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

Public observer slides – ACIC information redacted

Technology appraisal committee D [16 March 2023]

Chair: Stephen Smith

Lead team: Matt Bradley, Bernard Khoo, Malcolm Oswald

External assessment group: ScHARR

Technical team: Rachel Ramsden, Victoria Kelly, Jasdeep Hayre

Company: Ipsen

© NICE 2023. All rights reserved. Subject to Notice of rights.

Background on thyroid cancer

Causes

- Cause is often unknown, but risk factors include age, genetics and exposure to risk factors

Epidemiology

- ~3,900 new thyroid cancer cases in the UK every year
- Thyroid cancer more common in women than men, but in metastatic setting the proportions are similar
- Median age of diagnosis of thyroid cancer is 45 - 49 years

Diagnosis and classification

- Differentiated thyroid cancer is most common form of thyroid cancer, accounting for ~90-95% of all diagnosed cases

Symptoms and prognosis

- Symptoms include a painless lump in the front of the neck, difficulty swallowing, swollen glands in the neck, a sore throat and unexplained hoarseness that does not get better
- DTCs are typically curable, with 10-year survival ~85%
- Survival is related to stage at diagnosis (1yr age-standardised survival: 99% for stages 1-3, 77% for stage 4)
- For RAI-refractory DTC, the 5-year, 10-year and 15-year survival rates are 66%, 10% and 6% respectively

Abbreviations: DTC, differentiated thyroid cancer; RAI, radioactive iodine

Clinical perspectives

Submissions from NCRI-ACP-RCP-RCR and 2 clinical experts

Unmet need

- DTC affects people of working age and refractory disease poses huge challenges in terms of impacting on patient's ability to lead normal and productive lives
- Except for very small subset of patients who have targetable genetic alterations (NTRK and RET fusions), there is no other active treatment available, and prognosis is very poor
- Availability of cabozantinib would open another line of active treatment for this group of patients, extending PFS and potentially OS

"I cannot think of a single patient who has survived more than 2 years beyond progression on lenvatinib, unless further therapy has been available"

Benefits of cabozantinib

- Improvement in PFS is an important outcome for this group of patients. If disease is not progressing they are unlikely to develop new disease-related symptoms
- Data regarding the effect of this treatment on OS are difficult to interpret although there is likely to be a benefit for this group who otherwise have an extremely poor prognosis
- Will be prescribed in secondary care by thyroid oncologists with no additional investments required

Abbreviations: ACP, Association of Cancer Physicians; DTC, differentiated thyroid cancer; NCRI, National Cancer Research Institute; NTRK, neurotrophic tropomyosin receptor kinase; OS, overall survival; PFS, progression free survival; RCP, Royal College Of Physicians; RCR, Royal College of Radiologists; RET, rearranged during transfection

Equality and innovation considerations

Equality considerations

- **Company:** Females more likely to be diagnosed with thyroid cancer making up 72% of UK cases. Cabozantinib in DTC will reduce health inequalities for female thyroid cancer patients
- **EAG:** COSMIC-311 includes a comparatively lower proportion of women (53%). EAG's clinical advisors commented that proportions of men and women are similar in metastatic setting
- **Clinical experts:**
    - Men with thyroid cancer tend to have worse prognosis → numbers of men and women with the type of aggressive disease that requires this treatment are approximately equal as demonstrated in the trial population
    - Women have a higher prevalence of DTC compared to men. Offering this treatment to women with progressive and metastatic disease would improve outcomes in women and address the differential morbidity and mortality that women are exposed to, by virtue of higher prevalence in women

Innovation

- **Company:** No active treatment currently available for majority of these patients and their prognosis is very poor. It is addressing a significant unmet need

Does the committee consider that there are any relevant equality issues that it should consider in its decision making and, if so, how?

Abbreviations: DTC, differentiated thyroid cancer

Key issues

Key issues		Resolved?	ICER impact
DTC population included in model		No – for discussion	Large
Uncertainty around the effect of cabozantinib on overall survival		No – for discussion	Large
Uncertainty around the most appropriate health state utility values		No – for discussion	Small
Issues relating to resource use and costs	• Post-progression cabozantinib costs & TTD	No – for discussion	Small
	• Drug wastage costs	Yes	N/A
	• Drug cost adjustments using RDI	No – for discussion	Small
	• Monitoring cost assumptions	No – for discussion	Small
	• Concomitant medication costs	No – for discussion	Small

Abbreviations: DTC, differentiated thyroid cancer; ICER, incremental cost effectiveness ratio; N/A, not applicable; RDI, relative dose intensity; TTD, time to treatment discontinuation

Cabozantinib (Cabometyx®, Ipsen)

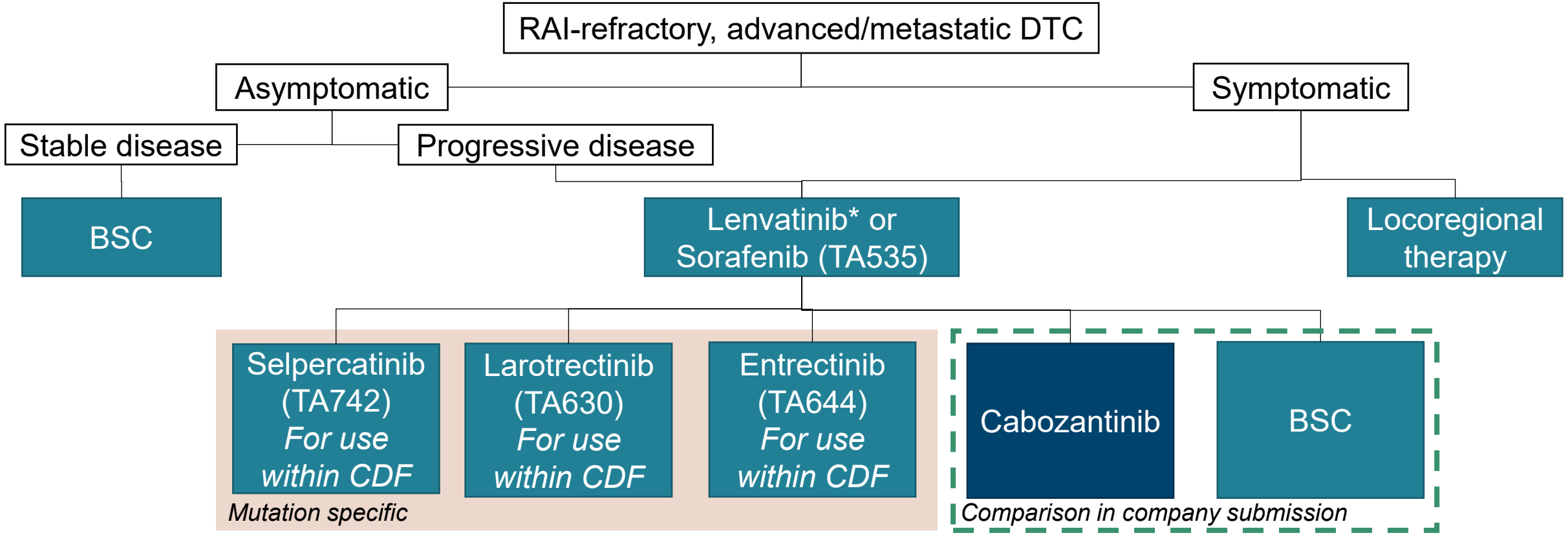
Technology details

Marketing authorisation	• Adult patients with locally advanced or metastatic DTC, refractory to or not eligible for RAI who have progressed during or after prior systemic therapy
Mechanism of action	• Cabozantinib is a multi-targeted inhibitor of RTKs, inhibiting several RTKs known to influence tumour growth, angiogenesis and cancer cell invasion or metastasis, including VEGFR2, RET, MET and AXL
Administration	• Oral administration • One 60 mg tablet to be taken once daily
Price	• List price: £5,143 per pack of 30 x 60 mg tablets • A simple patient access scheme discount is available

Abbreviations: AXL, growth arrest-specific protein 6 receptor; DTC, differentiated thyroid carcinoma; EMA, European Medicines Agency; MET, mesenchymal epithelial transition; MHRA, Medicines and Healthcare products Regulatory Agency; RAI, radioactive iodine; RET, rearranged during transfection; RTK, receptor tyrosine kinases; VEGFR2, vascular endothelial growth factor receptor 2

Treatment pathway

Company's revised base case positions cabozantinib as 2L treatment



*Some clinicians offer continued lenvatinib after progression but comparison to cabozantinib not included in final NICE scope or company submission. EAG considers there to be insufficient evidence to inform a reliable comparison

Is BSC the only relevant comparator? Should continued post-progression lenvatinib be considered as a potential comparator for 2L cabozantinib?

Abbreviations: 2L, second line; BSC, best supportive care; CDF, Cancer Drugs Fund; DTC, differentiated thyroid cancer; RAI, radioactive iodine

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial

Primary clinical evidence in company submission comes from COSMIC-311

	COSMIC-311 trial (XL184-311; NCT03690388)
Design	Phase 3, randomised, double-blind, controlled study
Population	Adults with RAI-refractory advanced DTC, who have progressed during or after previous systemic therapy
Intervention	Oral cabozantinib 60 mg once daily plus BSC (n=170; ITT, CCO2)
Comparator	Oral matched placebo once daily plus BSC (n=88; ITT, CCO2)
Median duration of follow-up	Primary CCO1 (data cut off 19 August 2020): 6.2 months Supportive CCO2 (data cut off 8 February 2021): 10.1 months
Primary outcomes	ORR, PFS
Key secondary outcomes	OS, DOR, time to objective response, safety and tolerability, HRQoL (EQ-5D-5L)
Locations	25 countries in Asia, North America, Europe, and the rest of the world
Used in model?	Yes

Crossover to open-label cabozantinib permitted upon radiographic PD (31% at CCO1 and 45% at CCO2)

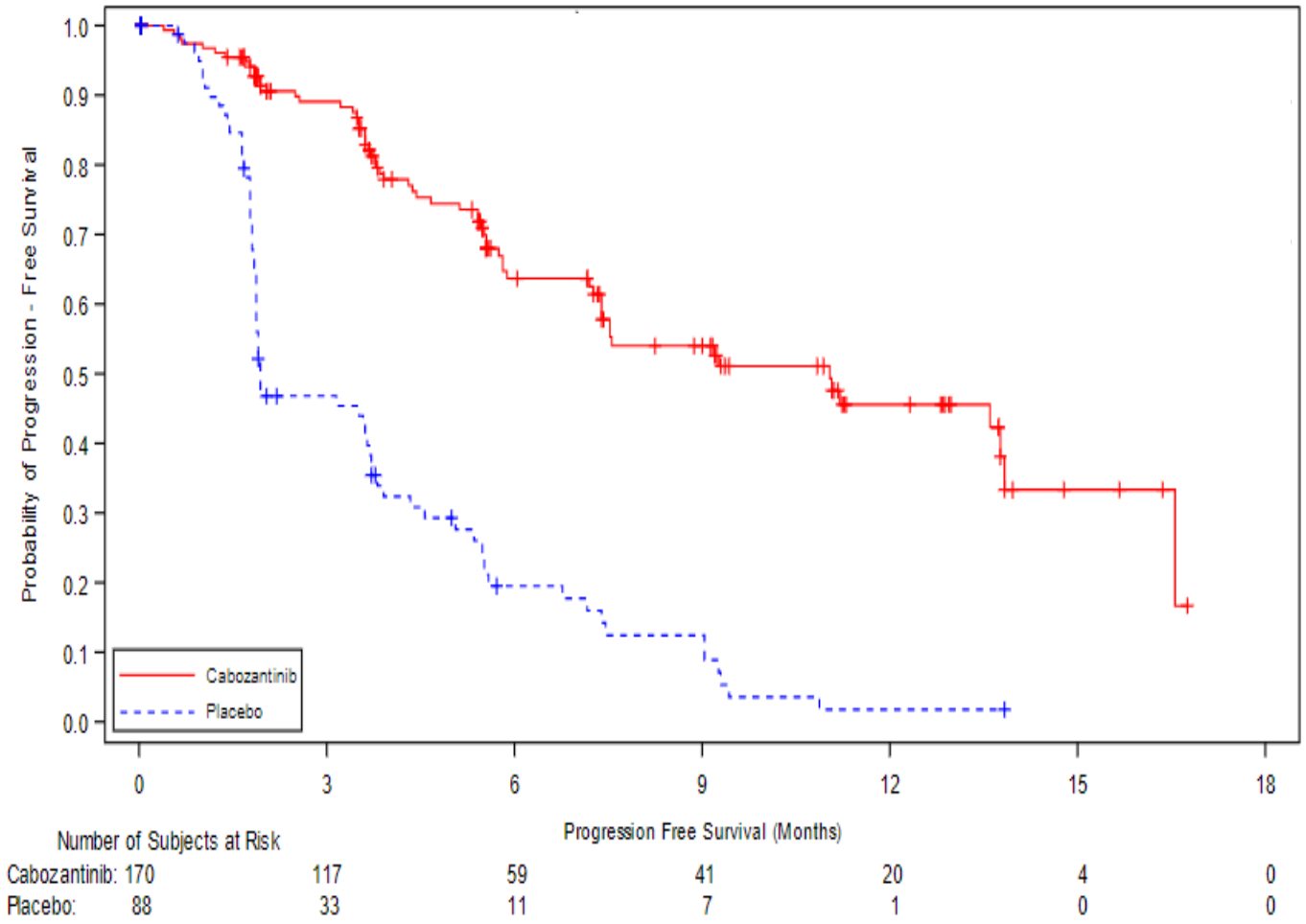
No planned further data-cuts

UK patients (CCO1): 4 in cabozantinib arm (3.2%) and 3 in placebo arm (4.8%)

Abbreviations: BSC, best supportive care; CCO, clinical cut-off; DOR, duration of objective response; DTC, differentiated thyroid carcinoma; EQ-5D-5L, EuroQoL-5-dimension with 5 levels; HRQoL, health-related quality of life; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD, progressed disease; PFS, progression free survival; RAI, radioactive iodine

COSMIC-311 results – PFS (ITT, CCO2)

Cabozantinib significantly extends PFS



	Cabozantinib (n = 170)	Placebo (n = 88)
Median PFS (months), 96% CI	11.0 (7.4, 13.8)	1.9 (1.9, 3.7)
HR (96% CI; stratified)	0.22 (0.15, 0.32)	
p-value (log-rank)	<0.0001	

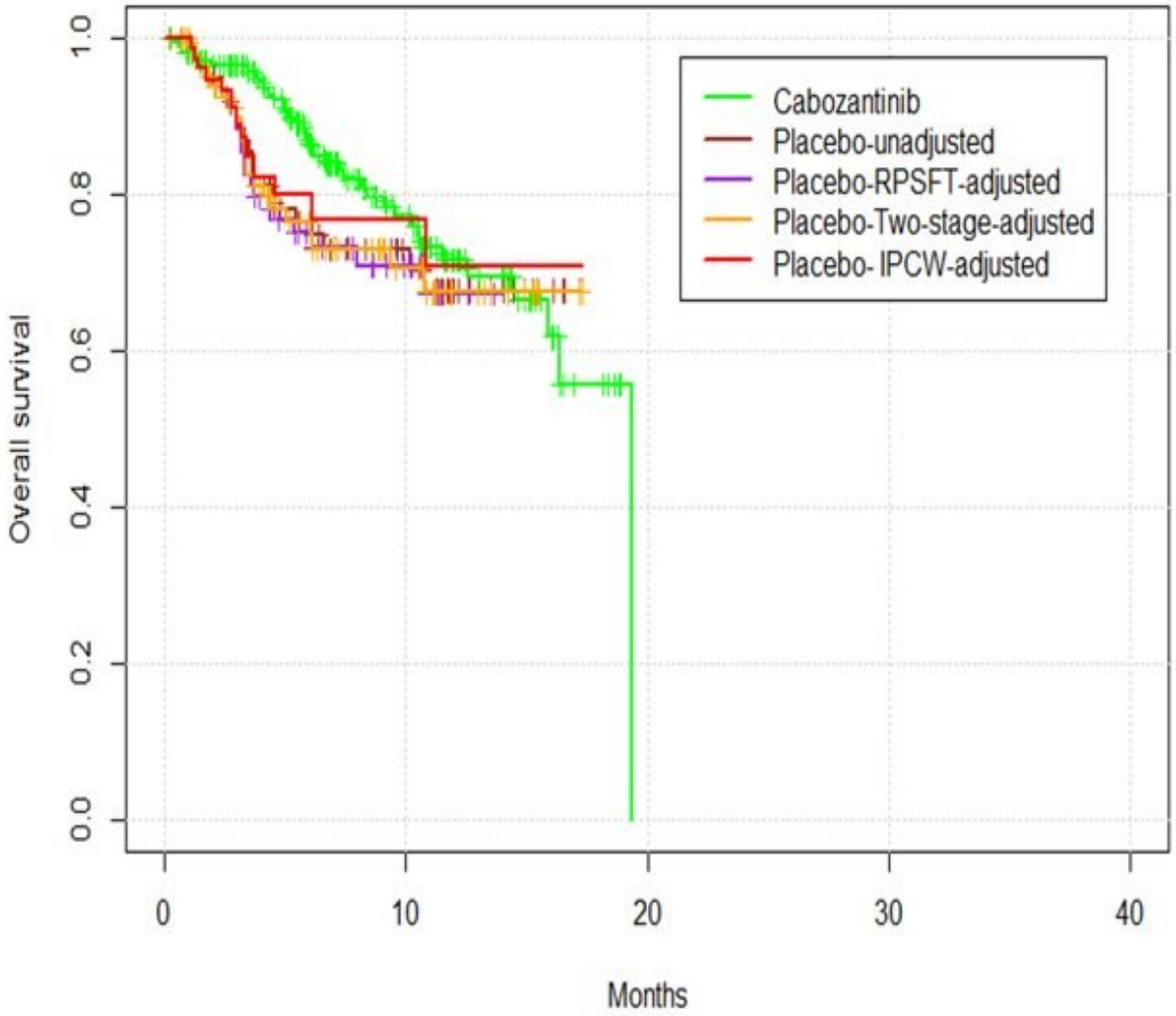
- Large proportion of patients had censored data (64% in cabozantinib arm, 22% in placebo arm)

NICE

Abbreviations: CCO, clinical cut-off; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; LR, log-rank test; PFS, progression-free survival

COSMIC-311 results – OS (ITT, CCO2) with crossover adjustment

Necessary to mitigate bias in OS results by adjusting for treatment switching in the placebo group



	Placebo-unadjusted	Placebo-RPSFT	Placebo-two-stage	Placebo-IPCW
Stratified HR (naïve 95% CI)	0.76 (0.45, 1.31)	0.65 (0.28, 1.53)	0.70 (0.41, 1.22)	0.68 (0.37, 1.27)
Mean survival, months	30.45	27.39	29.25	31.76

Background: 45% (n=40) of placebo arm switched to open-label cabozantinib upon progression

Company: Applied RPSFT in base case in line with previous NICE submissions, in particular TA535

- Difficulty justifying no unmeasured confounders assumption for IPCW and two-stage methods because limited covariates were included in the analysis
- IPCW may not be stable as only [redacted]
- [redacted]

EAG: RPSFT-adjusted data not very different from unadjusted data

NICE

Abbreviations: CCO, clinical cut-off; CI, confidence interval; HR, hazard ratio; IPCW, inverse-probability-of-censoring weighting; ITT, intention to treat; OS, overall survival; RPSFT, rank preserving structural failure time

Key issue: Population

Company's revised base case population at TE narrower than NICE scope

Background

- Company's ITT analysis reflected ITT population of COSMIC-311 (~76% previously received either sorafenib or lenvatinib and 24% received both)
- At TE, company's base case focused on a pure 2L population (only received 1 prior treatment)

Company

- Ideally receive positive NICE recommendation for whole population including second and subsequent lines
- 2L analysis performed to alleviate EAGs concern with application of 5-year death assumption in BSC arm
- 2L population demonstrates greater cost-effectiveness and unmet need in England and Wales

EAG comments

- 2L subgroup likely to better reflect population who would receive cabozantinib in the NHS in England
- Sample size reduced for 2L subgroup → greater uncertainty in model predictions
- Unclear how amending model population addresses uncertainty around model predictions for BSC
- Number of prior lines of therapy not a stratification factor in COSMIC-311 → unclear if treatment groups well balanced within 2L subgroup as 2L baseline characteristics not presented by company

Clinical experts

- Patients treated in NHS would not receive both lenvatinib and sorafenib
- COSMIC-311 conducted in exactly the setting in which we would plan to use this treatment in UK

NICE

Is the 2L subgroup of COSMIC-311 appropriate for decision making?

Abbreviations: 2L, second-line; BSC, best supportive care; ITT, intention to treat; TE, technical engagement

Comparison of 2L subgroup and ITT population, CCO2

Point estimates of HRs for PFS and OS between cabozantinib and BSC in 2L subgroup appear to be better than full ITT population

Population	Parameter	PFS		OS	
		Cabozantinib	Placebo	Cabozantinib	Placebo (RPSFT-adjusted)
2L subgroup (N=191)	Median duration (96% CI)	[redacted]	[redacted]	[redacted]	[redacted]
	HR (96% CI; stratified)		[redacted]		[redacted]
Full ITT population (N=258)	Median duration (96% CI)	11.0 (7.4, 13.8)	1.9 (1.9, 3.7)	19.4 (15.9, NE)	NE
	HR (stratified)		0.22 (0.15, 0.32)^		0.65 (0.28, 1.53)*

^ 96% CI; * inflated 95% CI

NICE

Abbreviations: 2L, second-line; BSC, best supportive care; CCO, clinical cut-off; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; NE, not estimatable; NR, not reported; OS, overall survival; PFS, progression-free survival; RPSFT, Rank-Preserving Structural Failure Time

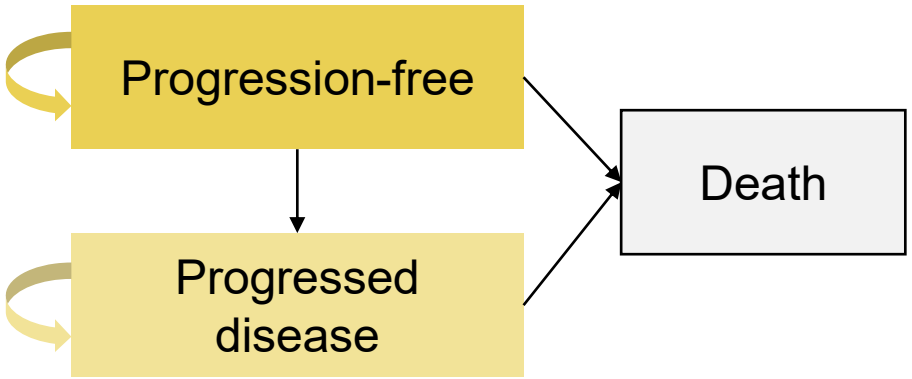
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

A three state partitioned survival model

Model structure



Technology affects **costs** by:

- Increasing overall costs due to acquisition cost of cabozantinib
- Increasing overall disease management costs due to extended OS
- Increasing costs associated with managing AEs

Technology affects **QALYs** by:

- Extending PFS
- Extending OS
- Increasing frequency of AEs

Assumptions with greatest **ICER** effect:

- Approach used to model OS in each treatment group
- Choice of utility values applied to progression-free and progressed disease health states
- Inclusion of post-progression cabozantinib costs

Abbreviations: AEs, adverse events; ICER, incremental cost effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year

How company incorporated evidence into model

EAG: company's model generally in line with Reference Case, except utility source

Input	Assumption and evidence source (company base case)
Baseline characteristics	COSMIC-311
Cabozantinib efficacy	COSMIC-311 (CCO2)
BSC efficacy – OS	2L model: COSMIC-311 (CCO2), with RPSFT adjustment
BSC efficacy - PFS	COSMIC-311 (CCO2)
Cabozantinib TTD	2L model: COSMIC-311 (CCO2), without PFS cap
Treatment effect waning	Constant treatment effect applied (no treatment waning)
Utilities	Health state utility values sourced from Fordham et al. 2015, with age-adjustment and adverse event disutilities
Costs	Resource use based on NICE TA742. Unit costs from NHS Reference Costs (2020-21), BNF, PSSRU and Georghiou et al. 2014 (end of life cost)

At TE, the company's revised base case population changed from the full ITT population to a pure 2L population

Abbreviations: 2L, second-line; BNF, British National Formulary; CCO, clinical cut-off; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; RPSFT, Rank Preserving Structural Failure Time; TE, technical engagement; TTD, time to treatment discontinuation

Key issue: Uncertainty around effect of cabozantinib on OS (1/4)

Long-term effect of cabozantinib on OS is highly uncertain

Background

- In company's 2L base case model, exponential functions are used to estimate OS for both treatment groups
- Clinical observations indicate that the exponential overestimates mean survival

	Cabozantinib			BSC		
	2 years	5 years	10 years	2 years	5 years	10 years
Mean of all clinical experts' estimates*	[redacted]					
Company's 2L model predictions	[redacted]					

*Includes company's and EAG's clinical advisors

Company:

- Unlikely to resolve uncertainty from current studies (no further planned data-cuts of COSMIC-311 beyond CCO2)
- All BSC OS functions overestimate mean survival expectations in later years
- Selected exponential function based on goodness of fit (AIC and BIC) and visual inspection

Abbreviations: 2L, second-line; AIC, Akaike information criterion; BIC, Bayesian Information Criterion; BSC, best supportive care; CCO, clinical cut-off; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; TE, technical engagement

Key issue: Uncertainty around effect of cabozantinib on OS (2/4)

EAG assessment of OS modelling

EAG comments

- EAG has several concerns regarding the OS modelling:
  - The exponential assumes PH, but the survival data from the trial indicates that the treatment effect for cabozantinib over BSC reduces over time (survival curves coming together)
  - EAG notes that more flexible parametric models would likely result in the OS curves for cabozantinib and BSC crossing, which is at odds with clinical expectations

- EAG explored 3 alternative approaches to modelling OS → ICER increased in scenario analyses
  1. EAG-preferred model (exponential) + treatment effect waning at 3 years
  2. Hybrid KM plus exponential tail after 12 months
  3. Hybrid KM plus BSC exponential tail after 12 months
- EAG noted that no analyses presented by them or the company are ideal
  ↳ See next slide

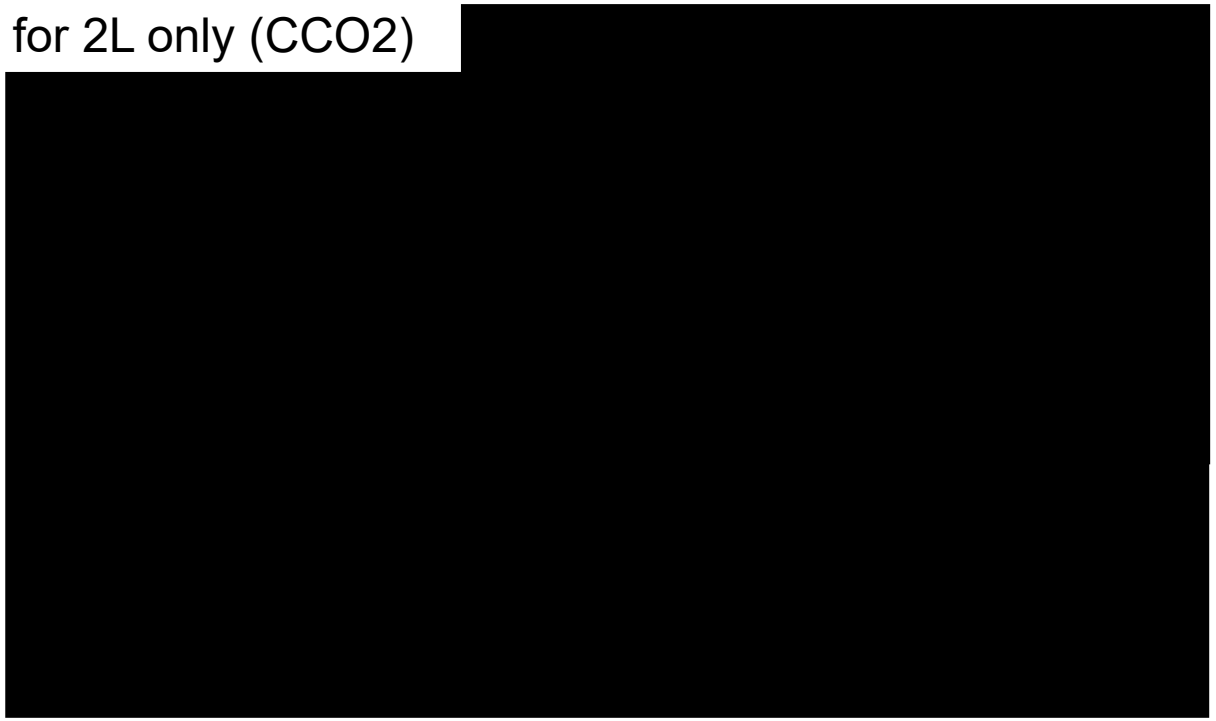
- Longer COSMIC-311 follow-up would help reduce uncertainty in OS estimates but no more data-cuts planned

Abbreviations: 2L, second-line; BSC, best supportive care; CCO, clinical cut-off; HR, hazard ratio; ICER, incremental cost effectiveness ratio; ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; TE, technical engagement

Key issue: Uncertainty around effect of cabozantinib on OS (3/4)

Alternative functions for modelling OS

Cabozantinib OS functions for 2L only (CCO2)



BSC OS functions for 2L only (CCO2)

EAG:

- Exponential is a poor fit for observed OS data and assumes PH
- Probably not possible to identify a fully parametric survival model which (i) provides good representation of underlying hazards and (ii) is clinically plausible

Abbreviations: 2L, second-line; BSC, best supportive care; CCO, clinical cut-off; KM, Kaplan-Meier; OS, overall survival; PH, proportional hazards

Key issue: Uncertainty around effect of cabozantinib on OS (4/4)

Clinical opinion regarding long-term effect of cabozantinib on OS

Company's clinical advisors:

- Not plausible that survivor functions for OS for cabozantinib and BSC would cross

Clinical experts (in response to technical engagement):

- Data regarding effect of this treatment on OS are difficult to interpret for all the reasons raised in EAG report, although there is likely to be a benefit for this group who otherwise have an extremely poor prognosis
- In the company's scenario analysis, there is an attempt to correct for the overestimated OS on BSC through applying a vertical drop in survival at 5 years
  - As indicated by the EAG this is not plausible, but neither is it that 10% of patients who progressed on lenvatinib and not received further treatment are still alive at 5 years
- Patients on BSC most likely to die within 3-5 years of disease progression. However, plausible that patients surviving >5 years may have different tumour biology characteristics
- Plausible cabozantinib continues to have same benefit compared to BSC for full duration of model, though in reality patients with radioiodine refractory, metastatic DTC unlikely to survive that long
- A fundamental problem is limited data to model OS, especially in BSC arm of COSMIC-311
  - Few patients, very short follow up for the majority make modelling OS difficult and lacking credibility

Company and EAG both use exponential models, though EAG notes that this has limitations and long-term effect of cabozantinib on OS is highly uncertain – what approach is appropriate for modelling OS?

Abbreviations: BSC, best supportive care; DTC, differentiated thyroid cancer; OS, overall survival

Key issue: Utilities (1/2)

Company prefers Fordham et al. adjusted utilities, EAG prefers unadjusted values

Background

- Company's base case model used utility values from Fordham et al. based on an adjusted regression analysis, in preference to mapped EQ-5D-5L data collected in COSMIC-311
- In addition, the EAG identified an error whereby general population utility cap had been overwritten in company's model. EAG corrected this error in all exploratory analyses undertaken by them

Utility values

	Fordham et al.		COSMIC-311	DECISION (TA535)	
	Adjusted	Unadjusted		TKI	BSC
PF	0.87	0.80	[redacted]	0.72	0.80
PD	0.52	0.50	N/A		0.64

Company

- Lack of validity in COSMIC-311 HRQoL as data collection stopped shortly after progression
- Agrees age-adjusted general population utility cap should be applied
- Adjusted utility values closer to those expected from a more normative UK sample

Abbreviations: BSC, best supportive care; EQ-5D-5L, EuroQoL-5-dimension with 5 levels; HRQoL, health related quality-of-life; N/A, not applicable; PD, progressed disease; PF, progression-free; TE, technical engagement; TKI, Tyrosine kinase inhibitor; TTO, time trade-off

Key issue: Utilities (2/2)

Company prefers Fordham et al. adjusted utilities, EAG uses unadjusted values

EAG comments

- Unadjusted Fordham et al. utilities applied in 3 previous NICE appraisals without trial EQ-5D data (TA516, TA550 and TA742)
- Agrees COSMIC-311 EQ-5D-5L data are limited but reasonable to consider, at least in sensitivity analyses
- Utility values deviate from NICE reference case as they were obtained from the Fordham et al. general population TTO study in preference to the EQ-5D-5L data collected in COSMIC-311
- That the company's PF utility value (0.87) is higher than that of the general population (0.82) lacks face validity
- Other HRQoL concerns:
  - Mean duration of AEs ([redacted] days) > duration of AE-related QALY losses (1 month) applied in company's model → may underestimate negative impact of treatment-related AEs
  - In TA535, treatment-specific utility values used to reflect lower HRQoL for patients receiving TKIs

EAG's clinical advisors

- Decrement associated with progression of 0.35 estimated by Fordham et al. is plausible

Clinical experts

- Agree with EAG not plausible this group of patients could have a higher utility value than UK general population
- More appropriate to use utility values collected in COSMIC-311
  - ↳ Patients in prior studies were receiving 1L and may have had lower symptom burden than 2L

Which utility values are appropriate?

Abbreviations: 1L, first-line; 2L, second-line; AE, adverse event; EQ-5D-5L, EuroQoL-5-dimension with 5 levels; HRQoL, health related quality-of-life; PF, progression-free; QALY, quality-adjusted life year; TKI, Tyrosine kinase inhibitor; TTO, time trade-off

Key issues: Resource use and costs

Issues relating to resource use and costs have small impact on ICER

Issue	Company model	EAG comments

Monitoring cost assumptions	• ECGs applied every 6 months for patients receiving cabozantinib
	• CT scans included for all patients receiving BSC
		• Explored in scenario analyses:
		  • ECG costs doubled
		  • CT scan costs for BSC removed
		• ICER not sensitive to these parameters

Concomitant medication costs	• Company's model does not include costs of concomitant therapies given as part of BSC in COSMIC-311
	  • Receipt was balanced between treatment arms
	  • Data only available for CCO1
		• Preferred company to have included costs
		• Minimal impact on ICER

Drug cost adjustments	• Drug costs should be adjusted using RDI (average amount of planned dose received) • Compliance estimate based on CCO1, RDI estimate is available from CCO2	• Prefers adjustment using compliance (proportion of days on which patients received treatment)

Abbreviations: BSC, best supportive care; CCO, clinical cut-off; CT, computerised tomography; ECG, electrocardiogram; ICER, incremental cost effectiveness ratio; RDI, relative dose intensity

Key issue: Post-progression cabozantinib costs (1/2)

Background

- In COSMIC-311, patients unmasked at radiographic PD in cabozantinib arm could continue to receive open-label cabozantinib (1.6% at CCO1 and 6.5% at CCO2 in ITT population)
- At TE, company agreed post-progression cabozantinib should be included in line with licence
  - ↳ Company presented revised TTD curve using generalised gamma
  - ↳ EAG's preferred analysis used Weibull model for TTD, without PFS cap

Company

- SmPC for cabozantinib: "patients should continue treatment until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs" (PFS is a proxy)
- Generalised gamma distribution has lowest AIC and BIC and best fit to KM compared with Gompertz

EAG comments

- Wording of SmPC not a strong rationale for assuming TTD must be similar to PFS
- Generalised gamma provides notably worse fit than other functions (including exponential, Weibull and Gompertz) when judged according to BIC
- Generalised gamma below PFS at all timepoints, implying no patient receives post-progression cabozantinib

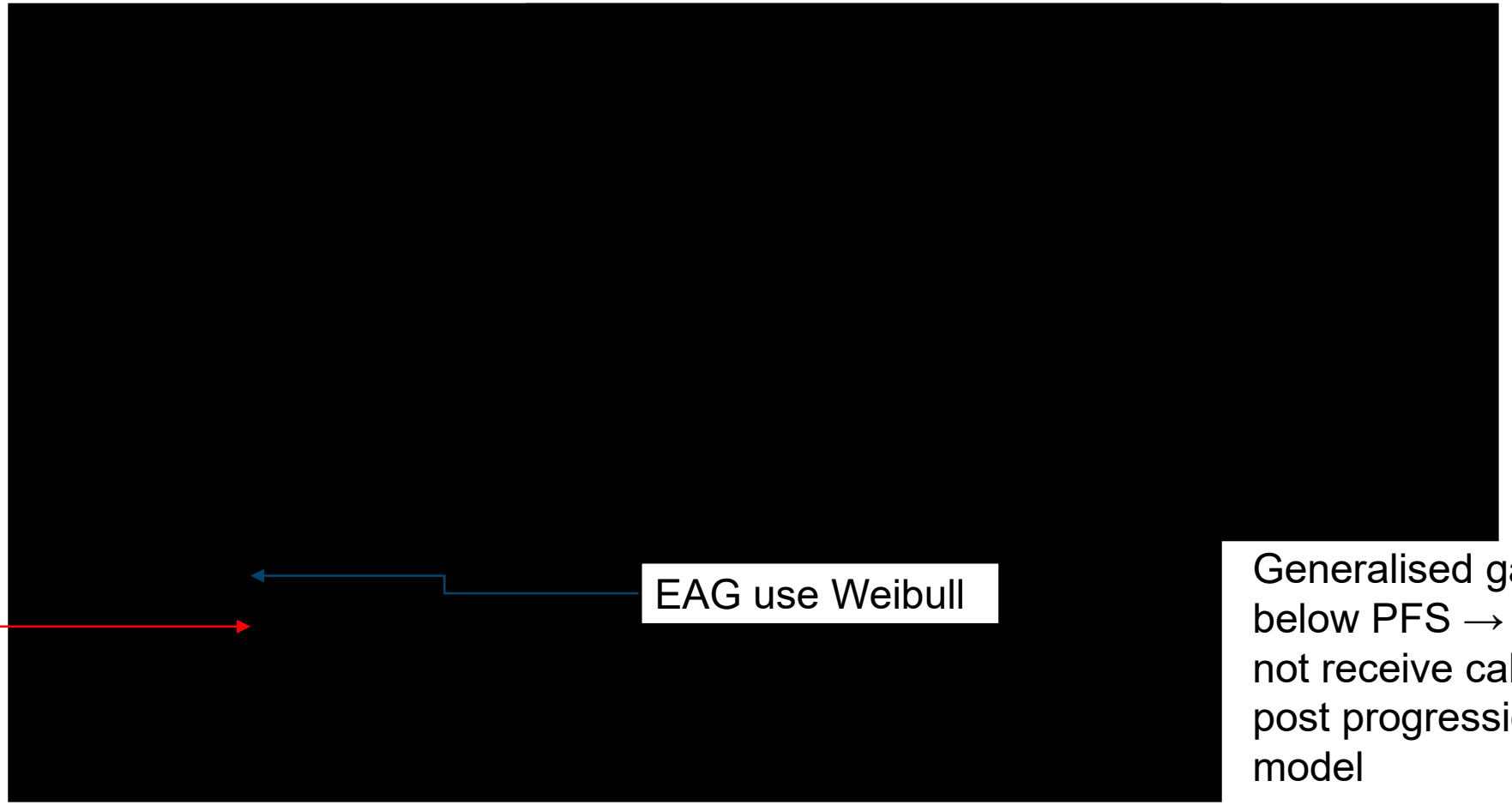
Clinical experts: Post-progression cabozantinib costs should be included as, in absence of other treatment lines, it is likely patients will continue cabozantinib for as long as they are considered to be deriving clinical benefit

Abbreviations: 2L, second-line; AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria; CCO, clinical cut-off; ITT, intention to treat; KM, Kaplan-Meier; PD, progressed disease; PFS, progression-free survival; SmPC, Summary of Product Characteristics; TE, technical engagement; TTD, time to treatment discontinuation

Key issue: Post-progression cabozantinib costs (2/2)

Comparison of modelled TTD and PFS for 2L, CCO2

Company apply generalised gamma



EAG use Weibull

Generalised gamma below PFS → patients do not receive cabozantinib post progression in the model

Company uses generalised gamma, EAG says exponential or Weibull may be more appropriate – which is more plausible?

Abbreviations: 2L, second-line; CCO, clinical cut-off; ITT, intention to treat; PFS, progression-free survival; TE, technical engagement; TTD, time to treatment discontinuation

Summary of company and EAG preferred assumptions

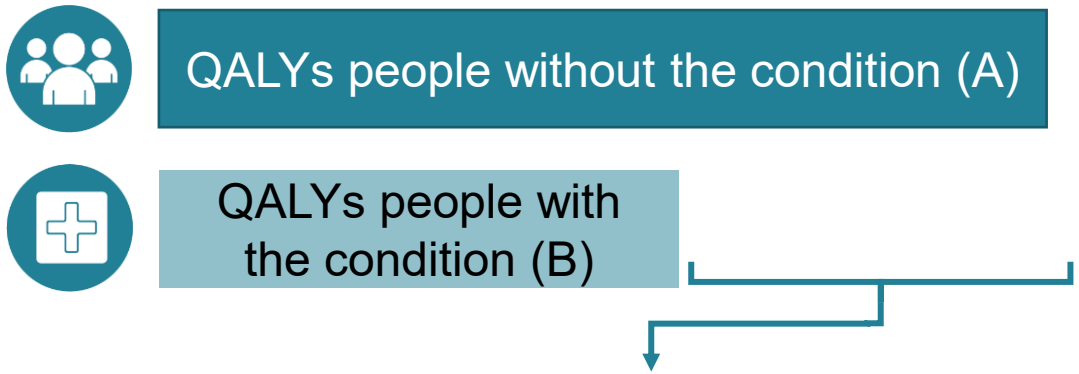
ICER particularly sensitive to alternative assumptions regarding OS

Assumption		Company's TE base case	EAG's preferred model
Population		2L	2L (with caveats for limitations in the 2L subgroup)
PFS	Cabozantinib	Weibull	Weibull
	BSC		
OS	Cabozantinib	Exponential	Exponential
	BSC	Exponential (RPSFT-adjusted)	Exponential (RPSFT-adjusted)
TTD	Cabozantinib	Generalised gamma	Weibull
	PFS cap	No	No
Cabozantinib drug costs	Adjustment	RDI	Compliance (as in company's ITT model)
	Wastage	Included	Included
Health state utility	Source	Fordham et al. (adjusted values)	Fordham et al (unadjusted values)
	Gen. pop. cap	Included (EAG corrected analysis)	Included

Abbreviations: 2L, second-line; BSC, best supportive care; Gen. pop., general population; ICER, incremental cost effectiveness ratio; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; RPSFT, rank-preserving structural failure time; TTD, time to treatment discontinuation

QALY weightings for severity (1/2)

New severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

QALY weightings for severity (2/2)

Background

- In its original submission, company concluded locally advanced or metastatic DTC patients, refractory or not eligible to RAI who have progressed during or after prior systemic therapy qualify for a 1.2 severity modifier
- Calculated using the York QALY shortfall calculator:
  - Trial baseline characteristics: 47% male, 65 year starting age (COSMIC-311 ITT, CCO2)
  - Utilities for people with the condition: PFS = 0.87, PD = 0.52 (Fordham et al)
- A severity modifier of 1.2 was also suggested across all EAG analyses, including for 2L
- Results are presented both with and without QALY weighting using a decision modifier of 1.2

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment	**Absolute QALY shortfall (has to be >12)**	**Proportional QALY shortfall (has to be >0.85)**
Company original base case	[redacted]	[redacted]*	[redacted]	[redacted]

*Total probabilistic BSC QALYs in EAG's preferred model are [redacted]. This does not affect the resulting shortfall or 1.2 QALY weighting for severity

Does the committee agree it is appropriate to apply a QALY weighting for severity?

Abbreviations: 2L, second-line; CCO, clinical cut-off; DTC, differentiated thyroid cancer; ITT, intention to treat; QALY, quality-adjusted life year; PD, progressed disease; PFS, progression-free survival; RAI, radioactive iodine

Company base case results (1/2)

Company's base case at technical engagement (2L)

Deterministic base case results

Technology	DM	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (excluding weighting)	ICER excluding QALY weighting (£/QALY)	ICER including QALY weighting (£/QALY)
BSC	1.2	[redacted]	[redacted]				
Cabozantinib		[redacted]	[redacted]	[redacted]	[redacted]	23,050^	19,208*

^ICER without QALY weighting, including EAG's error correction (general population utility cap) was £24,199/QALY

*ICER with QALY weighting, including EAG's error correction (general population utility cap) was £20,166/QALY

Probabilistic base case results

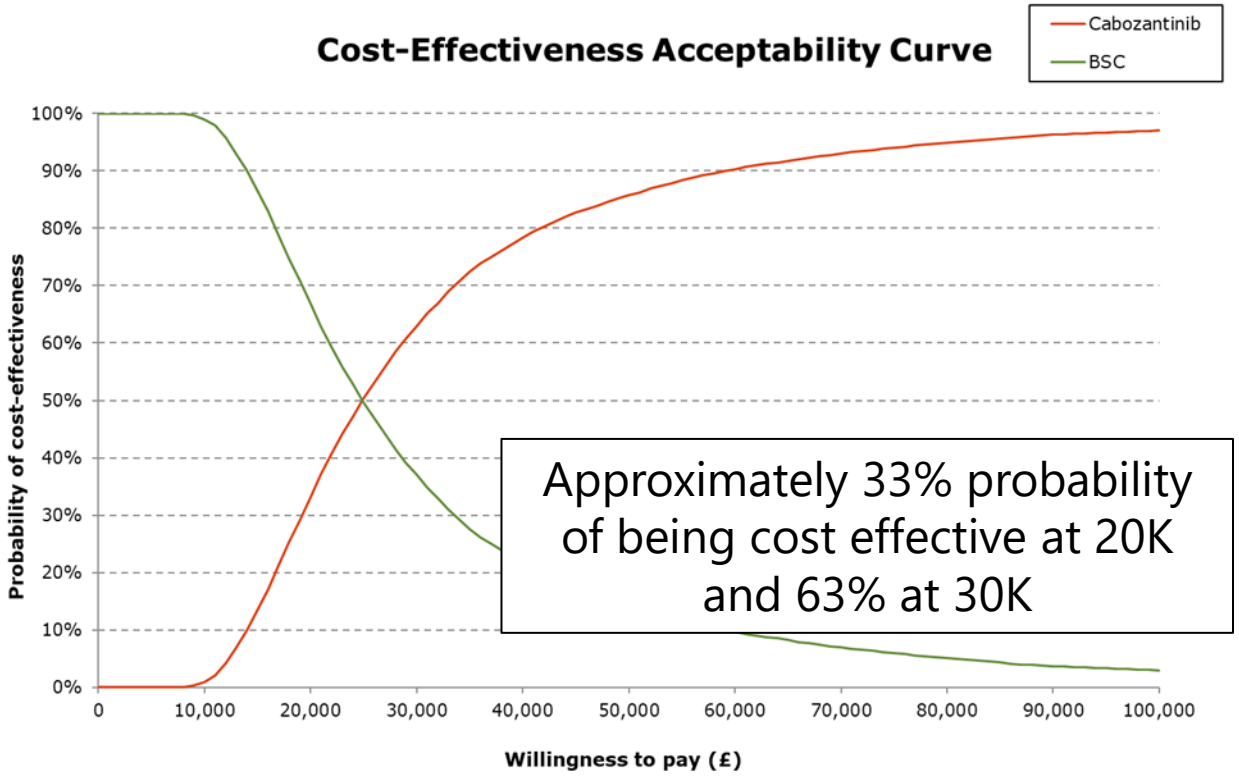
Technology	DM	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (excluding weighting)	ICER excluding QALY weighting (£/QALY)	ICER including QALY weighting (£/QALY)
BSC	1.2	[redacted]	[redacted]				
Cabozantinib		[redacted]	[redacted]	[redacted]	[redacted]	25,081	20,867

Abbreviations: 2L, second-line; BSC, best supportive care; DM, decision modifier; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

Company base case results (2/2)

Company's base case at technical engagement (2L)*

[redacted]



Results shown in incremental cost-effectiveness plane include QALY weighting

Results shown in cost-effectiveness acceptability curve exclude QALY weighting

*The results do not include the EAG's error correction for capping general population utility values. The company did not state if these values included the QALY weighting.

Abbreviations: 2L, second-line; BSC, best supportive care; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year

Company probabilistic scenario analysis

Scenario analyses for company's 2L base case model

No.	Scenario (applied to company base case)	Incremental costs (£) versus BSC	Incremental life years versus BSC	Incremental QALYs versus BSC (excluding weighting)	ICER excluding QALY weighting (£/QALY)	ICER including QALY weighting (£/QALY)
1	Company base case	[redacted]	[redacted]	[redacted]	25,081	20,867
2	Compliance	[redacted]	[redacted]	[redacted]	NR	23,308
3	5-year OS constraint for BSC	[redacted]	[redacted]	[redacted]	NR	19,015
4	OS curve: lognormal	[redacted]	[redacted]	[redacted]	NR	15,049
5	OS curve: Log-logistic	[redacted]	[redacted]	[redacted]	NR	22,221
6	PFS curve: lognormal	[redacted]	[redacted]	[redacted]	NR	17,474
7	PFS curve: Generalised gamma	[redacted]	[redacted]	[redacted]	NR	19,552
8	TTD curve: Exponential	[redacted]	[redacted]	[redacted]	NR	21,336
9	TTD curve: Gompertz	[redacted]	[redacted]	[redacted]	NR	10,122*

*Deterministic ICER including QALY weighting was £19,037/QALY

Abbreviations: 2L, second-line; BSC, best supportive care; ICER, incremental cost effectiveness ratio; NR, not reported; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year; TTD, time to discontinuation

EAG preferred analysis results

Analyses undertaken in 2L

Deterministic preferred analysis results

Technology	DM	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (excluding weighting)	ICER excluding QALY weighting (£/QALY)	ICER including QALY weighting (£/QALY)
BSC	1.2	[redacted]	[redacted]				
Cabozantinib		[redacted]	[redacted]	[redacted]	[redacted]	30,218	25,181

Probabilistic preferred analysis results

Technology	DM	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (excluding weighting)	ICER excluding QALY weighting (£/QALY)	ICER including QALY weighting (£/QALY)
BSC	1.2	[redacted]	[redacted]				
Cabozantinib		[redacted]	[redacted]	[redacted]	[redacted]	31,015	25,878

Abbreviations: 2L, second-line; BSC, best supportive care; DM, decision modifier; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

EAG deterministic scenario analysis (2L)

Analyses undertaken in 2L

No.	Scenario (applied to EAG preferred analysis)	DM	Incremental costs (£) versus BSC	Incremental life years versus BSC	Incremental QALYs versus BSC (excluding weighting)	ICER excluding QALY weighting (£/QALY)	ICER including QALY weighting (£/QALY)
1	EAG preferred analysis	1.2	[redacted]	[redacted]	[redacted]	30,218	25,181
2	Exponential OS with treatment effect waning at 3 years	1.2	[redacted]	[redacted]	[redacted]	39,157	32,630
3	Hybrid KM + exponential tail after 12 months, constant HR	1.2	[redacted]	[redacted]	[redacted]	31,084	25,904
4	Hybrid KM + exponential tail after 12 months, BSC hazard rate in both groups	1.2	[redacted]	[redacted]	[redacted]	59,448	49,540
5	COSMIC-311 utility value in progression-free state	1.2	[redacted]	[redacted]	[redacted]	33,840	28,200
6	DECISION trial utility values	1.2	[redacted]	[redacted]	[redacted]	31,617	26,348
7	AE QALY losses doubled	1.2	[redacted]	[redacted]	[redacted]	30,514	25,429
8	ECG costs doubled	1.2	[redacted]	[redacted]	[redacted]	30,684	25,570
9	CT scan costs removed for BSC	1.2	[redacted]	[redacted]	[redacted]	30,203	25,169

Abbreviations: 2L, second-line; AE, adverse event; BSC, best supportive care; CT, computerised tomography; DM, decision modifier; ECG, electrocardiogram; HR, hazard ratio; ICER, incremental cost effectiveness ratio; KM, Kaplan-Meier; OS, overall survival; QALY, quality adjusted life year

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Other considerations:

- Company state that no further data cuts from COSMIC-311 are planned
- The company are not proposing a managed access agreement

NICE National Institute for Health and Care Excellence

Thank you.

© NICE 2023. All rights reserved. Subject to Notice of rights.