NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

1 Recommendations

1.1 Lenvatinib and sorafenib are recommended as options for treating progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine, only if:

- they have not had a tyrosine kinase inhibitor before or
- they have had to stop taking a tyrosine kinase inhibitor within 3 months of starting it because of toxicity (specifically, toxicity that cannot be managed by dose delay or dose modification).

Lenvatinib and sorafenib are recommended only if the companies provide them according to the commercial arrangements (see section 2).

1.2 This recommendation is not intended to affect treatment with lenvatinib or sorafenib 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

Issue date: June 2018

Lenvatinib and sorafenib (tyrosine kinase inhibitors) are the only treatment options for progressive, locally advanced or metastatic differentiated thyroid cancer after surgery and radioactive iodine. For people who cannot have lenvatinib or sorafenib, best supportive care is the only option.

Clinical trial evidence shows that lenvatinib and sorafenib are both effective in delaying disease progression, but there is a higher response rate (that is, more tumours shrink) with lenvatinib and it may delay progression for longer. Clinical expert advice is that this response is associated with an improvement in symptoms, which is valued by patients. Lenvatinib and sorafenib also increase the length of time people live, but it is uncertain by how long.

The cost-effectiveness estimates are higher than what NICE normally considers acceptable, and lenvatinib and sorafenib do not meet NICE's end-of-life criteria. But the treatments do increase length of life and there are no other treatments available for the condition. Also, the cost-effectiveness estimates do not capture the benefits of people having a response to treatment, that is, an improvement in symptoms.

Taking all this into account, lenvatinib and sorafenib are recommended as treatment options for differentiated thyroid cancer after radioactive iodine. However, they are recommended only for people who have not had tyrosine kinase inhibitors before, or who have to stop them early because of tolerability (specifically, toxicity that cannot be managed by dose delay or dose modification). This is because there is not enough clinical evidence and no cost-effectiveness evidence to determine whether the treatments are effective when used sequentially.

2 Information about lenvatinib and sorafenib

	Lenvatinib (Lenvima, Eisai)	Sorafenib (Nexavar, Bayer)
Marketing authorisation indications	Adults with 'progressive, locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine'.	Adults with 'progressive, locally advanced or metastatic differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine'.
Dosage in the marketing authorisations	24 mg (2×10 mg capsules and 1×4 mg capsule) once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.	400 mg (2×200 mg tablets) twice daily (equivalent to a total daily dose of 800 mg). Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.
Prices	£1,437 per 30×10 mg pack and per 30×4 mg pack (excluding VAT; British national formulary online [accessed July 2017]). The company has a commercial arrangement (simple discount patient access scheme). This makes lenvatinib available to the NHS with a discount. 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.	£3,576.56 per 112×200 mg pack (excluding VAT; British national formulary online [accessed July 2017]). The company has a commercial arrangement (commercial access agreement). This makes sorafenib available to the NHS with a discount. 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 appraisal committee (section 6) considered evidence from a number of sources. See the committee papers for full details of the evidence.

Treating differentiated thyroid cancer

There is a need for active treatment options for disease that does not respond to radioactive iodine

3.1 The patient and clinical experts explained that differentiated thyroid cancer is rare. Surgery, followed by radioactive iodine (used to destroy

any remaining cancer cells) is the most common treatment. The clinical expert advised that disease that does not respond to radioactive iodine can sometimes remain stable for long periods. In clinical practice, best supportive care is offered until the disease starts to progress and symptoms occur, or there is rapid progression that is likely to become symptomatic. Lenvatinib and sorafenib are the only licensed disease-modifying treatments available in England. Sorafenib is available through the Cancer Drugs Fund for people with inoperable or metastatic papillary or follicular thyroid cancer that has not responded to radioactive iodine. Lenvatinib is available through a compassionate use programme for people who cannot tolerate sorafenib or who have disease that has progressed on sorafenib. The patient expert explained that people with progressive disease that does not respond to radioactive iodine often have reduced quality of life because of pain, fatigue and difficulty carrying out daily activities. Both lenvatinib and sorafenib allow people to return to work and take part in family life, while increasing their quality of life. The clinical expert explained that the only alternative to lenvatinib and sorafenib was best supportive care, which includes treatment such as palliative radiotherapy, analgesia and bisphosphonates. The committee concluded that there was a need for active treatment options for people with disease that does not respond to radioactive iodine.

Clinical evidence

The SELECT and DECISION trials are relevant to clinical practice

3.2 Two multicentre double-blind randomised controlled trials compared lenvatinib (SELECT) and sorafenib (DECISION) with placebo. Patients in both arms of the trials had best supportive care in addition to their randomised treatment. SELECT included 392 patients and DECISION included 417 patients; both trials included only patients with Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. In DECISION around 20% of patients had disease that was symptomatic at baseline but the proportion in SELECT was not clear. The clinical expert

advised that the trials included patients with recently progressed disease that was very likely to become symptomatic and that realistically, all patients who were included would become symptomatic. The clinical expert further explained that the trial populations were very similar to people having treatment in clinical practice (that is, people with progressive disease that is symptomatic or that will become symptomatic very quickly). The committee understood that in the marketing authorisations, both treatments are indicated for progressive disease and this is not restricted to symptomatic disease. The committee therefore concluded that the trials were relevant to clinical practice.

Progression-free survival results from SELECT and DECISION

Both treatments improve progression-free survival compared with placebo

3.3 In SELECT, lenvatinib statistically significantly improved median investigator-assessed progression-free survival compared with placebo (16.6 months for lenvatinib compared with 3.7 months for placebo; hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.16 to 0.35). Similar results were reported for independently-assessed progression-free survival. In DECISION, sorafenib statistically significantly improved median investigator-assessed progression-free survival compared with placebo (10.8 months for sorafenib compared with 5.4 months for placebo; HR 0.49, 95% CI 0.39 to 0.61). Similar results were reported for independently-assessed progression-free survival. The committee concluded that there was evidence to show that both treatments are clinically effective in improving progression-free survival compared with placebo.

Overall survival results from SELECT and DECISION

Lenvatinib and sorafenib improve overall survival but there is uncertainty from the crossover adjustment and anticancer treatment after progression

3.4 The proportion of people crossing over from placebo to active treatment after disease progression was 88% in SELECT and 75% in DECISION. The companies and the assessment group agreed that the rank preserving structural failure time (RPSFT) method was the most appropriate to adjust for the high level of crossover in both trials. In SELECT, median overall survival for lenvatinib was 41.6 months compared with 34.5 months for placebo. After correcting for crossover, there was a statistically significant overall survival benefit for lenvatinib compared with placebo (RPSFT-adjusted HR 0.54, 95% bootstrapping CI 0.36 to 0.80). In DECISION, the median overall survival for sorafenib was 39.4 months compared with 42.8 months for placebo. After correcting for crossover, there was no statistically significant improvement in overall survival for sorafenib compared with placebo (RPSFT-adjusted HR 0.77, 95% CI 0.58 to 1.02). The assessment group advised that the statistical assumption of proportional hazards (that is, there is a constant treatment effect over time) did not hold for any of the crossover corrected results for overall survival and these results should be interpreted with caution. Also, the committee noted that using anticancer treatments after progression in both trials may have confounded the overall survival results, although it could not be certain of the extent of this effect. The committee concluded that although lenvatinib and sorafenib improve overall survival, it was uncertain by how much because of the crossover adjustment and use of anticancer treatment after disease progression.

Indirect treatment comparison

An indirect treatment comparison is not appropriate to compare lenvatinib and sorafenib because of differences in the trials

3.5 Both companies carried out an indirect comparison to compare the clinical effectiveness of lenvatinib with sorafenib. The assessment group stated that an indirect comparison was not appropriate because:

- The risk of disease progression in patients in the 2 placebo arms of SELECT and DECISION was inconsistent over time and suggested there were differences in the patient groups in each trial.
- There were differences in trial characteristics, for example:
  - the use of anticancer treatment after disease progression in SELECT and DECISION
  - in DECISION, no patients had previously had tyrosine kinase inhibitors compared with 24% in SELECT
  - palliative radiotherapy (commonly used as part of best supportive care in clinical practice) was not allowed in SELECT.
- There were within and between trial differences in patient characteristics, such as geographical region and time from diagnosis.
- The statistical assumption of proportional hazards was not met for any outcome apart from unadjusted overall survival in DECISION.

As a result, the assessment group advised caution when interpreting the results from the companies' indirect comparisons and did not use these as part of its base case. The clinical expert noted that differences in patient characteristics were unlikely to explain the differences in the placebo arms across the 2 trials. However, the committee acknowledged that the Kaplan–Meier plots for progression-free survival in the placebo arms of the trials were different enough to suggest there were other important differences limiting the robustness of the indirect treatment comparisons (see section 3.3). It concluded that an indirect comparison of lenvatinib

and sorafenib using evidence from SELECT and DECISION was not appropriate.

Clinical evidence for sequential treatment

There is insufficient clinical trial evidence of the effectiveness of sequential treatment with lenvatinib and sorafenib

3.6 In SELECT 25% of patients in the lenvatinib arm had a previous tyrosine kinase inhibitor, including sorafenib, before having lenvatinib and some patients may have had sorafenib after progression on lenvatinib. However, previous treatment with a tyrosine kinase inhibitor was not allowed in DECISION. For the subgroup who had a previous tyrosine kinase inhibitor in SELECT, median progression-free survival for lenvatinib was 15.1 months compared with 3.6 months for placebo; the difference between the treatment groups was statistically significant (HR 0.22, 95% CI 0.12 to 0.41). Objective tumour response rate was 62.1% for lenvatinib compared with 3.7% for placebo. However, Eisai did not report overall survival results. The committee, noting that the subgroup included only about 25% of the patients in SELECT, acknowledged that lenvatinib appears to delay disease progression in this group of people. However, it had not seen any evidence of a survival benefit with lenvatinib or any benefit with sorafenib in this subgroup. Although the progression-free survival results and objective tumour response rates for the subgroup were similar to the results for the overall population in SELECT, the committee could not predict whether this would also apply to the overall survival results. The committee also noted that both Eisai and the assessment group had highlighted that the subgroup results should be treated with caution because of the small number of patients. Because of the uncertainty in the subgroup results, the assessment group considered that the most appropriate data for decision-making were the results from the intention-to-treat population. Because of the limitations and uncertainty in the subgroup data, the committee concluded that there was insufficient evidence to draw firm conclusions on whether the treatments

were effective when used sequentially after progression (see section 3.23).

The compassionate use programme for lenvatinib does not provide sufficient evidence for decision-making about sequential treatment

3.7 After the second committee meeting Eisai provided time-on-treatment data from a compassionate use programme, in which lenvatinib was available for 52 people in England who had either progressed after sorafenib, or could not have sorafenib because they could not tolerate it or it was contraindicated. Eisai acknowledged that the available data were limited, but argued that the estimated time on treatment for the 18 people who had stopped treatment (6.56 months) showed lenvatinib's benefit as a second-line treatment. The committee noted that Eisai had not presented any efficacy results from the compassionate use programme, so it was not possible to estimate the relative clinical effectiveness of lenvatinib in this subgroup. Therefore, the committee concluded that the time on treatment data from the compassionate use programme were not sufficient evidence for decision-making about whether lenvatinib was clinically effective when used after sorafenib.

Published audits of lenvatinib do not provide sufficient evidence of the effectiveness of sequential treatment with lenvatinib and sorafenib

3.8 Eisai also provided clinical effectiveness data from audits of lenvatinib in France (n=75), Switzerland (n=13) and Italy (n=12); 47% of people in these audits had taken at least 1 previous tyrosine kinase inhibitor. Eisai only reported efficacy results for the whole (intention-to-treat) study populations because subgroup results were not available in the published papers. The French and Swiss audits reported median progression-free survival as 10 and 7.2 months, respectively. The Swiss audit reported median overall survival as 22.7 months; median overall survival was not reached in the French audit. Progression-free survival and overall survival results were not reported for the Italian audit. Because these audits contained a higher proportion of patients who had a previous tyrosine

kinase inhibitor than in SELECT, Eisai stated that the efficacy results suggested a clinical benefit from the sequential use of lenvatinib. However, the assessment group was concerned that the efficacy results presented were for the whole study populations, rather than for the group of patients who had a previous tyrosine kinase inhibitor. Because of this, the assessment group considered that the audits did not provide enough evidence to draw conclusions about the effects of lenvatinib in this group. The assessment group also noted the large differences in patient characteristics across the studies (such as prognosis, sex, age, time from diagnosis and site of metastases), and advised that this would affect the interpretation of the efficacy findings. It emphasised that only 23% of the patients included in the French audit would have been eligible for inclusion in SELECT. It also stated that differences in the duration of treatment and length of follow-up between the studies would likely influence the survival estimates reported. The committee considered the company's data, but was aware that it had not seen efficacy results for the subgroup who had a previous tyrosine kinase inhibitor. Having also heard the assessment group's concerns about the heterogeneity between the studies, the committee concluded that the audits did not provide convincing evidence of the clinical effectiveness of sequential treatment with lenvatinib after sorafenib.

Adverse events

The decision to use lenvatinib or sorafenib is based on individual circumstances and consideration of the risks and benefits

3.9 Almost all patients in SELECT and DECISION had an adverse event while having lenvatinib (99.6%) or sorafenib (98.6%). Side effects such as sore hands and feet were more common with sorafenib and hypertension was more common with lenvatinib. The patient expert described how people may need to go to hospital because of side effects, but that these were manageable. The clinical expert explained that additional clinical monitoring visits are needed when starting both treatments and that there

is little effect on quality of life when treatment-related symptoms are quickly identified and treated. The clinical expert advised that the choice between lenvatinib or sorafenib depends on individual circumstances such as pain and location of lesions. However, clinical effectiveness, particularly response rates and toxicity profiles are also considered. The clinical expert explained that response rates suggested a larger benefit for lenvatinib (SELECT; objective tumour response 65%, DECISION; objective tumour response 12%). The clinical expert also noted the importance of balancing the risks and benefits when considering treatment. The committee concluded that the decision to use lenvatinib or sorafenib is based on individual circumstances and consideration of the risks and benefits.

Economic models

A model with 3 health states comparing each treatment with best supportive care is preferred for decision-making

3.10 Eisai's model for lenvatinib included 4 health states (stable disease, response, progressive and death) whereas Bayer's model for sorafenib included only 3 health states (progression-free, progressed and death). The assessment group was concerned that Eisai used a single aggregate ratio to estimate the number of patients in the response state for the sorafenib arm because no individual patient level data from DECISION were available. Eisai's approach excluded differences in the time and duration of response in DECISION and affected utility estimates. Therefore the assessment group used a 3-state model, similar to Bayer's. Clinical advice to the assessment group suggested there was no additional benefit from including a separate response health state in the economic model. However, the clinical expert at the committee meeting explained that for symptomatic disease, response to treatment substantially affects quality of life (see section 3.19). The committee noted the difference in opinion but considered that there were no data presented measuring the effect of a response health state on costs and utility values.

The assessment group's model used survival data and treatment duration taken directly from SELECT and DECISION and compared each treatment with best supportive care, whereas the company models also included an indirect comparison of lenvatinib and sorafenib. To assess the extent of the uncertainty when comparing the cost effectiveness of lenvatinib with sorafenib, the assessment group's model allowed a cross-trial comparison of the best supportive care arms from SELECT and DECISION and this had a large impact on the cost effectiveness of both treatments. The committee had previously concluded that an indirect comparison of lenvatinib and sorafenib was not appropriate (see section 3.5). Because there wasn't a 4-state model that modelled response for both treatments appropriately, the committee concluded that a 3-state model comparing each treatment with best supportive care was preferred for decision-making.

Extrapolating survival

The assessment group's method provided the best fit to the trial data but other extrapolations for progression-free survival are plausible

3.11 For progression-free survival, the assessment group used a single fitted exponential extrapolation that was unconstrained (that is, it did not pass through the origin) to extrapolate the trial data. In response to consultation, Bayer questioned this method because there was an artificial drop in the extrapolated portion of the curve for sorafenib, which underestimated long-term survival and was unlikely to reflect clinical practice. Bayer therefore presented 3 alternative approaches to estimate long-term progression-free survival. The assessment group criticised 2 of Bayer's alternative approaches because long-term survival was overestimated and the progression-free survival benefit therefore favoured sorafenib. It also noted that one of these alternative approaches, a piecewise extrapolation, was flawed because progression-free survival unexpectedly increased by around 35% at 16 months but time-to-event analyses can only decrease or remain constant over time. The

assessment group explained that there may have been a phase of increased risk of progression or death at the end of the trial that could continue beyond the trial period. Therefore it fitted an exponential extrapolation to the tail of the progression-free survival curve to make use of the observed trial data. The committee understood that the assessment group's approach provided a close fit to the final events of disease progression in the trial, with a mean progression-free survival estimate that was neither too generous nor too conservative. The committee concluded that the assessment group's method provided the best fit to the trial data but considered that some of Bayer's alternative extrapolations were also clinically plausible.

The assessment group's method provided the best fit to the trial data but other extrapolations for overall survival are plausible

3.12 For overall survival, the assessment group investigated longer-term survival trends in people with locally advanced or metastatic thyroid cancer in the US using the Surveillance, Epidemiology, and End Results (SEER) database. The database contains information on over 32,000 people who were followed up over 15 years. The assessment group explained that the SEER data followed a simple linear model that indicated that the risk of death was unchanged over the 15 years of follow-up. Therefore, the assessment group used a 2-phase exponential distribution in a piecewise model to extrapolate the Kaplan–Meier data from the trials. The clinical expert explained that historical data are unlikely to include the same population as the DECISION and SELECT trials. The assessment group also explored other parametric models and extrapolation methods for overall survival. It noted that the piecewise exponential model was the best-fitting option in 2 of the 4 trial arms, but no single extrapolation showed a clear advantage over another. Bayer used several alternative curves to extrapolate overall survival based on measures of fit to the trial data as well as published epidemiological evidence and clinical advice. Bayer considered that the fully parametric exponential and piecewise exponential models were similarly plausible,

but suggested that a single exponential curve fitted the survival estimates reported in a survey of 7 UK clinical experts better than the assessment group's approach. The committee understood that the cost effectiveness of sorafenib improved substantially using Bayer's alternative extrapolations in the assessment group's model. But it noted that the single exponential extrapolation was a poor fit to the trial data and appeared to be an outlier compared with other survival extrapolations. The committee concluded that the assessment group's method fitted the trial data well but Bayer's alternative extrapolations were also clinically plausible and improved the cost effectiveness of sorafenib.

Utility values

Using utility values from DECISION is the most appropriate

3.13 The models used utility values from health questionnaire (EQ-5D-3L) data collected in DECISION. Eisai explained that no EQ-5D data were collected for lenvatinib in SELECT, therefore its model used utility values from the best supportive care arm of DECISION and applied disutilities for adverse events as a weighted proportion using values from a vignette study (Fordham et al. 2015). The study included 100 people from the UK but the assessment group advised that their baseline utility values were higher than for a general UK population of a similar age. The model from the assessment group and Bayer assumed that disutilities were included in the EQ-5D values from DECISION. The assessment group preferred to use data from DECISION in its base case because it considered that evidence from people with differentiated thyroid cancer was more relevant to current practice than data from a vignette study. The assessment group explained that because there were no utility values for lenvatinib, utility values from DECISION were used for both treatments. The committee noted that this made lenvatinib more cost effective and sorafenib less cost effective. It recognised that utility values from DECISION did not adequately capture the different tolerability of the treatments and the different responses to treatment (see section 3.19) and so the utility

values for lenvatinib may have been underestimated. Because there were no other utility data the committee concluded that using utility values from DECISION was more appropriate than using the values from the vignette study.

Resource use

Changes to the assessment group's scenario analyses are clinically plausible and appropriate for decision-making

3.14 In its response to consultation, Eisai commented that the assessment group's estimates of resource use were not consistent with advice from 4 UK clinical experts. Eisai explained that in UK clinical practice hypertension is usually managed in primary care, bone scans are not carried out, there are fewer MRI scans and more frequent oncologist visits. The committee understood that when the estimates of resource used were changed in line with clinical practice in the assessment group's scenario analyses, both lenvatinib and sorafenib became more cost effective than best supportive care. The clinical expert confirmed that fewer investigations may be carried out in clinical practice than suggested in the assessment group's report, particularly before disease progression. The committee considered that resource use in the assessment group's base-case model may be overestimated. It concluded that the changes to the scenario analyses were clinically plausible and appropriate for decision-making.

Treatment after disease progression

The assessment group's model did not consistently include treatments taken after progression

3.15 In its response to consultation, Bayer commented that the assessment group's model included the cost of taking sorafenib after progression but it did not include the cost of taking other tyrosine kinase inhibitors after progression on lenvatinib. Bayer considered this to be inconsistent with

the clinical trials and UK clinical practice. The assessment group acknowledged that in SELECT, patients were allowed to take tyrosine kinase inhibitors other than lenvatinib after disease progression. However, there were no data available from SELECT on tyrosine kinase inhibitor use that could be incorporated in the economic model. The committee understood that both Bayer and the assessment group reported scenario analyses without the cost of sorafenib taken after progression. In the assessment group's analyses this scenario had little effect on its base case but there was a substantial improvement in the cost effectiveness of sorafenib using Bayer's alternative extrapolations (see sections 3.11 and 3.12). The committee acknowledged the lack of data but concluded that the assessment group's modelling of treatment after progression was not consistent for lenvatinib and sorafenib.

Revised base case

The assessment group's model is preferred for decision-making, but alternative assumptions may be plausible

3.16 The committee considered that the assessment group's model was the most reliable to estimate cost effectiveness. The model:

- compared each treatment with best supportive care only (assessment group's base case, see section 3.10)
- used a 3-state model that did not include a separate state for people with disease that responded to treatment (assessment group's base case, see section 3.10)
- used utility values from DECISION for both treatments (assessment group's base case, see section 3.13)
- used alternative resource use estimates for both treatments (assessment group's scenario analysis, see section 3.14).

After consultation, the assessment group revised its base case to correct the dose of lenvatinib, used another method to calculate costs for adverse

events and corrected a discounting error. The committee understood that in the assessment group's revised base case, the method and time point for extrapolating survival data was unchanged. It noted the uncertainty in the choice of survival extrapolation. Although the committee preferred the assessment group's method of extrapolation and agreed it would use it in its decision-making, it also recognised that some alternative extrapolations preferred by Bayer may be clinically plausible (see sections 3.11 and 3.12).

Cost-effectiveness results

The ICERs for lenvatinib and sorafenib are more than £30,000 per QALY gained

3.17 For lenvatinib compared with best supportive care, the incremental cost-effectiveness ratio (ICER) using the committee's preferred assumptions and including the confidential commercial arrangement was more than £30,000 per quality-adjusted life year (QALY) gained.

3.18 For sorafenib compared with best supportive care, the ICER using the committee's preferred assumptions and the confidential commercial arrangement was more than £30,000 per QALY gained.

Uncaptured benefits

There are some health-related benefits from response to treatment that are not captured in the preferred analyses, which could reduce the ICERs

3.19 The committee recognised that differentiated thyroid cancer is rare, and that lenvatinib and sorafenib are the only targeted treatments available. It noted that both drugs delayed disease progression compared with best supportive care. Despite some methodological uncertainty because the proportional hazards assumption was not met, the model predicted substantial overall survival benefit. The committee understood that although there was a statistically significant reduction in EQ-5D values in the sorafenib arm in DECISION, this difference was not considered clinically meaningful. However, the clinical and patient experts advised

that for symptomatic disease, response to treatment has a substantial effect on quality of life and this is valued by patients. This is particularly so for lenvatinib, which has a higher response rate than sorafenib (see section 3.9). The committee recalled that Eisai's model did not incorporate response appropriately for both treatments and recognised that the most plausible ICERs were based on the assessment group's model, which did not adequately capture this benefit. Therefore the committee concluded that there may be some additional health-related quality-of-life benefits from response to treatment that are not captured in the QALY calculations. It agreed that accounting for these uncaptured benefits could reduce the ICERs.

End of life

Both drugs meet the criterion for extension to life

3.20 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods. The assessment group's model estimated a mean survival benefit of 25 months for lenvatinib compared with best supportive care and 13 months for sorafenib compared with best supportive care. The committee recognised it was likely that both treatments provided a substantial overall survival gain compared with best supportive care. But it agreed there was uncertainty around how long people live with progressed disease. The committee agreed that the end-of-life criterion for extension to life (that is, a mean of at least 3 additional months) was met for both lenvatinib and sorafenib.

There is uncertainty about predicted overall survival and neither drug meets the criterion for short life expectancy

3.21 The assessment group's model predicted mean overall survival for best supportive care to be over 24 months (in the RPSFT-adjusted placebo arm in SELECT it was 30.2 months and in DECISION 43.8 months). However, the committee recalled that both lenvatinib and sorafenib

provided a substantial overall survival benefit compared with best supportive care that is not normally seen with other drugs for other cancers. The committee discussed whether it could accept a longer life expectancy of more than 24 months because of the substantial survival benefit, noting that the end-of-life criteria allowed this flexibility. However, it was concerned that survival of up to 43.8 months was not likely to be considered end of life. Also, it noted that the data were not robust enough to establish how long people live with progressive locally advanced or metastatic differentiated thyroid cancer. The clinical expert explained that although it is not possible to know the overall survival estimates for a population who has not had treatment, locally advanced or metastatic differentiated thyroid cancer is considered a terminal disease. The committee noted that in the assessment group's alternative extrapolations, the predicted overall survival estimates for the best supportive care arm after 10 years were consistently longer than 24 months. It understood that Bayer reported subgroup analyses in patients with symptomatic disease, but recalled the clinical expert's view that the trial populations were very similar to people having treatment in clinical practice, that is, people with progressive disease that is symptomatic or that will become symptomatic very quickly (see section 3.2). It noted that the subgroup analyses in patients with symptomatic disease from DECISION were post-hoc exploratory analyses that may not be reliable. Also, the assessment group's estimates of overall survival in this post-hoc subgroup were greater than 24 months. The committee debated whether it could apply flexibility when interpreting the end-of-life criteria but recognised that a high degree of certainty is needed. Based on the evidence presented, the committee concluded that neither lenvatinib nor sorafenib met the criterion for short life expectancy and therefore the end-of-life criteria did not apply.

Conclusions

Lenvatinib and sorafenib are recommended for treating differentiated thyroid cancer after radioactive iodine

3.22 The committee noted that there were additional considerations that could reduce the ICERs for lenvatinib and sorafenib compared with best supportive care, including:

- accounting for uncaptured benefit from response (see section 3.19)
- some of Bayer's alternative extrapolations of survival data for sorafenib may be plausible (see sections 3.11, 3.12 and 3.16).

The committee also considered the substantial modelled survival benefit (25 months for lenvatinib and 13 months for sorafenib) for people with this rare disease and that there are no other treatment options (see section 3.1). Taking all of this into account, the committee recommended lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine.

Lenvatinib and sorafenib are recommended only for people who have not had a tyrosine kinase inhibitor

3.23 Neither the companies nor the assessment group presented cost-effectiveness analyses according to previous tyrosine kinase inhibitor treatment. For sorafenib, this was not necessary because previous tyrosine kinase inhibitor treatment was not allowed in DECISION. Therefore sorafenib can only be considered and recommended by the committee as a first tyrosine kinase inhibitor treatment for this indication. Eisai's model for lenvatinib was based on the overall population from SELECT only. It did not present a cost-effectiveness analysis for the subgroup who had previous tyrosine kinase inhibitor treatment because of the small patient numbers. The assessment group did not have access to the overall survival results for this subgroup from SELECT, therefore it did not do a cost-effectiveness analysis for this group. However, it stated that

the uncertainties about the small numbers in the subgroup and the assumption of proportional hazards in the crossover-adjusted overall survival results for the overall population (see section 3.4) would not allow a robust estimate of cost effectiveness of lenvatinib in this subgroup. The committee would have preferred to see cost-effectiveness estimates according to previous tyrosine kinase inhibitor treatment, although it acknowledged that the estimates may not be robust. The committee was aware that the cost-effectiveness estimates provided were based on the overall SELECT population including the small number of patients who had previously had tyrosine kinase inhibitor treatment. However, because of the uncertainty about the clinical effectiveness (see sections 3.6 to 3.8) and the cost effectiveness of the drugs when used sequentially, the committee concluded that its recommendation for sorafenib and lenvatinib was limited to people who have not had previous treatment with a tyrosine kinase inhibitor.

The recommendation extends to people who have had to stop a tyrosine kinase inhibitor within 3 months of starting treatment because of toxicity

3.24 The committee was aware that some people who had a tyrosine kinase inhibitor as their initial treatment for differentiated thyroid cancer (after radioactive iodine) may have had to stop treatment because of toxicity. Aware of its recommendation about the sequential use of sorafenib and lenvatinib, the committee agreed that people who had to stop treatment with a tyrosine kinase inhibitor because of early intolerance would be considered as having had no previous treatment. The committee concluded that its recommendation extends to people who have had to stop a tyrosine kinase inhibitor within 3 months of starting treatment because of toxicity (specifically, toxicity that cannot be managed by dose delay or dose modification).

The recommendation does not include people having lenvatinib after disease progression on sorafenib (currently provided through compassionate use)

3.25 The committee discussed the issue of the compassionate use scheme for lenvatinib, in which the company is providing access to lenvatinib for people who cannot tolerate sorafenib or who have disease that has progressed on sorafenib. The committee acknowledged its recommendation does not include the latter group (people who have progressed on sorafenib). It understood from NHS England that patients who have commenced compassionate use treatment will be able to continue treatment as long as the patients and clinicians felt there was benefit.

Other factors

3.26 No equality issues were identified.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has progressive, locally advanced or metastatic

differentiated thyroid cancer (papillary, follicular or Hürthle cell) that does not respond to radioactive iodine and the doctor responsible for their care thinks that lenvatinib or sorafenib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on these technologies will be considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, Appraisal Committee
June 2018

6 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

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

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Project Manager

ISBN: [to be added at publication]