NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Cabozantinib is not recommended, within its marketing authorisation, for treating locally advanced or metastatic differentiated thyroid cancer (DTC) that is unsuitable for or refractory to radioactive iodine, and that has progressed after systemic treatment, in adults.

1.2 This recommendation is not intended to affect treatment with cabozantinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

There are no treatments available in the NHS that are specifically for advanced DTC that is unsuitable for, or does not respond (refractory) to, radioactive iodine, and that has got worse after systemic treatment. Standard treatment is best supportive care.

Clinical trial evidence shows that, compared with best supportive care, cabozantinib increases how long people have before their condition gets worse. But it is not clear if it increases how long people live. This is because people were not followed up for long enough, and because of how the trial was done.

Because it is not clear if cabozantinib increases how long people live, the cost-effectiveness estimates would need to be within the lower half of the range that NICE considers an acceptable use of NHS resources. But the most likely cost-effectiveness estimates are towards the higher end of the range that NICE considers an acceptable use of NHS resources. This is true when considering the condition's severity, its effect on quality and length of life, and the unmet need.

More evidence could help address the uncertainty about the benefits of cabozantinib, but the company has said that there would be no more evidence from the trial. So, cabozantinib is not recommended.

2 Information about cabozantinib

Marketing authorisation indication

2.1 Cabozantinib (Cabometyx, Ipsen) is indicated 'as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for cabozantinib.

Price

2.3 The list price of cabozantinib is £5,143 for a 30-tablet pack of 20 mg, 40 mg or 60 mg tablets (excluding VAT; BNF online accessed March 2023).

2.4 The company has a commercial arrangement. This makes cabozantinib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Ipsen, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical management

Clinical need

3.1 Differentiated thyroid cancer (DTC) is the most common form of thyroid cancer, accounting for around 90% to 95% of all diagnosed cases. More women than men are diagnosed with the condition. But the proportions of men and women are similar for people with metastatic disease. Treatment typically involves surgery, usually with the aim of curing the condition. Radioactive iodine may be used after surgery, to destroy any cancerous cells not removed by surgery and those that have spread beyond the thyroid. Radioactive iodine is an intensive intervention. But for between 5% and 15% of people with DTC their condition is refractory to radioactive iodine. The committee recalled at the second committee meeting that this is a small population, with fewer than 100 people a year estimated to have treatment for this indication. The clinical expert described previously treated locally advanced or metastatic DTC unsuitable for or refractory to radioactive iodine as a severe condition with a heavy symptom burden. Bone metastases can affect mobility, and prognosis is usually poor. For radioactive iodine-refractory locally advanced or metastatic DTC, NICE recommends first-line treatment with lenvatinib or sorafenib (see NICE's technology appraisal guidance on lenvatinib and sorafenib). But there are no NICE-recommended second-line treatments for people whose condition progresses on first-line treatment. The committee recognised that there is an unmet need and that the population is estimated to be small.

Treatment options

3.2 For people whose condition has progressed on lenvatinib or sorafenib, and who are no longer having treatment with these technologies, the only remaining option is best supportive care. This typically involves thyroid stimulating hormone suppression with an appropriate thyroid hormone treatment, and ongoing imaging, with palliative radiotherapy and symptom relief when necessary. NICE recommends selpercatinib for treating advanced RET (rearranged during transfection) fusion-positive thyroid cancer (see NICE's technology appraisal guidance on selpercatinib). NICE recommends entrectinib and larotrectinib for treating NTRK (neurotrophic tyrosine receptor kinase) fusion-positive solid tumours (see NICE's technology appraisal guidance on entrectinib and larotrectinib). DTC can be NTRK fusion positive. Selpercatinib, entrectinib and larotrectinib are all recommended for use in the Cancer Drugs Fund and are not part of routine NHS commissioning. Also, these drugs are only used if DNA analysis of the tumours identifies specific changes in the RET and NTRK genes, and these changes are uncommon in radioactive iodine-refractory locally advanced or metastatic DTC. The company selected best supportive care as the only comparator for cabozantinib. It said that there are no other routinely commissioned treatments recommended by NICE after first-line systemic treatment of radioactive iodine-refractory DTC. It also explained that lenvatinib and sorafenib can only be used at first line in clinical practice, and selpercatinib is only recommended in the Cancer Drugs Fund. This was confirmed by the clinical experts. NICE's health technology evaluations manual says that technologies that have been recommended by NICE with managed access (for example, in the Cancer Drugs Fund) are not considered established practice in the NHS and are not considered suitable comparators. The EAG noted that some clinicians may continue to offer lenvatinib after progression. But lenvatinib was not listed as a comparator in the final NICE scope. At the first committee meeting, the EAG considered that there was unlikely to be enough evidence for a reliable comparison between cabozantinib and continued lenvatinib used post-progression. The clinical experts acknowledged that lenvatinib may be continued after progression in clinical practice, but that this would be in very specific situations. The clinical experts confirmed that best supportive care was the only appropriate comparator. The committee

concluded that placebo plus best supportive care was the most appropriate comparator for cabozantinib plus best supportive care.

Positioning of cabozantinib

3.3 In the main clinical trial, COSMIC-311 (see section 3.4), approximately 76% of people had previously had either sorafenib or lenvatinib, and 24% had had both. The company proposed cabozantinib as a second-line treatment option for previously treated locally advanced or metastatic DTC unsuitable for or refractory to radioactive iodine. NHS England's Cancer Drugs Fund clinical lead confirmed that NHS England commissions only 1 of either lenvatinib or sorafenib for treating DTC after radioactive iodine. Lenvatinib is more frequently prescribed in clinical practice than sorafenib. The clinical expert agreed that people would not have both lenvatinib and sorafenib, unless they had had to stop taking either within 3 months of starting it because of toxicity. The marketing authorisation for cabozantinib included second-line or later-line treatment after prior systemic therapy (see section 2.1). The committee was also aware that there are no treatments recommended by NICE for after first-line systemic treatment of radioactive iodine-refractory DTC (see section 3.2). The committee concluded that the company's positioning of cabozantinib as a second-line treatment option was appropriate.

Clinical effectiveness

COSMIC-311 trial

3.4 The main evidence for cabozantinib came from COSMIC-311. This was a phase 3, randomised, double-blind, controlled study comparing cabozantinib plus best supportive care with placebo plus best supportive care. It included adults with radioactive iodine-refractory advanced DTC whose condition had progressed during or after previous systemic therapy. The primary endpoints were objective response rate and progression-free survival (PFS). COSMIC-311 reported 2 clinical cut-offs for data: the primary clinical cut-off (CCO1) in August 2020, and a secondary data cut-off (CCO2) in February 2021. CCO1 had a median

follow up of 6.2 months, and CCO2 had a median follow up of 10.1 months, for the full intention-to-treat (ITT) population. PFS significantly improved for cabozantinib compared with placebo in both data cuts. At CCO2 (n=258), the hazard ratio for PFS in the ITT population was 0.22 for cabozantinib compared with placebo (96% confidence interval [CI] 0.15 to 0.32, p<0.0001). The EAG noted that a large proportion of people in the study had censored data (64% in the cabozantinib group and 22% in the placebo group at CCO2). So, there was a lot of incomplete information for PFS and overall survival (OS) in the CCO2 follow up. There was no statistically significant difference in OS between the 2 treatment arms in either data cut-off. At CCO2, the hazard ratio for OS was 0.76 for cabozantinib compared with placebo (95% CI 0.45 to 1.31, p value is confidential and cannot be reported here). In response to consultation, the company noted that the ITT population in the trial was not powered for the exploratory endpoint of OS. The PFS and OS hazard ratios for cabozantinib compared with placebo in the second-line population were better than those estimated for the full ITT population. But the hazard ratios in the second-line population are confidential and cannot be reported here. The EAG was concerned that, because the second-line population was a subgroup of COSMIC-311, the sample size was smaller and there was greater uncertainty in the trial results. The EAG also cautioned that the integrity of the survival data was compromised by the large proportion of people having placebo who, on radiographic progression, had open-label cabozantinib (see section 3.5). The committee recognised that cabozantinib plus best supportive care showed a significant improvement in PFS compared with placebo plus best supportive care. But there was no statistically significant difference in OS. The clinical experts explained that it would be unusual for a PFS benefit not to translate into an OS benefit when there are limited treatment options available and there is otherwise a very poor prognosis. So, the clinical experts considered that it was likely that there would be an OS benefit for people treated with cabozantinib. But it was uncertain how much OS benefit there would be. The committee appreciated that the company had presented randomised controlled data collected in COSMIC-311. The committee also understood the limitations of the study and that by focusing on the relevant second-line population, it had reduced the evaluable sample. But it can only consider the data presented. The committee

acknowledged that there was a significant improvement in PFS for cabozantinib plus best supportive care, but the OS results were uncertain.

Crossover adjustment

3.5 The EAG assessed the risk of bias in the COSMIC-311 trial to be high because of deviations from the intended treatment. After radiographic progression, people having placebo could cross over, if eligible, to open-label cabozantinib. People having cabozantinib could also continue having open-label cabozantinib after radiographic progression if the investigator deemed that they were still getting clinical benefit. Large proportions of people in the placebo group switched treatment within a relatively short period from the start of the trial (31% at CCO1, and 45% at CCO2, in the ITT population). The company did crossover adjustment analyses on the OS data to estimate the unbiased survival benefit of cabozantinib treatment compared with the placebo arm. It explored 3 adjustment methods: rank-preserving structural failure time (RPSFT), two-stage estimation, and inverse-probability-of-censoring weightings. All 3 methods gave similar results. The company used the RPSFT method in its base case because it was in line with previous NICE submissions. The OS hazard ratio for cabozantinib compared with RPSFT-adjusted placebo in the ITT population was 0.65 (95% CI 0.28 to 1.53). The hazard ratio in the second-line population is confidential and cannot be reported here. But there was a non-statistically significant trend in improved OS for cabozantinib plus best supportive care compared with placebo plus best supportive care, with or without crossover adjustment. The committee understood that the OS results were confounded by the short time to progression in the placebo arm, combined with the high levels of censoring and crossover in COSMIC-311. It recognised the crossover adjustment methods explored by the company, and it was familiar with the uncertainty associated with them. The committee concluded that the OS data was uncertain, even after the company adjusted for crossover, and concluded that it would take this into account during its decision making.

Economic model

Company's modelling approach

3.6 The company used a partitioned survival model with 3 health states: progression-free disease, progressed disease, and death, to model the cost effectiveness of cabozantinib plus best supportive care. The company base-case analysis used the second-line subgroup of COSMIC-311 at CCO2, including the RPSFT-adjusted data for placebo plus best supportive care (see section 3.3 and section 3.5). The EAG considered the company's model to be generally in line with NICE's reference case. The committee concluded that the company's second-line subgroup model was acceptable for decision making.

Modelling overall survival

3.7 At the first committee meeting, the company fitted parametric survival models to the data for the second-line-only population in COSMIC-311. It selected the PFS and OS distributions based on visual and statistical fit to the observed data. The company also used clinical experts' expectations of OS at 2, 5 and 10 years in people with radioactive iodine-refractory DTC having cabozantinib or best supportive care. The company noted that all OS curves overestimated the clinical experts' survival expectations at 5 and 10 years. The parametric survival distributions for PFS and OS selected by the company for the second-line base-case analysis were the Weibull and the exponential, respectively. The EAG had several concerns about the company's modelling of OS. It explained that the company's model assumes proportional hazards. But the survival data from COSMIC-311 shows that the treatment effect for cabozantinib plus best supportive care compared with placebo plus best supportive care reduces over time. This is shown by the survival curves coming together, indicating that the proportional hazards assumption did not hold. The EAG also used exponential distributions to model OS for both cabozantinib plus best supportive care and placebo plus best supportive care in its preferred analysis. It noted that this gave the second most pessimistic survival curve for placebo plus best supportive care. The EAG explored applying

a treatment benefit cap. This analysis used the exponential models of its preferred analysis and applied the OS hazard rate for best supportive care to both groups after 36 months. But the EAG cautioned that the 36-month time point at which the treatment benefit cap was applied was arbitrary. The clinical experts noted that there was limited data from which to model OS, particularly in the placebo plus best supportive care group. The clinical experts described how low numbers at risk and a short follow up from COSMIC-311 explained why attempts to model OS lacked clinical plausibility. At the second committee meeting, the company revised its base-case model to include a blended survival analysis based on the second-line-only population in COSMIC-311 for both treatment arms. It explained that the survival estimates from the blended analysis were closer to the clinical experts' expectations of OS for both treatment arms than the survival estimates from the exponential parametric curve. The EAG was concerned that the OS curves from the blended survival analysis had a poor fit to the observed data from COSMIC-311. It was also concerned that the methodology had been insufficiently explained by the company. The EAG stressed that neither its analysis nor the company's analysis was ideal for modelling OS and that this was unresolvable given the limited and immature data available. The EAG considered that the uncertainty around the impact of cabozantinib on OS could not be resolved without additional data collection. But the company explained that no further data cuts were planned from COSMIC-311. The committee agreed that longer follow-up data from COSMIC-311 would be helpful for reducing uncertainty, but understood from the company that this would not be available in the future. The committee agreed that it was uncertain whether the OS models done by either the company or the EAG reflected the true long-term benefit of cabozantinib on OS. It acknowledged that the blended survival analysis based on the second-line-only population was helpful to consider as an alternative approach to modelling OS, but noted the resulting OS models did not fit the observed data well in this case. The curves appeared to have been manipulated to fit the clinical expert estimates of survival while ignoring the fit to the observed data from the trial. It was also unclear what function had been used to fit the observed data in the blended survival analysis. The company indicated that it was an exponential function but were unable to confirm that this was the case in the second committee meeting. The EAG noted that, if an

exponential function had been used, then it was unclear why the curve deviated significantly from the EAG model in the initial period, as both used an exponential function. The committee noted the lack of transparency around the blended survival analysis. Because of this, the committee concluded that the exponential function used by the EAG for modelling OS in both treatment arms was preferable for its decision making.

Modelling continued lenvatinib after progression

3.8 At the second committee meeting, the company explored the impact of continued lenvatinib after progression by applying associated treatment costs to the best supportive care arm. The EAG was concerned that the analysis did not consider the additional health gains that continued lenvatinib after progression may provide. So, it considered the analysis to likely be biased in favour of cabozantinib. The committee recalled that continued lenvatinib after progression would only be used in specific situations in clinical practice (see section 3.2). Given that the extra cost of continued lenvatinib after progression was included in the best supportive care arm but the potential health gains were not, the committee concluded that the results for this analysis were uncertain, and susceptible to bias. So, this analysis was not considered in the committee's decision making.

Utility values

Source of utility values

3.9 At the first committee meeting, the company's model used health-state utility values based on the adjusted regression model reported by Fordham et al. (2015). These values were a progression-free utility of 0.87, and a progressed-disease utility of 0.52. The EAG was concerned that the utility applied by the company in the progression-free state was higher than the age- and sex-matched EQ-5D-3L value for the general population. The general population utility was 0.82. At technical engagement, the company and the EAG agreed that an age-adjusted general population utility cap should be applied. This would ensure that

health-related quality of life in the radioactive iodine-refractory DTC population could not exceed health-related quality of life in the general population. The clinical experts also agreed that it was not plausible that people with radioactive iodine-refractory DTC would have a higher utility value than the UK general population. The company's second-line base-case model had mistakenly removed a constraint. This constraint had been applied to prevent the utility value for the progression-free health state from exceeding the estimated EQ-5D-3L utility value for the age- and sex-matched general population. So, the EAG corrected the model. The EAG explained that some NICE technology appraisal guidance on treatments for thyroid cancer had also applied utility values from Fordham et al. (2015). These were NICE's technology appraisal guidance on cabozantinib for medullary thyroid cancer, vandetanib for medullary thyroid cancer and selpercatinib for advanced thyroid cancer with RET alterations. But, in each of these technology appraisals, EQ-5D data had not been collected in the pivotal clinical trials, and the unadjusted utility values from Fordham et al. (2015) were used. These were a progression-free utility of 0.80 and a post-progression utility of 0.50. The EAG used the unadjusted utility values in its preferred analysis, for consistency with the previous appraisals. The clinical experts explained that people having treatment at second line were expected to have a poorer prognosis and lower health-related quality of life than at first line. So, they expected the utility value for people at second line to be lower. But the Fordham et al. (2015) utility values based on the adjusted regression model were higher than the unadjusted utility values used in the previous NICE appraisals for thyroid cancer. The committee considered that it would be more appropriate to use the utility estimate from COSMIC-311 than Fordham et al. (2015). It noted that the NICE health technology evaluations manual says that health-related quality of life should be measured directly by patients. The manual also advises using the EQ-5D measurement method to measure health-related quality of life in adults. The EQ-5D-5L data from the COSMIC-311 trial was mapped to EQ-5D-3L using the crosswalk approach by Hernandez Alava and Pudney (2017). The company noted at the first committee meeting that quality-of-life data collection stopped shortly after progression in COSMIC-311. It also noted that it preferred to use the same source for both the progression-free and the progressed-disease utility values. The EAG agreed it would be reasonable to consider the COSMIC-311 utility values. It recalled that it

had explored using the COSMIC-311 utility value for the progression-free state with its preferred unadjusted post-progression utility value from Fordham et al. (2015) in sensitivity analyses. At the first committee meeting, the committee concluded that it preferred using the COSMIC-311 utility value for the progression-free state because it was based on the population being appraised and because it used the same source as that used for the model's clinical efficacy inputs. It also recognised that the EQ-5D-5L data available from COSMIC-311 for informing the progressed-disease utility value was limited. So, it concluded that the unadjusted post-progression utility value from Fordham et al. (2015) was preferred for decision making. The company recognised the committee's preference for using the COSMIC-311 utility value for the progression-free state. In response to consultation, the company revised its base-case model to include the utility values from COSMIC-311 for both the progression-free and the progressed-disease health states. It recalled its preference for using the same source for both health-state utility values. It noted that combining COSMIC-311 and Fordham et al. (2015) would not present a clinically accurate reflection of the impact of cabozantinib. The EAG recalled the limitations of the progressed-disease utility from COSMIC-311. The committee agreed that their preference was to use utility data directly from the COSMIC-311 trial. But this data should be robust, free of bias and clinically plausible. The committee was not confident that this was the case for the utility value in the post-progression state. So, the committee still preferred the progression-free state utility value from COSMIC-311 and the unadjusted post-progression utility value from Fordham et al. (2015).

Costs

Post-progression cabozantinib costs

3.10 In COSMIC-311, 1.6% of people in the cabozantinib group had had post-progression open-label cabozantinib at CCO1 (see section 3.5). It was 6.5% of people at CCO2. The clinical experts considered it likely that, in clinical practice, some people would continue on cabozantinib beyond radiological progression if they were still benefiting from treatment. This is in the absence of any other further lines of treatment. At technical

engagement, the company agreed that the costs of post-progression cabozantinib should be included in the economic analysis. This would reflect the intention for cabozantinib to be used in line with its marketing authorisation. But the EAG was concerned that the company's selected model for time to treatment discontinuation (TTD), generalised gamma, remained lower than the modelled PFS function at all time points. This implied that people do not have post-progression cabozantinib. The EAG's preferred analysis used a Weibull model for TTD. But the EAG recognised that there were other functions that were equally plausible and that also gave TTD predictions that were above PFS. The Weibull was considered to be conservative compared with other alternatives. The committee understood that, in clinical practice, some people would continue on cabozantinib beyond radiological progression. So, the TTD curve should be above the PFS curve. In its response to consultation, the company included the Weibull model for TTD in its revised base-case analysis. The committee concluded that the Weibull model for TTD was appropriate for decision making.

Drug cost adjustments

3.11 In the company's base-case analysis, drug acquisition costs were adjusted based on relative dose intensity, which is the average amount of planned dose that the person had. The EAG considered it more appropriate to adjust cabozantinib costs based on adherence, given the flat pricing structure for cabozantinib. Adherence is the proportion of days on which people had treatment. The company recalled that previous NICE technology appraisals had used relative dose intensity to adjust drug acquisition costs. This was regardless of whether the technology had a flat pricing structure across different dosage strengths. The EAG explained that the issue having not been pursued in past appraisals was not sufficient justification for the inappropriate use of relative dose intensity adjustment in this appraisal. The company also noted that the adherence estimate was based on CCO1, whereas a relative dose intensity estimate was available from CCO2. In response to consultation, the company presented a real-world study in renal cell cancer which reported a lower relative dose intensity of cabozantinib in the real-world study than in the clinical trial. This was because of additional comorbidities in clinical practice that needed dosing schedule

adjustments to manage the side effects. So, the company suggested that adherence in the COSMIC-311 trial could be overestimating the true cost of cabozantinib in clinical practice. The EAG commented that the real-world study referred to the overestimation of relative dose intensity rather than adherence. It also cautioned that the real-world study did not consider the potential consequence that taking less cabozantinib in practice may also lead to lower comparative effectiveness compared with what has been observed in a clinical trial setting. The committee acknowledged that the relative dose intensity approach aligned with methods used in previous technology appraisals. But it concluded that the EAG's adjustment based on adherence was more appropriate for decision making, because it reflected the true drug acquisition cost of cabozantinib to the NHS.

Severity

QALY weighting

3.12 In its submission, the company provided evidence that previously treated locally advanced or metastatic DTC unsuitable for or refractory to radioactive iodine is a severe condition. The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (a severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The company's evidence to inform the QALYs of people without the condition was based on the COSMIC-311 ITT population at CCO2. This population had a mean baseline age of 65 years, and 47% were men. The company's evidence for QALYs of people with the condition on best supportive care was based on its preferred utility values from Fordham et al. (2015). These were based on an adjusted regression analysis (see section 3.9). The committee noted that the company's absolute QALY shortfall calculation results were below 12. Their proportional QALY shortfall calculation results were between 0.85 and 0.95. (The exact figures are confidential and so cannot be reported here.) The committee is allowed

to apply a greater weight to the QALYs for technologies indicated for conditions with a high degree of severity. The committee considered this advice on severity as a decision modifier. It noted that if either the absolute or the proportional QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply. The company said that the absolute QALY shortfall was less than 12, which would imply no QALY weight. But a proportional QALY shortfall between 0.85 and 0.95 implies a QALY weight of 1.2. The EAG's shortfall estimates agreed with the company's and supported a severity modifier with a 1.2 QALY weighting. The EAG confirmed that the 1.2 QALY weight also applied when considering both the second-line analyses (see section 3.3) and progression-free utility value based on COSMIC-311 (see section 3.9). So, the committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.13 NICE's health technology evaluations manual states that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, decisions about the acceptability of the technology as an effective use of NHS resources will consider the degree of uncertainty around the ICER and any benefits of the technology that were not captured in the QALY calculations. The committee will be more cautious about recommending a technology if it is less certain about the evidence presented. The committee noted that the size of the population estimated to have treatment for this indication per year was small (see section 3.1). Even so, the committee understood that enrolment of people to the COSMIC-311 trial was sufficient to generate an analysis population. The company also confirmed in response to consultation that the second-line population represented the majority (approximately 76%; see section 3.3) of the ITT population in the COSMIC-311 trial. It also confirmed that the trial was powered to detect a difference in PFS for the second-line population. The committee understood that evidence generation did not appear to have been particularly difficult as a result of a small population size. It recalled that uncertainty about the evidence

presented was related to crossover (see section 3.5) and limited follow up (see section 3.7). The committee noted that there are no NICE-recommended second-line treatments for locally advanced or metastatic DTC that is unsuitable for or refractory to radioactive iodine. So, it concluded that there is an unmet need in this population (see section 3.1). Section 6.2 in NICE's health technology evaluations manual explains that 'the extent of unmet health need is reflected within the severity definition'. The committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate for this appraisal (see section 3.12). Even so, the committee recognised the unmet need in this population and noted it would apply greater flexibility to reflect this. So, it considered the maximum acceptable ICER would be higher than £20,000 per QALY gained. The committee recalled that the effect of cabozantinib on OS and the resulting modelling of OS was uncertain (see section 3.4 and section 3.7). The committee recognised the need to balance the unmet need against the uncertainty in the cost-effectiveness estimates caused by crossover (see section 3.5) and limited follow up (see section 3.7). Because of this, the committee concluded that the maximum acceptable ICER would be within the lower half of the £20,000 to £30,000 per QALY gained range that is normally considered a cost-effective use of NHS resources.

Company cost-effectiveness estimates

3.14 In response to consultation, the company revised its base-case model. Its base-case ICER at the second committee was probabilistic because of the iterative methodology used to produce results from the blended survival analysis. So, the company's probabilistic base-case ICER for cabozantinib plus best supportive care compared with placebo plus best supportive care was £20,126 per QALY gained when the following were applied:

- the 1.2 severity weighting
- blended survival analysis in the second-line-only population for modelling OS (see section 3.7)
- the utility values from COSMIC-311 for both the progression-free and the progressed-disease health states (see section 3.9)

- a Weibull model to extrapolate TTD for cabozantinib (see section 3.10)
- relative dose intensity for adjusting drug acquisition costs for cabozantinib (see section 3.11).

Committee's preferred cost-effectiveness estimates

3.15 The committee preferred the exponential model for extrapolating OS in both treatment arms (see section 3.7) and the Weibull model for extrapolating TTD for cabozantinib (see section 3.10). It also agreed with the EAG's adherence approach for adjusting drug acquisition costs for cabozantinib (see section 3.11) and the unadjusted post-progression utility value from Fordham et al. (2015; see section 3.9). But the committee preferred to use the COSMIC-311 utility value for the progression-free health state (see section 3.9). The deterministic cost-effectiveness estimate generated by its preferred assumptions was £28,200 per QALY gained. The probabilistic ICER was £29,016 per QALY gained. It considered that when its preferred assumptions were incorporated, the cost-effectiveness estimate was towards the higher end of the range considered to be a cost-effective use of NHS resources. The ICER remained above £25,000 per QALY gained when the company's blended survival analysis was applied for modelling OS and all other assumptions preferred by the committee were held. The committee also recalled that the 3 alternative approaches to modelling OS explored by the EAG in scenario analyses in the first committee meeting gave ICERs ranging from £25,904 to £49,540 per QALY gained. The committee would prefer to see an ICER within the lower half of the range considered to be a cost-effective use of NHS resources (see section 3.13). The committee also considered the high likelihood of decision error and the inability to mitigate this because of the uncertainties in the available evidence (see section 3.7 and section 3.9). The committee was aware that the technology has potential benefits for people having it (see section 3.4). But it noted that there would be potential financial impacts for the NHS if a positive recommendation was given to the treatment. It noted there would also be a risk of displacing other cost-effective treatments offered by the NHS for other conditions. So, cabozantinib could not be recommended for treating locally advanced or metastatic DTC that is unsuitable for or refractory to

radioactive iodine, and that has progressed after systemic treatment.

Managed access

Recommendation with managed access

3.16 Having concluded that cabozantinib could not be recommended for routine commissioning, the committee then considered if it could be recommended with managed access for previously treated locally advanced or metastatic DTC unsuitable for or refractory to radioactive iodine. The company indicated that they were not planning further data collection from COSMIC-311 and did not submit an application for managed access. So, the committee concluded that managed access could not be considered.

Other factors

Equality issues

3.17 The committee noted the stakeholders' comments that women are more likely to be diagnosed with thyroid cancer. But the clinical experts explained that in metastatic DTC the proportions of men and women are similar (see section 3.1). This was seen in the trial population in COSMIC-311. No other equality or social value issues were identified.

Innovation

3.18 The committee considered if cabozantinib was innovative. It did not identify additional benefits of cabozantinib not captured in the economic modelling. So, the committee concluded that all additional benefits of cabozantinib had already been taken into account.

Conclusion

Recommendation

3.19 The committee concluded that there was uncertainty in the cost-effectiveness estimates. So, it considered that the maximum acceptable ICER would be within the lower half of the £20,000 to £30,000 range normally considered a cost-effective use of NHS resources. It considered that when its preferred assumptions were incorporated, the cost-effectiveness estimates for cabozantinib plus best supportive care were towards the higher end of the range considered to be a cost-effective use of NHS resources. So, cabozantinib is not recommended for treating locally advanced or metastatic DTC that is unsuitable for or refractory to radioactive iodine, and that has progressed after systemic treatment. Had cabozantinib been recommended by the committee it would have been limited to people whose condition has progressed after 1 systemic treatment.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Dr Stephen Smith
Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Rachel Ramsden
Technical lead

Victoria Kelly and Caron Jones
Technical advisers

Celia Mayers
Project manager

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Accreditation