Cabozantinib for previously treated advanced hepatocellular carcinoma (review of TA582). A Technology Appraisal

Addendum: Summary and critique of company's economic model

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Date completed	30th August 2022 (post-FAC version)

1. Introduction

In May 2022, the National Institute for Health and Care Excellence (NICE) informed the company (Ipsen) that cabozantinib had failed the scrutiny stage of the NICE Fast Track Appraisal (FTA) process. Subsequently, it was agreed between NICE, the company and the Evidence Review Group (ERG) that a proportionate approach to the appraisal should subsequently be pursued. It was agreed that this would involve the company extending their existing partitioned survival model, which had previously been presented as part of the company's response to clarification questions from the ERG[1] (question B6), to estimate incremental quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for cabozantinib versus regorafenib. This model is discussed briefly in Section 4.5.1 of the ERG report.[2] In July 2022, the company provided an updated version of their submission to NICE[3] and a fully executable health economic model programmed in Microsoft Excel.®

This ERG addendum provides a summary and critique of the company's economic model and presents the results of additional exploratory analyses undertaken by the ERG. Several aspects of the updated company's submission (CS), including the indirect treatment comparisons (ITCs), remain unchanged from the original CS; hence, these are not discussed in detail in this addendum. The ERG's critique of these analyses can be found in Section 3.3 of the ERG report.[2]

All cost-effectiveness results presented in this addendum include the Patient Access Scheme (PAS) price for cabozantinib (discount=[redacted]) and the list price for regorafenib. The results of the economic analyses including the PAS discounts for both of these products is provided in a separate confidential appendix.

2. Description of company's model

2.1 Economic analysis scope

The scope of the company's economic model is summarised in Table 1. The model assesses the incremental cost-effectiveness of cabozantinib versus regorafenib in adult patients with advanced hepatocellular carcinoma (HCC) who have received prior sorafenib treatment and progressed following at least one prior systemic treatment. The analysis adopts a National Health Service (NHS) and Personal Social Services (PSS) perspective over a lifetime horizon. Health outcomes and costs are discounted at a rate of 3.5% per annum. In line with the ITCs summarised in the original CS[4] and the company's clarification response,[1] cost-effectiveness estimates for cabozantinib versus regorafenib are presented across three efficacy scenarios which reflect the anchored and unanchored matching-adjusted indirect comparisons (MAICs) based on time-to-event data from the CELESTIAL and RESORCE trials.[5, 6]

Table 1: Scope of company's additional economic analyses

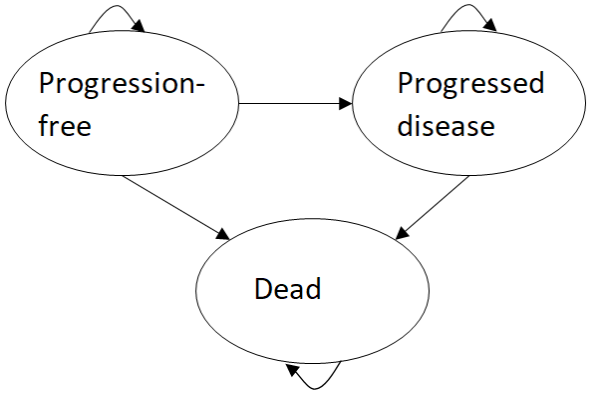
Population	Adult patients with advanced HCC who have received prior sorafenib treatment and progressed following at least one prior systemic treatment
Intervention	Cabozantinib 60mg QD
Comparator	Regorafenib 140mg QD for three weeks followed by one week off treatment
Outcome	Incremental cost per QALY gained
Time horizon	15 years (lifetime)
Perspective	NHS and PSS
Discounting	3.5% for health outcomes and costs
Efficacy scenarios considered	(1) Anchored MAIC, constant HRs (2) Anchored MAIC, time-varying HRs (3) Unanchored MAIC, independent models

HCC - hepatocellular carcinoma; mg - milligram; QD - once daily; QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services; MAIC - matching-adjusted indirect comparison; HR - hazard ratio

2.2 Model structure and logic

The company's economic model adopts a partitioned survival approach, including three health states: (i) progression-free; (ii) progressed disease, and (iii) dead (see Figure 1).

Figure 1: Company's economic model structure



The model logic operates as follows. Patients enter the model in the progression-free state and receive treatment with either cabozantinib or regorafenib. At any time *t*, health state occupancy is determined by the cumulative probabilities of overall survival (OS) and progression-free survival (PFS), whereby: the probability of being alive and progression-free is given by the cumulative probability of PFS; the probability of being alive following disease progression is calculated as the cumulative probability of OS minus the cumulative probability of PFS, and the probability of being dead is calculated as one minus the cumulative probability of OS. The company's model includes half-cycle correction, although this is subject to an error. Both cabozantinib and regorafenib are assumed to be given until disease progression or death, whichever occurs first; hence, time to treatment discontinuation (TTD) is assumed to be equivalent to PFS. Patients in both treatment groups are assumed to also receive best supportive care (BSC) in every model cycle, regardless of whether they have progressed. Following disease progression, patients are assumed not to receive any further active anticancer therapy in either treatment group (i.e., patients receive BSC alone).

The cumulative probabilities of OS and PFS for patients receiving cabozantinib and regorafenib are estimated using parametric survival models fitted to the observed/MAIC-adjusted data from the CELESTIAL and RESORCE trials.[5, 6] The model applies a structural constraint whereby the cumulative probability of PFS cannot be higher than the cumulative probability of OS at any timepoint. No other structural constraints are included in the model.

Health-related quality of life (HRQoL) is assumed to be determined by the presence/absence of disease progression and the incidence of adverse events (AEs). The utility values applied in the progression-free and progressed disease states are based on a statistical model fitted to Euroqol 5-Dimensions 5-Level (EQ-5D-5L) data from CELESTIAL[5] (mapped to the 3-level [3L] version). The same utility values are applied in each treatment group. The model also applies AE-related QALY losses in every model cycle whilst the patient is progression-free. Utility values are not adjusted for increasing age.

The model includes costs associated with: (i) drug acquisition; (ii) disease management (health state costs); (iii) tests associated with disease progression; (iv) the management of AEs and (v) end-of-life care costs. Drug acquisition costs for cabozantinib and regorafenib are modelled as a function of the PFS distribution, the treatment schedule and daily dose, relative dose intensity (RDI) and the costs of each product (including the PAS price for cabozantinib and the list price for regorafenib). Costs associated with wastage are not included in the base case analyses. Health state costs are applied in each model cycle. Costs associated with AEs, disease progression and end-of-life care are applied once-only (in the first model cycle, at the point of progression and at the point of death, respectively).

The incremental health gains, costs and cost-effectiveness for cabozantinib versus regorafenib are estimated over a 15-year time horizon using a 28-day cycle duration. No economic subgroup analyses are presented in the CS.[3]

Cost-effectiveness results for cabozantinib versus regorafenib are presented across three efficacy scenarios which were previously presented in the original CS and clarification response:[1, 4]

1. Anchored MAIC, constant hazard ratios (HRs) for PFS and OS (Weibull models for both endpoints)
2. Anchored MAIC, time-varying HRs for PFS and OS (log-logistic models for both endpoints)
3. Unanchored MAIC, independently fitted PFS and OS models (generalised gamma models for PFS, log-logistic models for OS).

2.3 Key model assumptions

The company's model applies the following assumptions:

- The three efficacy scenarios presented in the updated CS[3] assume that cabozantinib is not clinically equivalent to regorafenib. The anchored MAICs (Efficacy Scenarios 1 and 2) apply

HRs which favour cabozantinib for PFS, but favour regorafenib for OS. The unanchored MAIC (Efficacy Scenario 3) applies independently fitted models which suggest that cabozantinib improves both PFS and OS compared with regorafenib.

- Patients are treated with regorafenib and cabozantinib until disease progression.
- All patients receive BSC in every model cycle.
- The model includes a constraint which ensures that the cumulative probability of PFS cannot be higher than the cumulative probability of OS. No other constraints are included.
- Excluding the impact of AEs, health state utility values for the progression-free and progressed disease states are assumed to be the same for both treatment groups.
- HRQoL impacts associated with AEs are applied in every model cycle, based on the frequency of AEs and the median treatment exposure time for cabozantinib and regorafenib. A single common disutility value is applied to all AEs.
- Costs associated with AEs are applied once only in the first cycle.
- The model assumes that disease management costs are lower for the progression-free state compared with the progressed disease state. The same disease management costs are applied to health states for each treatment group.
- The model also includes once-only costs of progression and death which are applied when patients leave the progression-free state and die, respectively.

2.4 Evidence used to inform the company's model parameters

Table 2 summarises the evidence sources used to inform the company's model parameters. The derivation of the model parameter values is discussed in the subsequent sections.

Table 2: Summary of evidence sources used to inform the company's model

Model parameter/group	Source
PFS and OS	MAICs of cabozantinib versus regorafenib using time-to-event data from CELESTIAL and RESORCE[5, 6]
TTD	Assumed to be equivalent to PFS
AE frequency	MAIC using data from CELESTIAL[5] and RESORCE[6] converted to per-cycle probability
Health state utility values	Multivariable Tobit regression with repeated measurements fitted to EQ-5D-5L data from CELESTIAL[5] (mapped to the 3L version using van Hout *et al.*[7])
AE disutility	
Amount of drug received	Dosing based on SmPCs for cabozantinib and regorafenib.[8, 9] RDI based on CELESTIAL and RESORCE.[5, 6] Wastage not included (assumes pack-splitting).
Other resource use	Based on survey of 30 HCC physicians (Li *et al.*[10])
End of life care costs	Coyle *et al.*[11]
Unit costs	BNF,[12] eMIT,[13] NHS Reference Costs 2019/20,[14] and the PSSRU[15]

PFS - progression-free survival; OS - overall survival; MAIC - matching-adjusted indirect comparison; TTD - time to treatment discontinuation; AE - adverse events; EQ-5D-5L - Euroqol 5-Dimensions 5-Levels; 3L - level; SmPC - summary of product characteristics; RDI - relative dose intensity; HCC - hepatocellular carcinoma; BNF - British National Formulary; NHS - National Health Service; PSSRU - Personal Social Services Research Unit; eMIT - electronic Market Information Tool

Time-to-event outcomes

The company's approach to modelling PFS and OS differs across each of the three efficacy scenarios:

- *Efficacy Scenario 1: Anchored MAIC, constant HR*. This approach involved fitting parametric models for PFS and OS to data for each trial including treatment group as a covariate and applying the HR for regorafenib versus placebo to the weighted placebo arm of CELESTIAL.[5] PFS and OS are modelled using Weibull distributions.
- *Efficacy Scenario 2: Anchored MAIC time-varying HR*. This scenario applies time-varying HRs from the anchored MAICs. PFS and OS are both modelled using log-logistic models.
- *Efficacy Scenario 3: Unanchored MAIC*. This scenario uses the unanchored MAIC, based on independently fitted models applied to the cabozantinib arm of CELESTIAL[5] and the regorafenib arm of RESORCE.[6]

These ITCs have been described and critiqued previously in Section 3.3 of the ERG report.[2] Kaplan-Meier plots, hazard plots and goodness of fit statistics (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC] statistics) for the fitted parametric survival models are presented in the updated CS, the CS appendices and the clarification response.[1, 3, 16] The updated CS[3] states that parametric survival model selection was based on consideration of goodness-of-fit statistics, visual inspection and expert clinical input.[17, 18] A summary of the range of models considered, goodness-of-fit and clinical plausibility of the survival models fitted to the observed/MAIC-adjusted PFS and OS data is presented below.

Range of models assessed and goodness-of-fit

AIC and BIC statistics for the three efficacy scenarios can be found in CS Section B.3.3 (Tables 30, 31, 38 and 39) and CS Appendix L (Tables 51 and 52).[3, 16]

- *Efficacy Scenario 1 - Anchored MAIC, constant HR*
  - This analysis applies a constant HR to a baseline model; hence, the company only explored proportional hazards (PH) models within the analysis (the exponential, Weibull and Gompertz distributions).
  - The company selected the Weibull distribution for PFS and OS for both treatment groups. For both endpoints, the Weibull distribution is the best-fitting model in terms of both AIC and BIC for both treatment groups.
  - Based on visual inspection, the CS[3] comments that the PH assumption may not be appropriate and that modelled PFS and OS for the regorafenib group appear to be overestimated which biases against cabozantinib (see CS, Figures 32 and 35).

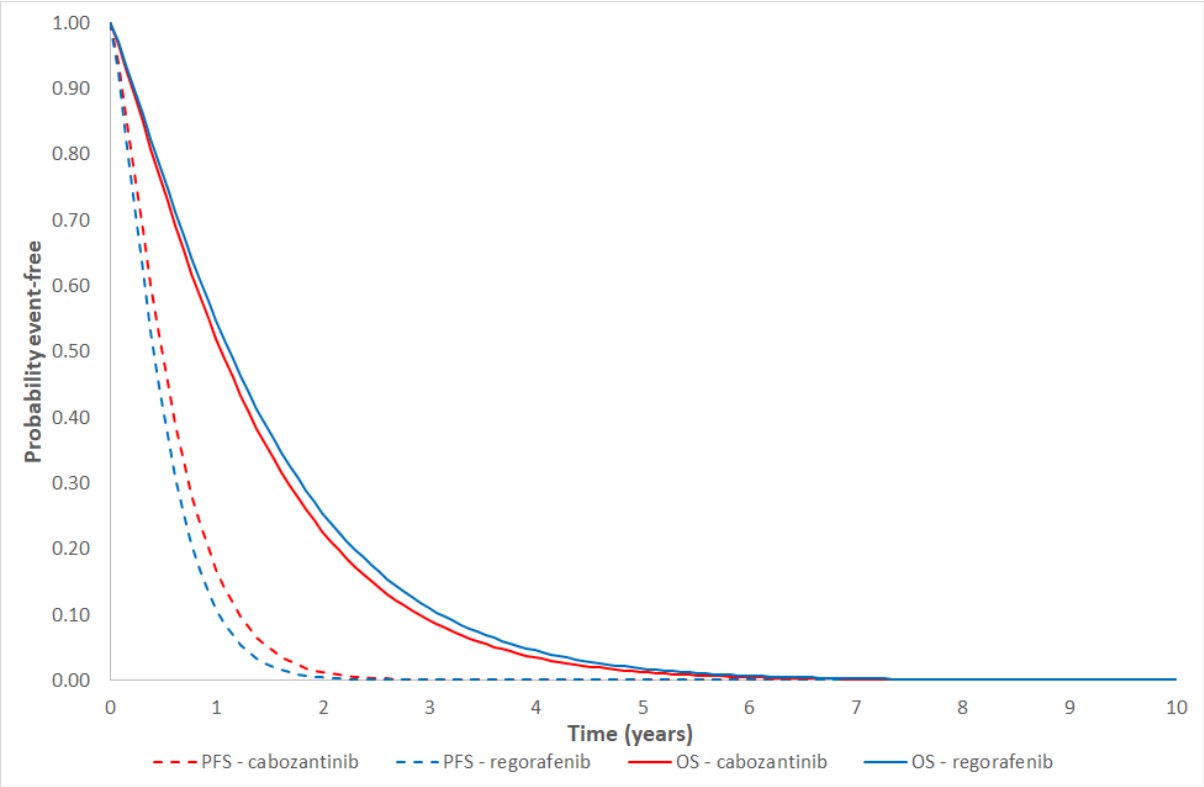
- *Efficacy Scenario 2 - Anchored MAIC, time-varying HR*
  - The company fitted six standard parametric survival models: the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions.
  - The company selected the log-logistic distribution for both PFS and OS for both treatment groups.
  - For PFS, the log-logistic distribution is the best-fitting model based on combined BIC and the second best-fitting model based on combined AIC.
  - For OS, the log-logistic distribution is the best-fitting model in terms of both AIC and BIC. The generalised gamma distribution has a similar AIC value, whilst the log-normal distribution has similar AIC and BIC values.
  - Based on visual inspection, the CS[3] comments that OS in the regorafenib group appears to be overestimated (see CS, Figure 33), but less so than in Efficacy Scenario 1 (anchored MAIC with constant HRs).

- *Efficacy Scenario 3 - Unanchored MAIC*
  - The company fitted six standard parametric survival models: the exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma distributions.
  - The company selected the generalised gamma model for PFS and the log-logistic model for OS. The same models are used in both treatment groups.
  - With respect to PFS, the generalised gamma distribution has the lowest AIC values. The log-logistic and log-normal models have lower BIC values for the cabozantinib and regorafenib arms, respectively. However, these differences are small.
  - With respect to OS, the log-logistic distribution is the best-fitting model for AIC and BIC in the cabozantinib arm, whereas the log-normal distribution is the best fitting model in the regorafenib arm.
  - The CS[3] does not comment on visual goodness of fit for this analysis; however, the ERG notes that the company's selected models appear to overestimate the tails of the distributions for the cabozantinib group, particularly for OS (see CS, Figures 25 and 26).

Summary of model-predicted PFS and OS

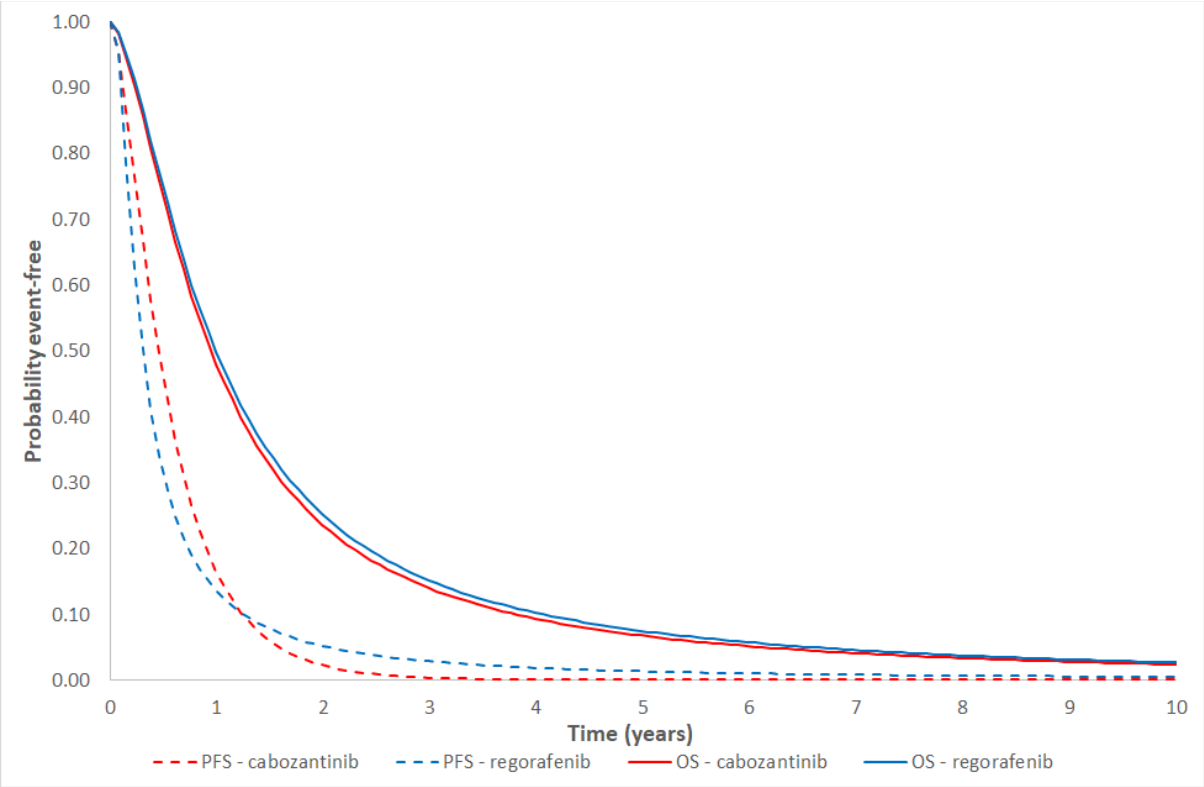
Model-predicted PFS and OS across the three efficacy scenarios are summarised in Figure 2, Figure 3 and Figure 4.

Figure 2: Modelled PFS and OS, Efficacy Scenario 1 – Anchored MAIC, constant HRs



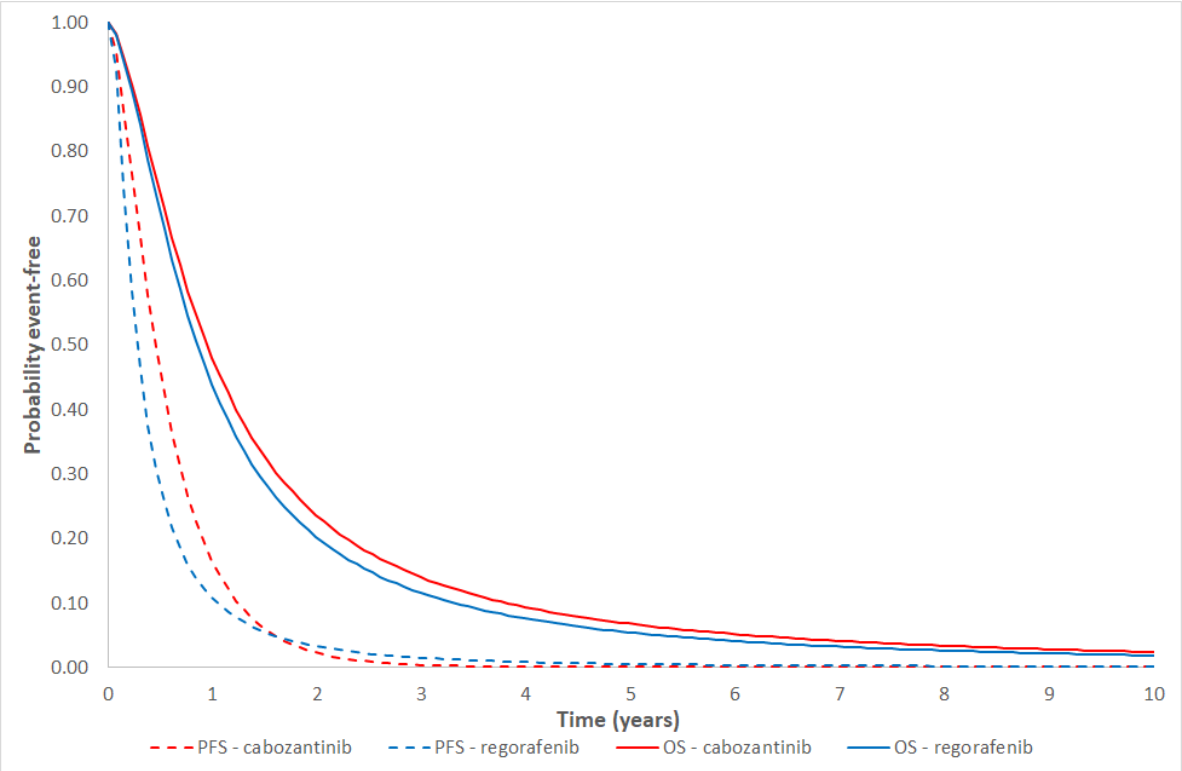
PFS - progression-free survival; OS - overall survival; MAIC- matching-adjusted indirect comparison; HR - hazard ratio

Figure 3: Modelled PFS and OS, Efficacy Scenario 2 – Anchored MAIC, time-varying HRs



PFS - progression-free survival; OS - overall survival; MAIC- matching-adjusted indirect comparison; HR - hazard ratio

Figure 4: Modelled PFS and OS, Efficacy Scenario 3 – Unanchored MAIC



PFS - progression-free survival; OS - overall survival; MAIC- matching-adjusted indirect comparison

Comparison of model predictions against external data

[redacted] One of the ERG's clinical advisors commented that they would expect 4-year OS in patients treated with regorafenib to be less than 5% - [redacted]. Efficacy Scenario 1 (anchored MAIC, constant HR) is broadly consistent with the ERG's

clinical advisor's estimate, whilst the other two scenarios produce higher 4-year OS estimates of 8-10%. The limitations of each of the ITC methods should be considered when interpreting the results of each of the three efficacy scenarios (see Section 3.3 of the ERG report[2]). As discussed in the ERG report, the ERG considers the anchored MAIC analyses to provide the most robust estimates of relative treatment effects between cabozantinib and regorafenib; however, there are concerns regarding the comparability of the anchor arm (placebo plus BSC) across the CELESTIAL and RESORCE trials[5, 6] and the CS highlights potential bias regarding the overestimation of PFS and OS for the regorafenib group.

Table 3: Company's clinical experts' estimates of PFS and OS and company's model predictions

Efficacy scenario	Treatment group	PFS		OS
		2 years	4 year	4 years
Company's clinical experts	-	[redacted]	[redacted]	[redacted]
1. Anchored MAIC, constant HR	Cabozantinib	1%	0%	3%
	Regorafenib	0%	0%	5%
2. Anchored MAIC, time-varying HR	Cabozantinib	2%	0%	9%
	Regorafenib	5%	2%	10%
3. Unanchored MAIC	Cabozantinib	2%	0%	9%
	Regorafenib	3%	1%	8%

PFS - progression-free survival; OS - overall survival; MAIC - matching-adjusted indirect comparison; HR - hazard ratio

Frequency of AEs

The frequency of individual AEs for each treatment group are based on MAICs presented in Table 12 of the ERG report.[2] The model applies different approaches to estimate the impact of AEs on QALYs and costs:

- The model applies QALY losses associated with Grade 3/4 AEs in each model cycle in which the patient remains progression-free. The company estimated the per-cycle AE probability based on the overall proportion of patients experiencing any Grade 3/4 AE and the median treatment exposure time for cabozantinib and regorafenib in CELESTIAL and RESORCE.[5, 6]
- The model assumes that all costs associated with managing AEs are incurred in the first model cycle, based on the frequency of each individual AE and its respective cost.

Table 4: AE frequency and per-cycle probabilities applied in company's model

AE type	Cabozantinib (median treatment exposure time = [redacted] months)		Regorafenib (median treatment exposure time = 3.60 months)	
	Frequency	Cycle probability	Frequency	Cycle probability
PPES	0.13	0.03	0.13	0.04
Hypertension	0.55	0.16	0.13	0.04
Elevated AST	0.11	0.02	0.05	0.01
Fatigue	0.07	0.02	0.06	0.02
Diarrhoea	0.12	0.03	0.02	0.01

AE - adverse event; PPES - palmar-plantar erythrodysaesthesia; AST - aspartate aminotransferase

HRQoL

Health utility and disutility values were estimated using EQ-5D-5L data collected in CELESTIAL;[5] these data were mapped to 3-level (3L) version using the algorithm reported by van Hout *et al*.[7] The updated CS[3] states that the company explored several potential models to estimate utility values using the EQ-5D data, including ordinary least squares (OLS) regression, Tobit regression with repeated measurements and mixed models with repeated measurements. The final selected model is a multivariate Tobit regression model for repeated measurements; the CS states that this model was selected because it had a lower AIC value compared with the mixed model. This appears to be a similar statistical model to that described in the additional analyses presented in the company's clarification response[1] (question B4). The utility and disutility values applied in the company's economic model are summarised in Table 5.

Table 5: Utility and disutility values applied in company's model (adapted from CS, Table 45)

Health state	Mean value	SE
Utility - progression-free	[redacted]	[redacted]
Disutility - progressed disease	[redacted]	[redacted]
Disutility - AEs	[redacted]	[redacted]

SE - standard error; AE - adverse event

Resource use and costs

The model includes costs associated with: (i) drug acquisition; (ii) disease management (health state costs); (iii) tests associated with disease progression; (iv) the management of AEs and (v) end-of-life care costs. The costs applied in the company's economic model are summarised in Table 6. These are described in further detail in the subsequent sections.

Table 6: Summary of costs applied in the company's model

Cost type	Cabozantinib	Regorafenib
Drug acquisition costs (per 28 days, progression-free state only)	[redacted]	List price: £3,371.94
BSC costs (per 28 days, both health states)	£1.72	
Health state cost - progression-free (per 28 days)	£926.49	
Health state cost - progressed disease (per 28 days)	£1,362.60	
AEs (once-only)	£489.64	£155.86
Progression (once-only)	£627.87	
End of life care (once-only)	£5,818.34	

PAS - Patient Access Scheme; BSC - best supportive care; AE - adverse event

Drug acquisition costs

The drug acquisition costs applied in the model are shown in Table 7. Drug acquisition costs for cabozantinib and regorafenib are modelled as a function of the PFS distribution, the treatment schedule

and daily dose, RDI and the costs of each product (including the PAS price for cabozantinib and the list price for regorafenib). Drug costs for cabozantinib and regorafenib were taken from the British National Formulary (BNF);[12] RDI was taken from the CELESTIAL and RESORCE trials.[5,6] The base case model assumes that packs of cabozantinib and regorafenib can be split and that no tablets are wasted (every tablet prescribed is taken). As both drugs are taken orally, administration costs are not included in the model.

Table 7: Drug acquisition costs per 28 days

	Cabozantinib	Regorafenib
List price	£5,143.00	£3,744.00
Tablets per pack	30	84
RDI	0.61	0.90
PAS discount	[redacted]	Not included
Cost per 28-day cycle	[redacted]	**£3,371.94**

RDI - relative dose intensity; PAS - Patient Access Scheme

BSC costs

The model includes the costs of concomitant BSC including: cyclizine hydrochloride; dexamethasone; lactulose; metoclopramide; morphine sulphate; omeprazole; oramorph; paracetamol and spironolactone. All drugs were costed using prices from the Commercial Medicines Unit (CMU) Electronic Market Information Tool (eMIT).[13] Further details regarding the costs of individual BSC drugs can be found in Table 46 of the updated CS.[3] A total cost of £1.72 per 28-day cycle is applied to all patients in each model cycle.

Health state management costs

Health state costs applied in each model cycle are summarised in Table 8. These costs include hospitalisations, clinical consultations, laboratory tests, scans and radiotherapy. The proportions of patients and frequencies of each resource item per 28-day cycle were based on a survey of 30 physicians treating advanced HCC patients undertaken in 2018.[10] Unit costs were taken from the NHS Reference Costs 2019/20[14] and the Personal Social Services Research Unit (PSSRU).[15] Further details of the NHS Reference Cost service codes can be found in Table 48 of the updated CS.[3] The total health state costs per 28-day cycle were estimated to be £926.49 for patients who are progression-free and £1,362.60 for patients with progressed disease.

Table 8: Health state costs per 28-day cycle

Resource component	Unit cost	Progression-free				Progressed disease				Unit cost source
		No.	% patients	Duration (days)	Expected cost	No.	% patients	Duration (days)	Expected cost	
Hospitalisations										
General ward	£676.48	1.00	0.17	4.89	£566.32	1.00	5.36	0.27	£971.38	NHS Reference Costs 2019/20[14]
A&E admission	£205.09	0.70	0.20	1.00	£27.95	0.70	1.00	0.26	£37.72	
ICU	£270.61	1.00	0.03	3.50	£29.74	1.00	3.57	0.05	£48.69	
Medical staff visits										
Oncologist	£204.48	1.14	0.57	-	£131.96	0.96	0.63	-	£123.04	NHS Reference Costs 2019/20[14]
Hepatologist	£174.44	0.30	0.05	-	£2.62			-	£0.00	
Gastroenterologist	£154.41	0.44	0.22	-	£14.87	0.33	0.19	-	£9.75	
Clinical nurse specialist	£44.00	1.10	0.41	-	£19.76	1.00	0.42	-	£18.43	PSSRU[15]
Palliative care team	£44.00	0.33	0.30	-	£4.40	2.00	0.80	-	£70.40	
Macmillan nurse	£44.00	0.95	0.37	-	£15.52	1.22	0.42	-	£22.49	
General practitioner	£39.00	1.00	0.38	-	£14.97	0.96	0.42	-	£15.84	
Laboratory tests										
AFP test	£8.56	0.95	0.70	-	£5.65	0.91	0.66	-	£5.12	NHS Reference Costs 2019/20[14]
LFT	£8.56	1.09	0.78	-	£7.30	0.96	0.70	-	£5.75	
Biochemistry	£1.20	1.13	0.80	-	£1.08	1.00	0.71	-	£0.86	
Complete blood count	£2.27	1.13	0.79	-	£2.01	0.96	0.72	-	£1.56	
INR	£2.27	1.14	0.64	-	£1.64	1.05	0.62	-	£1.48	
Radiological tests										
CT scan	£123.71	0.88	0.51	-	£55.60	0.46	0.43	-	£24.25	NHS Reference Costs 2019/20[14]
MRI scan	£273.25	0.33	0.18	-	£16.17	0.06	0.12	-	£1.98	
Procedures										
Radiotherapy fraction	£739.30	0.26	0.05	-	£8.92	0.11	0.05	-	£3.86	NHS Reference Costs 2019/20[14]
Total health state cost	-	-	-		**£926.49**	-	-	-	**£1,362.60**	

A&E - accident and emergency; ICU - intensive care unit; AFP - alpha-fetoprotein; LFT - liver function test; INR - international normalised ratio; CT - computerised tomography; MRI - magnetic resonance imaging; NHS - National Health Service; PSSRU - Personal Social Services Research Unit

Costs associated with disease progression

The costs associated with disease progression are summarised in Table 9. These are assumed to include alpha-fetoprotein (AFP) tests, liver function tests (LFTs), computerised tomography (CT) scans and magnetic resonance imaging (MRI) scans. Resource usage was based on the physician survey[10] and unit costs were taken from NHS Reference Costs 2019/20.[14] These costs are applied once-only to the proportion of patients leaving the progression-free state in each model cycle.

Table 9: Disease progression costs (once-only)

Cost component	Unit cost	No.	Proportion patients	Expected cost
AFP test	£8.56	5.17	0.79	£34.93
LFT	£8.56	2	1.00	£17.13
CT scan	£123.71	7.4	0.61	£555.12
MRI scan	£273.25	0.35	0.22	£20.70
Total cost	-	-	-	**£627.87**

AFP - alpha-fetoprotein; LFT - liver function test; CT - computerised tomography; MRI - magnetic resonance imaging

AE management costs

Costs associated with AEs are summarised in Table 10. The frequency of AEs was estimated using the company's MAICs (see ERG report,[2] Table 12). Unit costs were based on NHS Reference Costs 2019/20.[14] These costs are applied once-only in the first model cycle.

Table 10: AE costs (once-only)

AE	Unit cost	Frequency cabozantinib	Frequency regorafenib
PPES	£420.66	0.13	0.13
Hypertension	£638.81	0.55	0.13
Elevated AST	£0.00	0.11	0.05
Fatigue	£63.45	0.07	0.06
Diarrhoea	£629.69	0.12	0.02
Elevated bilirubin	£0.00	0.05	0.07
Expected cost	-	**£489.64**	**£155.86**

AE - adverse event; palmar-plantar erythrodysaesthesia; AST - aspartate aminotransferase

End of life care costs

The model includes a cost associated with end-of-life care of £5,818.34. This value was taken from Coyle *et al.*[11] and was uplifted to current values using inflation indices from the PSSRU.[15]

2.5 Model evaluation methods

The updated CS[3] presents base case cost-effectiveness results for each of the three efficacy scenarios using both the deterministic and probabilistic versions of the model. The probabilistic ICER is based on 1,000 Monte Carlo samples. The results of the probabilistic sensitivity analysis (PSA) for all efficacy scenarios are also presented using a cost-effectiveness plane and cost-effectiveness acceptability curves

(CEACs). The updated CS[3] presents the results of deterministic sensitivity analyses (DSAs) using tornado plots. The CS also reports the results of a range of deterministic scenario analyses exploring alternative assumptions regarding: the time horizon; treatment duration; the exclusion of RDI; discount rates; the use of list prices for both drugs; alternative parametric survival models; the use of Bucher ITCs rather than MAICs; the inclusion of wastage costs and alternative health state utility values.

2.6 Company's model results

Table 11 presents the central estimates of cost-effectiveness generated using the company's model across the three efficacy scenarios. All results include the PAS for cabozantinib and the list price for regorafenib. The results of the probabilistic analyses indicate that using the anchored MAICs, cabozantinib is expected to generate fewer QALYs and incur lower costs than regorafenib; the probabilistic ICERs are large and are in the South-West quadrant. The unanchored MAIC suggests that cabozantinib is expected to generate additional QALYs and cost-savings; hence, cabozantinib dominates regorafenib. The results generated using the deterministic version of the model for Efficacy Scenarios 1 and 3 are generally similar to those obtained from the probabilistic model; the probabilistic results for Efficacy Scenario 2 (MAIC with time-varying HR) suggest greater expected QALY losses and cost savings compared with the deterministic model.

Table 11: Summary of company's base case cost-effectiveness results

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
1. CEA, anchored MAIC, constant HRs (probabilistic)†							
Cabozantinib	1.43	[redacted]	[redacted]	-0.09	[redacted]	[redacted]	**£295,334 (SWQ)**
Regorafenib	1.53	1.05	£55,001	-	-	-	-
2. CEA, anchored MAIC, time-varying HRs (probabilistic)†							
Cabozantinib	1.81	[redacted]	[redacted]	-0.14	[redacted]	[redacted]	**£224,469 (SWQ)**
Regorafenib	1.95	1.27	£60,303	-	-	-	-
3. CEA, unanchored MAIC (probabilistic)†							
Cabozantinib	1.82	[redacted]	[redacted]	0.21	[redacted]	[redacted]	**Dominating**
Regorafenib	1.62	1.07	£55,409	-	-	-	-
1. CEA, anchored MAIC, constant HRs (deterministic)							
Cabozantinib	1.42	[redacted]	[redacted]	-0.10	[redacted]	[redacted]	**£290,383 (SWQ)**
Regorafenib	1.52	1.04	£55,669	-	-	-	-
2. CEA, anchored MAIC, time-varying HRs (deterministic)							
Cabozantinib	1.81	[redacted]	[redacted]	-0.10	[redacted]	[redacted]	**£300,170 (SWQ)**
Regorafenib	1.90	1.25	£60,496	-	-	-	-
3. CEA, unanchored MAIC (deterministic)							
Cabozantinib	1.81	[redacted]	[redacted]	0.19	[redacted]	[redacted]	**Dominating**
Regorafenib	1.62	1.07	£56,058	-	-	-	-

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; CEA - cost-effectiveness analysis; MAIC - matching-adjusted indirect comparison; HR - hazard ratio; SWQ – South-West quadrant
** Undiscounted*
† Based on a re-run of the probabilistic version of the model by the ERG, using 10,000 Monte Carlo simulations

Summary of other uncertainty analyses presented in the updated CS

The company's tornado plots for each efficacy scenario are presented in Figures 42, 43 and 44 of the updated CS.[3] These plots present the incremental net monetary benefit (NMB) for cabozantinib versus regorafenib assuming a willingness-to-pay (WTP) threshold of £30,000 per QALY gained. For brevity, these are not reproduced here. The company's plots consistently indicate that cabozantinib generates more NMB than regorafenib across all analyses, with the daily cost of regorafenib being the most influential model driver across all three efficacy scenarios.

The company's cost-effectiveness planes and CEACs for all three efficacy scenarios are presented in Figures 45 and 46 of the updated CS, respectively.[3] Assuming a WTP threshold of £30,000 per QALY gained, the probability that cabozantinib generates more net benefit than regorafenib is estimated to be approximately 0.94 or higher.

The results of the company's scenario analyses are summarised in Table 61 of the updated CS.[3] For brevity, these are not reproduced here. The economic conclusions suggested by these analyses are similar to those of the company's base case analyses (see Table 11), with the following exceptions:

- Using the list price for both cabozantinib and regorafenib results in substantially less favourable ICERs for cabozantinib (Efficacy Scenario 1: £25,227 per QALY gained [SWQ]; Efficacy Scenario 2: Dominated; Efficacy Scenario 3: £30,255 per QALY gained).
- The Bucher ITC results suggest that cabozantinib generates fewer QALYs and saves costs compared with regorafenib, leading to a South-West quadrant ICER of £162,411 per QALY gained.

These analyses indicate that the relative effectiveness of cabozantinib versus regorafenib and the prices of these products are key model drivers.

3. Critical appraisal by the ERG

3.1 Critical appraisal methods

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analysis and the underlying health economic model upon which this is based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists.[19, 20]
- Scrutiny of the company's model by the ERG.
- Double-programming of the deterministic version of the company's model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.

- Examination of the correspondence between the description of the model reported in the updated CS and the company's executable model.
- Replication of the base case results and PSA using the company's executable model.
- Where possible, checking of key parameter values used in the company's model against their original data sources.
- Clinical expert input to assess the plausibility of the model predictions.

3.2 Model verification

The ERG double-programmed the deterministic version of the company's model in order to check its implementation across all three efficacy scenarios. The results of the ERG's double-programmed model are very similar results to those generated using the company's model. During the process of rebuilding the company's model, the ERG identified several errors and other minor issues; these are described in Section 3.5.

Table 12: Comparison of results generated using the company's model and the ERG's double-programmed model, deterministic

Model outcome (incremental)	Company's model	ERG's double-programmed model
Efficacy scenario 1. Anchored MAIC, constant HRs		
Inc. LYGs	-0.10	-0.10
Inc. QALYs	[redacted]	[redacted]
Inc. costs	[redacted]	[redacted]
ICER	**£290,383 (SWQ)**	**£290,382 (SWQ)**
Efficacy scenario 2. Anchored MAIC, time-varying HRs		
Inc. LYGs	-0.10	-0.10
Inc. QALYs	[redacted]	[redacted]
Inc. costs	[redacted]	[redacted]
ICER	**£300,170 (SWQ)**	**£300,168 (SWQ)**
Efficacy scenario 3. Unanchored MAIC		
Inc. LYGs	0.19	0.19
Inc. QALYs	[redacted]	[redacted]
Inc. costs	[redacted]	[redacted]
ICER	**Dominating**	**Dominating**

ERG - Evidence Review Group; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; MAIC - matching-adjusted life year; HR - hazard ratio; SWQ - South-West quadrant

3.3 Adherence to the NICE Reference Case

Table 13 summarises the extent to which the company's model adheres to the NICE Reference Case.[21] The ERG has no major concerns and considers that the company's model is in line with the Reference Case.

Table 13: Adherence to the NICE Reference Case

Element of HTA	Reference Case	ERG comments
Defining the decision problem	The scope developed by NICE	The model compares cabozantinib against regorafenib in adult patients with advanced HCC who have had sorafenib. The final NICE scope[22] includes BSC as a comparator but this is not included in the economic model. As discussed in the ERG report,[2] the ERG agrees that BSC is not a relevant comparator for the population in whom regorafenib would otherwise be used.
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The model includes health gains accrued by patients.
Perspective on costs	NHS and PSS	
Types of economic evaluation	Cost-utility analysis with fully incremental analysis	The model is evaluated using a cost-utility approach.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 15-year time horizon. Across all three efficacy scenarios, virtually all patients (>98.5%) in the model have died by the final model cycle.
Synthesis of evidence on health effects	Based on systematic review	Modelled health outcomes have been estimated using ITCs comparing cabozantinib versus regorafenib using data from CELESTIAL and RESORCE.[5, 6] These trials were identified by the company's clinical effectiveness SLR.[3]
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health state utility values and a disutility value associated with AEs have been estimated using EQ-5D-5L data collected in CELESTIAL[5] (mapped to the 3L version using the algorithm reported by Van Hout *et al.*[7]).
Source of data for measurement of HRQoL	Reported directly by patients or carers, or both	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	No additional QALY weighting is applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The model includes costs borne by the NHS and PSS, valued using NHS Reference Costs and other standard costing sources.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Health outcomes and costs are discounted at a rate of 3.5% per annum.

HTA - health technology assessment; ERG - Evidence Review Group; NICE - National Institute for Health and Care Excellence; HCC - hepatocellular carcinoma; PSS - Personal Social Services; BSC - best supportive care; ITC - indirect treatment comparison; QALY - quality-adjusted life year; EQ-5D - Euroqol 5-Dimensions; 5L - 5-level; HRQoL - health-related quality of life; SLR - systematic literature review; AE - adverse event

3.4 Correspondence between model parameter values and evidence sources

Where possible, the ERG checked the parameter values used in the company's model against their original sources. The company's parametric survival models, HRs and HRQoL model were derived using individual patient data (IPD) which were not made available to the ERG; as such, the ERG cannot verify that these values have been estimated appropriately.

The ERG notes the following potential concerns regarding the other model parameters:

- The ERG was unable to find the number of patients attending A&E departments from the physician survey poster reported by Li *et al.*[10]
- The model worksheet "Cost inputs" suggests that the number of scans and tests incurred on disease progression were derived from the physician survey. However, these values are not reported by Li *et al.*[10] As such, the source of these values is unclear.
- The ERG was unable to identify or derive the company's unit cost estimates for hospitalisations from the NHS Reference Costs.[14]

The ERG believes that these issues are likely to be minor. The ERG was able to identify or derive all other cost and resource estimates used in the company's model.

3.5 Other issues identified from the ERG's critical appraisal

Other issues identified from the ERG's critical appraisal are summarised in Box 1. These issues are discussed below.

Box 1: Issues identified by the ERG's critical appraisal

(1) Model errors and other problems
(2) Issues relating to model parameter values
(3) Assumption of equivalent health state costs for cabozantinib and regorafenib
(4) Exclusion of wastage costs
(5) Discrepancy between probabilistic and deterministic results for Efficacy Scenario 2

(1) Model errors and other problems

The ERG identified five issues in the implementation of the company's model:

(a) The company's half-cycle correction is applied incorrectly as the first cycle is counted 1.5 times, rather than 0.5 times. This overestimates costs and health outcomes in both treatment groups.
(b) Costs associated with progression and end-of-life care are calculated based on the half-cycle corrected model trace. The ERG believes that it would be more appropriate to use the uncorrected trace for these costs.

(c) The physician survey poster (Li *et al.*[10]) reports resource use estimates per month, but the company's model applies these estimates in each 28-day model cycle. These costs should have been adjusted to reflect the 28-day cycle length (i.e., multiplied by 28/30.44).
(d) The model does not include a general population constraint.
(e) The model does not include age-adjustment of utility values or a cap to ensure that the modelled utility values for people with HCC remain lower than those for the general population.

These issues are addressed as part of the ERG's additional exploratory analyses (see Section 4).

(2) Issues relating to model parameter values

The ERG believes that the evidence sources used to inform the model parameters are generally appropriate.

The ERG does not have any major concerns regarding the company's survival analysis or model selection process, and the ERG broadly agrees with the final selected models included in each of the three efficacy scenarios. The three efficacy scenarios generate model predictions of PFS and OS which are broadly consistent with the views of clinical experts consulted by the company (see Table 3). Efficacy Scenario 1 appears to be most consistent with the ERG's clinical advisor's expectations of 4-year OS. The company has noted that OS appears to be overestimated in the regorafenib group in Efficacy Scenarios 1 and 2, whilst the ERG notes that OS appears to be overestimated for the cabozantinib group in Efficacy Scenario 3.

With respect to the HRQoL parameters, the ERG does not have any major methodological concerns regarding the company's analysis of the EQ-5D data from CELESTIAL,[5] but notes that the estimated disutility value associated with disease progression appears low (disutility = [redacted]). One of the ERG's clinical advisors commented that they would expect HRQoL to deteriorate more rapidly in patients with disease progression than in patients who are receiving an effective treatment - this deterioration does not appear to be fully reflected in the EQ-5D estimates used in the model. As such, the utility value for the progressed disease state (utility value = [redacted]) may not fully reflect the average level of HRQoL experienced by patients with advanced HCC who have failed two TKIs over their entire remaining lifetime. The ERG notes however that the post-progression utility values applied in the models used to inform NICE TA474[23] and TA514[24] also applied relatively high post-progression utility values based on analyses of EQ-5D data collected in the SHARP and RESORCE trials[6, 25] (utility values of 0.71 and 0.76, respectively). The ERG's exploratory analyses include a sensitivity analysis using a larger disutility value to explore its impact on the cost-effectiveness results (see Section 4).

The ERG also notes that the Coyle *et al.* study,[11] which used to inform the costs of end-of-life care, is more than 20 years old and that more recent sources are available (e.g., Round *et al.*[26]). However,

because virtually all patients in the model incur this cost, and most patients have a short survival time, this parameter has very little impact on the model results.

(3) Assumption of equivalent health state costs for cabozantinib and regorafenib

The company's model assumes that disease management costs in the progression-free health state are equivalent for cabozantinib and regorafenib. The ERG's clinical advisors commented that owing to its comparatively worse toxicity profile, cabozantinib is expected to lead to additional costs of monthly face-to-face visits whilst patients are still on treatment, which would otherwise have been managed remotely and less frequently (2-monthly) for patients receiving regorafenib. These additional costs are not included in the company's base case or sensitivity analyses. The ERG's exploratory analyses include additional monitoring costs for cabozantinib (see Section 4).

(4) Exclusion of wastage costs

The company's base case analyses assume that packs of treatment can be split and that every tablet prescribed is taken; hence, no wastage costs are included. This assumption particularly advantages the cabozantinib group because the mean RDI is much lower than that for regorafenib (0.61 vs 0.90). The ERG notes that some patients will incur wastage because they progress or die before completing a pack of treatment. The ERG believes that it would be more appropriate to include a level of drug wastage which is consistent with previous appraisals in HCC.[23, 24] These costs have been included in the ERG's exploratory analyses (see Section 4).

(5) Discrepancy between probabilistic and deterministic results for Efficacy Scenario 2

As shown in Table 11, the results of the probabilistic and deterministic results for the MAIC with time-varying HRs are noticeably different, with the former suggesting a comparatively greater loss in survival and QALYs than the latter. The ERG scrutinised the company's PSA sampling sub-routine and believes that this apparent discrepancy is due to uncertainty around the sampled survival model parameters rather than being the consequence of an error. Whilst the PSA results presented in the CS^3 are based on 1,000 Monte Carlo samples, all probabilistic results reported in this addendum use 10,000 samples.

4. Additional exploratory analyses undertaken by the ERG

4.1 ERG exploratory analysis - methods

The ERG undertook six sets of exploratory analyses (EAs) using the deterministic version of the company's model. These analyses are described below.

EA1: Correction of errors

This analysis includes the correction of three errors in the company's model:

(a) The half-cycle correction calculations were amended to count the first model cycle 0.5 times rather than 1.5 times.

(b) The calculations relating to the costs of progression and death were amended to use the uncorrected model trace.
(c) The health state cost calculations were amended to reflect a 28-day cycle duration.

These corrections were applied in all subsequent exploratory analyses.

EA2: Include general population mortality constraint

A general population mortality constraint was applied to the OS models to ensure that the risk of death with the disease in each cycle cannot be lower than the risk of all-cause death in the age- and sex-matched general population. This was done using a weighted survival model based on general population life tables for England,[27] together with information on the median age and proportion of female patients in the CELESTIAL trial (age=64 years; proportion female=0.18).[5]

EA3: Inclusion of age-adjusted utilities

Utility values were adjusted for increasing age based on a multiplicative approach using EQ-5D-3L estimates reported by Hernandez Alava *et al.*[28]

EA4: Inclusion of additional monitoring costs for cabozantinib

The health state cost calculations for the cabozantinib group were amended to include the cost of 0.5 additional oncologist visits per month (0.46 visits per 28-day model cycle).

EA5: Inclusion of wastage costs

The model was amended to include the costs of 7 days' worth of treatment in both treatment groups (adjusted for RDI). This was implemented using existing functionality contained in the company's model.

EA6: ERG-preferred model

The ERG's preferred model includes EA1-5. Results of this exploratory analysis are presented using both the deterministic and probabilistic versions of the model.

Additional sensitivity analyses

The ERG undertook four sets of additional sensitivity analyses using the ERG's preferred model (EA6).

ASA1: Alternative PFS models

The model was re-run using all alternative PFS models.

ASA2: Alternative OS models

The model was re-run using all alternative OS models.

ASA3: Post-progression utility value doubled

The disutility value associated with disease progression was doubled.

4.2 ERG exploratory analysis – results

ERG's preferred model results

The results of the ERG's preferred analyses for each of the three efficacy scenarios are presented in Table 14. The ERG's preferred model using the anchored MAICs suggests that compared with regorafenib, cabozantinib generates fewer QALYs and saves costs, leading to a high South-West quadrant ICERs of £254,307 and £202,316 saved per QALY lost for Efficacy Scenarios 1 and 2, respectively. The ERG's preferred model using the unanchored MAIC (Efficacy Scenario 3) suggests that cabozantinib generates additional QALYs and reduces costs, thereby dominating regorafenib.

Table 14: ERG preferred model results

Analysis	Incremental - cabozantinib versus regorafenib			
	Inc. LYGs	Inc. QALYs	Inc. costs	ICER
Efficacy scenario 1 – Anchored MAIC, constant HR				
Company's base case (deterministic)	-0.10	[redacted]	[redacted]	**£290,383 (SWQ)**
EA1 - Correction of errors	-0.10	[redacted]	[redacted]	£252,357 (SWQ)
EA2: General population mortality constraint	-0.10	[redacted]	[redacted]	£252,357 (SWQ)
EA3: Age-adjusted utilities	-0.10	[redacted]	[redacted]	£254,180 (SWQ)
EA4: Additional monitoring visit cost	-0.10	[redacted]	[redacted]	£241,519 (SWQ)
EA5: Wastage included	-0.10	[redacted]	[redacted]	£260,606 (SWQ)
EA6a: ERG-preferred model (deterministic)	-0.10	[redacted]	[redacted]	£251,572 (SWQ)
EA6b: ERG-preferred model (probabilistic)	-0.09	[redacted]	[redacted]	**£254,307 (SWQ)**
Efficacy scenario 2 – Anchored MAIC, time-varying HR				
Company's base case (deterministic)	-0.10	[redacted]	[redacted]	**£300,170 (SWQ)**
EA1 - Correction of errors	-0.10	[redacted]	[redacted]	£257,547 (SWQ)
EA2: General population mortality constraint	-0.10	[redacted]	[redacted]	£257,547 (SWQ)
EA3: Age-adjusted utilities	-0.10	[redacted]	[redacted]	£261,597 (SWQ)
EA4: Additional monitoring visit cost	-0.10	[redacted]	[redacted]	£243,674 (SWQ)
EA5: Wastage included	-0.10	[redacted]	[redacted]	£266,626 (SWQ)
EA6a: ERG-preferred model (deterministic)	-0.10	[redacted]	[redacted]	£256,727 (SWQ)
EA6b: ERG-preferred model (probabilistic)	-0.14	[redacted]	[redacted]	**£202,316 (SWQ)**
Efficacy scenario 3 – Unanchored MAIC				
Company's base case (deterministic)	0.19	[redacted]	[redacted]	**Dominating**
EA1 - Correction of errors	0.19	[redacted]	[redacted]	Dominating
EA2: General population mortality constraint	0.19	[redacted]	[redacted]	Dominating
EA3: Age-adjusted utilities	0.19	[redacted]	[redacted]	Dominating
EA4: Additional monitoring visit cost	0.19	[redacted]	[redacted]	Dominating
EA5: Wastage included	0.19	[redacted]	[redacted]	Dominating
EA6a: ERG-preferred model (deterministic)	0.19	[redacted]	[redacted]	Dominating
EA6b: ERG-preferred model (probabilistic)	0.21	[redacted]	[redacted]	**Dominating**

LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; EA - exploratory analysis; ERG - Evidence Review Group; MAIC - matching-adjusted indirect comparison; HR - hazard ratio

ERG's additional sensitivity analysis results

The results of the ERG's additional sensitivity analyses are summarised in Table 15. The economic conclusions remain consistent across all additional sensitivity analyses.

Table 15: ERG additional sensitivity analysis results

Analysis	**ICER – cabozantinib versus regorafenib**		
	1. Anchored MAIC, constant HR	**2. Anchored MAIC, time-varying HR**	**3. Unanchored MAIC**
ERG preferred model (deterministic)	**£251,572 (SWQ)**	**£256,727 (SWQ)**	**Dominating**
ASA1 – PFS = exponential	Not modifiable. Model uses Weibull distributions for PFS and OS.	£304,858 (SWQ)	Dominating
ASA1 – PFS = Weibull		£276,427 (SWQ)	Dominating
ASA1 – PFS = Gompertz		£282,716 (SWQ)	Dominating
ASA1 – PFS = log-normal		£243,518 (SWQ)	Dominating
ASA1 – PFS = log-logistic		£256,727 (SWQ)	Dominating
ASA1 – PFS = generalised gamma		£330,385 (SWQ)	Dominating
ASA2 – OS = exponential		£496,592 (SWQ)	Dominating
ASA2 – OS = Weibull		£297,850 (SWQ)	Dominating
ASA2 – OS = Gompertz		£64,981 (SWQ)	Dominating
ASA2 – OS = log-normal		£226,129 (SWQ)	Dominating
ASA2 – OS = log-logistic		£256,727 (SWQ)	Dominating
ASA2 – OS = generalised gamma		£132,798 (SWQ)	Dominating
ASA3 – progression disutility doubled	£271,009 (SWQ)	£292,878 (SWQ)	Dominating

ICER - incremental cost-effectiveness ratio; MAIC - matching-adjusted indirect comparison; HR - hazard ratio; ERG - Evidence Review Group; ASA - additional sensitivity analysis; PFS - progression-free survival; OS - overall survival; RDI - relative dose intensity; SWQ - South-West quadrant

5. End of life

The updated CS[3] states that cabozantinib does not meet NICE's End of Life criteria. The ERG agrees with the company's view.

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