Draft PROTOCOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Table of contents

ABBREVIATIONS LIST

AG	Assessment Group
CADTH	Canadian Agency for Drugs and Technologies in Health
DTC	Differentiated thyroid cancer
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FTC	Follicular carcinoma
HTA	Health technology assessment
LR*i*G	Liverpool Reviews and Implementation Group
LY	Life year
NICE	National Institute for Health and Care Excellence
PAS	Patient Access Scheme
PTC	Papillary carcinoma
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SMC	Scottish Medicines Consortium

1 TITLE OF PROJECT

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

2 ASSESSMENT GROUP

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3 PLAIN ENGLISH SUMMARY

Thyroid cancer is a rare cancer which affects the thyroid gland. The thyroid gland is located in the neck and produces hormones. Thyroid cancer is usually treated by surgery to remove the thyroid gland. Most cases of thyroid cancer are cured completely. However a small number of thyroid cancers return after treatment. Ninety per cent of thyroid cancers are referred to as differentiated thyroid cancer (DTC) and are treated in the same way.

Treatment for DTC involves surgery to remove all of the thyroid gland, followed by treatment with radioactive iodine (RAI) and oral thyroxine. The RAI aims to destroy any remaining cancer cells and the thyroxine is used to suppress hormones that stimulate the thyroid gland.

If the cancer continues to grow after RAI treatment, then only palliative treatment may be offered. However, there are newly available targeted therapies which may be suitable for the treatment of DTC that does not respond to RAI.

The aim of this review is to assess the clinical and cost effectiveness of two targeted therapies that are used to treat thyroid cancer that does not respond to RAI: lenvatinib and sorafenib. A systematic review of randomised controlled trials (RCTs) will be performed to assess the clinical effectiveness of these treatments in increasing overall survival and progression-free survival, the effect of the adverse events of treatment and impact on health-related quality of life. An economic model will be built to assess the cost effectiveness of treatments.

4 DECISION PROBLEM

4.1 Clarification of research question and scope

The remit of this review is to appraise the clinical and cost effectiveness of lenvatinib and of sorafenib within their respective European Medicines Agency (EMA) marketing authorisations for the treatment of patients with DTC whose disease is refractory to RAI.

4.2 Background

Thyroid cancer is caused by the growth of abnormal cells in the thyroid gland, a small gland at the base of the neck that secretes hormones to regulate the rate of a person's metabolism. The thyroid gland produces hormones: T3 (tri iodothyronine), T4 (thyroxine) and calcitonin. T3 and T4 control the rate of metabolism in the body, and calcitonin works with the parathyroid hormone to control the amount of calcium in the blood.[1]

Thyroid cancer is three times more common in women than men;[2] the reasons for this disparity are unclear.[3] The factors that can increase the risk of thyroid cancer, include:[4]

- other thyroid conditions, such as an inflamed thyroid (thyroiditis) or goitre (but not an overactive/underactive thyroid)
- a family history of thyroid cancer
- radiation exposure in childhood (e.g. radiotherapy)
- obesity
- a bowel condition called familial adenomatous polyposis
- acromegaly (a rare condition where the body produces too much growth hormone).

There are four main types of thyroid cancer: papillary carcinoma (PTC), follicular carcinoma (FTC), medullary carcinoma, and anaplastic carcinoma. There are other, rare types of thyroid cancer, which include Hürthle cell, tall cell, insular, and columnar. PTC and FTC are the most common types and are referred to as **differentiated** thyroid cancer. (Figure 1).

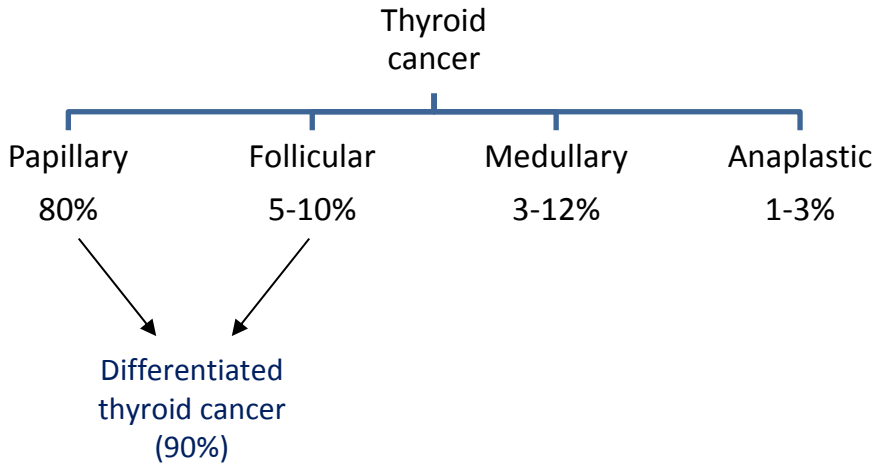

Figure 1 Types and prevalence of thyroid cancers

Source: Cancer Research UK[5]

The sub-types of DTC are similar in prognosis and are often treated in the same way. PTC usually affects people aged <40 years of age, and most often affects women; PTC is usually slow growing and can spread to lymph nodes in the neck.[4,5] FTC is most commonly diagnosed in older people, and, if it does spread beyond the thyroid, it is usually to the bones or lungs.[5] The long-term outcome for patients diagnosed with DTC is usually favourable, and most of these cancers are cureable.[5,6] There are a number of factors which have an effect on a patient's prognosis, including age, gender, histology (prognosis is better with PTC compared with FTC), and the extent of the tumour.[6]

4.2.1 Epidemiology

Thyroid cancer is a rare cancer, which in 2014 accounted for less than 1% of cancer deaths in the UK.[2] In the UK, thyroid cancer accounts for <1% of male cancer deaths, and <1% of

female cancer deaths; in England in 2014, there were 133 male and 188 female deaths caused by thyroid cancer.[2] In 2013, there were 3241 new cases of thyroid cancer, and thyroid cancer was the 19th most common cancer in the UK.[2] The figures for women diagnosed with thyroid cancer are significantly higher than those for men, with the men:women ratio being approximately 4:10; in 2013, 73% of cases were diagnosed in women.[2] Thyroid cancer is usually treatable, and in many cases is cured completely. However, even after treatment, the cancer can return.[4]

DTC accounts for around 90% of all thyroid cancers. For patients with DTC, the overall 10-year survival rate for middle-aged adults is 80-90%; however, between 5-20% of patients with DTC develop local or regional recurrences and 10-15% of patients develop distant metastases.[6] The overall 10-year survival rate for all patients with advanced or metastatic DTC falls to 76% for advanced DTC and 63% for metastatic DTC.[6]

4.2.2 Current treatment options

Treatments for thyroid cancer depend on factors including age, extent of disease, and histology. Treatment of DTC usually involves surgery to remove the thyroid gland (total thyroidectomy), which could also include removal of nearby lymph nodes.[4] Following surgery, it is usually recommended that the patient undergoes treatment with RAI, which can be used to treat residual, recurrent, or metastatic disease.[6] Patients ingest RAI, which is absorbed by thyroid cells and destroys the cancer cells. If the treatment with RAI is unsuccessful, the patient may be offered palliative radiotherapy.[4] For those patients who become refractory to RAI, the overall 10-year survival rate is only 10%.[7]

Recently, targeted therapies such as sorafenib have been used to treat thyroid cancer.[8] In the UK, the clinical pathway for treating progressive DTC that is refractory to RAI is currently limited to palliative radiotherapy and symptom relief, though sorafenib is currently available through the cancer drug fund for metastatic or inoperable papillary and follicular thyroid cancer, which is refractory to radioiodine.[8]

4.2.3 The technology

The two drugs under consideration in this review are both multi-kinase inhibitors (MKIs). Sorafenib (Nexavar), manufactured by Bayer HealthCare, is an oral MKI drug and targets B-type Raf kinase, the RET gene, vascular endothelial growth factor (VEGFR) 2 and 3 and platelet-derived growth factor (PDGF) beta.[9] The recommended dose for the treatment of patients with DTC is 400mg (two 200mg tablets) twice daily. Tablets should be taken without food or with a low fat meal. Adverse events can be managed through dose reduction.[10] Treatment is continued until disease progression.

Lenvatinib (Lenvima), manufactured by Eisai, is also an oral MKI drug but targets VEGF factors 1-3, fibroblast growth factor receptors (FGFR)1–4, PDGFRβ, the RET gene, and KIT.[9] The recommended dose for the treatment of DTC is 24mg (two 10mg capsules and one 4mg capsule) once daily. Adverse events can be managed through dose reduction and treatment is continued until disease progression or unacceptable toxicity.[11]

4.2.4 Regulation and guidance

Regulation

Sorafenib was approved for use in Europe in November 2013 for the treatment of "progressive, locally advanced or metastatic DTC refractory to RAI" (EMA[12]) and, in the US, "for the treatment of locally recurrent or metastatic, progressive, DTC refractory to radioactive iodine treatment" (FDA[13]). Both decisions were based on the results of one randomised controlled trial (RCT) (DECISION[14]) in which 417 patients were randomised to sorafenib or placebo at a ratio of 1:1.

Lenvatinib was approved for use in the US in February 2015, for the treatment of patients with "locally recurrent, progressive, RAI-refractory DTC" (the FDA[15]). The EMA approved lenvatinib[16] in May 2015 for the treatment of "adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine." Both decisions were based on the results of one RCT (SELECT[17]) in which 392 patients were randomised to lenvatinib or placebo at a ratio of 2:1.

Guidance

National guidance on the use of lenvatinib and sorafenib to treat DTC is available from the Scottish Medicines Consortium (SMC[18,19]) and the Canadian Agency for Drugs and Technologies in Health (CADTH[20,21]).

The SMC assessed both lenvatinib and sorafenib under the end of life and ultra-orphan process. In June 2015, sorafenib was approved for use in Scotland for the treatment of patients with progressive, locally advanced or metastatic DTC refractory to RAI contingent on a continuing Patient Access Scheme (PAS) price.[18] The SMC decision was based on results from the DECISION[14] trial. In September 2016, lenvatinib was approved for use in Scotland for the treatment of adult patients with progressive, locally advanced or metastatic DTC (papillary, follicular/ Hürthle cell) refractory to RAI contingent on a continuing PAS price.[19] The SMC decision was based on the results of the SELECT[17] trial.

In July 2015, the CADTH reviewed the effectiveness and safety of sorafenib in combination with best supportive care (BSC) for the treatment of patients with locally advanced or

metastatic, progressive DTC refractory to RAI[20] and identified one relevant RCT (DECISION[14]). The CADTH concluded that "there is a net overall clinical benefit of sorafenib compared to placebo in patients with clinically progressive radioactive iodine refractory metastatic DTC".[20] In September 2016, the CADTH evaluated the safety and efficacy of lenvatinib on patient outcomes for the treatment of patients with locally recurrent or metastatic, progressive, RAI refractory DTC[21] and identified one relevant RCT (SELECT[17]). The CADTH concluded that there was net clinical benefit to lenvatinib for the treatment of RAI refractory DTC.

4.3 The present appraisal

The present appraisal will be conducted in line with the decision problem set out in the final scope issued by NICE.[8] This is replicated in Table 1. The interventions under consideration are lenvatinib and sorafenib, and the population under consideration is adults with progressive, locally advanced or metastatic DTC that is refractory to RAI. The interventions will be compared to each other and with BSC. The outcome measures to be considered include survival (overall and progression-free), response rates, adverse effects of treatment and health-related quality of life. The cost effectiveness evidence will be expressed in incremental cost per quality adjusted life years (QALYs) gained. The time horizon for the economic evaluation will be sufficiently long so as to reflect any differences in costs or outcomes between technologies. Any PAS price in place will be taken into account in the analyses.

Table 1 Decision problem issued by NICE

Interventions	• Lenvatinib • Sorafenib
Population	Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine
Comparators	• The interventions listed above will be compared with each other • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	If the evidence allows, consideration will be given to subgroups based on previous treatment with tyrosine kinase inhibitors. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.

5 METHODS FOR SYNTHESISING CLINICAL EVIDENCE

5.1 Search strategy

The Assessment Group (AG) will identify clinical studies and systematic reviews by searching major medical databases including MEDLINE, EMBASE, PubMed and the Cochrane Library, from 1999 onwards, as scoping searches revealed no relevant studies prior to this date likely due to the newness of the drugs. Scoping searches also revealed a limited number of results, therefore no other search filters will be used, ensuring all relevant evidence will be identified. In addition, information on studies in progress will be sought by searching a range of relevant databases including Clinical trials.gov.uk, International Clinical Trials Registry Platform (ICTRP) and EU Clinical Trials Register (EU-CTR).

An example of the draft search strategy to be used in MEDLINE is presented in Appendix 1. Citation searches of key articles will be undertaken. A database of published literature will be assembled from the aforementioned sources and will be held in the Endnote X7 software package.

5.2 Study selection

Two reviewers will independently screen all titles and abstracts identified by the initial search. Full text copies of any titles/abstracts that may be eligible for inclusion will be obtained and will be assessed for inclusion by two reviewers using the inclusion and exclusion criteria listed in Table 2. Included studies will not be limited to full texts but will include conference abstracts, if sufficient data are included. Any discrepancies will be resolved by consultation with a third reviewer. Studies that do not meet the inclusion criteria will be excluded and their bibliographic details will be listed with reasons for exclusion.

Table 2 Inclusion criteria (clinical effectiveness)

	Inclusion
Study design	Randomised controlled trials Systematic reviews •Evidence submitted to the EMA
Patient population	Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine
Interventions	• Lenvatinib • Sorafenib
Comparators	• Lenvatinib • Sorafenib • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life
Limits	English language only

5.3 Data extraction and quality assessment strategy

Data relating to study characteristics and outcomes will be extracted by one reviewer and independently checked independently checked for accuracy by a second reviewer. Disagreement will be resolved through consensus, through consensus, and, if necessary, a third reviewer will be consulted. Time permitting, study authors will be study authors will be contacted for missing data. Data from multiple publications will be extracted and reported as extracted and reported as a single study. Examples of draft data extraction forms built in Microsoft Access are Microsoft Access are presented in

Appendix 2.

The quality of the included studies will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the RCTs and SRs will be assessed according to criteria based on Centre for Review and Dissemination's Guidance[22] for undertaking reviews in healthcare.

5.4 Methods of analysis/synthesis

The results of the data extraction and quality assessment for each included study will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Treatment effect estimates and corresponding 95% confidence intervals will be extracted from the full text papers, or calculated from data presented in the full text papers if sufficient data is available. Treatment effect estimates will be presented as hazard ratios for time-to-event data, relative risks for dichotomous data, or as mean differences for continuous data. Estimates of treatment effect will only be pooled when it is statistically and clinically meaningful to do so. Studies will be grouped according to the comparator used.

Heterogeneity between the included studies will be assessed by considering differences in (a) study population, (b) intervention, (c) outcome measures, and (d) study quality. In addition, where pooling is clinically and statistically meaningful, forest plots will be visually assessed for the presence of heterogeneity, the Chi-squared test will be performed ($p<0.1$) and the I^2 statistic will be calculated to quantify heterogeneity.

If direct comparisons between comparators are not possible then, if the data allow, indirect comparisons will be conducted. The AG will assess the feasibility of performing an indirect comparison by evaluating the clinical and methodological heterogeneity of the included studies with regards to (a) study population, (b) intervention, (c) outcome measures, and (d) study quality. If the AG determine that it is appropriate to do so, indirect comparisons will be performed using WinBUGS 1.4 software.[23] The outputs from the indirect comparisons will be the estimated treatment effects for each treatment relative to every other treatment included in the indirect comparison; treatment effect estimates will be presented as hazard ratios for time-to-event data, relative risks for dichotomous data, or as mean differences for continuous data.

If the evidence allows, the AG will perform indirect comparisons for subgroups of patients according to previous treatment with tyrosine kinase inhibitors.

6 METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

6.1 Identifying and systematically reviewing published cost studies

The purpose of the systematic literature review is two-fold: to identify published economic evaluations that could contribute to the evidence base for lenvatinib and sorafenib in comparison with BSC or each other for treating advanced or metastatic thyroid cancer, and to source published estimates to be considered for use as parameter values (e.g. resource use, costs and utilities) in any de novo economic modelling conducted by the AG.

6.2 Search strategy

The AG will identify economic evaluations using the search strategy detailed in Section 5 and by searching NHS EED and Econlit, from 1999 onwards only, due to the newness of the drugs. The search strategy has been designed to identify economic evaluations for inclusion in the cost effectiveness literature review. This search strategy will enable economic evaluations and other information sources, which may include data that can be used to populate a de novo economic model, to be identified. Other searching activities, including electronic searching of online health economics journals and contacting experts in the field will also be undertaken. Full details of the search process will be presented in the final report.

6.2.1 Study selection and inclusion criteria

In addition to the inclusion criteria outlined in Table 2, specific criteria required for the cost effectiveness review are described in Table 3.

Table 3 Inclusion criteria (cost effectiveness)

Study design	Full economic evaluations that consider both costs and consequences (cost effectiveness analysis, cost utility analysis, cost minimisation analysis and cost benefit analysis)
Outcomes	Incremental cost per life year (LY) gained and/or incremental cost per quality adjusted life year gained (QALYs)

Only full economic evaluations that compare two or more treatments and consider both costs and consequences (including cost effectiveness, cost utility and cost benefit analyses) will be included in the review of published literature. In addition, if appropriate, any economic models included in the company submission(s) will be included in the review. Studies that do not meet all of the criteria will be excluded and reasons for exclusion and bibliographic details will be provided.

6.2.2 Data extraction

Data relating to both study characteristics and outcomes will be extracted by one reviewer and independently checked for accuracy by a second reviewer. Disagreement will be resolved

through consensus and, if necessary, a third reviewer will be consulted. If time constraints allow, attempts will be made to contact authors for missing study data. Data from multiple publications will be extracted and reported as a single study.

6.2.3 Quality assessment

The quality of the individual cost effectiveness studies/models will be assessed by one reviewer, and independently checked for agreement by a second. Disagreements will be resolved through consensus and, if necessary, a third reviewer will be consulted. The quality of the reported cost effectiveness studies/models will be assessed according to the CHEERS checklist.[24] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[25]

Individual study data and quality assessment will be summarised in structured tables and as narrative descriptions. The potential effects of study quality on study results and review findings will be discussed.

To supplement findings from the economic literature review, additional cost and benefit information from other sources, including the company/sponsor submission(s) to NICE, will be collated and presented within the AG report, as appropriate.

6.3 Health economic modelling

6.3.1 Cost data

The primary perspective for the analysis of cost information will be that of the UK NHS. Where possible, the Personal Social Services perspective will also be considered. Cost data collection will focus on the marginal direct health service costs associated with the interventions. The relevant time horizon for the analysis will be a patient's lifetime. In line with guidance presented in the NICE Methods Guide[25] the costs of generic drugs will be taken from sources that reflect nationally available prices (e.g. the British National Formulary[26] and the NHS Electronic Marketing Information Tool [eMIT][27]). Any PAS price that is in place will be taken into account.

Quantities of resources used will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. Unit cost data will be extracted from the literature (e.g. Personal Social Services Research Unit[28]) or obtained from other relevant sources (drug price lists, NHS Reference Costs[29] and Chartered Institute of Public Finance and Accounting cost databases[30]).

Where appropriate, costs will be discounted at 3.5% per annum, the rate recommended in the NICE Methods Guide[25] for companies and sponsors of submissions.

6.3.2 Assessment of benefits

A balance sheet will be constructed to list benefits and costs arising from alternative treatment options. The AG anticipates that the main measure of benefit will be QALYs. Where appropriate, effectiveness and other measures of benefit will be discounted at 3.5% per annum, the rate recommended in the NICE Methods Guide[25] for companies and sponsors of submissions.

6.4 Modelling

The ability of the AG to construct an economic model will depend on the data available. An analysis of potential patient subgroups and meaningful treatment pathways for each group will be constructed and discussed with regard to the feasibility of modelling each pathway and the options for model design to achieve useful cost effectiveness results. This may be possible within a single decision model, or require multiple models to be developed. Where modelling is appropriate, a summary description of the model(s) and a critical appraisal of key structures, assumptions, resources, data and sensitivity analysis will be presented. In addition, the AG will provide an assessment of the model(s) strengths and weaknesses and discuss the implications of using different assumptions in the model(s). Reasons for any major discrepancies between the results obtained from the AG model(s) and the company model(s) will be explored.

If data are available, the results will be presented as incremental cost per QALY ratios for each option considered. If sufficient data are not available to construct these measures with reasonable precision, incremental cost effectiveness analysis or cost minimisation analysis will be undertaken. Any failure to meet the NICE Reference Case[25] will be clearly specified and justified, and the likely implications will, as far as possible, be quantified.

6.4.1 Sensitivity analysis

If appropriate, sensitivity analysis will be applied to the AG model in order to assess the robustness of the results to realistic variations in the levels of the underlying parameter values and key assumptions. Where the overall results are sensitive to a particular variable, the sensitivity analysis will explore the exact nature of the impact of variations.

Imprecision in the principal model cost effectiveness results with respect to key parameter values will be assessed by use of techniques compatible with the modelling methodology deemed appropriate to the research question and to the potential impact on decision making

for specific comparisons (e.g. multi-way sensitivity analysis, cost effectiveness acceptability curves).

7 HANDLING THE COMPANY SUBMISSIONS

All data submitted by the companies/sponsors will be considered if received by the AG no later than 18/04/2017. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submissions, provided they comply with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the AG judges that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a de novo model. Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the company check list, will be highlighted in blue and underlined in the AG's report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' data taken from a company submission, and specified as confidential in the company check list, will be highlighted in yellow and underlined in the AG's report (followed by an indication of the relevant company name e.g. in brackets).

8 EXPERTISE IN THE ASSESMENT GROUP AND COMPETING INTERESTS

This AG comprises the individuals listed in Table 4. A panel of clinical experts will also be consulted during the review process. The experts will provide insight into a range of issues relating to clinical practice, potential patient characteristics that may influence clinical heterogeneity and relevant patient subgroups.

Table 4 Assessment Group members

Juliet Hounsome	Team lead/clinical systematic reviewer
Gerlinde Pilkington	Systematic reviewer (clinical)
Rachel Houten	Systematic reviewer (economics) and economic modeller
Prof Adrian Bagust	Economic modeller
Eleanor Kotas	Information specialist
Marty Richardson	Statistician
Dr Angela Boland	HTA analyst
Sophie Beale	HTA analyst
Prof Rumona Dickson	Methods adviser/Director
Dr David Husband	Clinical adviser
Dr Aditya Shenoy	Clinical adviser

None of the review team has any competing interests. Any competing interests relating to any external reviewers will be declared in the final report. All e-mail correspondence should be sent to the team leader.

9 PROJECT TIMELINES

Table 5 Timetable/milestones

Submission and approval of final protocol	20/12/2016
Stakeholder information meeting	To be confirmed
Progress report to NETSCC, HTA	24/04/2017
Assessment Group report to be submitted	24/07/2017

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11 APPENDICES

Appendix 1: Draft search strategy

1 exp Thyroid Neoplasms/

2 ((thyroid* or papillar* or follicular*) adj4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*)).tw.

3 (DTC or FTC or PTC).tw.

4 adenocarcinoma, follicular/ or carcinoma, papillary, follicular/ or adenocarcinoma, papillary/

5 1 or 2 or 3 or 4

6 (Lenvatinib or Lenvima or E7080).tw.

7 (Nexavar or Sorafenib or bay439006).tw.

8 6 or 7

9 5 and 8

Appendix 2: Draft data extraction forms (clinical)

Study characteristics

Study ID	
Year	
Country	
Setting	
Number of centres	
Recruitment period	
Length of follow up	
Sponsorship/funding	
Conflict of interest	
Intervention name	
Intervention dose and schedule	
Comparator name	
Comparator dose and schedule	
Power calculation	

Primary outcome definition and measure	
Secondary outcomes definitions and measures	
Inclusion/exclusion criteria	

Participant characteristics

Study ID		
N enrolled		
N lost to follow up		
Attrition rate		
Average age (mean, median, sd, range)		
% male		
Ethnicity		
Previous treatments		
Average time from diagnosis (months)		
ECOG		
Histology		
Metastases		
FDG uptake		

Outcomes

Study ID		
Overall survival		
PFS		
RR		
AEs		
HRQoL		