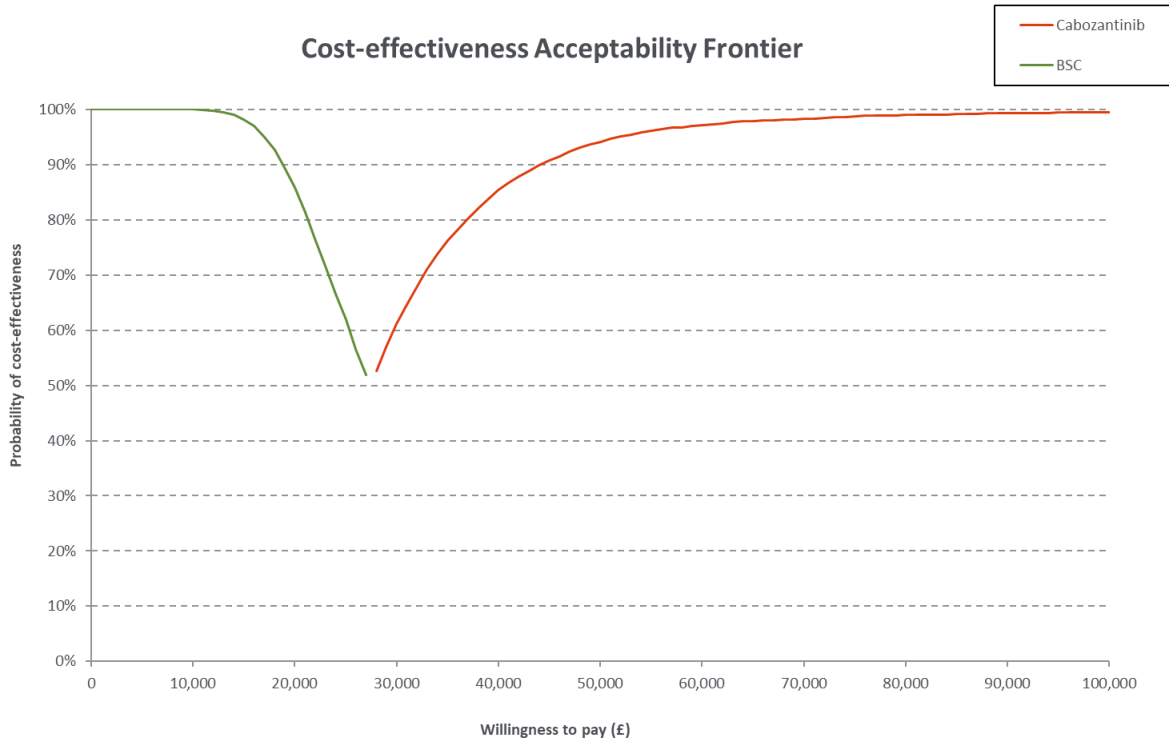
Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 22: Cost-effectiveness acceptability curve - Compliance dosing method – Scenario analysis



Abbreviations: BSC – Best supportive care

Figure 23: Cost-effectiveness acceptability frontier - Compliance dosing method – Scenario analysis



Abbreviations: BSC – Best supportive care

A.3.7. DECISION utilities – Scenario analysis

Table 13: Probabilistic results - DECISION utilities – Scenario analysis

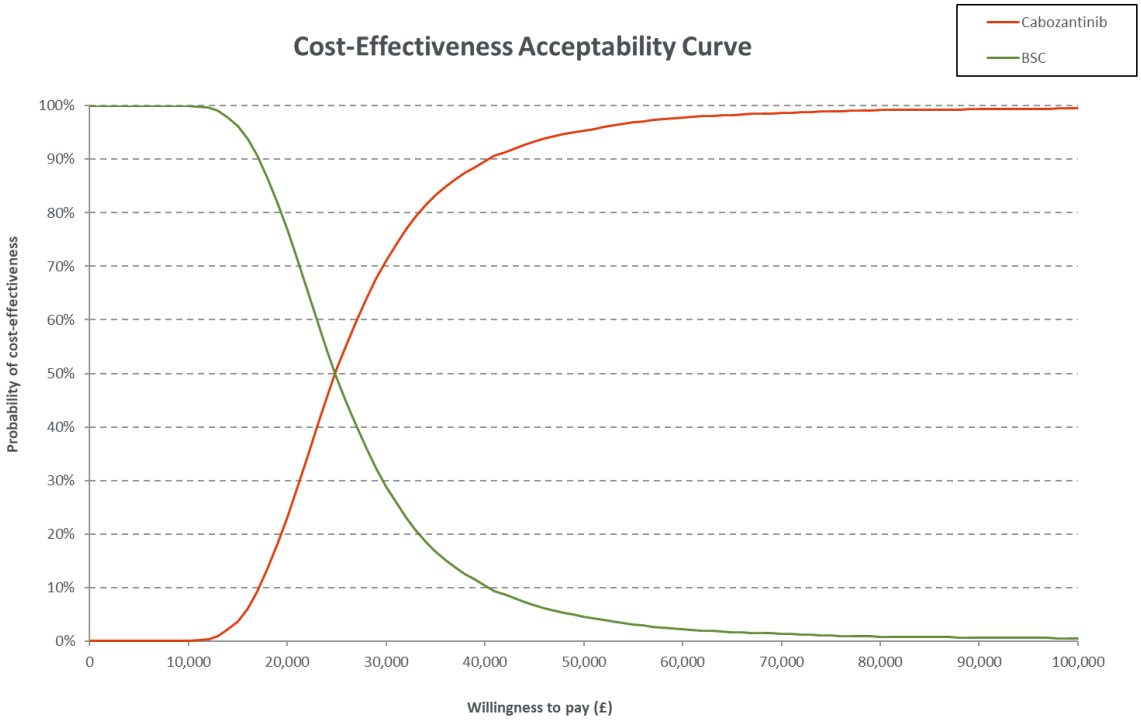
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,516

*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 24: Incremental cost-effectiveness plane – DECISION utilities – Scenario analysis

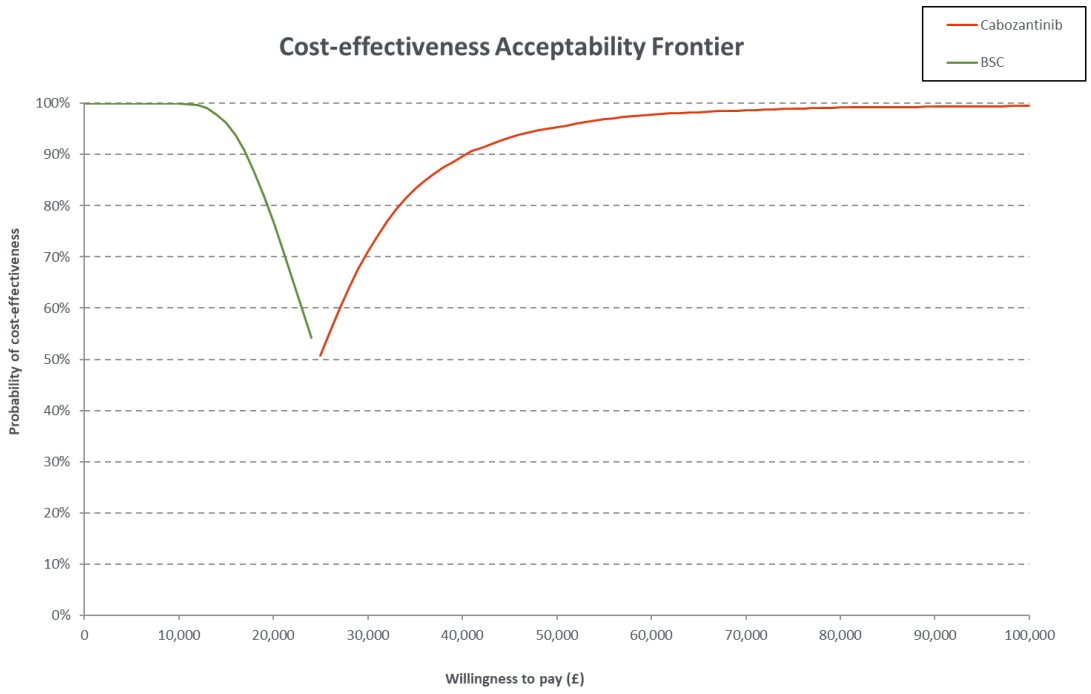
Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 25: Cost-effectiveness acceptability curve - DECISION utilities – Scenario analysis



Abbreviations: BSC – Best supportive care

Figure 26: Cost-effectiveness acceptability frontier - DECISION utilities – Scenario analysis



Abbreviations: BSC – Best supportive care

A.3.8. Lenvatinib cost addition – Scenario analysis

A lenvatinib cost was applied to the BSC arm for 4 cycles which aligns with the median PFS for BSC in the model. The TTD curve followed the PFS curve for four cycles.

Cost of lenvatinib is 3 capsules once per day (24 mg is the indicated dose) at a cost of £143.70 (BNF cost for Lenvatinib – flat pricing).[3] The RDI for Lenvatinib (71.666%, TA535), was applied.[4]

Table 14: Probabilistic results - Lenvatinib cost addition – Scenario analysis

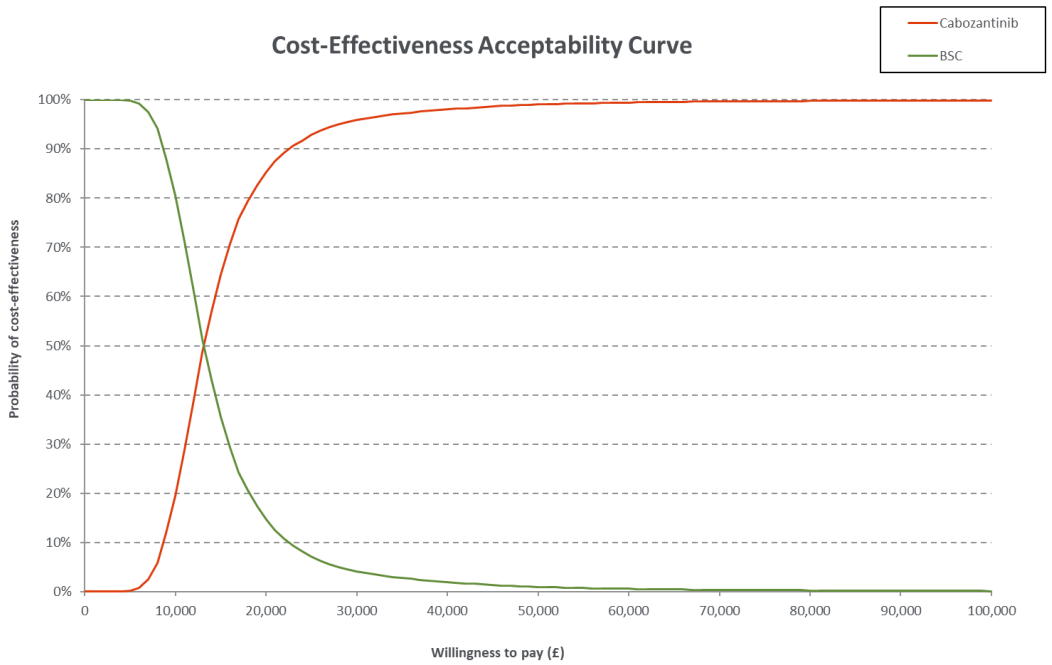
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,499

*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 27: Incremental cost-effectiveness plane – Lenvatinib cost addition – Scenario analysis

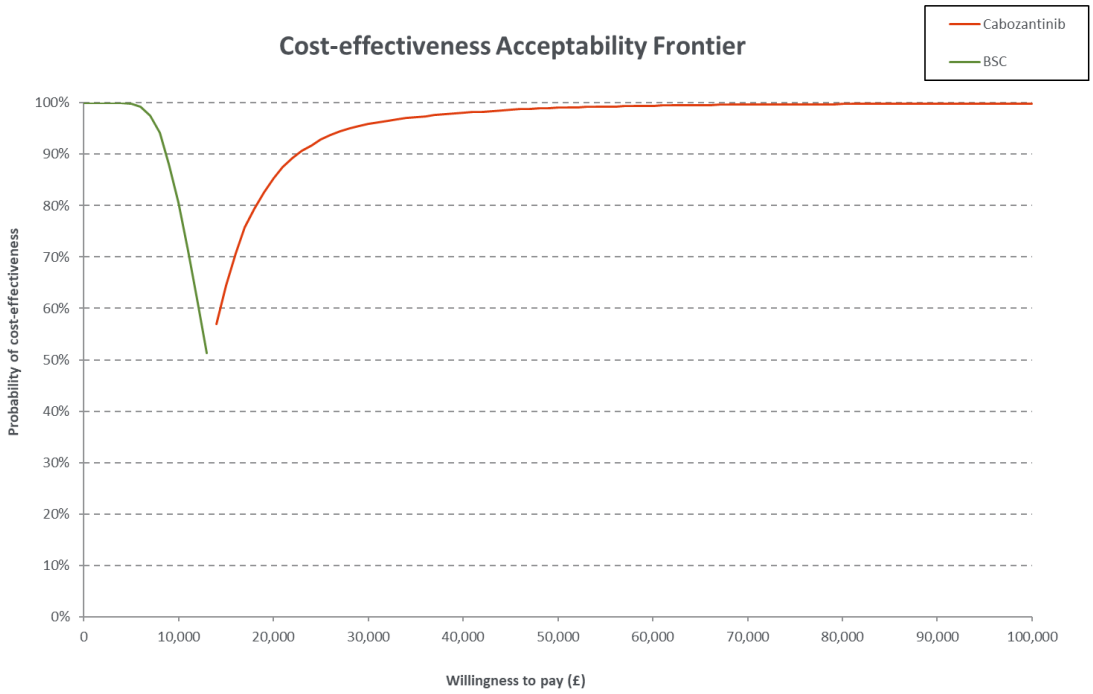
Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 28: Cost-effectiveness acceptability curve - Lenvatinib cost addition – Scenario analysis



Abbreviations: BSC – Best supportive care

Figure 29: Cost-effectiveness acceptability frontier - Lenvatinib cost addition – Scenario analysis



Abbreviations: BSC – Best supportive care

A.3.9. 2L population exponential parametric curves for OS (no blended analysis) – Scenario analysis

Table 15: Deterministic results – 2L population exponential parametric curves for OS (no blended analysis) – Scenario analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs excluding QALY weighting	ICER including QALY weighting (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,154

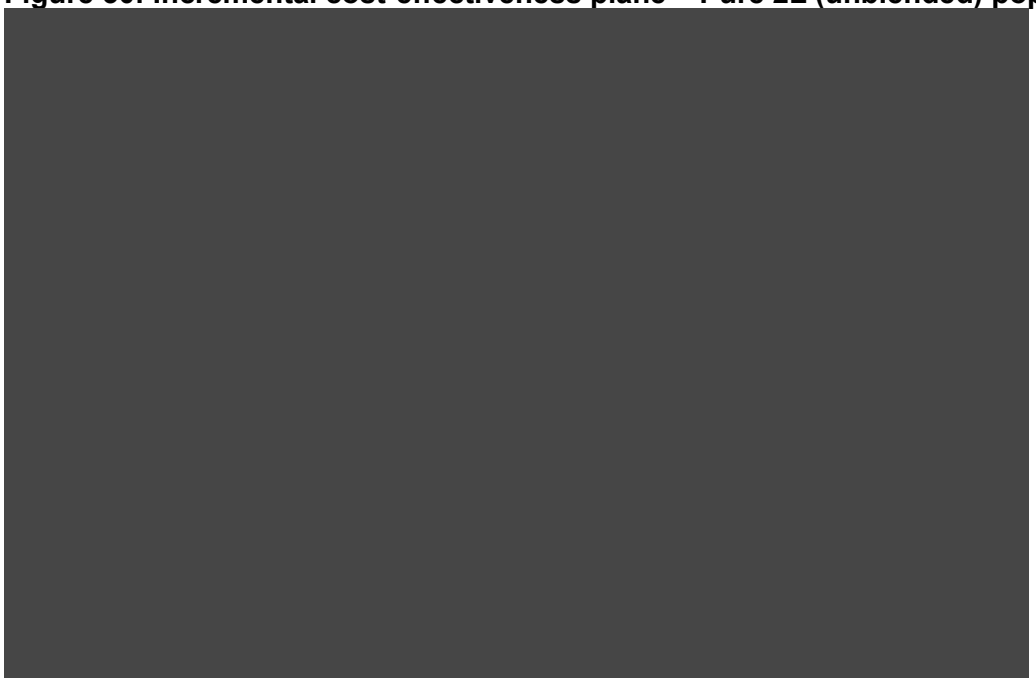
*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Table 16: Probabilistic scenario analysis results – 2L population exponential parametric curves for OS (no blended analysis) – Scenario analysis

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Severity ICER incremental* (£/QALY)
BSC	[redacted]	[redacted]	[redacted]				
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,776

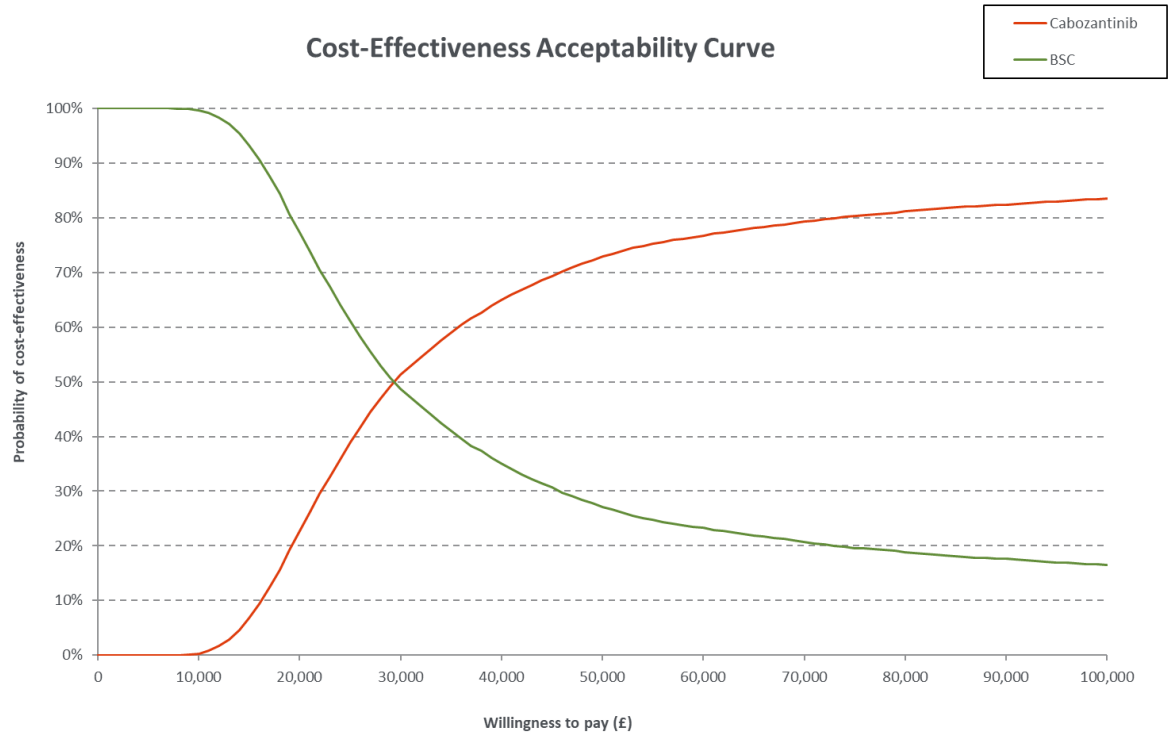
*Severity modifier of 1.2 has been applied to incremental QALYs
Abbreviations: BSC – Best supportive care; ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; QALYs – Quality-adjusted life years

Figure 30: Incremental cost-effectiveness plane – Pure 2L (unblended) population



Abbreviations: BSC – Best supportive care; PSA – Probabilistic sensitivity analysis

Figure 31: Cost-effectiveness acceptability curve - Pure 2L (unblended) population



Abbreviations: BSC – Best supportive care

Figure 32: Cost-effectiveness acceptability frontier - Pure 2L (unblended) population

Abbreviations: BSC – Best supportive care

A.4. References

(1) Che, Z.; Green, N.; Baio, G. Blended Survival Curves: A New Approach to Extrapolation for Time-to-Event Outcomes from Clinical Trials in Health Technology Assessment. https://doi.org/10.1177/0272989X221134545.
(2) Ipsen. Data on File. April 2023.
(3) Medicinal forms | Lenvatinib | Drugs | BNF content published by NICE. https://bnf.nice.org.uk/drugs/lenvatinib/medicinal-forms/ (accessed 2023-04-27).
(4) N.I.C.E. Lenvatinib and Sorafenib for Treating Differentiated Thyroid Cancer after Radioactive Iodine [ID1059. https://www.nice.org.uk/guidance/ta535/documents/committee-papers.

NICE National Institute for Health and Care Excellence

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 28 April 2023. Please submit via 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):	NCRI-ACP-RCP-RCR

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NICE National Institute for Health and Care Excellence

Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Friday 28 April 2023. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	None
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]

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.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
1	Radioiodine refractory differentiated thyroid cancer is associated with significant symptoms. The COSMIC-311 study demonstrated significant progression free survival, importantly in the second line setting. Patients who have progressed on first line treatment are more likely to develop symptoms that will require courses of radiotherapy, admission to hospital, and input from supportive care clinics. Treatment with cabozantinib after first line treatment may therefore alleviate these symptoms and in turn reduce the burden on other healthcare services.
2	We understand that the discontinuation of follow up of patients in the COSMIC-311 study has meant it is very difficult to comment on any benefit in overall survival for patients treated with cabozantinib, and consequently, cost effectiveness. If NICE were to approve use of cabozantinib in the Cancer Drug Fund for a time limited period this would allow more data to be collected which could help address this uncertainty.

Insert extra rows as needed

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Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

Draft guidance comments form

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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 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) 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 draft guidance 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.

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Cabozantinib for previously treated differentiated thyroid cancer unsuitable for or refractory to radioactive iodine [ID4046]

Addendum: EAG comments on the company's response to the draft guidance

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Authors	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK Kate (Shijie) Ren, Senior Research Fellow, ScHARR, University of Sheffield, Sheffield, UK Aline Navega Biz, Research Associate, ScHARR, University of Sheffield, Sheffield, UK Sarah (Sa) Ren, Research Associate, ScHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Paul Tappenden, Professor of Health Economic Modelling, ScHARR, University of Sheffield, Sheffield, UK
Date completed	4th May 2023

1. Introduction

In March 2023, the National Institute for Health and Care Excellence (NICE) published a negative recommendation for cabozantinib for the treatment of adults with locally advanced or metastatic differentiated thyroid cancer (DTC) that is unsuitable for or refractory to radioactive iodine (RAI), and that has progressed after systemic treatment.[1] The draft guidance (DG) highlights uncertainty around the expected overall survival (OS) gain associated with cabozantinib. Owing to this uncertainty around incremental OS benefit, the DG comments that the cost-effectiveness of cabozantinib is unclear. The DG states that the Appraisal Committee considered a cost-effectiveness threshold towards the lower end of its usual range to be appropriate and notes that the incremental cost-effectiveness ratios (ICERs) generated by the company and the External Assessment Group (EAG) were towards the higher end of the threshold range.

Section 3.6 of the DG[1] states that the Appraisal Committee considered the model based on the second-line subgroup of the COSMIC-311 trial[2] to be acceptable for decision-making. Section 3.14 of the DG[1] provides details of the Appraisal Committee's preferred analysis for the second-line subgroup:

- Use of exponential models for OS
- Use of the Weibull survival model for time to treatment discontinuation (TTD)
- Adjustment of cabozantinib acquisition costs using compliance (referred to as "adherence" in the DG)
- Inclusion of the Euroqol 5-Dimensions 3-Level (EQ-5D-3L) estimate derived from COSMIC-311[2] for the progression-free state (utility value = [redacted]) and the unadjusted "progressive disease" time trade-off (TTO) value reported by Fordham *et al.*[3] for the progressed disease state (utility value = 0.50).

The Appraisal Committee's preferred analysis is consistent with EAG Additional Sensitivity Analysis (ASA) 2a in the EAG's Technical Engagement (TE) response.[4] When a severity weighting of 1.2 is included in the analysis, the deterministic ICER was estimated to be £28,200 per quality-adjusted life year (QALY) gained.

In April 2023, the company submitted a response to the NICE DG.[5] The company's response consists of a written document, accompanying technical appendices and an updated version of the economic model. The company's written document explains that the company disagrees with the Appraisal Committee's preferred analysis and provides a new company base case which applies different OS models, a different utility value in the progressed disease state and a different acquisition cost adjustment approach (see Table 1). The company has not amended its Patient Access Scheme (PAS) discount, which remains at [redacted].

Table 1: Summary of Appraisal Committee's preferred analysis and company's new base case

Aspect of model	Appraisal Committee's preferred analysis	Company's new base case analysis	Is the new model in line with the Appraisal Committee's preferred analysis?
COSMIC-311 population	Second-line subgroup	Second-line subgroup	Yes
OS model	Exponential model (constant treatment effect)	Blended survival model	No
TTD model	Weibull model	Weibull model	Yes
Health utility values	Progression-free – COSMIC-311 Progressed disease – Fordham *et al.*(unadjusted)	Progression-free – COSMIC-311 Progressed disease – COSMIC-311	No
Cabozantinib cost adjustment	Compliance	RDI	No

DG - draft guidance; OS - overall survival; TTD - time to treatment discontinuation; RDI - relative dose intensity

This addendum provides a summary and critique of the company's response to the DG.[5] Section 2 summarises the results of the company's new base case analysis and additional scenario analyses presented in the appendices to the company's DG response. Section 3 provides a summary of the issues raised in the company's DG response together with a brief critique by the EAG. Section 4 presents additional analyses undertaken by the EAG which demonstrate the impact of reintroducing each of the Appraisal Committee's preferred assumptions into the company's new base case model.

2. Summary of results for company's new base case analysis and additional scenario analyses

Table 2 summarises the results of the Appraisal Committee's preferred analysis, the company's new base case analysis and the company's additional scenario analyses presented in the appendices to the company's DG response.[5] Based on the probabilistic version of the model, the company's new base case ICER is estimated to be £20,126 per QALY gained.

Table 2: Results of company's new base case model and additional scenarios* (includes PAS discount and QALY weighting of 1.2; based on company's DG response, Appendix C)

Option	LYGs†	QALYs	Costs	Inc. LYGs†	Inc. QALYs	Inc. Cost	ICER‡
Appraisal Committee's preferred analysis (deterministic)							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£28,200**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's new post-DG base case							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,126**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 1: Blending interval = 60 months							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,233**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 2: Blended survival weight function parameter (Rate: alpha=2, beta=5)							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,036**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 3: Blended survival high uncertainty							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,069**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 4: Blended survival low uncertainty							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,443**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 5: Inclusion of compliance instead of RDI							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,592**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 6: Inclusion of DECISION trial utility values							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,516**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 7: Inclusion of lenvatinib cost							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£11,499**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company scenario analysis 8: Exponential OS model							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£23,776**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

** All results from the company's DG response are based on the probabilistic version of the model*
† Undiscounted
‡ QALY weighting included in ICERs, but not included in absolute QALYs or incremental QALYs
Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care; RDI - relative dose intensity; OS - overall survival; DG - draft guidance

The EAG was unable to generate exactly equivalent results to those shown in Table 2 because the blended OS approach is probabilistic, and the company's model does not use a stored set of random numbers across analyses or a common random number stream. However, the EAG was able to generate the Appraisal Committee's preferred ICER of £28,200 per QALY gained by amending the drop-down menus within the deterministic version of the company's new model.

3. Summary and critique of the company's DG response

3.1 Focus on the second-line subgroup of COSMIC-311

The company's new base case analysis is focussed on the second-line subgroup of COSMIC-311.[2] The company's DG response[5] comments that this subgroup represents 75% of the intention-to-treat (ITT) population and that the trial has more than 100% power to detect a difference in the co-primary endpoint of progression-free survival (PFS) (hazard ratio [HR]=[redacted], 95% confidence interval [CI] [redacted]). The company's DG response also states that the second-line subgroup is representative of patients who would receive cabozantinib as second-line treatment in the NHS. The appendices to the company's DG response include a table of baseline characteristics for the second-line subgroup.

EAG comments:

The EAG notes the following points regarding the company's decision to focus on the second-line subgroup of COSMIC-311:[2]

- The EAG agrees that the second-line subgroup is consistent with the anticipated positioning of cabozantinib if it was recommended for use in the NHS.
- The EAG is unsure about the company's statements regarding the power of the COSMIC-311 study for the second-line patient population. Power is defined as the probability of avoiding a Type II error (a false-negative result) – as it is a probability, it must be bounded by 1.0 (or 100%). The Clinical Study Report (CSR) for clinical cut-off 1 (CCO1) in COSMIC-311[6] states that the trial was designed to have >90% power for overall response rate (ORR) in the overall response rate intention-to-treat (OITT) population and 90% power for PFS in the ITT population.
- At the TE stage of the appraisal, the EAG had some concerns that the company had not presented baseline characteristics for the second-line subgroup and that imbalances between the groups might result in confounding (see EAG TE addendum,[4] Section 2.1). These data have now been presented in Appendix B of the company's DG response.[5] However, the table provided in the appendix is incomplete, with no data presented on histological subtype, site of metastatic lesions, or median time from progression on the most recent prior non-radiation systemic anticancer regimen for DTC to randomisation. Data on prior lenvatinib and sorafenib use are also incomplete and difficult to interpret. The EAG is unsure why these data are missing or incomplete and cannot confirm that the treatment groups are adequately balanced across all factors.

3.2 Uncertainty around OS

Section 3.14 of the DG[1] states that the Appraisal Committee's preferred analysis includes the use of exponential models for OS. In contrast, the company's new base case analysis applies a blended survival modelling approach based on methods reported by Che *et al.*[7] This is similar to the analysis presented

in the company's TE response,[8] except that it now reflects the rank-preserving structural failure time (RPSFT)-adjusted second-line subgroup at clinical cut-off 2 (CCO2) in COSMIC-311,[2] rather than the ITT population of the trial. The blended survival approach has been applied to both treatment groups, with the Weibull distribution selected as the preferred function for the expert opinion survival curve (i.e., the external data extrapolation part). No details are provided about the distribution used for the observed data, the blending interval or the blending weight parameter used in the company's new base case analysis. The company's response document states that this approach reduces OS uncertainty.

The appendices to the company's DG response[5] present a range of scenarios exploring alternative specifications of the blended survival model which suggest ICERs in the range £20,126 to £22,069 per QALY gained (see Table 2, Base case and Scenarios 1-4). The appendices also include an additional scenario analysis in which OS is modelled using exponential distributions in both treatment groups; this increases the company's new base case ICER from £20,126 to £23,776 per QALY gained (see Table 2, Scenario 8).

EAG comments:

The EAG notes the following points regarding the company's updated survival analysis:

- The company's new blended survival analysis is not consistent with Appraisal Committee's preferred analysis.
- The blended survival analysis results in a greater incremental OS gain for cabozantinib versus BSC compared with the exponential model ([redacted] years versus [redacted] years). Whilst the blended analysis reduces the absolute OS in both groups, the reduction is greater in the BSC group than the cabozantinib group (see Figure 1, solid lines versus dashed lines).
- The company's blended survival analysis closely reflects the mean of the estimates obtained from the EAG's and the company's clinical advisors (see Table 3). However, the blended OS model does not provide a good representation of the RPSFT-adjusted OS data from COSMIC-311,[2] with OS for the cabozantinib group overestimated towards the tail of the distribution (after around 16 months) and OS in the BSC group underestimated from around 6 months onwards (see Figure 1). The EAG is unsure whether the blended survival approach has been implemented appropriately, as the model should reflect both the observed trial data and the external data. The EAG also notes that the model used for the first portion of the function (prior to blending) is unclear from the company's DG response; it may be the case that an alternative more flexible survival distribution could have provided a better fit to the trial data.
- As noted in the EAG report[9] and the EAG's TE response,[4] the exponential model also provides a poor representation of the observed trial data.

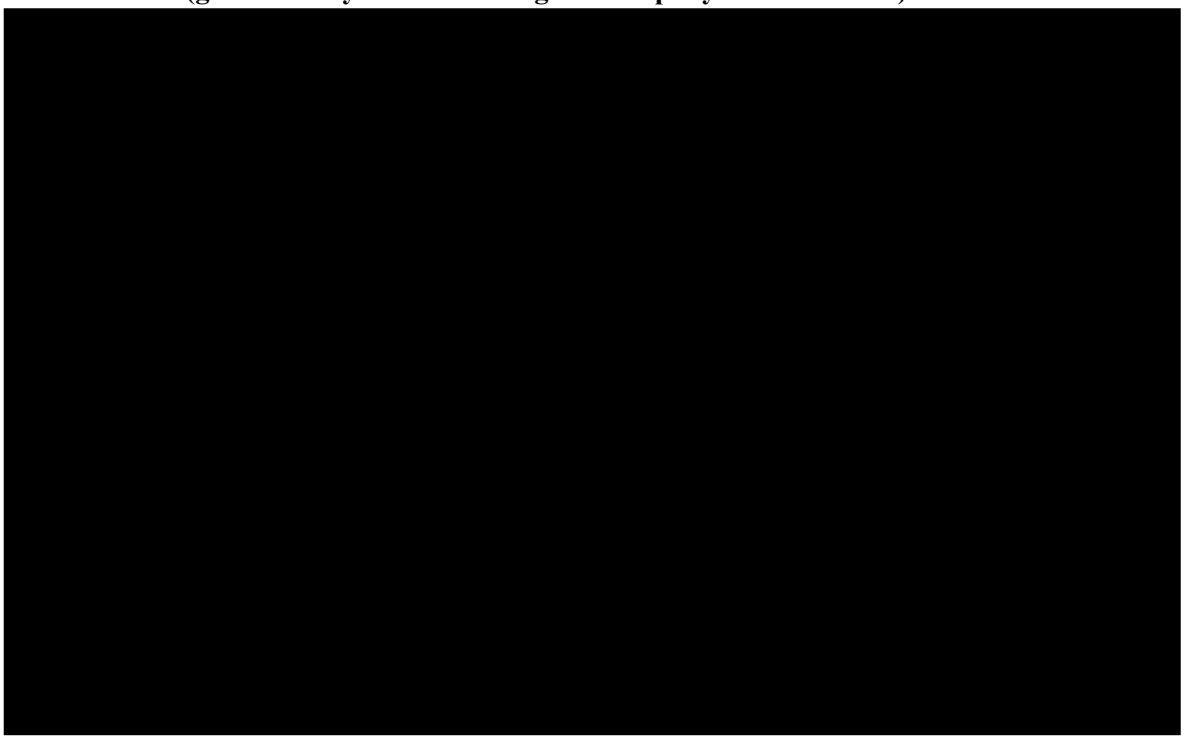
- The blended OS models and the exponential models appear optimistic in that both approaches suggest an increasing and prolonged separation of OS between the treatment groups which appears to be inconsistent with what has been observed in the trial.
- It remains the case that none of the analyses presented by the company or the EAG are ideal as they do not provide a good fit to both the observed data and the expectations of clinical experts.
- The EAG disagrees with the company's view that the blended survival approach reduces uncertainty. Whilst the EAG considers the blended survival analysis approach to be a novel means of synthesising observed data and clinical opinion within a combined model, it does not reduce clinical uncertainty - this is only possible through additional data collection. The EAG retains its view that the OS data from COSMIC-311 are limited and that the overall OS benefit for cabozantinib should be considered highly uncertain.

Table 3: Comparison of model predictions versus mean of experts' estimates

Estimate	Cabozantinib			BSC		
	2 years	5 years	10 years	2 years	5 years	10 years
Mean of EAG's and company's experts' values	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential model (Committee-preferred)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's new base case model predictions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC - best supportive care; EAG - External Assessment Group

Figure 1: Comparison of blended survival models, exponential models and observed survival in COSMIC-311 (generated by the EAG using the company's new model*†)



** Blended OS function shown reflects the mean of 100 samples*
† The Kaplan-Meier plot presented in this plot reflects the data for the second-line subgroup contained in the company's new model. The Kaplan-Meier plot in Figure 5 of the company's DG response is incorrect as it reflects the full ITT population.

3.3 Health utility values

Section 3.14 of the DG[1] states that the Appraisal Committee's preferred analysis includes the progression-free utility value from COSMIC-311[2] and the progressive disease utility value from Fordham *et al*.[3] In contrast, the company's new base case model applies EQ-5D-3L estimates from COSMIC-311 to the progression-free and progressed disease health states in the model. The company's DG response[5] argues that it is more appropriate to use the same source for both utility values applied in the progression-free and progressed disease health states and comments that the Fordham *et al.* valuation study is not consistent with the NICE Reference Case.[10] A scenario analysis using the utility values from the DECISION trial[11] is presented in the company's DG response appendices; this analysis increases the company's new base case ICER from £20,126 to £20,516 per QALY gained (see Table 2, Scenario 6).

EAG comments:

The EAG notes the following points regarding the company's updated choice of utility values included in the model:

- The company's updated base case analysis is not consistent with Appraisal Committee's preferred analysis.
- The pre- and post-progression EQ-5D-3L estimates from COSMIC-311[2] suggest that disease progression is associated with a negligible loss in HRQoL (progression-free utility = [redacted], progressed disease = [redacted], disutility for progression = [redacted]). This lacks clinical plausibility.
- The original company submission[12] (CS) and the minutes of the company's 2022 advisory board meeting[13] highlighted a number of problems associated with the available post-progression EQ-5D-3L data from COSMIC-311,[2] including the potential presence of informative censoring, selection bias and the likelihood that the post-progression utility value is not representative of mean utility for progressed patients over their remaining survival time. The concerns cited in the CS and the advisory board meeting minutes are reproduced below:
    - *"…the limited impact on utility associated with progression does not appear to be consistent, given the difference between PFS and PD states observed in other models and appraisals in advanced thyroid cancer, this inconsistency was also validated by UK clinicians in a recent advisory board."* (CS,[12] Section 3.4.1, page 107)
    - *"The limited impact of progression in the COSMIC-311 data was likely a result of limited follow-up in the PD state or missing data"* (CS,[12] Section B.3.4.1, page 106)
    - *"…it is likely that the PD value from the COSMIC-311 trial is not fully reflective of the PD state as a whole…"* (CS,[12] Section B.3.4.1, page 107)
    - *"Due to this lack of validity of the COSMIC-311 HRQoL data…"* (CS,[12] Section B.3.4.1, page 108).

- [redacted] (Company's advisory board meeting minutes,[13] page 15)
- [redacted] (Company's advisory board meeting minutes,[13] page 15).

- The EAG agrees that ideally, all utility values applied in the model would be: (i) unbiased; (ii) derived from the same study population and (iii) elicited from patients using a method that is consistent with the NICE Reference Case.[10] Given the problems with the COSMIC-311 post-progression utility value described by the company, the EAG believes that the most reasonable approach is to use Fordham *et al.* to inform the utility value for the post-progression state.

3.4 Adjustment of costs

Section 3.14 of the DG[1] states that the Appraisal Committee's preferred analysis includes the adjustment of cabozantinib acquisition costs using compliance. In contrast, the company's new base case analysis adjusts acquisition costs using relative dose intensity (RDI). The company's DG response[5] argues that:

- The analysis of compliance used to inform the EAG's preferred analyses is not reported in the CSRs for COSMIC-311,[6, 14, 15] whereas RDI values are reported in the CSRs.
- The compliance estimate is only available using data from CCO1, whereas RDI has been calculated using data from CCO2.
- Other appraisals of technologies for DTC with a flat pricing structure have included the adjustment of drug acquisition costs using RDI rather than compliance.
- Other appraisals of cabozantinib have included the adjustment of drug acquisition costs using RDI rather than compliance.
- In a real-world study in renal cell cancer (RCC), the RDI of cabozantinib was lower compared to that observed in the clinical trial due to additional comorbidities which required adjusted dosing schedules to manage side effects. As such, compliance in COSMIC-311 could be overestimating the true cost of cabozantinib in clinical practice.

The company's DG response[5] includes a scenario analysis which uses compliance instead of RDI; this increases the company's new base case ICER from £20,126 to £22,592 per QALY gained (see Table 2, Scenario 5).

EAG comments:

The EAG notes the following concerns regarding the company's preferred costing approach:

- The company's updated base case analysis is not consistent with Appraisal Committee's preferred analysis.

- Given the flat pricing structure for cabozantinib, the cost of treatment would be reduced if patients take fewer tablets, but would not be reduced if patients take the same number of tablets at a lower dose. Adjusting acquisition costs using compliance takes account of the number of days on which treatment was received. RDI accounts both for the number of days on which treatment was received as well as dose reductions on those treatment days. As such, adjusting costs by RDI will lead to the underestimation of the costs of cabozantinib, whereas adjusting costs using compliance will not.
- The EAG agrees that it would have been preferable for the economic analysis to include an updated compliance estimate based on CCO2. This issue was raised in Section 2.4 of the EAG's TE response.[4] However, the company has not provided this updated estimate. As discussed in the EAG's TE response, the compliance estimates reported in the CSRs for CCO1 and CCO2 are similar, with [redacted] of patients having any dose interruption. These values both differ slightly from the compliance estimate used in the model.
- The EAG believes that drug acquisition costs should have been adjusted using compliance in both TA535 and TA849. The fact that the issue was not raised, or at least not fully pursued, in either of these appraisals is not a sufficient justification for the inappropriate use of RDI adjustment in the current appraisal.
- The argument presented in the company's DG response regarding the real-world study in RCC refers to the overestimation of RDI rather than compliance, and does not account for the potential consequence that taking less cabozantinib in practice may also lead to lower comparative effectiveness compared with what has been observed in a clinical trial setting.

3.5 Post-progression lenvatinib scenario

The company's DG response[5] includes an additional scenario analysis which is intended to explore the impact of continued post-progression lenvatinib use. The company's analyses suggest that the ICER for cabozantinib versus continued post-progression lenvatinib is £11,499 per QALY gained (see Table 2, Scenario 7).

EAG comments:

The EAG notes that this additional scenario is the same as the company's new base case, except that additional costs of continued lenvatinib are included in the BSC group, without any consideration of additional health gains that continued post-progression tyrosine kinase inhibitor (TKI) therapy may provide. The EAG therefore considers that this analysis is likely to be biased that it should be disregarded.

3.6 Process-related issues raised in the company's DG response

The company's DG response[5] raises issues regarding the transparency of the deliberative process, the nature and extent of stakeholder involvement, insufficient time given to the company to review the EAG's TE response,[4] the need for a more pragmatic decision-making approach around managed access and a lack of transparency around the severity modifier.

The EAG considers that these are matters for NICE to address, but notes the following:

- The EAG's TE response[4] was submitted to NICE on the 6th February 2023, well in advance of the first ACM which was held on the 16th March 2023.
- At the first Appraisal Committee Meeting, the company indicated that they are not planning further data collection from COSMIC-311 and the company has not submitted an application for managed access. The EAG considers that the substantial uncertainty around OS benefits cannot be resolved without additional data collection.
- The severity modifier has been applied in line with the NICE Methods Manual[10] by both the company and the EAG and this has been accounted for in the draft recommendation (see DG,[1] Section 3.11). The EAG also notes that under NICE's previous End-of-Life criteria, it was necessary that *"the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival"* (NICE Methods Guide 2013,[16] Section 6.2.10). Given the uncertainty around the OS benefits of cabozantinib, it is unclear whether cabozantinib would have satisfied the EoL criteria. Nonetheless, the company and the EAG are aware that the 2022 NICE Methods Manual applies to this appraisal.

4. Additional analysis undertaken by the EAG

Table 4 summarises the cumulative impact of reintroducing the Appraisal Committee's preferred assumptions into the company's new base case model. As shown in the table, re-applying each of Appraisal Committee's preferred assumptions increases the ICER for cabozantinib versus BSC.

Table 4: Cumulative impact of re-applying changes to the company's new base case to return to the Committee's preferred analysis (probabilistic)

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER†
Company's new base case							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£20,217**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's new base case + compliance							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£22,651**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Company's new base case + compliance + Fordham PD utility value							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£25,608**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-
Committee preferred analysis (EAG ASA2a)							
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,016†**
BSC	[redacted]	[redacted]	[redacted]	-	-	-	-

** Undiscounted*
† QALY weighting included in ICERs, but not included in absolute QALYs or incremental QALYs
LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care; PD - progressed disease; ASA - additional sensitivity analysis

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