Cabozantinib for previously treated advanced hepatocellular carcinoma (review of TA582 – terminated appraisal)

Part 1 public observer slides – contains redacted information

Technology appraisal committee C [04 October 2022]

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Company: Ipsen

NICE

Appraisal history

Cost-comparison

- Company submitted cost-comparison approach for cabozantinib

Scrutiny step

- NICE informed the company that cabozantinib had failed the scrutiny stage of the NICE cost-comparison process due to uncertainties about whether cabozantinib and regorafenib have similar health effects
- A cost-utility model would be needed to explore the potential differences

Proportionate approach

- It was agreed that a proportionate approach to the cost-utility modelling should be pursued
- The company extended their existing partitioned survival model, to estimate incremental QALYs and ICERs for cabozantinib versus regorafenib

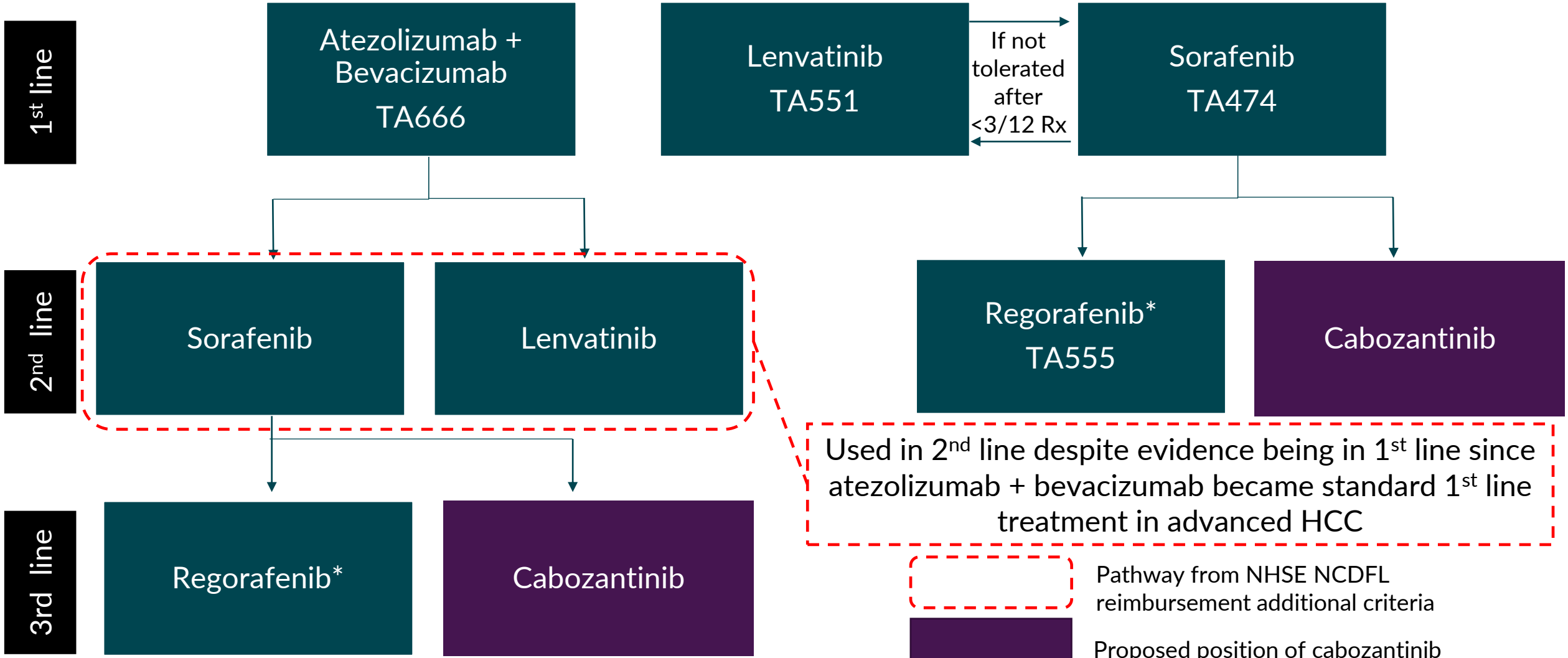
Abbreviations: ICER, incremental-cost effectiveness ratio; QALY, quality-adjusted life year

Background on hepatocellular carcinoma

- HCC is commonest subtype of primary hepatic cancer ~ 80% liver cancer cases in the UK
  - predominantly in people with underlying chronic liver disease especially those with cirrhosis
  - typically associated with: viral hepatitis, long-term alcohol consumption, non-alcoholic fatty liver disease and heritable diseases such as haemochromatosis
  - symptoms are a combination of pre-existing liver disease and HCC
- 6,214 new cases in UK (2016-2018): 66% cases in males; 43% >75+ years of age
- Overall prognosis for HCC depends on the severity of underlying liver dysfunction at the time of diagnosis as defined by the disease stage
  - most people are diagnosed in the advanced stages of the disease (BCLC stage C): cirrhosis is present, surgery is rarely an option, and treatment options are not curative
- 4,758 deaths are caused by liver cancer in England every year (2017-19)
  - age-standardised net survival rate at 1 year is 38.1%, and the net survival rate at 5 years is 12.7% for liver cancer, in England
- Fewer than 100 people per year are likely to have treatment with cabozantinib (maximum uptake of treatment in eligible population per Blueteq figures provided by NHSE&I)

Abbreviations: BCLC, Barcelona Liver Clinic Cancer; HCC, hepatocellular carcinoma

Treatment pathway & proposed position



*ERG agrees that regorafenib is an appropriate comparator

Abbreviations: HCC, hepatocellular carcinoma; NCDFL, National Cancer Drug Fund List; Rx, prescription

Patient and professional organisation perspectives

Submissions from British Liver Trust, British Association for the Study of the Liver, National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians and Royal College of Radiologists

- HCC commonly diagnosed at advanced stage with few treatment options
- People with advanced HCC report being extremely unwell, tired and weak. Survey responses show they live with "uncertainty, hopelessness and often stigma and isolation due to the [public] image of liver cancer"
    - significant impact on quality of life of patients, families and carers
- Unmet need for patients - limited treatment options available for those who have progressed on, or are intolerant of, sorafenib
- Cabozantinib offers people with advanced HCC a meaningful improvement in overall survival
    - age profile 'younger than for other cancers'. Extra time is valued by "people who may have young families and working lives to put in order before death"
    - "patients are desperate for any new treatments and were encouraged by the data that has been published in peer review journals"
- Wide variation of care across England and Wales with patients experiencing different standards of care depending on where they live.

"Every time I put my head up above water I got shot down."

Relatives [describe HCC] as "brutal—the worst possible way to go"

"He was put on the waiting list, then… taken off the list as the cancer had grown whilst waiting"

Abbreviations: HCC, hepatocellular carcinoma

Clinical expert perspectives

Submissions from Christie NHS foundation trust, University College London

- Advanced HCC has limited treatment options for patients and a poor prognosis
- Currently in the UK, regorafenib is only approved for use after sorafenib: it's not available for people who have lenvatinib
- Cabozantinib has "broader applicability than regorafenib" which was only evaluated in sorafenib-tolerant population
  - "sorafenib is often poorly tolerated and [~]20% of patients discontinue treatment due to poor tolerance"
  - "toxicity profile is well defined and side effects can be managed as an outpatient with low cost supportive medication when needed."
  - "by delaying progression, disease related symptoms will be delayed."
  - "absolute benefit is less in those with impaired liver function…Confining treatment to those with Child Pugh A liver disease would seem appropriate."
- Approval of atezolizumab and bevacizumab as first line therapy means fewer patients are treated with sorafenib
  - size of patient population for which cabozantinib may be considered has reduced as a consequence

"Improving the efficacy of systemic therapy is critical for delivery of better outcomes in advanced HCC and remains a significant unmet need."

"If approved, [cabozantinib] is likely to become the drug of choice as second line therapy following sorafenib."

Key issues

Model driver
Unknown impact
Small/Moderate impact

Issue	Questions for discussion	ICER impact
Comparative efficacy and safety	• Can the MAICs for second-line treatment be used to inform recommendations for third line? • Are the results from the MAICs appropriate for decision making? • Which MAIC method is most appropriate?	Large
Appropriateness of costs	• Is it appropriate to include additional monitoring costs for cabozantinib? • Is it appropriate to include wastage costs?	Large

Abbreviations: MAIC, matching-adjusted indirect comparison

Cabozantinib (Cabometyx, Ipsen)

Marketing authorisation (MHRA)	Monotherapy for the treatment of hepatocellular carcinoma (HCC) in adults who have previously been treated with sorafenib
Mechanism of action	Multi-targeted TKI that potently inhibits several RTKs known to influence tumour growth, metastasis and angiogenesis, including MET, VEGFR2 and AXL
Dose	60mg daily
Administration	Tablets, taken orally
List price	£5,143 per 30 tablet pack £4,800 per 28-day cycle (unadjusted for RDI) £62,573 per annum (unadjusted for RDI) Company has agreed a confidential patient access scheme for cabozantinib

Abbreviations: MET, mesenchymal epithelial transition factor; RDI, relative dose intensity; RTK, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor

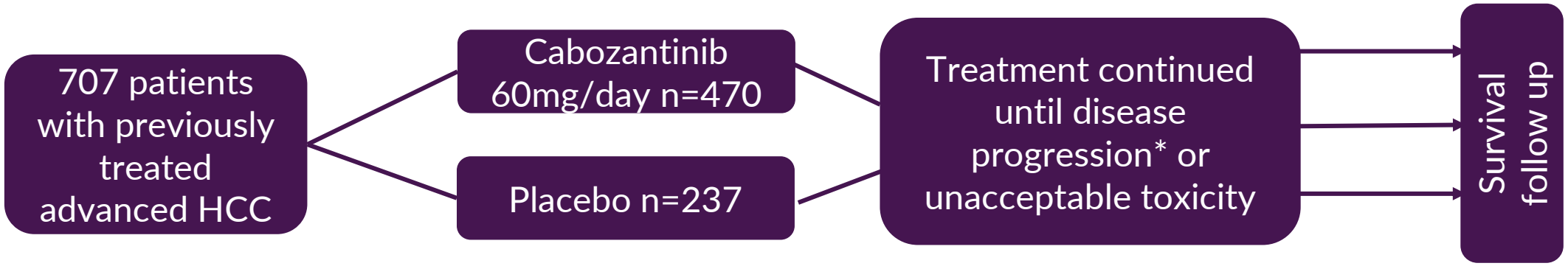
Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial - CELESTIAL

CELESTIAL phase III trial- conducted between September 2013 – June 2017

	CELESTIAL randomised, double-blind, placebo-controlled trial
Population	Patients with HCC on second or third-line treatment (sorafenib tolerant and intolerant) with an ECOG PS 0 or 1, and Child-Pugh status A
Intervention	Cabozantinib 60mg once daily plus BSC
Comparator(s)	Placebo once daily plus BSC
Primary outcome	Overall survival
Key secondary outcomes	Progression-free survival, objective response rate
Locations	Multicentre (Europe, North America, Australia, New Zealand, Asia)



*Patients could continue to receive treatment beyond disease progression at discretion of clinician

Abbreviations: BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma

CELESTIAL trial results - efficacy

Absence of direct evidence comparing cabozantinib against regorafenib.

CELESTIAL trial results

Outcome	Cabozantinib (n=470)	Placebo (n=237)
Median OS (95% CI)	10.2 months (9.1, 12.0)	8.0 months (6.8, 9.4)
OS HR (95% CI)	0.76 (0.63, 0.92)	
Median PFS (95% CI)	5.2 months (4.0, 5.5)	1.9 months (1.9, 1.9)
PFS HR (95% CI)	0.44 (0.36, 0.52)	
ORR [CR+PR], % (95% CI)	4 (2.3, 6.0)	0.4 (0.0, 2.3)
Odds ratio (95% CI)	9.4 (1.2, 71.0)	

CELESTIAL trial ad hoc subgroup results

Subgroups	Median OS		Median PFS	
	Cabozantinib	Placebo	Cabozantinib	Placebo
Second line	11.4 months (n=335)	7.7 months (n=174)	5.5 months (n=335)	1.9 months (n=174)
Second line HR (95% CI)	0.74 (0.59-0.92)		0.43 (0.35-0.52)	
Third line	8.6 months (n=130)	8.6 months (n=62)	3.7 months (n=130)	1.9 months (n=62)
Third line HR (95% CI)	0.90 (0.63-1.29)		0.58 (0.41-0.83)	

Abbreviations: CI, confidence interval; CR, complete response; HCC, hepatocellular carcinoma; PFS, progression-free survival; PR, partial response; ORR, objective response rate; OS, overall survival

Key evidence source - comparator

Absence of direct evidence comparing cabozantinib against regorafenib. Company did a series of indirect treatment comparisons (ITCs) of these treatments. Comparator evidence from RESORCE trial.

RESORCE phase III trial- conducted between May 2013 – February 2016

	RESORCE randomised, double-blind, placebo-controlled trial
Population	Patients with HCC on second-line treatment (sorafenib tolerant) with an ECOG PS 0 or 1, and Child-Pugh status A
Intervention	Regorafenib 160mg once daily plus BSC during weeks 1-3 of each 4-week cycle
Comparator(s)	Placebo once daily plus BSC during weeks 1-3 of each 4-week cycle
Primary outcome	Overall survival
Key secondary outcomes	Time to progression, progression-free survival, objective response rate, disease control rate
Locations	Multicentre (Europe, North America, Australia, South America, Asia)

Abbreviations: BSC, best supportive care; HCC, hepatocellular carcinoma; ITC, indirect treatment comparison

ITC analyses methods - cabozantinib vs. regorafenib

Company explored a number of ITC approaches

Bucher approach (placebo plus BSC as common comparator arm)

- Used aggregate data from the CELESTIAL and RESORCE trials
- Company and ERG agree results not sufficiently robust because effect modifiers assumption unlikely to be satisfied given the cross-trial differences . Not explored further

MAIC approaches

Anchored MAIC, constant HR

- Parametric models fitted to data for each trial (weighted data for CELESTIAL) including treatment group as a covariate then HR for regorafenib versus placebo applied to weighted placebo arm of CELESTIAL

Anchored MAIC (placebo plus BSC as common comparator arm), time varying HR

- Independent parametric models fitted to the weighted cabozantinib arm and the regorafenib arm to estimate a time-varying HR

Unanchored MAIC (no common comparator arm)

- Independent parametric models fitted to the weighted cabozantinib arm and the regorafenib arm to estimate absolute treatment effect.

MAICs use IPD from CELESTIAL trial (subpopulation of second-line patients) and aggregate data from RESORCE trial (ITT population of second-line patients). ITCs in the third-line population not possible because RESORCE trial was restricted to second-line.

Abbreviations : BSC, best supportive care; HR, hazard ratio; IPD, individual patient level data; PH, proportional hazards

MAIC results - efficacy

- The anchored MAIC results suggest a PFS benefit for cabozantinib but an OS benefit for regorafenib.
- The unanchored MAIC shows cabozantinib may have a similar OS and longer PFS compared with regorafenib.

	Cabozantinib vs regorafenib efficacy outcomes, HR (95% CI)	
Analysis	OS	PFS
Anchored MAIC, constant HR	1.09 (0.73, 1.62)	0.80 (0.55, 1.15)
Anchored MAIC, time varying HR	• Time-varying HR>1.0 → improved OS for regorafenib • Results across models show HR is not statistically different from 1.0 over time (95% CI includes a time-varying HR of 1.0)	• Time-varying HR<1.0 → improved PFS for cabozantinib • Results across models show HR over time is not statistically different from 1.0 (95% CI includes a time-varying HR of 1.0)
Unanchored MAIC	Large amount of overlap until year 1 when cabozantinib begins to show a relatively small benefit over regorafenib.	Statistically significant benefit for cabozantinib until approximately 1 year when the PFS curves show minimal difference for the rest of time horizon.

HR<1.0 favours cabozantinib over regorafenib

Abbreviations: CI, confidence interval; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; PH, proportional hazards; OS, overall survival

MAIC results - safety

- When using the MAIC methodology, only diarrhoea shows statistically significant differences at the 5% level
- ERG noted that the sum of probabilities of the individual grade 3/4 AEs in the model is 1.03 for cabozantinib and 0.46 for regorafenib

	Cabozantinib vs regorafenib safety outcomes, OR (95% CI)					
Analysis	Hypertension	Elevated AST	Fatigue	Elevated bilirubin	Diarrhoea	PPE syndrome
Anchored MAIC, constant HR	8.17 (0.90, 73.70)	2.20 (0.63, 7.84)	1.09 (0.17, 6.96)	0.78 (0.07, 9.30)	-	-
Unanchored MAIC	-	-	-	-	5.70 (2.72, 11.94)	1.05 (0.67, 1.65)

OR<1 favour cabozantinib over regorafenib

Abbreviations: AE, adverse event; AST, aspartate transaminase; MAIC, matching-adjusted indirect comparison; PPES, palmar-plantar erythrodysaesthesia syndrome; OR, odds ratio

MAIC- ERG comments

Issue	ERG comments
Lack of 3rd line comparative evidence	• Not possible to do ITCs in the third-line subgroup because the RESORCE trial was restricted to second-line, but regorafenib is now used in clinical practice in both second- and third-line
Potentially important cross-trial differences not addressed in the MAIC	• Anchored MAICs: concerns with the comparability of the placebo arms across both trials → assumption of transitivity may be violated if there are systematic differences in the placebo arm of each trial • Unanchored MAICs: relies on assumption that all prognostic factors and treatment effect modifiers accounted for → assumption rarely met, meaning the unanchored comparisons may not be robust
Which method more reliable?	• Unanchored MAIC limited by lack of preservation of trial randomisation and the potential problem of residual confounding • **Anchored MAIC with time varying HR may be the most appropriate** (based on violation of proportional hazards assumption for PFS and time-varying HR plots showing HR not constant for a number of parametric models).

- Can the MAICs for second-line treatment be used to inform recommendations for third line?
- Are the results from the MAICs appropriate for using in the economic model?
- Which MAIC method is most appropriate?

Abbreviations: BSC, best supportive care; HR, hazard ratio, ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; PH, proportional hazards

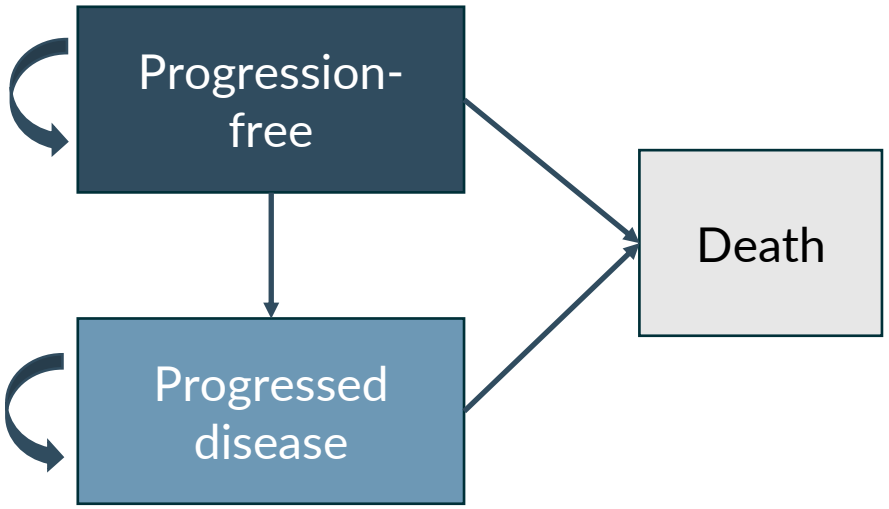
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's updated economic analysis

Model type	Three state partitioned survival model
Population	Adult patients with advanced HCC who have had prior sorafenib treatment and progressed following at least one prior systemic treatment
Intervention	Cabozantinib 60mg once daily
Comparator	Regorafenib 160mg once daily for 3 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

Three state partitioned survival model structure



Three efficacy scenarios presented by company:
(1) Anchored MAIC, constant HRs
(2) Anchored MAIC, time-varying HRs
(3) Unanchored MAIC, independent models

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PSS, personal social services; QALY, quality-adjusted life year

Evidence used in company's economic model

Modelled patient characteristics	CELESTIAL ITT population
PFS & OS	MAICs of cabozantinib versus regorafenib using time-to-event data in second-line treatment from CELESTIAL and RESORCE
Time to treatment discontinuation	Assumed to be equivalent to PFS
Adverse event frequency	MAIC using data from CELESTIAL and RESORCE converted to per-cycle probability
Health state utility and adverse event disutility	Multivariable Tobit regression with repeated measurements fitted to EQ-5D-5L data from CELESTIAL (mapped to the 3L version using van Hout *et al*)
Costs included	• Drugs acquisition costs (dosing based on SmPCs for cabozantinib and regorafenib. Relative dose intensity based on CELESTIAL and RESORCE) • Health state resource use costs (based on survey of 30 HCC physicians) • Adverse event treatment costs • End of life costs

Abbreviations: AE, adverse event; HCC, hepatocellular carcinoma; ITT, intention-to-treat; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; OS, overall survival; RDI, relative dose intensity; TTD, time-to-treatment discontinuation

Extrapolation of PFS and OS

Analysis	PFS	OS	ERG comments on extrapolation based on visual inspection
Anchored MAIC, constant HR	Weibull	Weibull	• Proportional hazards assumption may not be appropriate • Modelled PFS and OS for the regorafenib group appear to be overestimated which biases against cabozantinib
Anchored MAIC, time-varying HR	Log-logistic	Log-logistic	OS in the regorafenib group appears to be overestimated but less so than in scenario with anchored MAIC with constant HR
Unanchored MAIC	Gen. gamma	Log-logistic	Selected models appear to overestimate the tails of the distributions for the cabozantinib group, particularly for OS

Efficacy scenario	Treatment group	PFS		OS
		2 yrs	4 yrs	4 yrs
Company's clinical experts	Cabozantinib	[redacted]	[redacted]	[redacted]
ERG's clinical advisor	Regorafenib	-	-	<5%
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%

Company: parametric model selection based on goodness-of-fit statistics, visual inspection and clinical input

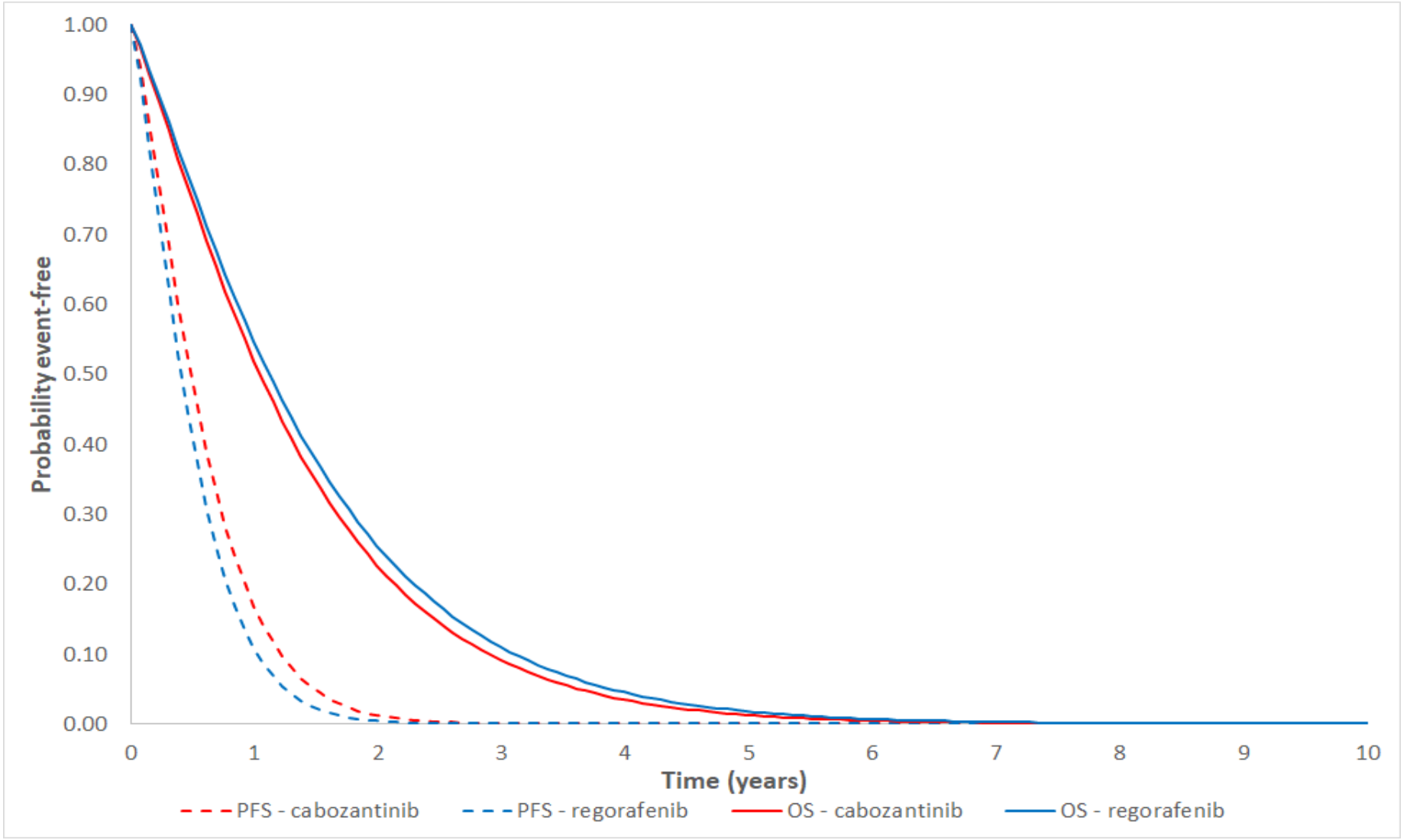
ERG: company's estimates from the three MAICs broadly consistent with clinical opinion from company's clinical experts.

- Scenario 1 is broadly consistent with the ERG's clinical advisor's estimate for 4-year OS, whilst the other two scenarios produce higher estimates of 8-10%.

Abbreviations: CI, confidence interval; CR, complete response HCC, hepatocellular carcinoma; PFS, progression-free survival; PR, partial response; ORR, objective response rate; OS, overall survival

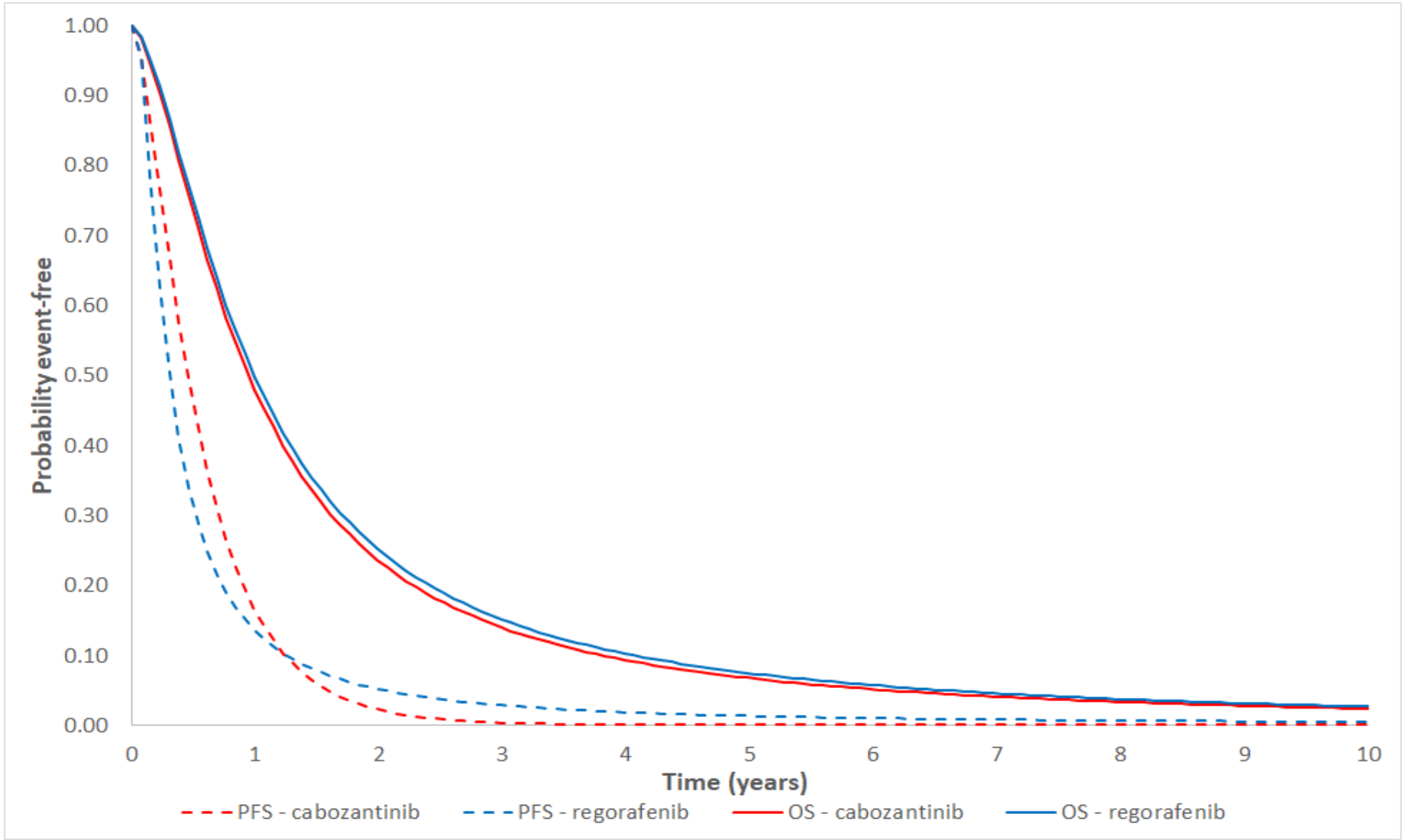
Extrapolation of PFS and OS- efficacy scenario 1

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



Extrapolation of PFS and OS- efficacy scenario 2

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



Key issue: Monitoring costs

Background

Company assumes disease management costs in the progression-free health state are equivalent for cabozantinib and regorafenib

Company

- Monitoring costs are equivalent due to equal efficacy
- The safety profile of cabozantinib is generally similar to that of other VEGFR-targeting TKIs

ERG comments

- ERG's clinical advisors commented that due to its comparatively worse toxicity profile, cabozantinib is expected to lead to additional costs of monthly face-to-face visits, which would otherwise have been managed remotely and less frequently (2-monthly) for patients receiving regorafenib
- Presented preferred analyses with additional monitoring costs for cabozantinib

Is it appropriate to include additional monitoring costs for cabozantinib?

Abbreviations: TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor

Key issue: Wastage costs

Background

Company's base case analyses assume that packs of treatment can be split and that every tablet prescribed is taken; so no wastage costs are included company's base case

Company

- Relative dose intensity (RDI) used to calculate drug costs. TA555 guidance indicates full pack dosing was "unlikely to reflect clinical practice, because the dose reductions in the trial were planned, so it was more likely that wastage would be minimised in clinical practice"
- Wastage costs included in scenario analysis

ERG comments

- Exclusion of drug wastage costs particularly advantages the cabozantinib group because the mean RDI is much lower than that for regorafenib (0.61 vs 0.90).
- Wastage could occur if patients progress or die before completing a pack
- More appropriate to include a level of drug wastage which is consistent with previous appraisals in HCC (TA474 and TA555) - including 7 days' drug wastage adjusted for RDI
- Presented preferred analyses with wastage costs included

Is it appropriate to include wastage costs?

Abbreviations: RDI, relative dose intensity

Other considerations

Equality considerations

- Liver disease and liver cancer disproportionally affects the poorest in society. Many patients with liver cancer come from disadvantaged backgrounds and have complex lives (British Liver Trust submission).
- Fewer people from ethnic minority backgrounds are able to access a liver transplant because of the lack of suitable donors, potentially increasing the likelihood of requiring systemic treatment.

Innovation

- Cabozantinib and regorafenib belong to the same drug class of TKIs. They inhibit multiple receptor tyrosine kinases implicated in tumour growth, metastasis, and angiogenesis. Cabozantinib is currently the only therapy developed for HCC that inhibits the MET and AXL, and thereby provides additional inhibitory effects beyond that of currently approved TKIs. Due to this unique molecular pathway, cabozantinib may be able to break TKI resistance established in the first line of treatment (company submission).

Are there any benefits not captured in the QALY calculations?
Are there any equality considerations relevant to the recommendations?

Abbreviations: OS, overall survival; ICER, incremental-cost effectiveness ratio; MET, mesenchymal epithelial transition factor; TKI, tyrosine kinase inhibitor

ERG base case

The ERG's preferred modelling included 5 updates to the company's base-case analyses (presented for all MAIC analyses):

1. **Correction of errors**
    - Half-cycle correction calculations were amended to count the first model cycle 0.5 times rather than 1.5 times.
    - Costs associated with progression and end-of-life care were amended to be calculated based on the uncorrected trace rather than the half-cycle corrected model trace
    - Health state cost calculations were amended to reflect a 28-day cycle duration
2. **Include general population mortality constraint (very minor impact on results)**
    - 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
3. **Inclusion of age-adjusted utilities (very minor impact on results)**
    - Adjusted for increasing age based on a multiplicative approach using EQ-5D-3L estimates
4. **Inclusion of additional monitoring costs for cabozantinib**
    - Amended to include the cost of 0.5 additional oncologist visits per month
5. **Inclusion of wastage costs**
    - Amended to include the costs of 7 days' worth of treatment in both groups (adjusted for RDI)

Abbreviations: MAIC, matching-adjusted indirect comparison; OS, overall survival; RDI, relative dose intensity

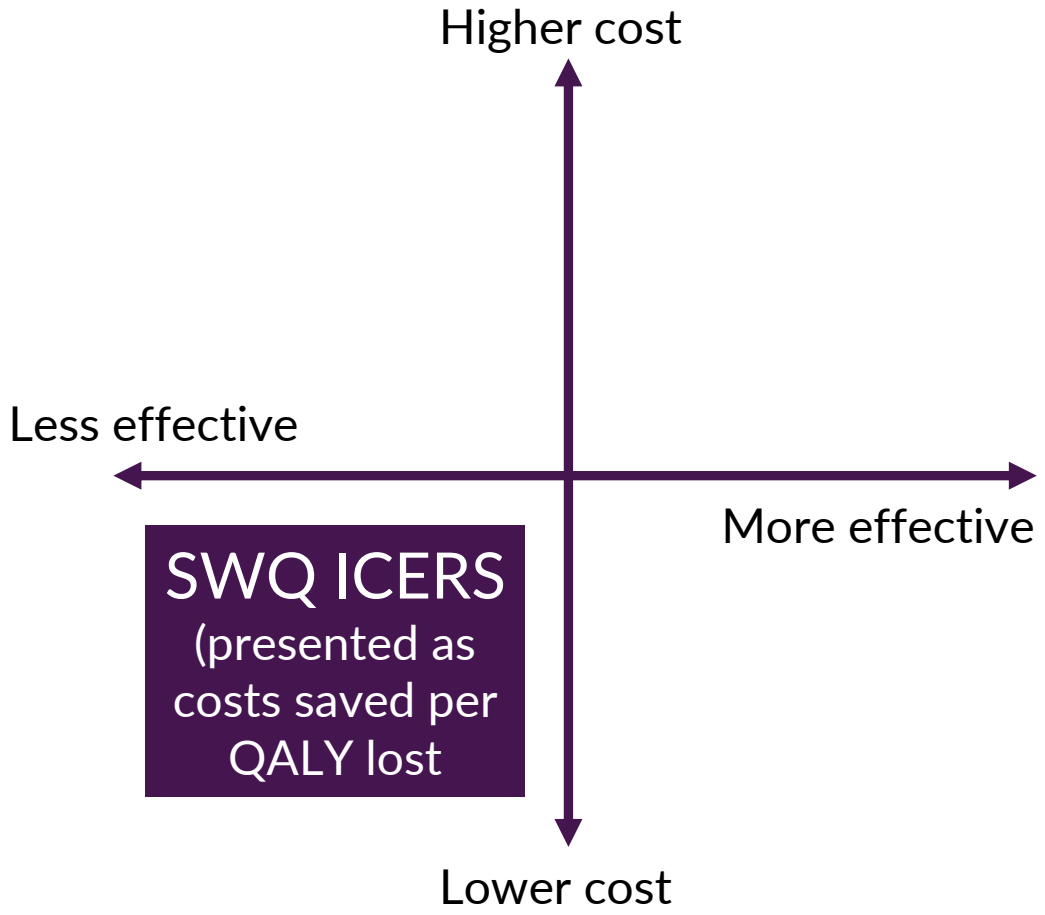
Cost-effectiveness results

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- Many of the company and ERG analyses suggest cabozantinib is associated with lower costs and QALYs than regorafenib

Abbreviations: ICER, incremental cost effectiveness ratio; PFS, progression-free survival; OS, overall survival

Decision-making with south-west quadrant ICERs

- When a treatment has lower costs and is less effective than a comparator, the ICERs are in the south-west quadrant of the cost-effectiveness plane
- South-west quadrant ICERs are presented as costs saved per QALY lost.
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed.
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss. Usually, SWQ ICERs have led to positive recommendations when ICERs are substantially above £30,000 per QALY lost.



Abbreviations: OS, overall survival; ICER, incremental-cost effectiveness ratio; SWQ, south-west quadrant

Explanation of cost-effectiveness results

Anchored MAIC results lead to ICERs in the southwest quadrant

Model parameter	Impact on incremental costs/QALYs
Costs	
Drug	**Lower for cabozantinib,** primarily driven by lower RDI for cabozantinib than regorafenib (61% in CELESTIAL vs 90.1% in RESORCE)
Health state	**Slightly lower for cabozantinib** in company base case; **higher for cabozantinib** in ERG base case
Adverse events	AEs more frequent for cabozantinib, so the costs are higher for cabozantinib, but this is **not a key driver** as these costs are applied once-only
Progression	**very similar for both groups** (because almost everyone in model cohort progresses or dies)
Death	**very similar for both groups** (because almost everyone in model cohort dies)
Health outcomes	
OS and PFS	The **incremental QALYs are negative** because of the loss in QALYs due to shorter OS outweighs the gain in QALYs due to longer PFS for cabozantinib
AEs	Slightly greater QALY losses for cabozantinib (AEs more frequent for cabozantinb). **Not a key driver**

Abbreviations: AE, adverse event; RDI, relative dose intensity; OS, overall survival; ICER, incremental-cost effectiveness ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival, QALY- quality-adjusted life year

Back up slides

MAIC approaches

ITC method	Outcomes assessed	Method description
Anchored MAIC, constant HR	• Efficacy: OS, PFS • Safety: Increased AST, elevated bilirubin, fatigue, hypertension	• Efficacy: constant HR applied to baseline model (weibull models for OS and PFS) • Safety: weighted OR (where weights are estimated from matching on trial baseline characteristics)
Anchored MAIC, time varying HR	• Efficacy: OS, PFS	• Efficacy: company selected a log-logistic model as the best fitting model to estimate a time-varying HR for both OS and PFS
Unanchored MAIC	• Efficacy: OS, PFS • Safety: Diarrhoea, PPES	• Efficacy: company selected a log-logistic model for OS and generalised gamma model for PFS fitted to weighted cabozantinib and regorafenib arms • Safety: Weighted OR (where weights are estimated from matching on trial baseline characteristics)

Abbreviations: AST, aspartate transaminase; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; PFS, progression-free survival; PH, proportional hazards; PPES, palmar-plantar erythrodysaesthesia syndrome; OR, odds ratio; OS, overall survival