NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lenvatinib and sorafenib in the NHS in England. The appraisal committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: October 2017

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using lenvatinib and sorafenib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 10 November 2017

Second appraisal committee meeting: 23 November 2017

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Lenvatinib and sorafenib are not recommended, within their marketing authorisations, 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.

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 these recommendations 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

Lenvatinib and sorafenib 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 suggests that lenvatinib and sorafenib are both effective in delaying disease progression, but there is a higher response to lenvatinib and it may delay progression for longer. Both trials allowed patients who had placebo to have active treatment after disease progression (called cross-over). The survival results from the trial needed adjusting to account for this. Although using methods to adjust for this cross-over introduces some uncertainty, the evidence shows that lenvatinib prolongs survival but the survival benefit with sorafenib is less convincing.

Cost-effectiveness estimates for both lenvatinib and sorafenib are much higher than what NICE normally considers to be an acceptable use of NHS resources. Neither treatment meets NICE's end-of-life criteria or is

suitable for use in the Cancer Drugs Fund. Therefore, neither lenvatinib nor sorafenib can be recommended.

2 The technologies

	Lenvatinib (Lenvima, Eisai)	Sorafenib (Nexavar, Bayer)
Marketing authorisations	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.
Recommended doses and schedules	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 30×4 mg pack (excluding VAT; British national formulary online [accessed July 2017]). The company has agreed a patient access scheme with the Department of Health. If lenvatinib had been recommended, this scheme would provide a simple discount to the list price of lenvatinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.	£3,576.56 per 112×200 mg pack (excluding VAT; British national formulary online [accessed July 2017]). The company has a commercial access agreement with NHS England. If sorafenib had been recommended, this agreement would make sorafenib available at a reduced cost. The financial terms of the agreement are commercial in confidence.

3 Committee discussion

The appraisal committee (section 5) 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 ablation (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 without progression for long periods. In clinical practice, best supportive care is offered until 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 on 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 access programme for people who cannot tolerate sorafenib or 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 a 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 is best supportive care, which includes treatment such as palliative radiotherapy, analgesia and bisphosphonates. The committee concluded that there is a need for active treatment options for people with disease that is not responding to radioactive iodine treatment.

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 and best

supportive care. 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 subgroup analyses in patients with symptomatic disease from DECISION were post-hoc exploratory analyses that may not be reliable. The clinical expert advised that the trials included patients with recently progressed disease that is 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 but lenvatinib shows a larger benefit

3.3 In SELECT, the median investigator-assessed progression-free survival for lenvatinib was 16.6 months compared with 3.7 months for placebo. Lenvatinib improved investigator-assessed progression-free survival (hazard ratio [HR] 0.24, 95% confidence interval [CI] 0.16 to 0.35) compared with placebo and similar results were reported for independently-assessed progression-free survival. In DECISION, the median investigator-assessed progression-free survival for sorafenib was 10.8 months compared with 5.4 months for placebo. Sorafenib also improved investigator-assessed progression-free survival (HR 0.49, 95% CI 0.39 to 0.61) compared with placebo, and similar results were reported for independently-assessed progression-free survival. The committee

concluded that there is evidence to show that both treatments are clinically effective in improving progression-free survival and lenvatinib shows a larger benefit.

Overall survival results from SELECT and DECISION

Lenvatinib improves overall survival but the magnitude of benefit for sorafenib is less convincing

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 an 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 with 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. In addition, the committee noted that the use of 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 impact. The committee concluded that there is uncertainty in the magnitude of overall survival benefit. However, there is some evidence to show that lenvatinib is clinically effective in improving overall survival but the survival benefit with sorafenib is less convincing.

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 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 in the use of anticancer treatment after disease progression in SELECT and DECISION. In DECISION, patients who had previously had vascular endothelial growth factor receptor inhibitors were not included compared with 24% who had previous treatment in SELECT, and 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). For these reasons, the committee concluded that an

indirect comparison of lenvatinib and sorafenib using evidence from SELECT and DECISION was not appropriate.

Adverse events

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

3.6 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 impact 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, but that clinical effectiveness, in particular, response rates, and toxicity profiles are also considered. The response rate for lenvatinib in SELECT (objective tumour response 65%) was higher than for sorafenib in DECISION (objective tumour response 12%) and suggested a larger benefit for lenvatinib. They also explained the importance of balancing the risks and benefits when considering either treatment. The committee concluded that the decision to use lenvatinib or sorafenib is based on individual circumstances and careful 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

3.7 The model submitted by Eisai for lenvatinib included 4 health states (stable disease, response, progressive and death) whereas Bayer's model

for sorafenib and the assessment group's model included only 3 health states (progression-free, progressed and death). The assessment group did not include a separate health state for people responding to treatment because clinical advice suggested there was no additional benefit from including this state in the economic model. The clinical expert explained that for symptomatic disease, response to treatment substantially affects quality of life (see section 3.11). The committee noted the difference in opinion but considered that there were no data presented measuring the impact of a response health state on costs and utility values. The committee also understood that Eisai's model did not incorporate the duration of response appropriately and therefore questioned the validity of the model. The assessment group's model also 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 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). In the absence of a 4 state model that modelled response appropriately, the committee concluded that a model with 3 health states comparing each treatment with best supportive care was preferred for decision-making.

Extrapolation of overall survival

There is no justification to favour one overall survival extrapolation approach over the other

3.8 Bayer (sorafenib) used a fully parametric exponential model to extrapolate overall survival based on measures of fit to the trial data as well as published epidemiological evidence and clinical advice. The assessment

group investigated longer-term survival trends in people with locally advanced or metastatic thyroid cancer in the USA 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 simple exponential distribution in a piecewise model to extrapolate overall survival Kaplan-Meier data from the trials. The company agreed that an exponential model was appropriate but commented that the assessment group's approach lacked face validity and overestimated the treatment duration for sorafenib, while underestimating that for lenvatinib. The committee questioned whether alternative parametric models and extrapolation methods were explored in the assessment group's analyses. The assessment group explained that fully parametric curves did not fit the long-term data well. The assessment group also stated that using the piecewise model allowed the observed trial data to be used directly to predict the long-term survival estimates from the economic model. The committee would have preferred to have seen overall survival extrapolations that used both piecewise and fully parametric curves and a range of alternative statistical distributions. The committee acknowledged the merits of the different approaches used by the companies and the assessment group, but concluded, based on the evidence it had been presented with, there was no sufficient justification to favour one approach over the other.

Utility values

Using utility values from DECISION is the most appropriate

3.9 The models used utility values from 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 the baseline utility values in Fordham et al. (2015) were higher compared with the general population in the UK of a similar age. The model from the assessment group and Bayer (sorafenib) 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 in the absence of similar evidence for lenvatinib, utility values from DECISION were used for both treatments. The committee noted that using the alternative utility values made lenvatinib more cost effective but sorafenib became less cost effective. It recognised that utility values from DECISION did not adequately capture the different side effects of the treatments and the different response to treatment (see section 3.6) and this may have underestimated utility values for lenvatinib. In the absence of alternative utility data the committee concluded that using utility values from DECISION was more appropriate than using the values from the vignette study.

Cost-effectiveness results

The most plausible ICERs for lenvatinib and sorafenib are higher than the range normally considered cost effective

3.10 The committee noted the uncertainty in the choice of overall survival extrapolation (see section 3.8). However, it considered the most reliable evidence on which to estimate the cost-effectiveness was the assessment group's model, which consistently applied methods for both treatments and which:

- compared each treatment with best supportive care only (see section 3.5)

- used a 3-state model that did not include a separate state for people responding to treatment (see section 3.7)
- used a simple exponential distribution in a piecewise model to extrapolate overall survival (see section 3.8)
- used utility values from DECISION for both treatments (see section 3.9).

Including the confidential patient access scheme discount for lenvatinib and the commercial access agreement for sorafenib, the incremental cost-effectiveness ratio (ICER) for each treatment compared with best supportive care was considerably higher than £30,000 per quality-adjusted life year (QALY) gained (the exact ICERs are commercial in confidence and cannot be reported here). The committee concluded that the most plausible ICERs were much higher than what NICE normally considers to be a cost-effective use of NHS resources (that is, between £20,000 and £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

3.11 The committee recognised that differentiated thyroid cancer is rare, and that lenvatinib and sorafenib are the only targeted treatments available for this indication. It noted the advice from NICE's social value judgements: principles for the development of NICE guidance, that NICE should evaluate drugs to treat rare conditions in the same way as any other treatment. It noted that both drugs delayed disease progression compared with best supportive care and 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 experts advised that for

symptomatic disease, response to treatment has a substantial impact on quality of life, particularly with lenvatinib, which has a higher response rate than sorafenib (see section 3.6). The committee recalled that Eisai's model did not incorporate response appropriately and recognised that the most plausible ICERs were based on a model that 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 not already captured in the QALY calculations. It agreed that accounting for these uncaptured benefits could reduce the ICERs but had not been presented evidence demonstrating this, and it could not make a judgement about the impact on the ICER.

End of life

Both drugs meet the criterion for extension to life

3.12 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 agreed there was uncertainty around how long people live with progressed disease and it had not seen lifetime survival estimates using alternative parametric extrapolations. 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

3.13 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 treatments 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. In addition, 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 understood that the median overall survival in the placebo arms of the trial was over 24 months but explained that in clinical practice, although some people may live longer, at least 50% will not live longer than 2 years. Because there were no lifetime survival estimates exploring a range of alternative parametric extrapolations, the committee felt that it did not have enough information to judge the survival prospects for this group of people. 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 and this could be resolved by further information on overall survival. Based on the evidence presented to it, 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.

Recommendations

Lenvatinib and sorafenib cannot be recommended for routine commissioning

3.14 The committee could not recommend lenvatinib and sorafenib as a cost-effective use of NHS resources for treating differentiated thyroid cancer, because the ICERs for each drug were significantly higher than £30,000 per QALY gained, and neither drug met the end-of-life criteria.

Cancer Drugs Fund

The companies did not consider either treatment to be suitable for the Cancer Drugs Fund

3.15 Having concluded that lenvatinib and sorafenib could not be recommended for routine use, the committee then considered if they could be recommended for treating progressive, locally advanced or metastatic, differentiated thyroid cancer that does not respond to radioactive iodine within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. The companies stated that there are no significant ongoing trials that would provide further evidence on overall survival in the Cancer Drugs Fund. Therefore, the drugs should be considered for routine use only. Because there will be no further data collection to address the clinical uncertainty, data collected from the Cancer Drugs Fund is unlikely to address the key uncertainties and there was no plausible potential for cost effectiveness, the committee concluded that lenvatinib and sorafenib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Other factors

3.16 No equality issues were identified.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is 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
October 2017

5 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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