Public observer slides – ACIC information redacted

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

Technology appraisal committee D [11 May 2023]

Chair: Stephen Smith

External assessment group: ScHARR

Technical team: Rachel Ramsden, Caron Jones, Jasdeep Hayre

Company: Ipsen

Background on thyroid cancer

RECAP

Causes

- Often unknown, but risk factors include age, genetics and exposure to risk factors

Epidemiology

- ~3,900 new thyroid cancer cases/year in UK; median age of diagnosis is 45-49 years

Diagnosis and classification

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

Treatment options

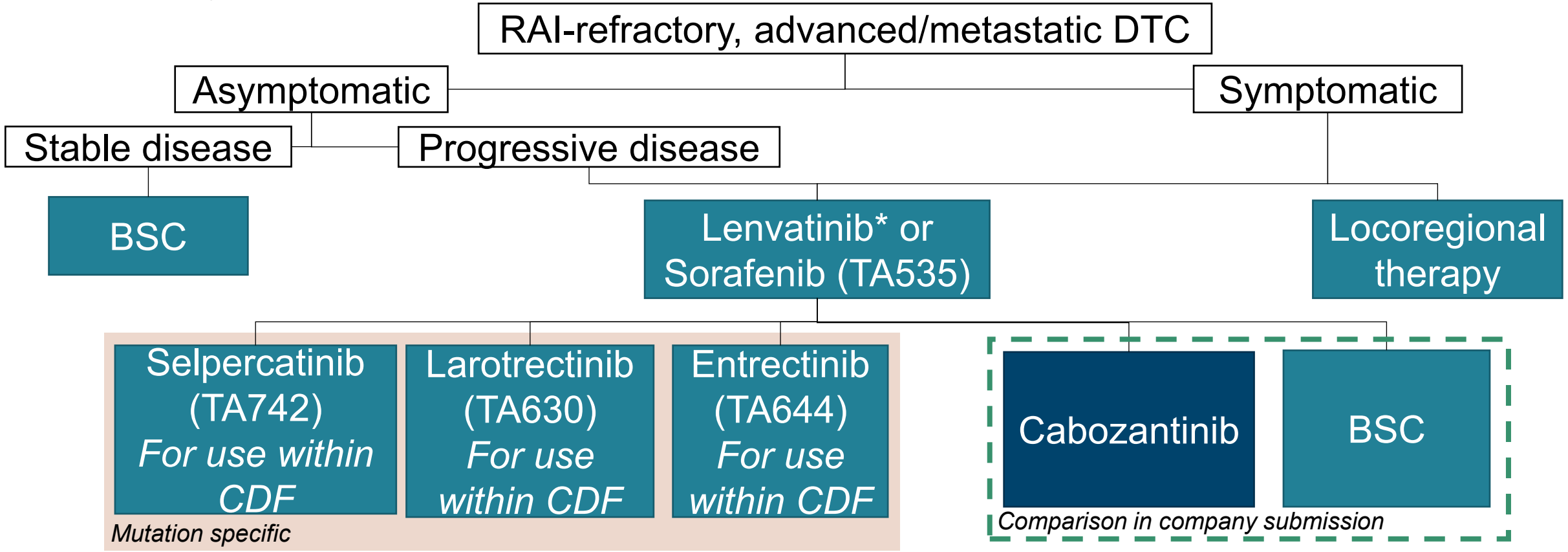
- No active treatment currently available for previously treated DTC unsuitable for or refractory to RAI

NICE

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

Treatment pathway

Company positions cabozantinib as 2L treatment



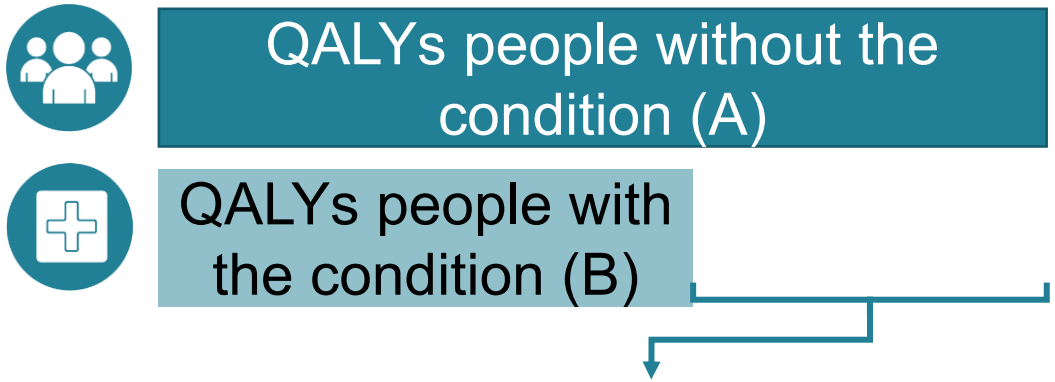
*Some clinicians offer continued lenvatinib after progression but comparison to cabozantinib not included in final NICE scope or original company submission. EAG considers there to be insufficient evidence to inform a reliable comparison

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

RECAP

QALY weightings for severity

New severity modifier calculations and components:



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

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

Draft guidance 3.11: Committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate

Abbreviations: QALY, quality-adjusted life year

Draft guidance

Recommendation (routine use): Cabozantinib is not recommended, within its marketing authorisation, for treating locally advanced or metastatic DTC that is unsuitable for or refractory to RAI, and that has progressed after systemic treatment, in adults

Why the committee made this decision:

- Effect of cabozantinib on OS is uncertain (DG 3.4)
- Uncertain if OS modelling extrapolations done by the company or EAG reflected the true long-term benefit of cabozantinib on OS (DG 3.7)
- ICER for committee's preferred assumptions was at higher end of range considered to be a cost-effective use of NHS resources. Committee preferred to see it towards lower end of the range, because of the uncertainty

Recommendation (managed access): Managed access could not be considered

Why the committee made this decision:

- Company not planning further data collection from COSMIC 311 and so did not submit an application for managed access (DG 3.15)

Consultation responses received from Ipsen (company) and NCRI-ACP-RCP-RCR (professional group)

Abbreviations: DG, draft guidance; DTC, differentiated thyroid cancer; ICER, incremental cost-effectiveness ratio; OS, overall survival; RAI, radioactive iodine

Summary of NCRI-ACP-RCP-RCR response

Theme	NCRI-ACP-RCP-RCR comments
Reduction in symptoms and healthcare resource use at 2L	• COSMIC-311 demonstrated significant PFS in 2L • Patients who progress on 1L treatment are more likely to develop symptoms that will require courses of radiotherapy, admission to hospital, and input from supportive care clinics • Treatment with cabozantinib after 1L treatment may therefore alleviate these symptoms and in turn reduce the burden on other healthcare services
CDF	• Understand it is very difficult to comment on any benefit in OS and, consequently, cost effectiveness due to discontinuation of COSMIC-311 follow up • If NICE approved cabozantinib in the CDF, more data could be collected to help address this uncertainty

Abbreviations: 1L, first line; 2L, second line; ACP, Association of Cancer Physicians; CDF, Cancer Drugs Fund; NCRI, National Cancer Research Institute; OS, overall survival; PFS, progression free survival; RCP, Royal College Of Physicians; RCR, Royal College of Radiologists

Addressing committee's preferred assumptions (DG 3.14)

Theme	Committee's preferred assumption	Company's DG response model	Aligned?
COSMIC-311 population	2L subgroup	2L subgroup	Yes
OS models	Exponential	Blended survival	No
Health state utility	PF: COSMIC-311 ([redacted]) PD: unadjusted Fordham et al. (0.50)	PF: COSMIC-311 ([redacted]) PD: COSMIC-311 ([redacted])	No
TTD model	Weibull	Weibull	Yes
Cabozantinib cost adjustment	Compliance	RDI	No

Committee's preferred deterministic ICER = £28,200/QALY gained (including 1.2 QALY weighting)

Abbreviations: 2L, second line; DG, draft guidance; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PF, progression-free; QALY, per quality-adjusted life year; RDI, relative dose intensity; TTD, time to treatment discontinuation

Summary of company DG response and EAG critique (1/4)

DG section	Company comments	EAG comments
3.2 - continued lenvatinib post-progression	• Explored the addition of a continued lenvatinib cost applied to the BSC arm for 4 cycles (TTD curve followed PFS curve) in scenario analysis	• Analysis does not consider additional health gains that continued TKI therapy after progression may provide • Analysis is likely biased in favour of cabozantinib and should be disregarded

Abbreviations: BSC, best supportive care; DG, draft guidance; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation

Summary of company DG response and EAG critique (2/4)

DG section	Company comments	EAG comments

3.7 – modelling OS	• Included blended survival analysis (2L) for both the cabozantinib and BSC arms in new base case
	  • Reduces uncertainty
	  • Closer to expert estimates for both cabozantinib and BSC, than exponential parametric curve (no blended analysis)
		• Blended model not a good fit to RPSFT-adjusted OS data
		  • Unsure if implemented correctly
		• Blended model does not reduce uncertainty
		  • Substantial uncertainty around OS gains cannot be resolved without additional data collection
		• Maintains none of the analyses presented by the company or EAG are ideal
		• OS benefit for cabozantinib highly uncertain

Abbreviations: 2L, second-line; BSC, best supportive care; DG, draft guidance; OS, overall survival; RPSFT, rank-preserving structural failure time

Company's blended survival analysis for OS

Mean blended survival curve for cabozantinib and BSC (company base case)

[redacted]

EAG:

- Blended OS overestimated for cabozantinib after ~16 months and underestimated for BSC after ~6 months
- Blended OS and exponential appear optimistic, suggesting an increasing & prolonged separation of OS between treatment groups (appears inconsistent with what was observed in trial)

	Cabozantinib			BSC		
	2 years	5 years	10 years	2 years	5 years	10 years
Mean of all clinical experts' estimates*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's base case (blended analysis)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential parametric curve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Includes company's and EAG's clinical advisors

Abbreviations: BSC, best supportive care; KM, Kaplan-Meier; OS, overall survival

Summary of company DG response and EAG critique (3/4)

DG section	Company comments	EAG comments
3.8 – utility values	• Committee's preference to combine TTO vignette study data (Fordham et al.) and EQ-5D data not a clinically accurate reflection of the impact of cabozantinib • New base case includes COSMIC-311 values for both PF and PD states • Presented scenario analysis using utility values from DECISION	• COSMIC-311 utilities suggest progression gives negligible loss in HRQoL (lacks clinical plausibility) • Concerns with COSMIC-311 PD utility reported in company's original submission and advisory board: • Potential presence of informative censoring, selection bias and likelihood not representative of mean utility over remaining survival time • Most reasonable approach is to use Fordham et al. to inform PD utility

	Fordham et al. (unadjusted)	COSMIC-311	DECISION (TKI)	DECISION (BSC)
PF	0.80	[redacted]	0.72	0.80
PD	0.50	[redacted]		0.64

Abbreviations: BSC, best supportive care; DG, draft guidance; EQ-5D, EuroQoL-5-dimension; HRQoL, health-related quality of life; PD, progressed disease; PF, progression-free; TKI, tyrosine kinase inhibitor; TTO, time trade-off

Concerns cited in the company submission and advisory board meeting minutes

1. “…the limited impact on utility associated with progression does not appear to be consistent, given the difference between PFS and PD states observed in other models and appraisals in advanced thyroid cancer, this inconsistency was also validated by UK clinicians in a recent advisory board.” (CS, Section 3.4.1, page 107)
2. "The limited impact of progression in the COSMIC-311 data was likely a result of limited follow-up in the PD state or missing data" (CS, Section B.3.4.1, page 106)
3. "…it is likely that the PD value from the COSMIC-311 trial is not fully reflective of the PD state as a whole…" (CS, Section B.3.4.1, page 107)
4. "Due to this lack of validity of the COSMIC-311 HRQoL data…" (CS, Section B.3.4.1, page 108).
5. [redacted] (company’s advisory board meeting minutes,13 page 15)
6. [redacted] (company’s advisory board meeting minutes,13 page 15).

Abbreviations: CS, company submission; HRQoL, health-related quality of life; PD, progressed disease; PFS, progression-free survival

Summary of company DG response and EAG critique (4/4)

DG section	Company comments	EAG comments

3.10 - cabozantinib drug cost adjustment	• RDI is most appropriate method due to:
	  • uncertainty around validity of the compliance figure
	  • consistency with past NICE appraisals (TA535 and TA849)
	• Compliance in COSMIC-311 may overestimate cost, based on RDI of cabozantinib in a real world study < RDI in clinical trial in RCC
		• Given flat pricing structure for cabozantinib, adjusting by RDI underestimates cabozantinib costs but adjusting by compliance does not
		• Compliance estimates reported in CSRs for CCO1 and CCO2 are similar (values differ slightly from value used in model)
		• This issue not being fully pursued in past appraisals is not sufficient justification for inappropriate use of RDI adjustment in the current appraisal
		• Real-world study in RCC refers to overestimation of RDI rather than compliance, and does not consider that taking less cabozantinib in practice may lead to lower comparative effectiveness than observed in a clinical trial setting

Abbreviations: CCO, clinical cut-off; CSR, clinical study report; DG, draft guidance; RCC, renal cell cancer; RDI, relative dose intensity

Summary of other company responses (1/2)

Theme	Company comments	EAG comments
Severity weighting	• Lack of transparency in new severity QALY weighting concept limits discussion from those without HEOR knowledge • Cabozantinib would have met the previously adopted EoL criteria and thus qualified for a decision making threshold of £50,000 per QALY	• Severity modifier applied in line with NICE Methods Manual by both the company and EAG and has been accounted for in the draft recommendation (DG 3.11) • Unclear if cabozantinib would have satisfied the EoL criteria given the difficulty in robustly estimating the OS benefit of cabozantinib • Company and EAG are aware that the 2022 NICE Methods Manual applies to this appraisal

Abbreviations: 2L, second line; DG, draft guidance; EoL, end of life; HEOR, health economics and outcomes research; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

Summary of other company responses (2/2)

Theme	Company comments

Decision making and transparency	• Considering NICE Methods Guide Section 6.2.7 and 6.2.8:
	  • Unclear from DG to what extent lack of alternative treatments was taken into account in committee decision making
	  • Concerned no patient submissions made, no patient organisation representation at committee meeting and unclear how company's SIP deployed
	  • Do not know if or how patient organisations or clinicians were engaged during technical engagement

Timing	• Company received EAG's critique on the company's technical engagement response <48 hours before ACM1 and the EAG updated model after ACM1 giving the company little/no time to prepare

Abbreviations: ACM1, first committee meeting; CDF, Cancer Drugs Fund; DG, draft guidance; SIP, Summary of Information for Patients

Key issues

Key issues at ACM1		Resolved?	ICER impact
DTC population included in model		Yes	N/A
Uncertainty around the effect of cabozantinib on overall survival		No	Biggest
Uncertainty around the most appropriate health state utility values		No	Small
Issues relating to resource use and costs	• Post-progression cabozantinib costs & TTD	Yes	N/A
	• Drug wastage costs	Yes	N/A
	• Drug cost adjustments using RDI	No	Small
	• Monitoring cost assumptions	Yes	N/A
	• Concomitant medication costs	Yes	N/A

Abbreviations: ACM1, first appraisal committee meeting; DTC, differentiated thyroid cancer; ICER, incremental cost effectiveness ratio; N/A, not applicable; RDI, relative dose intensity; TTD, time to treatment discontinuation

Preferred analysis results (1/2)

Committee's preferred analysis results at ACM1 (deterministic)

Technology	DM	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (excluding weighting)	ICER including QALY weighting (£/QALY)
BSC	1.2	[redacted]	[redacted]			
Cabozantinib		[redacted]	[redacted]	[redacted]	[redacted]	28,200

Company's base case results (probabilistic*)

Technology	DM	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (excluding weighting)	ICER including QALY weighting (£/QALY)
BSC	1.2	[redacted]	[redacted]			
Cabozantinib		[redacted]	[redacted]	[redacted]	[redacted]	20,126

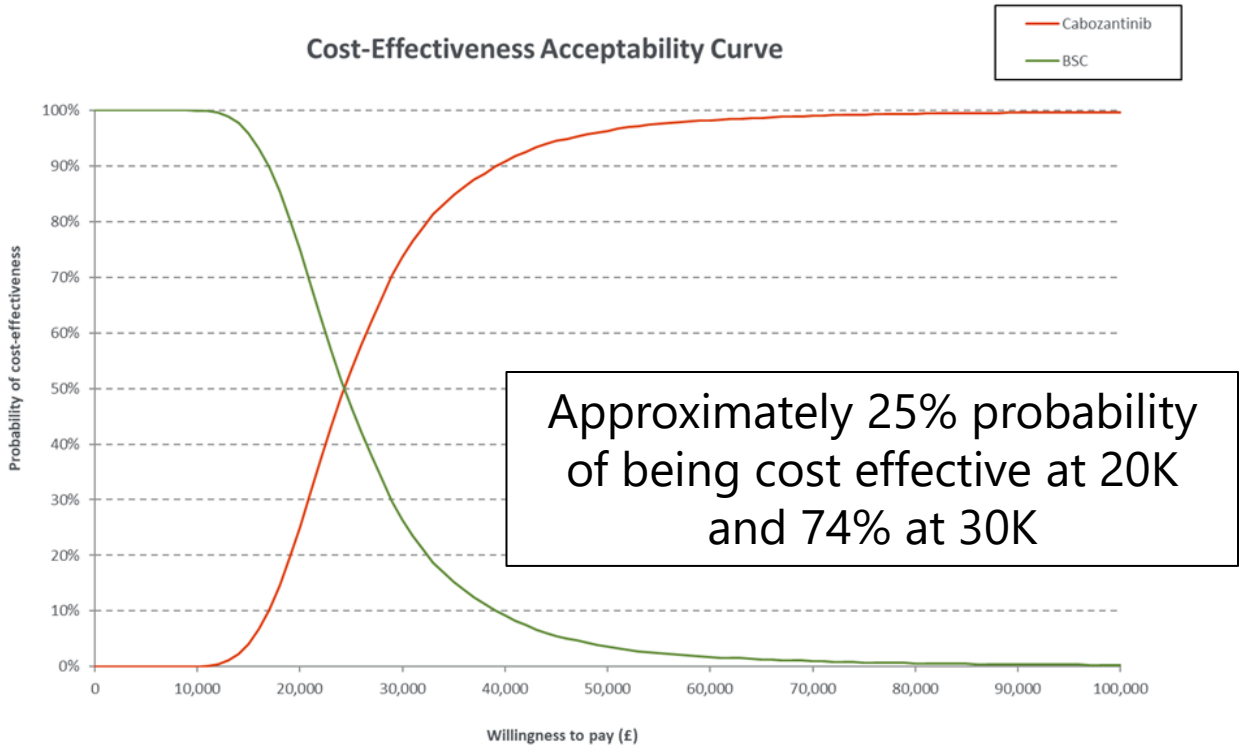
*Results are probabilistic as the blended analysis produced 100 curves; probabilistic method runs through the 100 curves multiple times to show the impact of the blended analysis

Abbreviations: ACM1, first appraisal committee meeting; BSC, best supportive care; DM, decision modifier; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

Company base case results (2/2)

[redacted]

Results shown in incremental cost-effectiveness plane include QALY weighting



Results shown in cost-effectiveness acceptability curve exclude QALY weighting

Abbreviations: BSC, best supportive care; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year

Company probabilistic scenario analysis

No.	Scenario (applied to company base case)		Incremental costs (£) versus BSC	Incremental life years versus BSC	Incremental QALYs versus BSC (excluding weighting)	ICER including QALY weighting (£/QALY)
1	Company base case		[redacted]	[redacted]	[redacted]	20,126
2	Compliance		[redacted]	[redacted]	[redacted]	22,592
3	OS: exponential parametric curves (no blended analysis)		[redacted]	[redacted]	[redacted]	23,776
4	Inclusion of lenvatinib cost		[redacted]	[redacted]	[redacted]	11,499
5	DECISION utilities		[redacted]	[redacted]	[redacted]	20,516
6	Blended survival	Blending interval (60 months)	[redacted]	[redacted]	[redacted]	20,233
7		Parameter for weight function (rate: α=2, β=5)	[redacted]	[redacted]	[redacted]	20,036
8		High uncertainty	[redacted]	[redacted]	[redacted]	22,069
9		Low uncertainty	[redacted]	[redacted]	[redacted]	20,443

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; OS, overall survival; QALY, quality adjusted life year

Additional analysis by EAG (probabilistic)

Re-applying each of committee's preferred assumptions increases the ICER

No.	Scenario (applied to company base case)	Incremental costs (£) versus BSC	Incremental life years versus BSC	Incremental QALYs versus BSC (excluding weighting)	ICER including QALY weighting (£/QALY)
1	Company base case	[redacted]	[redacted]	[redacted]	20,126
2	Company base case (run by EAG)*	[redacted]	[redacted]	[redacted]	20,217
3	Company's base case + compliance	[redacted]	[redacted]	[redacted]	22,651
4	Company's base case + compliance + Fordham PD utility value	[redacted]	[redacted]	[redacted]	25,608
5	Company's base case + compliance + Fordham PD utility value + exponential models for OS (no blended analysis) (Committee's preferred assumptions at ACM1)	[redacted]	[redacted]	[redacted]	29,016

*Not equivalent to company's reported results because blended OS approach is probabilistic, and the company's model does not use a constant set of random numbers across analyses

Abbreviations: ACM1, first appraisal committee meeting; BSC, best supportive care; ICER, incremental cost effectiveness ratio; OS, overall survival; PD, progressed disease; 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**.

Company:

- No further data cuts from COSMIC-311 are planned
- Not proposing a managed access agreement
- A more pragmatic approach to a CDF consideration should be taken by NICE committees, especially given the unmet need and very small patient population

Abbreviations: CDF, Cancer Drugs Fund

NICE National Institute for Health and Care Excellence

Thank you.