

# Lenvatinib and sorafenib for differentiated thyroid cancer after radioactive iodine: a systematic review and economic evaluation

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## Scientific summary

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# Scientific summary

## Background

Thyroid cancer is a rare cancer, accounting for only 1% of malignancies in England and Wales. Differentiated thyroid cancer (DTC) accounts for approximately 94% of thyroid cancers. For patients with DTC, the overall 10-year survival rate for middle-aged adults is 80–90%.

Treatment of DTC usually involves surgery. Following surgery, it is generally recommended that patients undergo treatment with radioactive iodine. Treatment for DTC refractory to radioactive iodine [radioactive iodine-refractory DTC (RR-DTC)] is often limited to best supportive care (BSC).

Two oral anti-cancer treatments for RR-DTC, used within their licensed indications, are the focus of this review: lenvatinib (Lenvima®; Eisai Ltd, Hertfordshire, UK) and sorafenib (Nexar®; Bayer HealthCare, Leverkusen, Germany). Both are types of tyrosine kinase inhibitors (TKIs) known as multikinase inhibitors.

Clinical advice to the Assessment Group (AG) is that in clinical practice there are concerns about the toxicity of TKI therapy in patients and consequent effects on the quality of life of patients with asymptomatic disease. This means that treatment tends to be given only to patients who are symptomatic or only when clinically significant progressive disease develops.

## Objectives

The remit of this research was to assess the clinical effectiveness and cost-effectiveness of lenvatinib and sorafenib within their European Union marketing authorisations for the treatment of patients with RR-DTC.

## Review methods

The research involved systematic reviews of clinical and cost-effectiveness evidence, including evidence provided by the companies that manufacture lenvatinib (Eisai Ltd) and sorafenib (Bayer HealthCare). The AG also carried out its own evidence review and developed a de novo economic model.

Five electronic databases were searched (on 10 January 2017) for randomised controlled trials (RCTs), systematic reviews, prospective observational studies and economic evaluations. References in the systematic reviews identified during the AG's review and the professional stakeholder submissions, received as part of the National Institute for Health and Care Excellence (NICE)'s multiple technology appraisal process, were cross-checked to identify any relevant studies that the AG's search may have missed. Only studies of lenvatinib or sorafenib for treating RR-DTC were included. Clinical effectiveness outcomes included overall survival (OS), progression-free survival (PFS), objective tumour response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL). Cost-effectiveness outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts, applied inclusion criteria to relevant publications, and quality assessed the included studies. The results of the data extraction and quality assessment were summarised in structured tables and by narrative description. The AG constructed a de novo economic model comparing the cost-effectiveness of lenvatinib and sorafenib with BSC.

## Results from the systematic reviews

### Evidence from randomised controlled trials

Two relevant Phase III, multicentre, double-blind RCTs were identified: SELECT (Study of [E7080] Lenvatinib in 131I-refractory differentiated Cancer of the Thyroid) (lenvatinib vs. placebo) and DECISION (Study of sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory thyroid cancer) (sorafenib vs. placebo).

The proportions of patients in these trials who were asymptomatic at baseline are unknown; however, the European Public Assessment Report for sorafenib reports that 20% of patients in DECISION were retrospectively considered to be symptomatic.

The AG considered both trials to be well conducted and of good quality; however, there were some differences in trial and patient characteristics, both within and across the two trials. Owing to event hazards being proportional over time only for DECISION-unadjusted OS, all other hazard ratio results from SELECT and DECISION should be interpreted with caution.

The primary outcome in both trials was PFS, assessed by blinded independent review, using data from the first data cut-off point (after a median of 17 months' follow-up in both trials). Results from SELECT show that treatment with lenvatinib improved median PFS compared with placebo (18.3 vs. 3.6 months, respectively). Results from DECISION show that treatment with sorafenib improved median PFS compared with placebo (10.8 vs. 5.8 months, respectively). Results from the post hoc subgroup analyses of data collected from symptomatic and asymptomatic participants show that median PFS for asymptomatic and symptomatic participants treated with sorafenib is similar (10.8 vs. 10.7 months, respectively); however, for participants treated with placebo, the median PFS of asymptomatic participants is twice that of symptomatic participants (7.2 vs. 3.6 months, respectively).

The OS results from SELECT and DECISION at the third data cut-off point (after approximately 38 and 36 months' follow-up, respectively) showed no statistically significant differences between trial arms; however, patient crossover was high ( $\geq 75\%$ ) in both trials, confounding OS estimates. When OS results from both trials were adjusted for treatment crossover, the only statistical difference between arms was in SELECT, favouring lenvatinib over placebo.

The ORR in both trials was reported based on data from the first data cut-off point. ORR in SELECT was 64.8% in the lenvatinib arm and 1.5% in the placebo arm. ORR results for the sorafenib and placebo arms of DECISION were 12.2% and 0.5%, respectively.

Analyses of safety data from SELECT and DECISION were reported from the first data cut-off point. Results show that treatment with both lenvatinib and sorafenib led to an increase in the incidence of AEs versus treatment with placebo (in particular, hypertension and hand-foot syndrome, respectively). The median time to onset of AEs suggests that most AEs typically occur early, with a decrease in incidence, prevalence and severity over time. Dose reductions were frequent ( $> 60\%$ ) in both trials.

Health-related quality-of-life data were collected only as part of DECISION. At baseline, HRQoL scores were considered to be comparable to a normative adult cancer population; however, at the first assessment (cycle 2, day 1), HRQoL scores worsened in the sorafenib arm whereas the scores for the placebo arm remained very similar to the baseline score. Thereafter, the sorafenib arm scores remained similar to the scores at first assessment, whereas the placebo arm scores remained similar to the baseline scores.

Prespecified subgroup analyses were conducted for OS, PFS and ORR in SELECT and for PFS in DECISION. All findings favoured the intervention (lenvatinib or sorafenib) when compared with placebo.

Both trials also included extended open-label phases including patients who had crossed over from placebo to lenvatinib or sorafenib on disease progression. The extended open-label phase of DECISION also involved patients who received additional sorafenib on disease progression. The efficacy findings for PFS from the extended phase of SELECT and DECISION were similar to the findings reported in the randomised phase of the trials. The incidence of AEs for patients treated with lenvatinib and sorafenib in the open-label phases of the two trials tended to be slightly lower than the incidence of those reported during the double-blind phase.

### **Indirect comparison**

In the absence of direct clinical evidence comparing treatment with lenvatinib with treatment with sorafenib, the AG considered whether or not it would be appropriate to undertake an indirect treatment comparison. As SELECT and DECISION shared a common comparator (placebo), it is possible to construct a network; however, differences in participant characteristics, both within and between the trials, raised concerns about whether or not this approach was appropriate. The AG examined the PFS Kaplan–Meier data and concluded that the risk profiles of the populations in the two placebo arms were not comparable. In view of these issues, the AG concluded that it was not appropriate to undertake an indirect comparison, and considered that the results generated by any indirect comparison that included data from SELECT and DECISION should be interpreted with caution. Therefore, the AG could not conclude whether the effectiveness of treatment with lenvatinib and effectiveness of treatment with sorafenib are similar or different.

### **Evidence from other reviews and prospective observational studies**

Thirteen studies were included in the AG's review of systematic review evidence, including those reviews conducted by Eisai Ltd and Bayer HealthCare, provided within their company submissions. Nine studies were included in the AG's review of prospective observational studies. Unadjusted median OS estimates for patients treated with lenvatinib and sorafenib in SELECT and DECISION tended to be higher than those reported in the reviewed prospective observational studies, whereas median PFS and ORR estimates tended to be lower. Results from indirect comparisons conducted by the authors of systematic reviews showed PFS (but not OS) to be statistically significantly improved with lenvatinib, when compared with sorafenib. Overall, the safety findings from the RCTs were consistent with the findings from the prospective observational studies and systematic reviews of lenvatinib and sorafenib. Results from indirect comparisons conducted by the authors of two systematic reviews showed lenvatinib to result in statistically significantly fewer cases of alopecia but statistically significantly more cases of hypertension, serious adverse events, treatment-related serious adverse events and withdrawals owing to AEs, when compared with sorafenib.

### **Evidence from cost-effectiveness studies**

The two submitting companies and the AG agreed that there are no published cost-effectiveness studies relevant to the decision problem set out in the final scope issued by NICE.

## **Company submissions (economics)**

Both companies submitted economic evidence generated by de novo economic models. Using list prices, the Eisai Ltd base-case incremental cost-effectiveness ratio (ICER) for the comparison of treatment with lenvatinib and treatment with sorafenib is £22,491 per QALY gained; for the comparison of treatment with lenvatinib and BSC, it is £48,569 per QALY gained. The analyses carried out by Bayer HealthCare used the Commercial Medicines Unit price for sorafenib and the list price for lenvatinib. The Bayer HealthCare ICERs per QALY gained for the comparison of treatment with sorafenib and treatment with lenvatinib, and treatment with sorafenib and BSC, are commercial in confidence and cannot be reported. Using the list price for sorafenib, the AG found that Bayer HealthCare's model generates an ICER per QALY gained of £56,417 for the comparison of treatment with sorafenib versus BSC.

## Summary of the Assessment Group's cost-effectiveness results

The AG considered that it was inappropriate to compare data from SELECT and DECISION in the same evidence network, and concluded that it was not possible to carry out a cost-effectiveness analysis of lenvatinib versus sorafenib for patients with RR-DTC. Instead, the AG used a standard partitioned survival model structure, applied to the patient population specified in the final scope issued by NICE, to consider the cost-effectiveness of lenvatinib and sorafenib separately in comparison with BSC (as represented by the placebo arms of SELECT and DECISION, respectively). The design of the AG's model allowed each intervention to be represented in its natural time metric: 30-day cycles for lenvatinib and 28-day cycles for sorafenib. This involved creating two parallel models using the same assumptions and model parameters, but each with its own placebo arm calibrated from its respective clinical trial data.

The AG's base-case analysis, using list prices only, for the comparison of the cost-effectiveness of treatment with lenvatinib and BSC yields an ICER per QALY gained of £65,872, and for the comparison of sorafenib and BSC it yields an ICER per QALY gained of £85,644. The AG's deterministic sensitivity analysis involved varying 18 parameters, and the results of these analyses show that none of the variations lowers the AG's base-case ICERs below £50,000 per QALY gained. The AG's probabilistic sensitivity analysis results show that, compared with BSC, the probability of sorafenib being cost-effective at a threshold of £50,000 per QALY gained is < 0.05%, and the probability of lenvatinib being cost-effective is 5.4%.

When the AG compared the cost-effectiveness of lenvatinib and BSC using placebo data from DECISION, and the cost-effectiveness of sorafenib and BSC using placebo data from SELECT, the ICERs per QALY gained approximately doubled (to £130,592) and halved (to £41,716), respectively. These results highlight that the choice of BSC comparator is very influential in this appraisal.

## Discussion

### Strengths

A key strength of this review is that it has brought together all the available relevant evidence (RCTs, observational studies, systematic reviews, indirect comparisons and cost-effectiveness studies) for assessing the clinical effectiveness and cost-effectiveness of treatment with lenvatinib versus sorafenib in patients with RR-DTC. The AG considered that SELECT and DECISION are good-quality, well-conducted trials.

### Weaknesses and areas of uncertainty

Owing to a lack of confidence in any results generated by an indirect comparison, the AG considered that it is not possible to compare the relative effectiveness of treatment with lenvatinib with the relative effectiveness of treatment with sorafenib.

The generalisability of the findings of SELECT and DECISION to NHS clinical practice is questionable, as, in clinical practice, concerns about the toxicity of TKI therapy in patients, and consequent effects on the quality of life of patients with asymptomatic disease, means that treatment is generally only given to patients who are symptomatic or when clinically significant progressive disease develops. However, results from a post hoc analysis of DECISION data showed no difference in median PFS between symptomatic and asymptomatic patients (retrospectively categorised) treated with sorafenib.

Owing to a lack of HRQoL studies, there is considerable uncertainty around the HRQoL of patients with RR-DTC in general.

## Conclusions

Compared with placebo, treatment with lenvatinib and sorafenib results in an improvement in PFS, ORR and possibly OS; however, compared with placebo, treatment with both drugs increases the incidence of AEs. Dose reductions with both drugs are, therefore, frequently required.

The AG considered that it is not possible to compare the clinical effectiveness or cost-effectiveness of lenvatinib with the clinical effectiveness or cost-effectiveness of sorafenib. This is primarily because the risk profiles of the participants in the placebo arms of SELECT and DECISION do not appear to be comparable.

Using list prices, compared with BSC, both treatments exhibit estimated ICERs of > £50,000 per QALY gained. Compared with BSC, the probability of sorafenib and lenvatinib being cost-effective at a threshold of £50,000 per QALY gained is < 0.05% and 5.4%, respectively.

## Recommendations for research

These recommendations are ranked in order of priority.

1. Future clinical effectiveness research should focus on a head-to-head RCT that includes lenvatinib, sorafenib and BSC, and addresses the following questions:
  - i. Should both symptomatic and asymptomatic patients be treated with lenvatinib and/or sorafenib?
  - ii. How does treatment with lenvatinib and sorafenib affect the HRQoL of patients (progressed and non-progressed, and symptomatic and asymptomatic)?
  - iii. What is the clinical effectiveness of lenvatinib and sorafenib compared with BSC and compared with each other?
  - iv. How should lenvatinib, sorafenib and BSC be positioned in the treatment pathway?
2. The AG considered that it is important to explore more than just standard differences in participant and trial characteristics when considering the heterogeneity of studies that may be included in an indirect comparison. The AG suggests that, before undertaking an indirect comparison, the risk profiles of patient populations for the relevant outcome should be checked to confirm that they are proportional both within and across all trials that are being considered for inclusion in the network. This assessment would avoid generating indirect comparison results that are of unknown reliability.

## Study registration

This study is registered as PROSPERO CRD42017055516.

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