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Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [ID1059]

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MTA report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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

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The following data reported in the clinical study report for the SELECT trial was previously marked as commercial in confidence but which Eisai Ltd agreed could be cited in this report without confidentiality restrictions:

1. Table 11: Demographic and Baseline Characteristics – Full Analysis Set for data on age
2. Table 14.3.8.1 Post Randomization Anti-Cancer Therapy - Full Analysis Set
3. Table 33: Grade 3 or 4 Treatment-Emergent Adverse Events Occurring in at Least 2% of Subjects in Either Treatment Arm by System Organ Class and Preferred Term – Safety Analysis Set for incidence of hypocalcaemia
4. Table 34: Treatment-Related, Treatment-Emergent Adverse Events Occurring in at Least 10% of Subjects in Either Treatment Arm (All Grades and Grade 3 or Higher) by System Organ Class and Preferred Term – Safety Analysis Set for data on rash.

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1. Table 14.1.2 / 11: Systemic anti-cancer therapy during follow up: overview (full analysis set)
2. Table 14.3.3 / 3: Overview of treatment-emergent adverse events during double blind treatment period (safety analysis set) for data on treatment-related adverse events
3. Table 14.3.3 / 4: Treatment-emergent adverse events by CTCAE and worst CTCAE grade during double blind treatment period (safety analysis set) for data on proteinuria and dysphagia
4. Table 14.3.3 / 18: Treatment-emergent adverse events by MedDRA during double blind treatment period (safety analysis set) for data on asthenia.

In addition, Bayer Healthcare confirmed that all results using data from the third data cut (unadjusted and adjusted overall survival; progression-free survival; objective tumour response rate) could be cited in this report without confidentiality restrictions.

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors

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Data sharing statement
All available data can be obtained by contacting LRiG

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ABSTRACT

Background

Thyroid cancer is a rare cancer representing only 1% of all malignancies in England and Wales. Differentiated thyroid cancer (DTC) accounts for ~94% of all thyroid cancers. Patients with DTC often require treatment with radioactive iodine. Treatment for DTC refractory to radioactive iodine (RR-DTC) is often limited to best supportive care (BSC).

Objectives

We aimed to assess the clinical and cost effectiveness of lenvatinib and sorafenib for the treatment of patients with RR-DTC.

Methods

Five electronic databases were searched for randomised controlled trials (RCTs), systematic reviews, prospective observational studies and economic evaluations of lenvatinib or sorafenib. In addition, we constructed a *de novo* economic model to compare the cost effectiveness of lenvatinib and sorafenib with BSC.

Results

Two phase III multi-centre double-blind RCTs were identified: the SELECT and DECISION trials. Lenvatinib and sorafenib were both reported to improve median progression-free survival (PFS) when compared with placebo (18.3 months versus 3.6 months, and 10.8 months versus 5.8 months, respectively). Patient crossover was high (≥75%) in both trials and confounded estimates of overall survival (OS). Using OS data adjusted for crossover, the trial authors reported a statistically significant improvement in OS for patients treated with lenvatinib versus placebo (SELECT trial) but not for sorafenib versus placebo (DECISION trial). Lenvatinib and sorafenib also increased the incidence of adverse events (AEs) and >60% of patients required dose reductions. The results from nine prospective observational studies and 13 systematic reviews of lenvatinib and sorafenib were broadly comparable with those from the RCTs. However, median PFS tended to be higher, and median OS lower, than reported in the RCTs. Health related quality of life (HRQoL) data were only collected in the DECISION trial.

We considered the feasibility of comparing lenvatinib with sorafenib via an indirect comparison but concluded that this would not be appropriate due to differences in trial and participant characteristics, risk profiles of the patients in the placebo arms and because the proportional hazard assumption was violated for five of the six survival outcomes available from the trials.

The base case analysis, using list prices only, for the comparison of the cost effectiveness of treatment with lenvatinib versus BSC yields an incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained of £65,872, and for the comparison of sorafenib versus BSC yields an ICER of £85,644 per QALY gained. The deterministic sensitivity analyses show that none of the variations lowered the base case ICERs to below £50,000 per QALY gained.

Conclusions

Compared with placebo, treatment with lenvatinib and sorafenib result in an improvement in PFS, ORR and possibly OS. However, both drugs also increase the incidence of AEs. Compared with BSC, using list prices, both treatments exhibit estimated ICERs >£50,000 per QALY gained. We consider it is not possible to compare the clinical or cost effectiveness of lenvatinib with sorafenib.

Study registration

This review is registered as PROSPERO CRD42017055516

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SCIENTIFIC SUMMARY

Background

Thyroid cancer is a rare cancer representing 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% to 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 (RR-DTC) is often limited to best supportive care (BSC).

Two oral anti-cancer treatments for RR-DTC, used within their respective licensed indications, are the focus of this review: lenvatinib (Lenvima®, Eisai Ltd) and sorafenib (Nexar®, Bayer Healthcare). Both are types of tyrosine kinase inhibitors (TKIs) known as multi-kinase 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 only be given to patients who are symptomatic or when clinically significant progressive disease develops.

Aims and objectives

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

Methods

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

Five electronic databases were searched 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 NICE MTA 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 (LY) 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 multi-centre double-blind RCTs were identified: the SELECT trial (lenvatinib versus placebo) and the DECISION trial (sorafenib versus 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 of good quality and well conducted. However, there were some differences in trial and patient characteristics, both within and across the two trials. Due to event hazards only being proportional over time for DECISION trial unadjusted OS, all other HR results from the SELECT and DECISION trials should be interpreted with caution

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

OS results from the SELECT and DECISION at the third data-cut (occurring after approximately 38 and 36 months follow-up, respectively) showed no statistically significant differences between trial arms. However patient crossover was high (≥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 the SELECT trial, favouring lenvatinib over placebo.

ORR was reported based on data from the first data-cut. ORR in the SELECT trial was 64.8% for lenvatinib versus 1.5% in the placebo arm. ORR results for the sorafenib and placebo arms of the DECISION trial were 12.2% and 0.5% respectively.

Analyses of safety data from the SELECT and DECISION trials were reported from the first data-cut. 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.

HRQoL data were only collected as part of the DECISION trial. At baseline, HRQoL scores were considered to be comparable to comparable to a normative adult cancer population. However, at the first assessment (cycle 2, day 1), HRQoL scores worsened in the sorafenib arm while 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, whilst the placebo arm scores remained similar to the baseline scores.

Pre-specified subgroup analyses were conducted for OS, PFS and ORR in the SELECT trial and PFS in the DECISION trial. 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 the DECISION trial also involved patients who received additional sorafenib on disease progression. The efficacy findings for PFS from the extended phase of the SELECT and DECISION trials 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 those reported during the double-blind phase.

Indirect comparison

In the absence of direct clinical evidence comparing treatment with lenvatinib versus sorafenib, the AG considered whether it is appropriate to perform an indirect treatment comparison As both the SELECT and DECISION trials shared a common comparator (placebo), it is possible to construct a network. However, differences in participant characteristics, both within and

across the trials, raised concerns about whether this approach was appropriate. The AG examined the PFS Kaplan-Meier (K-M) 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 the SELECT and DECISION trials should be interpreted with caution. Therefore the AG could not conclude whether the effectiveness of treatment with lenvatinib and 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 performed by Eisai and Bayer, 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 the SELECT and DECISION trials tended to be higher than those reported in the reviewed prospective observational studies, whilst 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 was 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 systematic reviews showed lenvatinib to result in statistically significantly less alopecia but statistically significantly more hypertension, Grade ≥3 AEs and SAEs when compared with sorafenib.

Evidence from cost effectiveness studies

The two submitting companies and the AG agree 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 base case incremental cost effectiveness ratio (ICER) for the comparison of treatment with lenvatinib versus sorafenib is £22,491 per QALY gained and, for the comparison of treatment with lenvatinib versus BSC, is £48,569 per QALY gained. The analyses carried out by Bayer used the Commercial Medicines Unit price for sorafenib and the list price for lenvatinib. The Bayer ICER for the comparison of treatment with sorafenib versus lenvatinib is £[redacted] per QALY gained and, for the comparison of sorafenib versus BSC, is [redacted] per QALY gained.

Summary of the Assessment Group's cost effectiveness results

The AG considered it was inappropriate to compare data from the SELECT and DECISION trials 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 the SELECT and DECISION trials 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 versus BSC yields an ICER per QALY gained of £65,872, and for the comparison of sorafenib versus BSC 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 lower the AG's base case ICERs below £50,000 per QALY gained. The AG's probabilistic sensitivity analysis (PSA) results show that, compared to BSC, the probability of sorafenib being cost effective at a threshold of £50,000 per QALY gained is less than 0.05% and the probability of lenvatinib being cost effective is 5.4%.

When the AG compared the cost effectiveness of lenvatinib versus BSC using placebo data from the DECISION trial, and sorafenib versus BSC using placebo data from the SELECT trial, the ICERs per QALY gained approximately doubled (£130,592) and halved (£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 and cost effectiveness of treatment with lenvatinib versus sorafenib in patients with RR-DTC. The AG considers that the SELECT and DECISION trials are good quality, well-conducted trials.

Weaknesses and areas of uncertainty

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

The generalisability of the SELECT and DECISION trials findings 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 trial data showed no difference in median PFS between symptomatic and asymptomatic patients (retrospectively categorised) treated with sorafenib.

Due 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 result 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 considers it is not possible to compare the clinical or cost effectiveness of lenvatinib with sorafenib. Primarily this is because the risk profiles of the patients in the placebo arms of the SELECT and DECISION trials do not appear to be comparable.

Using list prices, compared with BSC, both treatments exhibit estimated ICERs >£50,000 per QALY gained. Compared to 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.

Implications for service provision

As the administration and AE profiles of lenvatinib and sorafenib are in line with those of other TKIs used to treat patients with cancer, clinical advice to the AG is that there would be no major implications for service provision if NICE were to recommend these drugs.

Recommendations for research (numbered in priority order)

1. Future clinical effectiveness research should focus on a head-to-head RCT that includes lenvatinib, sorafenib and BSC and addresses the following issues:

    a) Should both symptomatic and asymptomatic patients be treated with lenvatinib and/or sorafenib?

    b) How does treatment with lenvatinib and sorafenib affect the HRQoL of patients (progressed and non-progressed, symptomatic and asymptomatic)?

    c) What is the clinical effectiveness of lenvatinib and sorafenib versus BSC and versus each other?

    d) How should lenvatinib, sorafenib and BSC be positioned in the treatment pathway?

2. Further statistical research is needed to develop reliable methods of undertaking indirect comparisons in cases where the proportional hazard assumptions are violated.

Study registration

This review is registered as PROSPERO CRD42017055516

PLAIN LANGUAGE SUMMARY

What was the problem?

Differentiated thyroid cancer is common type of thyroid cancer. For many patients, radioactive iodine is an effective treatment. However, for some patients, the treatment stops working or becomes unsafe. Two new drugs, lenvatinib and sorafenib, may be new treatment options.

What did we do?

We reviewed the clinical evidence of lenvatinib and sorafenib. We also estimated the costs and benefits of treatment.

What did we find?

Compared with no treatment, treatment with lenvatinib or sorafenib may increase the time that people live with thyroid cancer before their disease gets worse. However, both drugs are expensive and may have unpleasant side effects.

What does this mean?

At their published (undiscounted) prices, lenvatinib or sorafenib may not be considered to provide good value for money to the NHS.

LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse event
AG	Assessment Group
BNF	British National Formulary
BSC	Best Supportive Care
BTA	British Thyroid Association
CADTH	Canadian Agency for Drugs and Technologies in Health
CDF	Cancer Drugs Fund
CEAC	Cost effectiveness acceptability curves
CI	Confidence interval
CMU	Commercial Medicines Unit
CSR	Clinical study report
CT	Computed tomography
DECISION	Stu**D**y of soraf**E**nib in lo**C**ally advanced or metastat**I**c patient**S** with radioactive **I**odine-refractory thyr**O**id ca**N**cer
DTC	Differentiated thyroid cancer
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol five dimensions questionnaire
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	US Food and Drug Administration
FDG	Fludeoxyglucose F18
FTC	Follicular carcinoma
HCC	Hepatocellular carcinoma
H-H	Cumulative hazard versus cumulative hazard
HR	Hazard ratio
HRQOL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IPE	Iterative parameter estimation
ITC	Indirect treatment comparison
ITT	Intention-to-treat
K-M	Kaplan-Meier
LY	Life year
MAIC	Matched adjusted indirect comparison
MCi	Millicurie
mg	Milligram(s)
MKI	Multiple kinase inhibitor
MRI	Magnetic resonance imaging
MTA	Multiple technology appraisal
N	Number of patients
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

Abbreviation	Description
ORR	Objective tumour response rate
OS	Overall survival
PAS	Patient Access Scheme
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazard
PPS	Post-progression survival
PR	Partial response
PS	Performance Status
PSA	Probabilistic sensitivity analysis
PTC	Papillary carcinoma
QALY	Quality adjusted life year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RPSFTM	Rank preserving structural failure time method
RR-DTC	Radioactive iodine refractory differentiated thyroid cancer
SAE	Serious adverse event
SELECT	**S**tudy of [**E**7080] **LE**nvatinib in 131I-refractory differentiated **C**ancer of the **T**hyroid
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
UK	United Kingdom
USA	United States of America
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

1 BACKGROUND

1.1 Thyroid cancer: overview

Thyroid cancer is a rare cancer representing only 1% of all malignancies in England and Wales.[1] It is caused by the growth of abnormal cells in the thyroid gland, a small gland at the base of the neck that secretes three 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.[2] Thyroid cancer is usually asymptomatic and is often discovered incidentally via imaging studies (e.g., sonograms, computed tomography [CT] scans and magnetic resonance imaging [MRI]) performed for another reason, or when patients present with a large palpable nodule in the neck.[3] The actual diagnosis of thyroid cancer is usually made via ultrasound and biopsy (typically, a fine needle aspiration).[4]

The incidence of thyroid cancer is increasing world-wide.[4-10] In the UK, between the period 2003 to 2005, and the period 2012 to 2014, thyroid cancer incidence rates increased by 74% (Figure 1).[1]

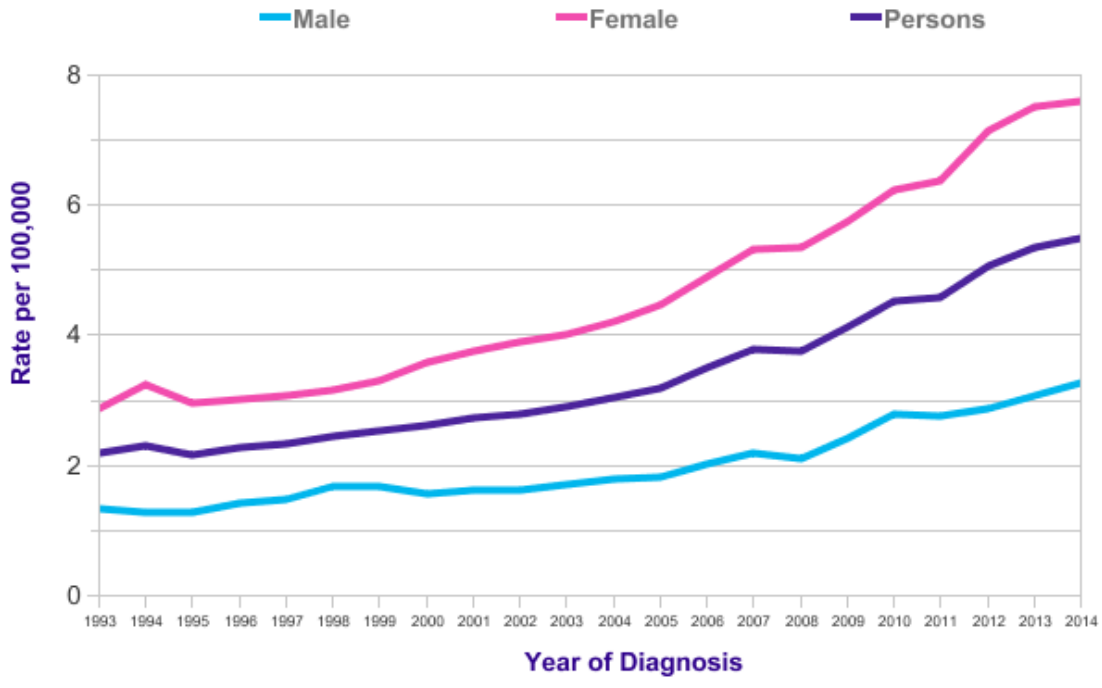

Figure 1 Average number of new cases per year per 100,000 population, UK

Source: Cancer Research UK[1]

In 2014, there were 3404 patients diagnosed with thyroid cancer in the UK, 2941 of whom were diagnosed in England, and 123 in Wales.[1] The reasons for the increase in incidence are unknown, but are thought, at least in part, to be due to improved diagnostic and detection techniques.[11]

The incidence of thyroid cancer is 2.5 times greater in women than in men.[1] The reasons for this disparity are unclear.[12] Thyroid cancer incidence is strongly related to age, with the highest incidence rates being in older males, and the highest incidence rates in females being in younger and middle-aged women (Figure 2).

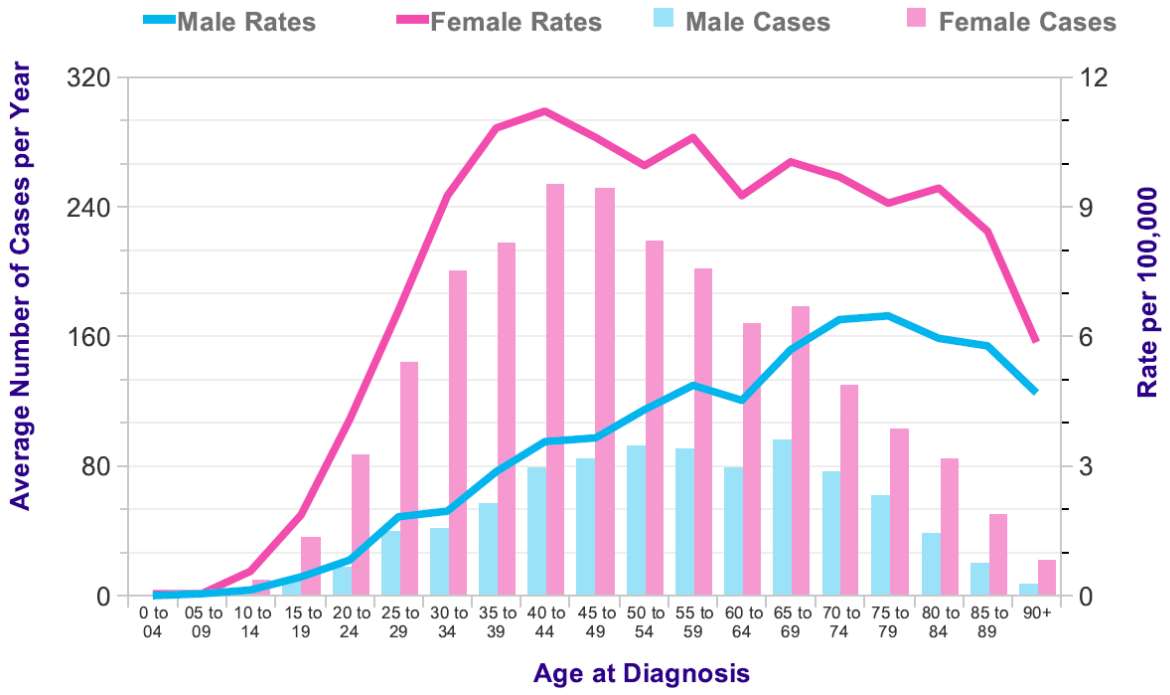

Figure 2 Age-specific incidence rates per 100,000 population, UK

Source: Cancer Research UK[1]

In the UK, thyroid cancer accounts for <1% of male cancer deaths, and <1% of female cancer deaths.[13] Mortality rates in the UK are reported to be <1 death per 100,000 people. In 2014, there were 376 thyroid cancer deaths in the UK: 154 (41%) in males and 222 (59%) in females, giving a male:female ratio of around 7:10. In England and Wales, there were 331 thyroid cancer deaths, 137 in males and 194 in females.[13]

While the incidence of thyroid cancer in the UK increased between the period 2003 to 2005 and the period 2012 to 2014, overall mortality rates remained stable during this time (Figure 3).[13] However, between 1970 and 2014, thyroid cancer mortality rates decreased by 46% in

the UK, the decrease being most marked in females (54%) compared with males (24%)[13] Mortality rates for thyroid cancer are projected to rise in the future: in the UK, it is expected that, between 2014 and 2035, mortality will increase by 7%. However, the overall rate will remain relatively low at 1 death per 100,000 people.[13]

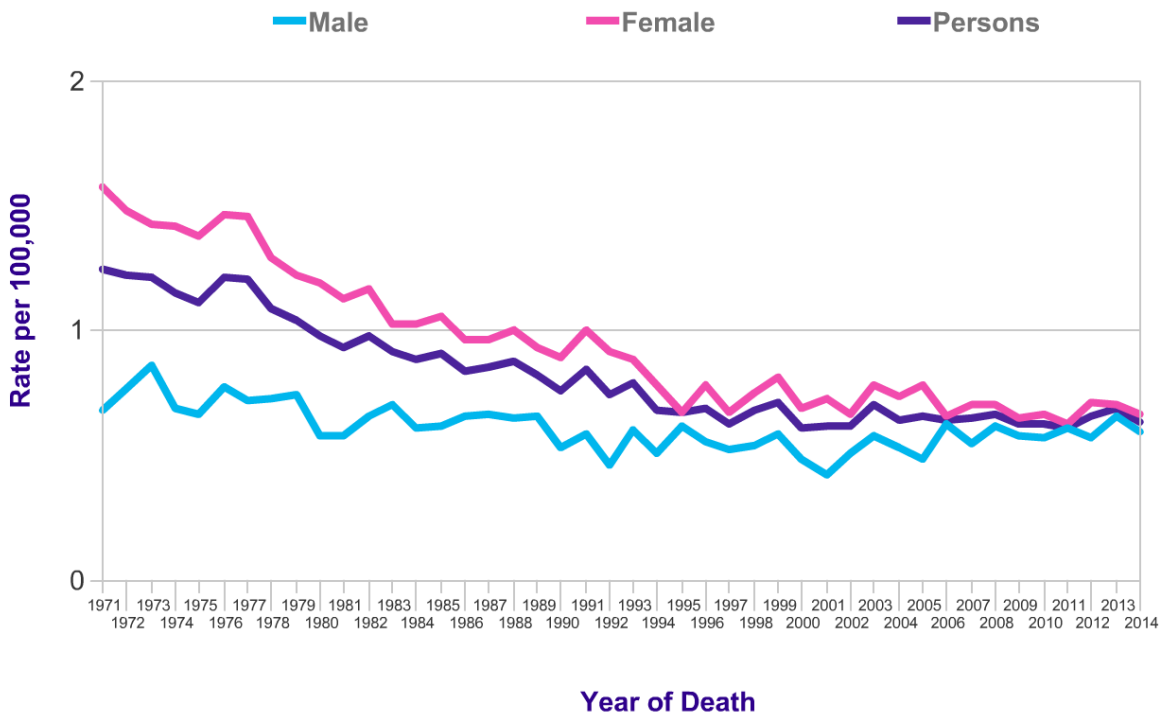

Figure 3 Thyroid Cancer, European Age-Standardised Mortality Rates, UK, 1971-2014

Source: Cancer Research UK[13]

1.2 Differentiated thyroid cancer

The most common form of thyroid cancer is differentiated thyroid cancer (DTC); DTC is reported to account for approximately 94% of thyroid carcinomas.[14,15] Less common types of thyroid cancer include medullary carcinoma and anaplastic carcinoma; these have been reported to account for approximately 4% and approximately 2% of all thyroid carcinomas, respectively.[15]

DTC is a specific type of thyroid cancer made up of different subtypes including papillary carcinoma (PTC), follicular carcinoma (FTC) and Hürthle cell carcinoma. PTC is the most common type of DTC, accounting for approximately 83%[15] to 86%[16] of all cases, FTC accounts for approximately 10%[16] to 13%,[15] and Hürthle cell carcinoma accounts for approximately 3%[15] to 4%.[16] Hürthle cell carcinomas are usually grouped with FTCs because they present and behave similarly.[17]

The median age for all patients with DTC is reported to be 45 years.[18] However, estimates for the median age of onset for the subtypes of DTC have been reported to vary:

- PTC often affects people aged <40 years[17] but it is also reported that the median age of patients with PTC is 45 years[19]
- The peak age for the onset of FTC has been stated to be between 40 and 60 years[20] but again, the median age has been reported to be approximately 45 years[21]
- The median age of patients with Hürthle cell carcinoma has been reported to be 55 years old.[21]

In general, the prognosis for patients with DTC is relatively good. The overall 10-year survival rate for middle-aged adults is reported to be 80% to 90%.[4] It has also been reported that >85% of patients with DTC have a 'normal' life expectancy.[22] However, the prognosis generally gets worse with increasing age at the time of diagnosis, particularly for patients aged ≥45 years.[4] In addition, young children (<10 years) are at higher risk of recurrence than older children.[4] Prognosis may also be affected by DTC subtype (histology). An analysis of US National Cancer Data Base data on 41,375 patients with DTC treated between 1985 and 1995 has shown the 10-year relative survival for patients with PTC is 93%, whilst for patients with FTC it is 85%, and for patients with Hürthle cell carcinoma it is 76%.[15]

The size and spread of the tumour affects prognosis. Studies cited by the British Thyroid Association[4] (BTA) are reported to show that the risk of recurrence and mortality correlates with the size of the primary tumour. Extra-thyroidal invasion, lymph node metastases and distant metastases are also reported to be important prognostic factors.[4]

1.3 First-line treatment options for patients with differentiated thyroid cancer

There are currently no NICE guidance or guidelines for treating patients with DTC or any other type of thyroid cancer. Other, clinical guidelines do, however, present some recommendations. In chronological order from date of publication, relevant clinical guidelines include: European Society of Medical Oncology (ESMO) guidelines (2012),[23] BTA guidelines,[4] American Thyroid Association (ATA) guidelines (2015)[24] and National Comprehensive Cancer Network (NCCN) guidelines (2017).[25]

Due to the indolent course of the disease, many patients with DTC, even if they have metastatic disease, do not require therapy for several years after diagnosis.[26] Treatments for DTC depend on factors including age, extent of disease, and histology, but usually involve surgery to remove all or part of the thyroid gland (thyroidectomy) followed by lifelong thyroxine

for thyroid stimulating hormone (TSH) suppression from the low normal to fully suppressed range dependent upon risk factors.[4,23-25]

1.4 Treatment options for patients with differentiated thyroid cancer that has progressed following surgery

Following initial surgery, it is estimated that between 5% and 20% of patients with DTC develop local or regional recurrences (approximately two-thirds involve cervical lymph nodes[27]) and between 10% and 15% of patients with DTC develop distant metastases.[4,24] The most common sites for metastases are reported to be the lungs (50%), bones (25%), lungs and bones (20%), or at other sites (5%).[24] It has been noted that the presence of bone metastases has been associated with a worse prognosis than metastases in other sites.[23]

The sites that DTC is most likely to spread to vary by histology. For patients aged >40 years, it has been reported that 10% of patients with PTC, 25% of patients with FTC and 35% of patients with Hürthle cell carcinoma develop distant metastases.[28,29] PTC tends to spread to lymph nodes in the neck, whereas FTC usually spreads to the bones or lungs.[17] Hürthle cell carcinoma is more likely than FTC to spread to lymph nodes in the neck.[30]

A radioactive iodine uptake test is commonly used to determine whether DTC has spread. The test involves a patient being given a liquid or capsule containing radioactive iodine (I-123) to swallow. Two separate uptake measurements are then commonly obtained at different times within a 24-hour period. The patient is then scanned to see how much of this radioactive iodine has been absorbed by the thyroid (radioactive uptake). Positive results (evidence of I-123 uptake) denote the presence of disease whereas negative results (no radioactive uptake) denote the absence of disease.

It is recommended in clinical guidelines[4,23-25] that patients with DTC and evidence of radioactive iodine uptake should undergo treatment with radioactive iodine (also known as radioactive iodine ablation) to treat residual, recurrent, or metastatic disease. Patients are typically tested 1 to 2 months after surgery. Radioactive iodine treatment has been used for over 60 years. It is administered in hospital (inpatient stay) and can be given to patients on more than one occasion, as necessary.[4]

Like the radioactive iodine uptake test used to diagnose DTC, radioactive iodine treatment involves swallowing radioactive iodine in either liquid or capsule form. However, the radioactive iodine is a different form (I-131) to that used for scans (I-123), the purpose of radioactive iodine treatment is to destroy cancerous cells. Thus, patients with I-131 uptake are responsive to treatment, which can be confirmed by imaging studies.

Approximately 33% of patients with advanced disease can be cured and many others achieve long-term disease stabilisation.[31] From published French registry data,[32] the 10-year survival rate for patients with distant metastases who successfully responded to treatment with radioactive iodine is 92%.[32]

1.5 Radioactive iodine refractory differentiated thyroid cancer

While for many patients, treatment with radioactive iodine is an effective treatment, some patients become resistant to the treatment (decreased or no radioactive iodine uptake), or are unable to safely tolerate additional doses. These patients are considered to have radioactive iodine refractory differentiated thyroid cancer (RR-DTC) and are the focus of this MTA.

While clinical criteria and algorithms have been developed and reported in clinical guidelines,[4,23-25] there is no agreed precise definition of RR-DTC.[33] However, a review of the literature published in February 2017[31] highlights key features which can be considered in defining RR-DTC:

- metastatic disease that does not take up radioactive iodine at the time of the first radioactive iodine treatment
- ability to take up radioactive iodine has been lost after previous evidence of uptake of radioactive iodine
- radioactive iodine uptake is retained in some lesions but not in others
- metastatic disease that progresses despite substantial uptake of radioactive iodine
- absence of complete response to treatment after >600 mCi of cumulative activity of radioactive iodine
- high uptake of Fludeoxyglucose F18 (FDG) on positron emission tomography (PET) or CT scan; importantly, however, the authors of this review[31] state that this feature alone should not be used to abandon radioactive iodine treatment.

Before deciding whether a patient's disease can be described as being RR-DTC, it is important to determine that decreased radioactive iodine uptake is not due to iodine contamination or to insufficient TSH.[34]

RR-DTC is a life-threatening form of thyroid cancer with a tendency to progress and metastasise.[14] From published French registry data,[32] the 10-year survival rate and median OS for patients with distant metastases who failed to respond to treatment (no I-131 uptake) was 10% and 3 years, respectively. For those who appear to respond to radioactive iodine treatment (I-131 uptake) but who did not then attain negative imaging studies, the 10-year survival and median OS was 29% and 6 years, respectively. A separate analysis of patients with lung and/or bone metastases[35] found that 10-year survival and median OS for those who

did not have a complete response to treatment with radioactive iodine was 14% and 5 years, respectively. Data from Canada have suggested the median OS for patients with RR-DTC may be between 2.5 and 3.5 years.[5]

The proportion of patients whose disease becomes refractory to treatment with radioactive iodine is relatively small, and so RR-DTC is described as an ultra-orphan condition.[7,8] Estimates of the proportion of patients who become refractory vary but commonly lie within the range of 5% to 15%.[7,8,14,16,32,35-37]

As with early stage DTC, many patients with RR-DTC are initially asymptomatic. As highlighted in a literature review published by Schmidt et al 2017,[31] even patients with distant metastases may have a disease that does not progress for many years. However, as noted by Thyroid Cancer Canada, the cancer continues to progress 'silently'.[5]

For patients with rapidly progressing disease, which is characterised by symptomatic disease, the symptoms of RR-DTC can be severe, profoundly debilitating and result in patients becoming increasingly dependent on carers.[8] Clinical advice to the AG is that this is likely to be approximately 25% to 30% of patients with RR-DTC. As a result of their symptoms, patients with clinically significant progressive RR-DTC may suffer a poor quality of life and the psychological impact of the disease can also be substantial, resulting in low mood and fatigue.[38] It has also been stated that patients with RR-DTC often experience multiple complications.[39]

1.6 Treatment options for patients with radioactive iodine refractory differentiated thyroid cancer

RR-DTC is typically asymptomatic but symptoms start to occur as the disease progresses. Symptoms associated with lymph nodes of the neck include difficulty swallowing and/or breathing, pain or sensitivity in the front of the neck or throat, hoarseness or other voice changes, and swelling of the lymph nodes in the neck.[4] Symptoms associated with lung metastases also include swallowing and breathing difficulties.[26] Pain often presents as the principal symptom of metastatic bone involvement.[29,40] Fractures and spinal cord compression are also associated with bone metastases.

Since many treatments, particularly systemic treatments, can have severe side effects and impact significantly on health-related quality of life (HRQoL), clinical advice to the AG is that best supportive care (BSC) tends to be the preferred treatment option, at least until symptoms occur. BSC typically entails TSH suppression therapy and imaging every 3 to 12 months. Palliative radiotherapy and symptom relief are also offered when necessary.

Patients experiencing RR-DTC symptoms and/or those with rapidly progressing disease are those in need of systemic treatment,[31] as reflected in clinical guidelines.[4,23-25] The aim of systemic treatment for patients with rapidly progressing and/or symptomatic RR-DTC is to gain local disease control in the neck and manage systemic disease.[41] Another important objective of treatment is to prolong survival.[27] However, treatment options for patients with RR-DTC are limited. Within the ESMO guidelines published in 2012[23] it is stated that chemotherapy should not be given to patients with RR-DTC as it is associated with significant toxicity with no proven evidence of effectiveness. The authors of these guidelines stated that surgical resection and external beam radiotherapy represented the only therapeutic options and strongly encouraged enrolment of patients in experimental trials with targeted therapy. Similarly, the authors of the guidelines published by the BTA in 2014 [4] only recommended chemotherapy for patients with rapidly progressive, symptomatic RR-DTC who have good performance status (PS) and only when access to targeted therapies in clinical trials is unavailable, or where targeted therapies have proved unsuccessful. The authors of the more recent US guidelines published by the ATA and NCCN recommend that patients with RR-DTC should usually avoid treatment with chemotherapy.[24,25] Clinical advice to the AG is that chemotherapy is rarely used to treat RR-DTC in UK NHS practice.

Targeted therapies were not widely available and were only the subject of clinical trials between 2012 and 2014 when the ESMO guidelines[23] and the BTA guidelines[4] were published. The authors of the BTA guidelines[4] considered the most promising targeted therapies to be lenvatinib and sorafenib at the time.[4] By 2017, the authors of the NCCN guidelines[25] recommended lenvatinib or sorafenib as the treatment of choice for patients with progressive and/or symptomatic disease; lenvatinib is stated to be the 'preferred' option but the authors state that the decision should be based on the individual patient, taking into account the likelihood of response and comorbidities.[25] In cases where lenvatinib or sorafenib are not available or not appropriate, drugs not regulated by the US Food and Drug Administration (FDA) but used in the context of clinical trials, are also recommended by the authors of the NCCN guidelines.[25]

1.7 Description of technology under assessment

The two interventions under consideration in this MTA are lenvatinib (Lenvima) manufactured by Eisai, and sorafenib (Nexavar) manufactured by Bayer. Both are a type of tyrosine kinase inhibitor (TKI) known as multi-kinase inhibitors (MKIs).

A brief comparison of the key features of the two interventions is given in Table 1. The AG notes that lenvatinib and sorafenib appear to have slightly different mechanisms of action.[42] Both drugs have been approved for treating RR-DTC in the US[43,44] and Europe,[45,46] with

sorafenib being the first of the two agents to be approved in both jurisdictions. In the US and Europe, the marketing indications for both lenvatinib and sorafenib are for identical patient populations. Approval in the US and Europe was based largely on evidence from two phase III randomised controlled trials (RCTs); the SELECT trial[47] in which lenvatinib was compared with placebo, and the DECISION trial[48] in which sorafenib was compared with placebo.

Approval for use in NHS Scotland was granted to sorafenib in June 2015 [49] and to lenvatinib in September 2016.[38] Both approvals are for the treatment of patients with progressive, locally advanced or metastatic RR-DTC. In NHS Scotland, the use of both lenvatinib and sorafenib is contingent upon the continuing availability of patient access scheme (PAS) prices that have been assessed by the Patient Access Scheme Assessment Group (PASAG).

In England, since July 2016, sorafenib has been available to the NHS via the Cancer Drugs Fund (CDF). According to Bayer, sorafenib has now became the standard of care, replacing BSC.[7] Lenvatinib is not currently available to patients treated by the English or Welsh NHS.

Eisai[8] has estimated the incidence of patients in England and Wales with RR-DTC eligible for treatment with lenvatinib or sorafenib to be approximately 280 patients each year. Bayer[7] has estimated the incidence to be approximately 225 patients. The AG notes that the estimates made by the companies differ in how they are calculated but that neither estimate appears to account for the fact that lenvatinib and sorafenib are likely only to be preferred for patients with symptomatic and/or rapidly progressing disease. The estimated number of patients eligible for treatment each year may therefore be markedly lower.

Table 1 Comparison of the key features of lenvatinib and sorafenib

Feature	Lenvatinib	Sorafenib
Brand name	Lenvima	Nexavar
Manufacturer	Eisai	Bayer
Class of drug	Oral MKI	Oral MKI
Mechanism of action	Targets VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, PDGFR beta, RET and KIT[42]	Targets BRAF, RET, VEGFR2 and VEGFR3[42]
US marketing indication	For the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (15 February 2015)[44]	For the treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment (22 November 2013)[43]
European Union marketing indication	For the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine (28 May 2015)[50]	For the treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine (25 January 2015)[51] In addition to RR-DTC, sorafenib is also indicated for treatment of hepatocellular carcinoma and the treatment of advanced renal cell carcinoma.[51]
Dose information for treating RR-DTC	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[50]	400mg (two 200mg tablets) twice daily taken without food or with a low-fat meal Adverse events can be managed through dose reduction and treatment is continued until disease progression or unacceptable toxicity [51]
Important identified risks	Important risks highlighted by the EMA[27] include: Hypertension; proteinuria; renal failure or impairment; hypokalaemia; cardiac failure; posterior reversible encephalopathy syndrome; hepatotoxicity; hemorrhagic events; arterial thromboembolic events); QTC prolongation; hypocalcaemia Further information, including how to manage some of the risks (e.g., the use of hypertensives for hypertension) is provided in the SmPC[51]	Important risks highlighted by the EMA[26] include: Severe skin adverse events, hand-foot syndrome; hypertension; posterior reversible encephalopathy syndrome; haemorrhage including lung haemorrhage, gastrointestinal haemorrhage and cerebral haemorrhage; arterial thrombosis (myocardial infarction) congestive heart failure; squamous cell cancer of the skin; gastrointestinal perforation; symptomatic pancreatitis and increases in lipase and amylase; hypophosphatemia; renal dysfunction; interstitial lung disease-like events; drug-induced hepatitis Further information, including how to manage some of the risks (e.g., the use of topical therapies, temporary treatment interruption and/or dose modification or treatment discontinuation for hand-foot syndrome) is provided in the SmPC[51]
List price per pack	£1,437.00 for the 4mg and 10mg packs[8]	£3,576.56 for a pack of 112 x 200mg tablets[52]
Cost per year*	£52,307[38]	£38,746[49]

BRAF= B-type rapidly accelerated fibrosarcoma; EMA=European Medicines Agency; FGFR=fibroblast growth factor receptors; MKI=multi-kinase inhibitor; PDGFR=platelet-derived growth factor receptor; RET=rearranged during transfection; RR-DTC=radioactive iodine refractory differentiated thyroid cancer; SmPC=summary of product characteristics; VEGFR=vascular endothelial growth factor receptor
*All costs are presented based on the list price

2 DEFINITION OF THE DECISION PROBLEM

The decision problem for this appraisal, as described in the final scope issued by NICE,[53] is summarised in Table 2.

Table 2 Decision problem summarised in the final scope issued by NICE and addressed by the AG

Parameter	In scope	Addressed by AG
Interventions	• Lenvatinib • Sorafenib	As per scope
Population	Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine	As per scope
Comparators	• The interventions listed above will be compared with each other • Best supportive care (BSC)	• Explore the feasibility of comparing lenvatinib with sorafenib • Comparisons of interventions with BSC
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	As per scope
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.	As per scope
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	As per scope

2.1.1 Decision problem addressed by the Assessment Group

The decision problem addressed by the AG reflects that described in the final scope issued by NICE.[53]

2.1.2 Overall aims and objectives of assessment

The aim of this research was to assess the clinical and cost effectiveness of lenvatinib versus sorafenib, within their respective EU marketing authorisations,[50,51] for the treatment of patients with RR-DTC. The research objectives were to:

- carry out systematic reviews to compare the clinical and cost effectiveness of treatment with:
    - lenvatinib versus sorafenib for RR-DTC
    - lenvatinib versus BSC for RR-DTC
    - sorafenib versus BSC for RR-DTC
- develop an economic model to compare the cost effectiveness of treatment with:
    - lenvatinib versus sorafenib for RR-DTC
    - lenvatinib versus BSC for RR-DTC
    - sorafenib versus BSC for RR-DTC.

3 METHODS FOR REVIEWING CLINICAL EFFECTIVENESS LITERATURE

3.1 Search strategy

The AG identified clinical studies and systematic reviews by searching Embase, MEDLINE, PubMed and the Cochrane Library, from 1999 onwards. All databases were searched on 10 January 2017. Based on the fact that the FDA approved sorafenib for its first indication in 2005, and lenvatinib in 2015, the AG considered that this date span would allow all relevant clinical evidence to be identified. Searches were restricted to publications in English. The AG did not use any other search filters. The search strategies used by the AG are provided in Appendix 1.In addition to the electronic database searches, information on studies in progress was sought (on 16 May 2017) by searching the clinicaltrials.gov website, the International Clinical Trials Registry Platform (ICTRP) and the EU Clinical Trials Register (EU-CTR). The references in the systematic reviews included in the AG's review of systematic reviews and those listed in the submissions from professional stakeholders that were submitted to NICE as part of the NICE MTA process, were cross-checked to identify any relevant studies not retrieved from the electronic database searches. Literature search results were uploaded to, and managed using EndNote X7.4 software.

3.2 Study selection

The eligibility criteria listed in Table 3 were used to identify studies for inclusion in the AG's literature review.

Table 3 Eligibility criteria (clinical effectiveness)

Criteria	Inclusion	Exclusion
Patient population	Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine	Patients with other types of thyroid cancer or diseases
Interventions	Lenvatinib or sorafenib monotherapy (or in combination with best supportive care)	Lenvatinib or sorafenib in combination with other agents
Comparators	Lenvatinib or sorafenib monotherapy (or in combination with best supportive care), best supportive care, placebo	A comparator other than lenvatinib, sorafenib, best supportive care, placebo
Outcomes	The outcome measures to be considered include: overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life	No study was excluded based on outcomes
Study design	Randomised controlled trials, systematic reviews, prospective observational studies	Retrospective cohort studies, case series, case reports, comments, letters, editorials, in vitro, animal, genetic or histochemical studies
Restrictions	English language only	Non-English studies

Two reviewers (JH/RH) independently screened all titles and abstracts that were identified by the initial searches (screening stage 1). Based on the titles and abstracts, full-text papers that appeared to be relevant were obtained and assessed for inclusion by the same two reviewers according to the AG's eligibility criteria (screening stage 2). Where necessary, discrepancies were resolved by consultation with a third reviewer (NF). At both stages of screening, studies that did not meet the inclusion criteria were excluded and, at screening stage 2, the reasons for excluding studies were noted.

The eligibility criteria in Table 3 differ slightly to those specified in the AG's systematic review protocol.[54] The AG, responding to a suggestion from NICE in relation to the final protocol,[54] agreed to include evidence from prospective observational studies that had been submitted to the European Medicines Agency (EMA). However, as only reviewing studies included in the EMA submissions[26,27] would have introduced selection bias, the AG included all prospective observational studies of patients with RR-DTC identified by its searches.

3.3 Data extraction and quality assessment strategy

Data relating to RCT study characteristics and outcomes were extracted by one reviewer (NF) and independently checked for accuracy by a second reviewer (YD). Data relating to study characteristics and outcomes of systematic reviews and observational studies were extracted by one reviewer (JH/NF) and independently checked for accuracy by a second reviewer (JG). In all cases, a consensus was reached. Study data reported in multiple publications were extracted and reported as a single study. Data were extracted into tables in Microsoft Office Word.

As specified in the AG's systematic review protocol,[54] the quality of included RCTs and systematic reviews was assessed according to the criteria set out in the Centre for Review and Dissemination's Guidance[55] for undertaking reviews in healthcare. The quality of the included RCTs was assessed by one reviewer (YD) and independently checked for agreement by a second reviewer (NF). In all cases, a consensus was reached. The quality of the included systematic reviews was assessed by one reviewer (JG) and independently checked for agreement by a second reviewer (YD). Where necessary, discrepancies were resolved by consultation with a third reviewer (MR).

3.4 Methods of analysis/synthesis

The AG's data extraction and quality assessment results are presented in structured tables and as a narrative summary. Data from RCTs are considered to provide primary clinical effectiveness evidence, with data from systematic reviews and observational studies considered to provide supporting evidence.

As the available evidence did not include two or more RCTs comparing the same intervention the AG was not able to conduct a meta-analysis of RCT data.

The AG assessed the feasibility of performing an indirect comparison of effectiveness data (including a comparison to assess effectiveness according to previous treatment with TKIs) by evaluating the clinical and methodological heterogeneity of the included RCTs. Heterogeneity was assessed by comparing (a) trial characteristics, (b) participant characteristics, (c) outcome data, and (d) study quality.

4 FINDINGS FROM THE SYSTEMATIC REVIEW OF CLINICAL EFFECTIVENESS LITERATURE

4.1 Quantity and quality of research available

4.1.1 Included studies

The process of study selection is shown in Figure 4. The electronic searches yielded 2358 papers and six additional references[5-8,56,57] were identified through other sources. In total, the AG included 93 papers[5-8,33,47,48,56-141] reporting on 24 separate studies and reviews: two unique RCTs,[47,48] 13 unique systematic reviews[5-8,33,56,60,92,96,103,126,137,140] and nine unique prospective observational studies. [58,76,77,80,87,100,102,125,134]

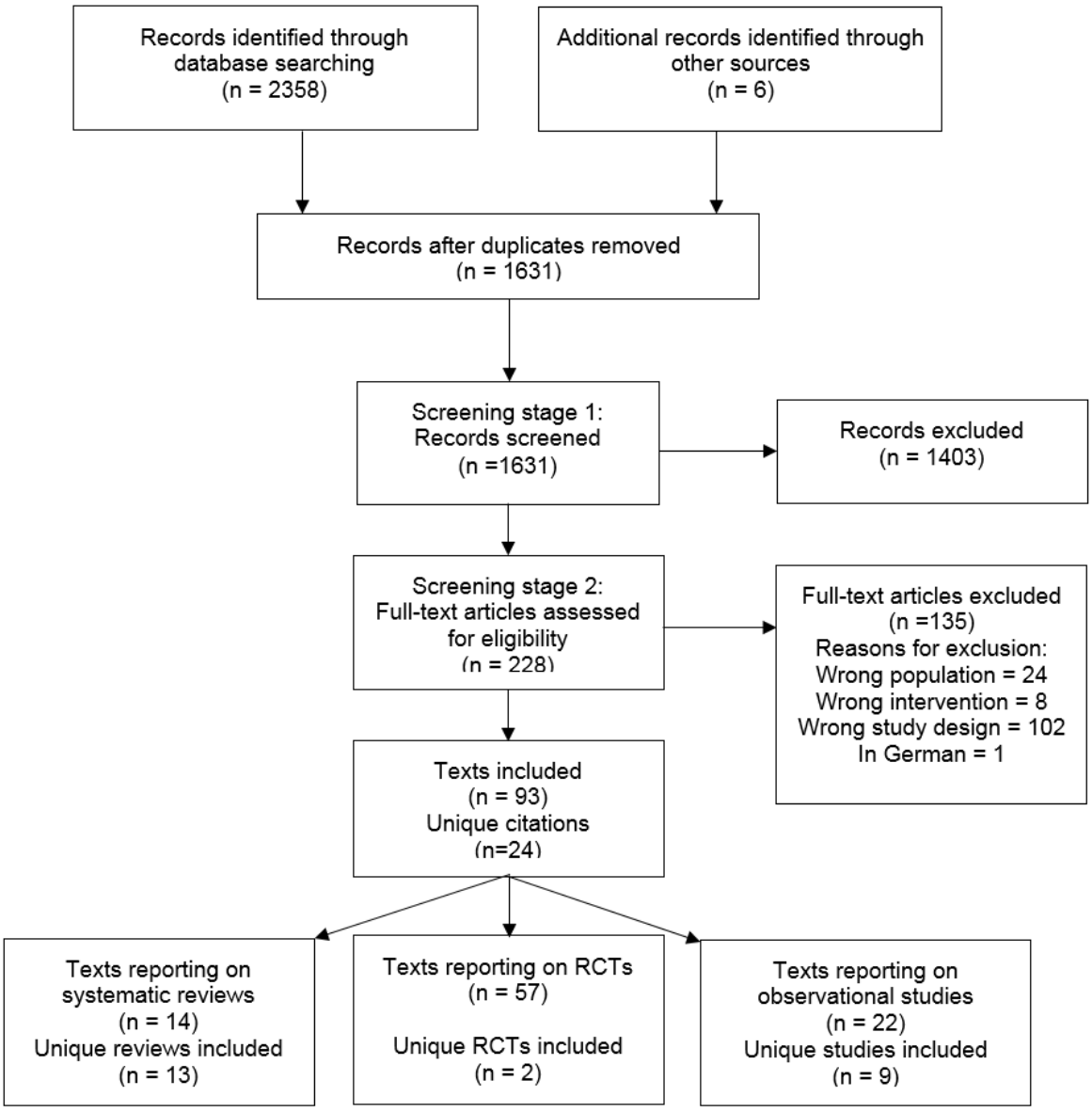

Figure 4 PRISMA flow diagram: studies included in AG's systematic review

4.1.2 Excluded studies

A full list of studies excluded at stage 2 with reasons for exclusion is presented in Table 54 in Appendix 2.

4.2 Evidence from randomised controlled trials

Only two RCTs were identified as relevant for inclusion in the AG's systematic review: the SELECT trial and the DECISION trial. Except where stated otherwise, all information about these two trials has been extracted from the two key trial publications.[47,48]

4.2.1 Trial characteristics

A summary of the characteristics of the two included trials is provided in Table 4. Both trials were phase III multi-centre double-blind RCTs designed to compare the intervention of interest (lenvatinib or sorafenib) with placebo. Subjects were randomised 2:1 to the intervention and comparator arms of the SELECT trial, whereas they were randomised 1:1 in the DECISION trial. In both trials the primary outcome was progression-free survival (PFS) assessed by blinded independent review. Both trials also reported investigator assessed PFS. Unless otherwise specified, in the remainder of this AG report on clinical effectiveness, PFS refers to PFS assessed by blinded independent review.

Analysis of clinical efficacy

All efficacy outcomes from both trials, including tumour response evaluations in the SELECT trial, were undertaken using data from the intention-to-treat (ITT) population. Tumour response evaluations in the DECISION trial were undertaken using data from the per protocol population, i.e., randomised patients who were evaluable for tumour response with imaging data, had received intervention or placebo as allocated, and no major protocol deviations.

Analysis of safety

Safety analyses for both trials were undertaken using data from the population who were randomised and received at least one dose of study drug and had at least one post-baseline safety evaluation. In the SELECT trial, the numbers of patients included in the ITT and safety populations were identical.

Table 4 Characteristics of the SELECT and DECISION trials

Parameter	SELECT trial	DECISION trial
Primary reference	Schlumberger et al 2015[47]	Brose et al 2014[48]
Number of centres	117	81
Stratification factors	Subjects were stratified according to age (≤65 years or >65 years), geographical region (Europe, North America, Other) and receipt or non-receipt of prior VEGFR targeted therapy (0, 1)	Subjects were stratified according to age (<60 years vs. ≥60 years) and geographical region (North America, Europe, and Asia)
Country	Centres distributed as follows: Europe, 60 (51.3%), North America, 31 (26.5%), Asia Pacific, 13 (11.1%), Japan, 6 (5.1%) and Latin America, 7 (6.0%)	18 countries from: Europe (59.7%) (Austria, Belgium, Bulgaria, Denmark, France, Germany, Italy, Poland, Russia, Spain, Sweden, Netherlands, United Kingdom), United States (USA; 17.3%) and Asia (23%) (China, Japan, South Korea, Saudi Arabia)
Recruitment period	5 August 2012 to 4 October 2012	5 November 2009 to 29 August 2012
Participants (n)	612 assessed, 392 randomised	556 enrolled, 419 randomised
Intervention dose and schedule (n)	Lenvatinib 24 mg (two 10mg capsules and one 4mg capsule) continuous once daily (n=261)	Sorafenib 400 mg (two 200mg tablets) twice daily for a total daily dose of 800 mg (n=207)
Comparator arm (n)	Placebo (n=131)	Placebo (n=210)
Primary outcome	Progression-free survival, assessed every 8 weeks* and determined by blinded independent imaging review conducted by the imaging core laboratory using RECIST 1.1	Progression-free survival, assessed every 8 weeks by central independent blinded review using RECIST 1.0
Relevant secondary outcomes	Overall survival, measured from the date of randomisation until date of death from any cause Investigator assessed progression-free survival Objective tumour response rate (defined as the proportion of subjects who had best overall response of complete response or partial response as determined by blinded independent imaging review using RECIST 1.1) and related outcomes including duration of response, stable disease, disease control rate and clinical benefit rate Safety	Overall survival, measured from the date of randomisation until date of death from any cause Investigator assessed progression-free survival Objective tumour response (defined as the proportion of subjects who had best overall response of complete response or partial response as determined by blinded Independent Imaging Review using RECIST 1.0) and related outcomes including duration of response, stable disease and disease control rate Safety Health-related quality of life
Primary analysis	≥214 progression events or deaths	~267 progression events
Data-cuts	November 2013 June 2014 August 2015	August 2012 May 2013 July 2015

GBq=gigabecquerels; RECIST=Response evaluation criteria in solid tumours; VEGFR=vascular endothelial growth factor receptor
*Every 12 weeks in the extended open-label phase of the trial
Source: Schlumberger et al 2015,[47] Eisai 2017,[8] Brose et al 2014[48] and Bayer 2017[7]

Patients eligible for inclusion

A summary of the criteria describing patient eligibility for entry into the SELECT and DECISION trials is presented in Table 5. Both trials only included patients with RR-DTC and who had Eastern Cooperative Oncology Group (ECOG) PS 0 to 2. As highlighted in the Background of this report (Section 1.5), there is no universally agreed definition of RR-DTC. The definitions used to define RR-DTC in the two trials were broadly similar (see Table 6 for definitions employed by the trials for RR-DTC).

The main difference in trial eligibility was that the SELECT trial permitted the enrolment of patients who had been previously treated with a vascular endothelial growth factor receptor (VEGFR)-targeted therapy (including sorafenib) and the DECISION trial did not. Age, region and VEGFR-targeted therapy were stratification factors in the SELECT trial, whereas age and region were stratification factors in the DECISION trial.

Table 5 Patients included and excluded in the SELECT and DECISION trials

Criteria	SELECT trial	DECISION trial
Inclusion	• Adults with histologically or cytologically confirmed diagnosis of differentiated thyroid cancer • Measurable disease as confirmed by central radiographic review within the past 13 months • Radioactive iodine-refractory/resistant (see Table 6 for definition) • Disease progressed within 12 (+1) months according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans • Eastern Cooperative Oncology Group performance status 0 to 2 • 0 or 1 prior VEGFR-targeted therapy • Adequately controlled blood pressure with or without antihypertensive medications • Adequate bone marrow, blood coagulation, liver and renal function	• Adults with differentiated and poorly differentiated thyroid cancer • ≥1 measurable lesion by CT or MRI according to RECIST 1.0 • Disease progressed within the past 14 months according to RECIST 1.0 • Radioactive iodine resistant (see Table 6 for definition) • Eastern Cooperative Oncology Group performance status 0 to 2 • Patients must not be candidates for curative surgery or radiation therapy • Adequate TSH suppression (<0.5 mU/L) • Adequate bone marrow, liver and renal function
Exclusion	• Anaplastic or medullary carcinoma of the thyroid • Active malignancy (except for differentiated thyroid carcinoma, or definitively treated melanoma in-situ, basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix) within the past 24 months • Prior treatment with lenvatinib • ≥2 prior VEGFR-targeted therapy or any ongoing treatment for RR-DTC other than TSH-suppressive thyroid hormone therapy • Major surgery within 3 weeks prior to the first dose of study drug • Subjects with urine protein ≥1 g/24h • Gastrointestinal malabsorption or any other condition in the opinion of the investigator that might affect the absorption of lenvatinib • Significant cardiovascular impairment • Prolongation of QTC interval to >480 ms • Bleeding or thrombotic disorders or use of anticoagulants, such as warfarin, or similar agents requiring therapeutic international normalized ration (INR) monitoring (Treatment with low molecular weight heparin is allowed) • Active haemoptysis within 3 weeks prior to the first dose of study drug • Active infection (any infection requiring treatment) • Any medical or other condition which, in the opinion of the investigator, would preclude participation in a clinical trial • Women who are pregnant or breastfeeding • Known intolerance to any of the study drugs (or any of the excipients)	• Concurrent cancer distinct in primary site or histology from thyroid cancer ≤5 years prior to randomisation (except for cervical cancer in situ, treated basal-cell carcinoma, and superficial bladder tumours) and patients with foci of undifferentiated thyroid cancer • Patients who had received previous targeted therapy, thalidomide, or chemotherapy for thyroid cancer (low-dose chemotherapy for radio sensitisation was allowed) • Patients who undergo major surgery, open biopsy, or significant traumatic injury ≤30 days prior to randomisation • Presence of a non-healing wound, ulcer, bone fracture, or grade ≥2 infection according to NCI-CTCAE v3.0[142] • Grade ≥3 haemorrhage or bleeding event according to NCI-CTCAE ≤3 months prior to randomization • Evidence or history of bleeding diathesis or coagulopathy; or the presence of tracheal, bronchial, or oesophageal infiltration with significant risk of bleeding (but without having received local treatment prior to enrollment in the study) • Patients with clinically significant cardiac disease and/or uncontrolled hypertension (>150/90 mm Hg) despite optimal treatment • Patients known to be infected with HIV or hepatitis B or C virus • Women who are pregnant or breastfeeding • Patients with a known or suspected allergy to sorafenib or hypersensitivity to sorafenib or any agent given during the course of the study

CT=computed tomography; HIV=human immunodeficiency virus; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST=response evaluation criteria in solid tumours; RR-DTC=radioactive iodine refractory differentiated thyroid cancer; TSH=thyroid-stimulating hormone; VEGFR=vascular endothelial growth factor receptor
Source: Schlumberger et al 2015[47] including supplementary material (protocol), Brose et al 2011[71] and Brose et al 2014[48]

Table 6 Definitions of differentiated thyroid cancer refractory to radioactive iodine employed by the SELECT and DECISION trials

Criteria	SELECT trial	DECISION trial
To be classified as having differentiated thyroid cancer refractory to radioactive iodine, patients were required to meet at least one of the criteria specified	• ≥1 measurable lesions that do not demonstrate iodine uptake on any radioactive iodine scan • ≥1 measurable lesions that had progressed, according to RECIST 1.1, within 12 months of radioactive iodine therapy, despite demonstration of radioiodine avidity at the time of that treatment by pre- or post-treatment scanning (These were subjects who were not eligible for possible curative surgery) • Cumulative activity of radioactive iodine of >600 mCi or 22 GBq, with the last dose administered at ≥6 months prior to study entry	• ≥1 target lesion without iodine uptake • Tumours had iodine uptake and progressed after one radioactive iodine treatment (≥3.7 GBq [≥100 mCi]) within the past 16 months • Disease progression after each of two radioactive iodine treatments (≥3.7 GBq [≥100 mCi]) within 16 months of each other (with the last such treatment administered >16 months ago) • Cumulative radioactive iodine activity of at least ≥22.2 GBq (≥600 mCi)

GBq=gigabecquerels; mCI=millicurie; MRI=Magnetic resonance imaging; RECIST= Response evaluation criteria in solid tumours
Source: Schlumberger et al 2015[47] including supplementary material (protocol), Brose et al 2011[71] and Brose et al 2014[48]

Dose modifications/interruptions and concomitant therapy

In both trials, the starting dose for treatment with lenvatinib or sorafenib was the licensed dose (24mg and 800mg, respectively). Both trials permitted dose modifications or interruptions. The criteria were not stated in the protocol for the SELECT trial but the Summary of Product Characteristics (SmPC)[50] includes a dose/toxicity management plan for lenvatinib. For the DECISION trial, Brose et al 2011[7] stated that dose modifications or interruptions were allowed, based on specific criteria, for Grade 2 to Grade 3 hand-foot syndrome and other AEs.

A summary of the concomitant therapies permitted and prohibited in each trial is presented in Table 7. While neither trial describes BSC for patients in either arm, permitted concomitant therapies could be considered to be BSC and were available to patients in both arms of both trials. The main difference between the two trials is that palliative radiotherapy, which is commonly available as part of BSC in UK NHS clinical practice, was not permitted in either arm of the SELECT trial.

Table 7 Concomitant treatment available to patients in the SELECT and DECISION trials

Concomitant treatment allowed and disallowed	SELECT trial	DECISION trial
Permitted	• Thyroxine suppression therapy • Over the counter medications • Treatment of complications or adverse events or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs) may be given at investigator discretion, unless expected to interfere with the evaluation of (or to interact with) study drug • Aspirin, nonsteroidal anti-inflammatory drugs and low molecular weight heparin are permissible but should be used with caution • G-CSF or equivalent may be used in accordance with ASCO, institutional, or national guidelines • Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell counts	• Thyroid hormone replacement with suppressed thyroid stimulating hormone levels (target <0.5 mU/l) • Treatment with non-conventional therapies (for example herbs with the exception of St. John's Wort or acupuncture) and vitamin/mineral supplements provided that they do not interfere with the study endpoints, in the opinion of the investigator • Bisphosphonate treatment in subjects with bone metastasis on discretion of the investigator • G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator; however they may not be substituted for a required dose reduction (Subjects taking chronic erythropoietin are permitted) • Narrow therapeutic index medication (e.g. warfarin) permitted with monitoring
Prohibited	• Anti-cancer therapies such as chemotherapy, palliative radiotherapy or immunotherapy	• Concomitant radioactive iodine, chemotherapy or other investigational therapy • Substances known to induce CYP3A4

ASCO=American Society of Clinical Oncology; G-CSF=Granulocyte colony-stimulating factor
Source: Schlumberger et al 2015,[47] supplementary material (protocol), Brose et al 2011[71] and Bayer 2015[143]

Subgroup analyses

In the SELECT trial, subgroup analyses were pre-specified for patients previously treated with a VEGFR-targeted therapy and for those who were not. Both trials also included pre-specified subgroup analyses for age, region, gender and histology. Subgroup analyses were pre-specified for PFS, OS and objective tumour response rate (ORR) in the SELECT trial but only for PFS in the DECISION trial. Other pre-specified subgroup analyses in the SELECT trial were for race and for patients whose TSH level was highest prior to progression. Other pre-specified subgroup analyses in the DECISION trial included site of metastasis, FDG take-up, prior radioactive iodine cumulative dosing, tumour burden as measured by number of target or non-target lesions and as measured by sum of target diameters. Many other post-hoc subgroup analyses were also conducted for both trials (see Appendix 4, Table 55).

Follow-up, dose intensity and treatment crossover and other subsequent therapy received

At the time of the primary data-cuts for both trials, OS data were immature. Therefore, for both trials, OS was updated at two subsequent data-cuts. The median duration of follow-up at each data-cut was similar for both trials (see Table 8).

Table 8 Length of follow-up and average dose intensity in the SELECT and DECISION trials

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
First data-cut	November 2013		August 2012	
Length of follow up, median, months (95% CI)	17.1 (16.0 to 17.6)	17.4 (15.9 to 19.0)	17.4 (CIs NR)	NR
Average dose, mg	17.2	NR	651	793
Dose intensity (% of maximum dose)	71.7%	NR	81.4%	99.1%
Second data-cut	June 2014		May 2013	
Length of follow up, median, months (95% CI)	23.6 (22.7 to 24.5)	24.1 (22.1 to 26.1)	24.1 (CIs NR)	NR
Average dose, mg	NR	NR	NR	NR
Dose intensity (% of maximum dose)	NR	NR	NR	NR
Third data-cut	August 2015		July 2015	
Length of follow up, median, months (95% CI)	37.8 (CIs NR)	37.9 (CIs NR)	36.0 (CIs NR)	NR
Average dose, mg	17.4	NR	651.2mg	793.6mg
Dose intensity (% of maximum dose)	72.5%	NR	81.4%	99.2%

CI=confidence interval; NR=not reported
Source: Schlumberger et al 2015,[47] Eisai 2017,[8] Brose et al 2014[48] and Bayer 2017[7]

Patients were eligible to receive treatment (intervention or placebo) in both trials until disease progression. An important feature of both trials is that, on disease progression, patients were unblinded and permitted to cross over from the placebo arm to the active treatment arm. In both trials, patients who crossed over were entered into an open-label extension phase of the same trial. In the DECISION trial, patients who had progressed on sorafenib were also eligible to enter the open-label extension phase of the trial and receive further sorafenib until further disease progression. Patients who progressed on lenvatinib in the SELECT trial were however not permitted to receive additional lenvatinib in the open-label extension phase. Information on treatment crossover and subsequent treatment received is reported in Table 9 where it is evident that the majority of patients in both placebo arms, but in particular in the placebo arm of the SELECT trial, crossed over to receive lenvatinib or sorafenib.

Table 9 Treatment crossover in the SELECT and DECISION trials (those who entered the extended open-label phase of the trials)

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
Number (%) of patients who crossed-over: First data-cut	n/a	109 (83.2)	55 (26.6)*	150 (71.4)
Number (%) of patients who crossed-over: Second data-cut	n/a	115 (87.8)	NR	157 (74.8)
Number (%) of patients who crossed-over: Third data-cut	n/a	115 (87.8)	NR	158 (75.0)

*Patients did not crossover from the sorafenib arm to the placebo arm in the DECISION trial but were permitted to receive additional sorafenib, data reported here is for those who received additional sorafenib
Source: Schlumberger et al 2015,[47] Eisai 2017,[8] including Appendix 4, Brose et al 2014[48] and Bayer 2017[7]

In addition, some patients received subsequent anti-cancer treatments, not part of the trial protocols, on disease progression (Table 10). In the SELECT trial, at the first data-cut (November 2013) 15.7% of patients randomised to lenvatinib and 12.2% of patients randomised to placebo received subsequent treatment. In the DECISION trial, at the first data-cut (August 2012), 20.3% of patients randomised to sorafenib and 8.6% of patients randomised to placebo received subsequent treatments. For the most part, subsequent treatment in both trials constituted antineoplastic and immunomodulating agents. The specific antineoplastic and immunomodulating agents were only reported for the SELECT trial. Most commonly, patients received pazopanib (17.1% and 18.8% of patients who received subsequent therapy in the lenvatinib and placebo arms, respectively) and/or sorafenib (14.6% and 12.5% of patients who received subsequent therapy in the lenvatinib and placebo arms, respectively).

Table 10 Subsequent treatment received in the SELECT and DECISION trials following disease progression (first data-cuts)

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
Any anti-cancer treatment	41 (15.7)	16 (12.2)	42 (20.3)	18 (8.6)
Antineoplastic and immunomodulating agents	29 (11.1)	13 (9.9)	38 (18.4)	17 (8.1)
Various*	17 (6.5)	5 (3.8)	4 (1.9)	2 (1.0)

Source: SELECT trial clinical study report, Table 14.3.8.1 and DECISION trial clinical study report, Table 14.1.2 / 11
*Various includes the following categories: other therapeutic radiopharmaceuticals; all other therapeutic products; diagnostic agents; diagnostic radiopharmaceuticals

Methods used for adjusting for treatment crossover

As patients in both trials were permitted to cross over to receive the intervention drug on disease progression, the OS results are likely to be confounded. The authors of the SELECT trial publication[47] employed the Rank Preserving Structural Failure Time Model (RPSFTM) to adjust the OS results for patient crossover. The OS results from the DECISION trial have been adjusted using both the RPSFTM and the Iterative Parameter Estimation (IPE). The

unadjusted and adjusted OS analyses have been reported in conference abstracts for the SELECT trial,[86] DECISION trial[57,67,109] and in the company submissions.[7,8]

As patients were not censored when they received post-progression treatments, the RPSFTM and IPE methods implicitly included all subsequent therapies as an inherent part of the intervention/control treatment effect. In other words, it is assumed that the subsequent therapy administered to patients in each arm of the trial is reflective of the subsequent therapy that would have been offered to patients receiving the same treatment in clinical practice.

The RPSFTM and IPE methods also both rely critically on the 'common treatment effect' assumption, that is, the effect of receiving the experimental treatment is the same when received on diagnosis (i.e. in patients initially randomised to the experimental arm) as it is in treatment switchers (i.e. patients from the control arm who switch to receive the experimental treatment). In practice, it is unlikely that the 'common treatment effect' assumption will ever be exactly true. However, it is appropriate to use RPSFTM/IPE methods if the assumption is likely to be approximately true.[144] Clinical advice to the AG was that for both the SELECT and DECISION trials, it is reasonable to assume that patients who switched from the placebo arm to receive the experimental treatment (i.e. lenvatinib/sorafenib) would experience the same treatment effect as patients who were originally randomised to the experimental arm.

In addition to the assumptions that are common to both the RPSFTM and the IPE methods, the IPE method also assumes that survival times follow a parametric distribution. To implement this method, a suitable parametric model must be identified, which can be problematic. The AG has been unable to identify information on how the IPE analysis was performed using data from the DECISION trial, including details of the parametric model chosen, and so is not able to comment on the suitability of this method.

Generally, the key assumption of a 'common treatment effect' that underpins the RPSFTM method appears to be valid, and due to the fact that a large number of placebo patients crossed over to active treatment in both trials, the AG is of the opinion that the RPSFTM method is the most suitable method for adjusting for treatment switching in the SELECT and DECISION trials. However, a caveat to the use of the RPSFTM adjusted OS results for both trials is that differences in post-study (post-progression) anti-cancer treatments administered to patients in each treatment arm are not accounted for in this analysis.

4.2.2 Participant characteristics

Overall, the baseline characteristics of patients included in the SELECT trial and in the DECISION trial were balanced between treatment arms (Table 11). Nevertheless, there are a few notable differences between treatment arms and also across trials.

In the SELECT trial, there were proportionately fewer males in the lenvatinib arm (47.9%) than in the placebo arm (57.3%). Median time from diagnosis of DTC to randomisation was shorter in the lenvatinib arm than in the placebo arm (66.0 months versus 73.9 months). Compared with the placebo arm, a smaller proportion of patients in the lenvatinib arm had metastases in the lung (86.6% versus 94.7%) or liver (16.5% versus 21.4%).

In the DECISION trial, a higher proportion of patients in the sorafenib arm had metastases in the lymph node (54.6%) or pleura (19.3%) than in the placebo arm (48.1% and 11.4% respectively). There were proportionately more males in the sorafenib arm (50.2%) than in the placebo arm (45.2%).

As previously highlighted, patients in the SELECT trial could have been previously treated with a VEGFR-targeted therapy (including sorafenib) prior to trial entry whereas patients in the DECISION trial could not. Approximately one quarter (23.7%) of patients in the SELECT trial had received prior treatment with a VEGFR-targeted therapy. In the lenvatinib arm, of 66 patients previously treated with a VEGFR-targeted therapy, 51 patients (77.2%) were treated with sorafenib. In the placebo arm, of 27 patients previously treated with a VEGFR-targeted therapy, 21 patients (77.8%) were treated with sorafenib. Other VEGFR-targeted therapies used prior to trial entry to the SELECT trial included sunitinib and pazopanib. The median duration of any prior therapy was approximately 11 months in both arms.

In the SELECT trial, a higher proportion of enrolled patients were from North America than in the DECISION trial (29.6% versus 17.3%, respectively) and a lower proportion of patients were from Europe in the SELECT trial than in the DECISION trial (49.7% versus 59.7%, respectively). A greater proportion of patients were white in the SELECT trial (79.3%) compared to the DECISION trial (60.2%). A higher proportion of patients in the SELECT trial had bone metastases than in the DECISION trial (38.8% versus 27.1%, respectively).

Table 11 Participant characteristics in the SELECT and DECISION trials

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
Median age, years (minimum to maximum)	64 (27 to 89)	61 (21 to 81)	63 (24 to 82)	63 (30 to 87)
Number (%) male	125 (47.9)	75 (57.3)	104 (50.2)	95 (45.2)
Ethnicity				
White	208 (79.7)	103 (78.6)	123 (59.4)	128 (61.0)
Black of African American	4 (1.5)	4 (3.1)	6 (2.9)	5 (2.4)
Asian	46 (17.6)	24 (18.1)	47 (22.7)	52 (24.8)
Other	3 (1.2)	0	2 (1.0)	2 (1.0)
Missing or uncodeable	n/a	n/a	29 (14.0)	23 (11.0)
Region, n (%)				
Europe	131 (50.2)	64 (48.9)	124 (59.9)	125 (59.5)
North America	77 (29.5)	39 (29.8)	36 (17.4)	36 (17.1)
Other	53 (20.3)	28 (21.4)	47 (22.7)	49 (23.3)
Median time from diagnosis of DTC to randomisation, months (range)	66 (0.4 to 573.6)	73.9 (6.0 to 484.8)	66.2 (3.9 to 362.4)	66.9 (6.6 to 401.8)
ECOG performance status, n (%)				
0	144 (55.2)	68 (51.9)	130 (62.8)	129 (61.4)
1	104 (39.8)	61 (46.6)	69 (33.3)	74 (35.2)
2	12 (4.6)	2 (1.5)	7 (3.4)	6 (2.9)
3	1 (0.4)	0	0	0
Not available	0	0	1 (0.5)	1 (0.5)
Histology, n (%)				
Papillary	132 (50.6)	68 (51.9)	118 (57.0)	119 (56.7)
Poorly differentiated	28 (10.7)	19 (14.5)	24 (11.6)	16 (7.6)
Follicular, not Hürthle cell	53 (20.3)	22 (16.8)	13 (6.3)	19 (9.0)
Hürthle cell	48 (18.4)	22 (16.8)	37 (17.9)	37 (17.6)
Other	0	0	2 (1.0)	5 (2.4)
Missing or non-diagnosed	0	0	13 (6.3)	14 (6.7)
Metastases, n (%)				
Locally advanced	4 (1.5)	0	7 (3.4)	8 (3.8)
Distant	257 (98.5)	131 (100)	200 (96.6)	202 (96.2)
Metastases site, n (%)				
Lung	226 (86.6)	124 (94.7)	178 (86.0)	181(86.2)
Lymph node	138 (52.9)	64 (48.9)	113 (54.6)	101(48.1)
Bone	104 (39.8)	48 (36.6)	57 (27.5)	56 (26.7)
Pleura	46 (17.0)	18 (13.7)	40 (19.3)	24 (11.4)
Head and neck	Not reported	Not reported	33 (15.9)	34 (16.2)
Liver	43 (16.5)	28 (21.4)	28 (13.5)	30 (14.3)
Thyroid surgery	261 (100)	131 (100)	207 (100)	208 (99.0)
Median cumulative radioiodine activity, mCI	350		400	376
Target tumor size, n (%)				
<35	65 (25)	28 (21)	44 (21)	51 (24)
36-60	72 (28)	32 (24)	34 (16)	48 (23)
61-92	63 (24)	34 (26)	51 (25)	34 (16)
>92	61 (23)	37 (28)	78 (38)	77 (37)
Prior VEGFR-targeted therapy	66 (25.3)	27 (20.6)	0	0

DTC=differentiated thyroid cancer; ECOG=Eastern Cooperative Oncology Group; mCI=millicurie; VEGFR=vascular endothelial growth factor receptor

Source: Schlumberger et al 2015,[47] EPAR for lenvatinib,[27] Brose et al 2014[48] and Bayer 2017,[7] appendix 7.5 (Table 12)

4.2.3 Comparison of assessments of risk of bias

A summary of the risk of bias assessments for both trials is reproduced in Table 12. Overall, the AG considered the risk of bias to be low in both trials.

Table 12 Risk of bias assessment of the SELECT and DECISION trials

Parameter	SELECT	DECISION
Was the method used to assign participants to the treatment groups really random?	✓	✓
Was the allocation of treatment concealed?	✓	✓
Was the number of participants who were randomised stated?	✓	✓
Were details of baseline comparability presented in terms of prognostic factors?	✓	✓
Was baseline comparability achieved in terms of prognostic factors?	✓/✗ [a]	✓/✗ [a]
Were the eligibility criteria for study entry specified?	✓	✓
Were any co-interventions identified that may influence the outcomes for each group?	✓	✓
Were the outcome assessors blinded to the treatment allocation?	✓	✓
Were the individuals who administered the intervention blinded to the treatment allocation?	✓ [b]	✓
Were the participants who received the intervention blinded to the treatment allocation?	✓ [c]	✓ [d]
Was the success of the blinding procedure assessed?	✗	✗
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	✓	✓
Were the reasons for withdrawals stated?	✓	✓
Is there any evidence to suggest that the authors measured more outcomes than they reported?	✓	✓
Was an intention to treat analysis included?	✓	✓

✓ yes (item properly addressed) ✗ no (item not properly addressed) ✓/✗ partially (item partially addressed)
a In the SELECT trial, median time from diagnosis of DTC to randomisation was shorter in the lenvatinib arm than in the placebo arm (66.0 months versus 73.9 months). Compared with the placebo arm, a smaller proportion of patients in the lenvatinib arm had metastases in the lung (86.6% versus 94.7%) or liver (16.5% versus 21.4%). In the DECISION trial, a higher proportion of patients in the sorafenib arm had metastases in the lymph node (54.6%) or pleura (19.3%) than in the placebo arm (48.1% and 11.4% respectively).
b Study drugs administered by clinicians who remained unaware of the study-drug assignments until the occurrence of unacceptable toxic effects or disease progression as assessed by independent radiologic review
c If independent radiologic review confirmed disease progression, the patients who were receiving placebo could elect to enter the open-label lenvatinib phase
d In the event of protocol-defined progression determined by the investigator, treatment could be unmasked and patients from both groups could begin open-label sorafenib and continue until treatment was no longer beneficial, based on investigator judgment

4.2.4 Consideration of proportional hazards assumption

Cox proportional hazard (PH) modelling was used to generate PFS, unadjusted OS and adjusted OS HRs from data collected during the SELECT and DECISION trials. The validity of this method relies on the event hazards associated with the intervention and comparator data being proportional over time within each trial. The AG assessed the validity of the PH assumption for all analyses, where possible, provided in the submissions from Eisai 2017[8] and

Bayer 2017[7] that included a HR result (see Appendix 3 for methods and results). The AG concluded that the PH assumption was not valid for PFS, unadjusted OS or RPSFTM adjusted OS in the SELECT trial or for PFS or RPSFTM adjusted OS in the DECISION trial.

4.2.5 Overall survival

A summary of the unadjusted and adjusted OS findings from the most recent data-cuts from both trials is presented in Table 13. The findings for all data-cuts are summarised in Appendix 4 (Table 56).

Table 13 Overall survival findings from the SELECT and DECISION trials

Outcome	SELECT trial		DECISION trial	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
Data-cut*	Third data-cut (August 2015)		Third data-cut (July 2015)	
Number of deaths (%)	121 (46.4)	70 (53.4)	103 (49.8)	109 (51.9)
Median OS in months (95% CI)	41.6 (31.2 to NE)	34.5 (21.7 to NE	39.4 (32.7 to 51.4)	42.8 (34.7 to 52.6)
Unadjusted HR (95% CI) p value	0.84 (0.62 to 1.13) nominal p=0.2475		0.92 (0.71 to 1.21) one-sided p=0.28	
RPSFTM adjusted HR (95% CI) p value (Bootstrapping 95% CI)	0.54 (CIs NR) nominal p=0.0025 (0.36 to 0.80)		0.77 (0.58 to 1.02) NR (0.42 to 1.79)	
IPE adjusted HR (95% CI) p value (Bootstrapping 95% CI)	n/a		0.80 (0.61 to 1.05) NR (0.48 to 1.71)	

CI=confidence interval; HR=hazard ratio; IPE=Iterative Parameter Estimation; NE-not estimable; NR=not reported; OS=overall survival; RPSFTM=Rank Preserving Structural Failure Time Model
*See Section 5.3.4 for details of the data-cuts used in the AG's economic model
Source: Eisai 2017,[8] adapted from Table 8 and Bayer 2017,[7] text on page 28

In both trials, there was no statistically significant difference in unadjusted OS between trial arms. However, when the RPSFTM was used, patients in the lenvatinib arm had a statistically significant improvement in OS when compared to patients in the placebo arm in the SELECT trial. The difference in OS between sorafenib and placebo was not reported to be statistically significant when using either the RPSFTM or IPE method in the DECISION trial.

4.2.6 Progression-free survival

In both trials, the primary outcome was PFS by blinded independent review. The findings for PFS reported in the SELECT and DECISION trials are summarised for the first data-cuts (November 2013 and August 2012, respectively) in Table 13 since this was the only data-cut for which PFS results have been published for both trials.

Table 14 Progression-free survival findings from the SELECT and DECISION trials

Outcome	SELECT trial		DECISION trial	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
Data-cut	First data-cut (November 2013)		First data-cut (August 2012)	
Progression-free survival by blinded independent review				
Number of events (%)	93 (35.6)	109 (83.2)	113 (54.6)	137 (65.2)
Died before progression	14 (5.4)	4 (3.1)	NR	NR
Median PFS in months (95% CI)	18.3 (15.1 to NE)	3.6 (2.2 to 3.7)	10.8	5.8
Stratified HR (95% CI)* p value	0.21 (0.14 to 0.31) p<0.001		0.59 (0.45 to 0.76) p<0.0001	
Investigator assessed progression-free survival				
Number of events (%)	91 (34.9)	104 (79.4)	140 (67.6)	184 (87.6)
Died before progression	16 (6.1)	6 (4.6)	NR	NR
Median PFS in months (95% CI)	16.6 (4.8 to NE)	3.7 (3.5 to NE)	10.8	5.4
Stratified HR (95% CI)* p value	0.24 (0.16 to 0.35) p<0.001			

CI=confidence interval; HR=hazard ratio; IPE=Iterative Parameter Estimation; NE=not estimable; NR=not reported; PFS=progression-free survival

*Stratification factors for the SELECT trial were age (≤65 years or >65 years), geographical region (Europe, North America, Other) and receipt or non-receipt of prior VEGFR-targeted therapy (0, 1); stratification factors in the DECISION trial were age (<60 years or ≥60 years) and geographical region (North America, Europe, Asia)

Source: Schlumberger et al 2015[47] and Brose et al 2014[48] with additional data from Eisai 2017[8] and Bayer 2017[7]

In the SELECT trial there was a 14.7 months improvement in PFS (blinded independent review) with lenvatinib when compared to placebo. In the DECISION trial there was a 5 months improvement in PFS (blinded independent review) with sorafenib when compared with placebo. The differences in median PFS assessed by investigators were marginally decreased in the SELECT trial (12.9 months) and marginally increased in the DECISION trial (5.4 months). However, the HRs in both trials were similar to those from the assessments by blinded independent review.

The SELECT trial is the only trial that also reports PFS for another data-cut.[84,85] This was available for investigator assessed PFS at the third data-cut (August 2015). Compared to the first data-cut, median PFS was reported to be slightly higher in the lenvatinib arm at the third data-cut (19.4 months) but the median PFS remained the same in the placebo arm (3.7 months), a difference of 15.7 months. However, for both data-cuts, the HR between arms was identical (0.24) and reported to be statistically significant (p<0.001).

The findings for all data-cuts are summarised in Appendix 4 (Table 57 and Table 58).

4.2.7 Objective tumour response

The findings for objective tumour response are reported in Table 15. In both trials, the tumour response assessment was conducted by blinded independent review at the first data-cut and favoured patients in the intervention arms compared with patients in the placebo arms. It is noticeable that the difference in ORR between the intervention and placebo arms was much greater for patients treated with lenvatinib in the SELECT trial (63.2%) than those treated with sorafenib in the DECISION trial (11.7%). This is attributable to the much higher proportion of patients who were treated with lenvatinib and had a partial response in the SELECT trial compared to patients treated with sorafenib in the DECISION trial. Complete responses were only reported for patients treated with lenvatinib, albeit in very few patients (1.5%). ORR was statistically significantly improved in both trials for patients treated with either lenvatinib or sorafenib when compared with placebo.

The objective tumour response evaluations for the SELECT trial were conducted using an ITT analysis. In the DECISION trial, patients for whom it was not possible to evaluate a tumour response were excluded from the analysis (as per the requirements of a per protocol analysis). If all patients are included in the evaluations using ORR data from the DECISION trial, the ORR is marginally decreased in both arms: 11.6% for sorafenib versus 0.5% for placebo.

Time to response was only reported for the SELECT trial. For patients treated with lenvatinib the median was 2.0 months compared to 5.6 months in the placebo arm. The median duration of response was not estimable for patients in the SELECT trial, however, for those treated with lenvatinib, the restricted mean was 17.34 months. Time to response was not reported in the DECISION trial but the duration of response was 10.2 months for patients treated with sorafenib.

Table 15 Objective tumour response findings from the SELECT and DECISION trials, first data-cut

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=196	Placebo N=201
ORR, % (95% CI)	64.8 (59.0 to 70.5)	1.5 (0.0 to 3.6)	12.2 (8.0 to 17.7)	0.5 (0.0 to 2.7)
Difference, % (95% CI)	63.2 (57.1 to 69.4)		11.7	
Odds Ratio (95% CI) P value	28.87 (12.46 to 66.86) p<0.0001		NR <0.0001	
Complete response, n (%)	4 (1.5)	0	0	0
Partial response, n (%)	165 (63.2)	2 (1.5)	24 (12.2)	1 (0.5)
Stable disease ≥4 weeks	≥7 weeks: 60 (23.0)	≥7 weeks: 71 (54.2)	145 (74.0)	149 (74.1)
Durable stable disease (stable disease ≥23 weeks or 6 months)	40 (15.3)	39 (29.8)	82 (41.8)	67 (33.2)
Progressive disease, n (%)	18 (6.9)	52 (39.7)	20 (10.2)	46 (22.9)
Patients unevaluable for response / not known, n (%)	1 (0.4) / 13 (5.0)	2 (1.5) / 4 (3.1)	n/a per protocol analysis*	n/a per protocol analysis*
Time to response, months Median (95% CI) Restricted mean (SD)	 2.0 (1.9 to 3.5) 3.38 (0.18)	 5.6 (1.8 to 9.4) 5.63 (3.79)	 NR NR	 NR NR
Duration of response, months Median (95% CI) Restricted mean (SD)	 NE (16.8 to NE) 17.34 (0.76)	 NE NE	 10.2 (7.4 to 16.6) NR	 NR NR

n/a=not applicable; NR=not reported; SD=standard deviation
*Unlike the SELECT trial, patients who were unevaluable for response were excluded from the analyses in the DECISION trial. There were 18 (4.3%) patients who were excluded from the objective tumour response analyses in the DECISION trial, 9 (4.3%) patients in each arm
Source: Eisai 2017,[8] text on page 25 and Bayer 2017,[7] adapted from Table 5

Both trials also assessed disease control rates (complete response + partial response + stable disease) and the SELECT trial reported clinical benefit rate (complete response + partial response + durable stable disease). In each trial, the findings were statistically significantly in favour of lenvatinib or sorafenib compared with placebo. However, comparisons between trials cannot be easily made as the definition of disease control rate differed across trials due to differences in the length of stable disease required for control. The SELECT trial required a stable disease of ≥7 weeks whereas the DECISION trial required a length of ≥4 weeks. Both trials did however report stable disease ≥6 months. This was similar in the placebo arms of both trials (SELECT: 29.8%; DECISION: 33.2%), 15.3% for patients treated with lenvatinib and 41.8% for patients treated with sorafenib. Therefore, a clinical benefit at 6 months was reported by 79.5% of patients treated with lenvatinib versus 31.3% with placebo in the SELECT trial and 54.0% patients treated with sorafenib versus 33.7% with placebo in the DECISION trial. In the submission from Bayer 2017,[7] it is noted that most sorafenib-treated

patients (77%) experienced target lesion tumour shrinkage compared to 28% of patients in the placebo arm.

4.2.8 Safety findings

Safety data from the SELECT and DECISION trials were reported for the first data-cut (November 2013 and August 2012, respectively). For the individual types of AEs experienced by patients, the published paper for the SELECT trial presented data for treatment-related AEs whereas the published paper for the DECISION trial presented data for any treatment-emergent AEs. Therefore, data for specific types of treatment emergent AEs were extracted from the pharmaceutical company submission (Eisai 2017[8]) for the SELECT trial.

All-Grade and Grade ≥3 adverse events

Nearly all of the patients who received lenvatinib or sorafenib reported an AE and approximately 90% of patients who received placebo reported an AE. AEs that were reported by ≥30% and Grade ≥3 AEs that were reported by ≥1.5% of patients in any of the arms are summarised in Table 16 and Table 17. All types of AEs were more common in patients treated with lenvatinib or sorafenib compared with patients in the placebo arms of both trials. Hand-foot syndrome was reported by approximately three-quarters of patients in the DECISION trial. Approximately two-thirds of patients reported all-Grade hypertension or diarrhoea when treated with lenvatinib in the SELECT trial, similar to the proportion treated with sorafenib reporting all-Grade diarrhoea or alopecia in the DECISION trial. Weight loss was reported by approximately half of all patients treated with either lenvatinib or sorafenib. By far the most common Grade ≥3 AEs were hypertension and hand-foot syndrome for patients treated with lenvatinib (>40%) and sorafenib (>20%) respectively.

Table 16 All-Grade adverse events reported by ≥30% of patients in any arm of the SELECT and DECISION trials

Outcome, n (%)	SELECT trial		DECISION trial	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=209
Any adverse event	260 (99.6)	118 (90.1)	204 (98.6)	183 (87.6)
Hypertension	181 (69.3)	19 (14.5)	84 (40.6)	26 (12.4)
Diarrhoea	173 (66.3)	22 (16.8)	142 (68.6)	32 (15.3)
Decreased appetite / anorexia	139 (53.3)	24 (18.3)	66 (31.9)	10 (4.8)
Weight loss	132 (50.6)	19 (14.5)	97 (46.9)	29 (13.9)
Nausea	121 (46.4)	33 (25.2)	43 (20.8)	24 (11.5)
Fatigue	110 (42.1)	32 (24.4)	103 (49.8)	53 (25.4)
Headache	100 (38.3)	15 (11.5)	37 (17.9)	15 (7.2)
Stomatitis (oral mucositis)	93 (35.6)	9 (6.9)	48 (23.2)	7 (3.3)
Vomiting	92 (35.2)	19 (14.5)	23 (11.1)	12 (5.7)
Proteinuria	84 (32.2)	4 (3.1)	2 (1.0)	0
Hand-foot syndrome	84 (32.2)	1 (0.8)	158 (76.3)	20 (9.6)
Dysphonia	82 (31.4)	7 (5.3)	25 (12.1)	6 (2.9)
Rash or desquamation	48 (18.4)	2 (1.5)	104 (50.2)	24 (11.5)
Alopecia	32 (12.3)	7 (5.3)	139 (67.1)	16 (7.7)

Source: Eisai 2017[8] and Brose et al 2014[48](with additional data on proteinuria from the clinical study report for the DECISION trial, Table 14.3.3 / 4)

Table 17 Grade ≥3 adverse events reported by ≥1.5% of patients in any arm of the SELECT and DECISION trials

Outcome, n (%)	SELECT trial		DECISION trial	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=209
Any Grade ≥3 adverse event	223 (85.4)	39 (29.8)	133 (64.3)	63 (30.1)
Hypertension	112 (42.9)	5 (3.8)	20 (9.7)	5 (2.4)
Weight loss	31 (11.9)	1 (0.8)	12 (5.8)	2 (1.0)
Proteinuria	26 (10.0)	0	0	0
Diarrhoea	22 (8.4)	0	12 (5.8)	2 (1.0)
Decreased appetite / anorexia	15 (5.7)	1 (0.8)	5 (2.4)	0
Asthenia	15 (5.7)	3 (2.3)	0	0
Fatigue	12 (4.6)	2 (1.5)	12 (5.8)	3 (1.4)
Stomatitis (Oral mucositis)	11 (4.2)	0	2 (1.0)	0
Hand-foot syndrome	9 (3.4)	0	42 (20.3)	0
Headache	8 (3.1)	1 (0.8)	0	0
Nausea	6 (2.3)	1 (0.8)	0	0
Hypocalcaemia	14 (5.4%)	0	19 (9.2)	3 (1.4)
Dyspnoea	4 (1.5)	4 (3.1)	10 (4.8)	6 (2.9)
Dysphagia	4 (1.5)	4 (3.1)	3 (1.4)	2 (1.0)
Rash / desquamation	1 (0.4)	0	10 (4.8)	0

Source: Eisai 2017,[8] Brose et al 2014[48] and Worden et al 2015[138] (with additional data from the clinical study report for the SELECT trial, Table 33 and from the clinical study report for the DECISION trial, Table 14.3.3 / 4 and Table 14.3.3 / 1)

Serious adverse events (including fatal adverse events)

Serious adverse events (SAEs) reported in the SELECT and DECISION trials are summarised in Table 18. In the SELECT trial, approximately half of the patients in the lenvatinib arm reported a SAE. Just over a third of patients reported a SAE in the sorafenib arm of the DECISION trial. Approximately a quarter of patients in the placebo arms of both trials reported a SAE. The only SAE reported by ≥2% in both trials was dyspnoea, which was at least as common for patients who received placebo as lenvatinib or sorafenib. The most common SAEs (≥3%) reported for patients treated with lenvatinib in the SELECT trial were pneumonia and hypertension. The most common SAEs (≥3%) reported by patients treated with sorafenib in the DECISION trial were secondary malignancy and pleural effusion.

Deaths from AEs were reported by 7.7% of patients treated with lenvatinib and 4.6% of patients in the placebo arm of the SELECT trial. Fatal AEs in the DECISION trial were reported by 5.8% of patients treated with sorafenib and 2.9% of patients in the placebo arm of the DECISION trial.

Table 18 Serious adverse events reported by ≥2% of patients in any arm of the SELECT and DECISION trials

Outcome, n (%)	SELECT trial*		DECISION trial	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=209
SAEs	133 (51.0)	31 (23.7)	77 (37.2)	55 (26.3)
Pneumonia	10 (3.8)	3 (2.3)	<2%†	<2%†
Hypertension	9 (3.4)	0	<2%†	<2%†
Dehydration	7 (2.7)	0	<2%†	<2%†
General physical health deterioration	6 (2.3)	0	<2%†	<2%†
Dysphagia	3 (1.1)	3 (2.3)	<2%†	<2%†
Dyspnoea	3 (1.1)	5 (3.8)	7 (3.4)	6 (2.9)
Haemoptysis	0	3 (2.3)	<2%†	<2%†
Secondary malignancy	<2%†	<2%†	9 (4.3)	4 (1.9)
Pleural effusion	<2%†	<2%†	6 (2.9)	4 (1.9)

SAE=serious adverse event
*SAEs only reported as treatment-related AEs for the SELECT trial
†Not reported in source documents so assumed to be <2%
Source: Eisai 2017[8] and Brose et al 2014[48]

Treatment-related adverse events

A summary of treatment-related AEs is presented in Table 19. A very high proportion of all-Grade AEs (≥96%) were considered treatment-related with lenvatinib or sorafenib. The proportion considered to be treatment-related was also high (>50%) in the placebo arms of both trials.

Table 19 Treatment-related adverse events in the SELECT and DECISION trials

Outcome, n (%)	SELECT trial		DECISION trial	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=209
Treatment related all-Grade AEs	254 (97.3)	78 (59.5)	200 (96.6)	112 (53.6)
Treatment related Grade ≥3 AEs	198 (75.9)	13 (9.9)	113 (54.6)	15 (7.2)
Treatment related SAEs	79 (30.3)	8 (6.1)	26 (12.6%)	8 (3.8)
Treatment related fatal AEs	6 (2.3)	0	1 (0.5)	1 (0.5)

AE=adverse event; SAE=serious adverse event
Source: Schlumberger et al 2015[47] and Brose et al 2014[48] (with additional data from the clinical study report for DECISION trial, Table 14.3.3 / 3)

In the SELECT trial, the causes of death considered to be treatment-related in the lenvatinib arm were: one case each of pulmonary embolism, haemorrhagic stroke and general deterioration of physical health; three cases were reported as deaths or sudden deaths (not otherwise specified). The DECISION trial was the only trial in which a patient in the placebo arm was considered to have died because of a treatment-related AE. The cause of death for this patient was subdural haematoma. Cause of death for a patient in the sorafenib arm that was considered to be treatment-related was myocardial infarction.

Timing of adverse events

In both trials, there have been subsequent analyses of the timing of AE occurrences in the treatment cycle reported. For the SELECT trial, Haddad et al 2015[90] reported the incidence and timing of five AEs: proteinuria, diarrhoea, fatigue / asthenia / malaise, rash and hand-foot syndrome. Hypertension was a notable AE omitted from the analysis. For the DECISION trial, detailed analysis of the AE occurrence patterns in patients is published in a peer-reviewed paper by Worden et al 2015.[138] Findings from the two trials cannot be easily compared as Haddad et al 2015[90] reported their findings as median time to first onset and median time to last resolution, whereas Worden et al 2015[138] reported the proportion of AEs occurring during each cycle. The AEs reported included: hand-foot syndrome, rash / desquamation, diarrhoea, fatigue, hypertension, weight loss, increased TSH levels and hypocalcaemia. Increased TSH levels were described as a 'study specific' AE, with a maximum severity of Grade 1; this AE was reported by 69 (33.3%) patients treated with sorafenib.[138]

In the SELECT trial, Haddad et al 2015[90] found that generally AEs for patients treated with lenvatinib occurred early in the treatment process and were resolved. Median time to onset for patients treated with lenvatinib ranged from 3 weeks with fatigue / asthenia / malaise to 12.1 weeks with diarrhoea. With regards to resolution, this ranged from a median of 5.9 weeks with rash to a median of 20.0 weeks with hand-foot syndrome.

In the DECISION trial, Worden et al 2015[138] found that in patients treated with sorafenib, the incidence of AEs was usually highest in the first cycle or first two cycles. Severity tended to diminish with each cycle (over the first nine cycles). The prevalence of AEs tended to remain stable. Diarrhoea and TSH were notable exceptions in that prevalence steadily increased over the first five or six cycles, at which point the prevalence peaked. Only weight loss, which was primarily Grade 1 or Grade 2 and highest in the first four cycles, tended to increase in severity over time (from Grade 1 to Grade 2: a greater proportion of patients experienced Grade 2 toxicity in cycle 9 compared with cycles 1 and 2). The authors noted that in general, AEs with sorafenib were manageable over time following dose modification and/or concomitant medications such as anti-diarrhoeals, anti-hypertensives or dermatologic preparations.

Dose modifications

Dose modifications as a result of AEs were more common for patients treated with lenvatinib and sorafenib than for those who received placebo (Table 20). Of note, the incidence of dose interruptions with lenvatinib in the SELECT trial was higher than with sorafenib in the DECISION trial. The incidence of dose interruptions and dose reductions were lower in the placebo arm of the SELECT trial than in the DECISION trial.

Table 20 Dose modifications because of an adverse event in the SELECT and DECISION trials

Outcome, n (%)	SELECT trial		DECISION trial	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=209
Dose interruptions because of an adverse event	215 (82.4)	24 (18.3)	137 (66.2)	54 (25.8)
Dose reductions because of an adverse event	177 (67.8)	6 (4.6)	133 (64.3)	19 (9.1)
Discontinued treatment because of an adverse event	43 (16.5)	6 (4.6)	39 (18.8)	8 (3.8)

Source: Schlumberger et al 2015[47] and Brose et al 2014[48]

It is reported that, in the SELECT trial, the most common AEs developing during treatment that led to a dose interruption or reduction among patients receiving lenvatinib were diarrhoea (22.6%), hypertension (19.9%), proteinuria (18.8%), and decreased appetite (18.0%). It is also noted that four patients in the lenvatinib arm (1.5%) required dose adjustments owing to hypocalcaemia. In the submission from Eisai 2017,[8] it is further noted that 1.1% of patients discontinued treatment due to hypertension. In the DECISION trial, it is reported that hand-foot syndrome was the most common reason for sorafenib dose interruptions (26.6%), reductions (33.8%), and withdrawals (53%).

4.2.9 Health-related quality of life findings

It was reported in the EPAR[27] that while HRQoL data were not collected in the randomised part of the SELECT trial,[47] HRQoL would be assessed in 30 patients who participated in the open-label extension phase of the trial. The AG is unaware whether these findings have been published.

For the DECISION trial, HRQoL was reported in a conference abstract by Schlumberger et al 2013.[119] More detailed HRQoL results were also reported in the submission from Bayer 2017.[7] Cancer-specific HRQoL was measured using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire[145] and general health status was measured using the generic EuroQol five dimensions, three levels questionnaire (EQ-5D-3L) and EQ-5D visual analogue scale (VAS).[146] The FACT-G questionnaire is a validated 27-item questionnaire designed to assess the following dimensions in cancer patients: physical well-being, social / family well-being, emotional well-being and functional well-being. FACT-G total score ranges from 0 to 108 with higher scores representing a better HRQoL. Similarly, the EQ-5D is a validated instrument in which higher scores represent better health status.

All questionnaires were self-administered at baseline and day 1 of every 28-day cycle. The overall questionnaire completion rate during the trial was reported by the authors to be 96%.[119] However, the actual number of patients completing the questionnaires reduces with each cycle since only patients who are progression-free disease are asked to complete the questionnaires. Thus, as shown in the submission from Bayer 2017[7] by the response to one of the physical well-being questions, by cycle 13 the number of patients who responded was 87, 40.1% of all patients enrolled into the trial.

FACT-G

Minimally important differences in the FACT-G total score, i.e. a difference considered to be clinically meaningful, ranges between 3 and 7 points.[145] At baseline, it was reported[7,119] that FACT-G scores were comparable to a normative adult cancer population, the mean +/- standard deviation scores being 81+/-15 in the sorafenib arm and 82+/-14 in the placebo arm. However, at the first assessment (cycle 2, day 1), the score for the sorafenib arm had fallen to 76+/-15 while the score in the placebo arm remained very similar to baseline. The authors of the conference abstract[119] reported that the scores in the sorafenib arm thereafter remained similar to the scores at first assessment whilst in the placebo arm the scores remained similar to the baseline scores. A mixed linear model estimated that, compared with placebo, the FACT-G score was 3.45 points lower in the sorafenib group (p=0.0006) representing a clinically meaningful difference between arms in favour of the placebo arm. The authors attributed the diminished HRQoL score to AEs. Indeed, the submission from Bayer 2017[7]

noted that in response to the FACT-G physical well-being domain question 'I am bothered by side effects', the proportion of patients in the sorafenib arm who replied 'quite a bit' or 'very much' increased from 1.5% at cycle 1, to 29.6% at cycle 2. However, this proportion gradually diminished over time and by cycle 6 was 16.8% and by cycle 13 was 8.0%.

EQ-5D Index and VAS

A change of at least 0.10 to 0.12 points on the EQ-5D index has been reported to be clinically meaningful (using ECOG PS as the anchor).[147] Similarly, the same study reported a change of at least seven points on the VAS to be clinically meaningful.[147] It was reported[7,119] that the patterns for EQ-5D index and VAS were similar to that of the FACT-G; after the first assessment, the scores in the sorafenib arm were lower than the scores in the placebo arm. While the between arm differences were statistically significant ($p<0.0001$ for both EQ-5D index and VAS), the treatment effects (-0.07 and -6.75, respectively) were of a small magnitude and did not reach the threshold for a clinically meaningful difference. It is reported in the submission from Bayer 2017[7] that dimensions in the EQ-5D index that are sensitive to AEs include mobility, usual activities and pain / discomfort.

4.3 Subgroup analyses from randomised controlled trials

Only subgroup analyses considered by the AG to be of direct relevance to the decision problem have been reported in the remainder of this report. The AG considered the following subgroup analyses to be relevant (with rationale given):

- patients previously treated and not previously treated with TKIs (pre-specified subgroup in the NICE scope[53] and AG decision problem)
- patients with and without symptomatic disease at baseline (as highlighted in the background section to this AG report, systemic treatment is recommended for patients who have symptomatic disease)
- analyses of subgroups that were pre-specified in the trials and where there appeared to be differences in baseline characteristics within or across trials (as differences in baseline characteristics may influence results).

As previously highlighted, the AG concluded that the assumption of PH does not hold in any of the analyses that they were able to check other than unadjusted OS in the DECISION trial. This means that the majority of the survival HRs generated using data from the SELECT and DECISION trials and, consequently, statements about the statistical significance of results should be interpreted with caution.

Patients previously treated and not previously treated with tyrosine kinase inhibitors

Subgroup analyses have been reported for patients previously treated with a TKI (e.g. VEGFR-targeted therapy) in the SELECT trial but only for PFS and ORR.[47,104,105] No patients in the DECISION trial had received prior treatment with a TKI.

Results from subgroup analyses using data from the SELECT trial[47,104,105] showed that for patients previously treated with VEGFR-targeted therapy (including sorafenib), PFS was statistically significantly longer for patients treated with lenvatinib compared with placebo (Table 21). For patients who were VEGFR-targeted therapy naïve, PFS was also statistically significantly longer for patients treated with lenvatinib compared with placebo.

Table 21 Progression-free survival findings in patients previously and not previously treated with VEGFR-targeted therapy in the SELECT trial, first data-cut (November 2013)

Outcome	Prior treatment with VEGFR-targeted therapy		No prior treatment with VEGFR-targeted therapy	
	Lenvatinib (n=66)	Placebo (n=27)	Lenvatinib (n=195)	Placebo (n=104)
Number of events (%)	31 (47.0)	25 (92.6)	76 (39.0)	88 (84.6)
Median progression-free survival in months	15.1	3.6	18.7	3.6
Hazard ratio (95% confidence interval)	0.22 (0.12 to 0.41)		0.20 (0.14 to 0.27)	

VEGFR=vascular endothelial growth factor receptor
Source: Schlumberger et al 2015,[47] supplementary appendix

Compared to patients in the placebo arm, ORR was statistically significantly improved for patients treated with lenvatinib whether or not they had been previously treated with a VEGFR-targeted therapy (Table 22).[47,104,105] Objective tumour response rates were similar in both subgroups to the ORRs observed in the overall trial population (lenvatinib: 64.8%; placebo: 1.5%).

Table 22 Tumour objective response findings in patients previously and not previously treated with VEGFR-targeted therapy in the SELECT trial, first data-cut (November 2013)

Outcome	Prior treatment		No prior treatment	
	Lenvatinib (n=66)	Placebo (n=27)	Lenvatinib (n=195)	Placebo (n=104)
Objective tumour response rate, % (95% confidence interval)	62.1 (50.4 to 73.8)	3.7 (0.0 to 10.8)	65.6 (59.0 to 72.3)	1.0 (0.0 to 2.8)
Hazard ratio (95% confidence interval)	15.57 (4.06 to 59.72)		58.88 (18.95 to 182.91)	

VEGFR=Vascular endothelial growth factor receptor
Source: Schlumberger et al 2015,[47] supplementary appendix

Newbold et al 2015[104,105] reported that any all-Grade and Grade ≥3 AEs were similar in the two subgroups of patients receiving lenvatinib (prior VEGFR-targeted therapy: 100.0% and 87.9% respectively; no prior VEGFR-targeted therapy: 99.5% and 86.7% respectively). However, SAEs were more common in the lenvatinib arm amongst patients who had received prior VEGFR-targeted therapy (60.6%) than those who had not (50.8%). For patients in the

placebo arm, the opposite was the case, SAEs being less common amongst patients who had received prior VEGFR-targeted therapy (18.5%) than those who had not (25.0%).

Patients who had not received prior VEGFR-targeted therapy were treated with more cycles of lenvatinib (median 16 cycles) than those who had received prior VEGFR-targeted therapy (median 12.5 cycles). The proportion of patients who had at least one lenvatinib dose reduction was also similar between subgroups (prior VEGFR-targeted therapy: 81.8%; no VEGFR-targeted therapy: 86.7%;). Patients with no prior VEGFR-targeted therapy had an earlier median time-to-first dose reduction (8.9 weeks) compared with patients with prior VEGFR-targeted therapy (14.8 weeks). Patients with no prior VEGFR-targeted therapy also had a lower median daily dose of lenvatinib (16.1mg versus 20.1mg).

Patients with and without symptomatic disease at baseline

Subgroup analyses were not conducted for patients with symptomatic or asymptomatic disease at baseline in the SELECT trial. In the DECISION trial, median PFS for patients who were retrospectively categorised as being symptomatic at baseline was longer for patients who were asymptomatic than those who were symptomatic in the placebo arm but was similar in the intervention arm (Table 23). Patients were assessed as being symptomatic if they had symptoms / findings that were consistent with RR-DTC reported in the medical history or pre-treatment AE dataset at trial entry.[112,118] It is noted in the EPAR[26] for sorafenib that approximately 20% of patients had symptoms likely to be related to thyroid cancer at baseline.

Table 23 Progression-free survival findings in symptomatic and asymptomatic patients in the DECISION trial, first data-cut (August 2012)

Outcome	Symptomatic (~20%)		Asymptomatic (~80%)	
	Sorafenib	Placebo	Sorafenib	Placebo
Number of events (%)	NR	NR	NR	NR
Median progression-free survival in months*	10.7	3.6	10.8	7.2
Hazard ratio (95% confidence interval)	0.386 (0.207 to 0.720)		0.602 (0.448 to 0.807)	

NR=not reported
*Reported in source documents in days, converted to months by dividing by 365.25 and multiplying by 12
Source: Bayer 2017,[7] appendix 7.3 and European Public Assessment Report for sorafenib[26]

While subgroup analyses have not been reported for tumour response for patients with symptomatic or asymptomatic disease at baseline, Bayer 2017[7] has noted: “Of note, tumour shrinkage in symptomatic patients was often sufficient to alleviate symptoms, despite often

not being sufficient to class as a confirmed response." Further evidence has not been presented to support this statement.

Safety analyses for patients with symptomatic or asymptomatic disease at baseline have not been reported in the SELECT or DECISION trials.

Other subgroup analyses of interest

Some OS subgroup analyses in the SELECT trial have been reported in conference abstracts.[66,72,81,88] No OS subgroup analyses have been reported using data from the DECISION trial. For OS (first data-cut, November 2013) in the SELECT trial, it has been reported:

- there was no statistically significant difference in OS between older and younger lenvatinib-treated patients (HR=0.78, 95% CI: 0.49 to 1.26; p=0.304) but there was a statistically significant difference in the placebo arm, favouring younger patients (HR=0.48, 95% CI: 0.27 to 0.85; p=0.010)[66,72]
- median OS was not reached in either arm in patients treated in North America[88]
- a statistically significant OS advantage was observed in patients with FTC treated with lenvatinib compared with placebo (HR=0.41, 95% CI: 0.18 to 0.97).[81]

In addition to the subgroup analyses, Haddad et al 2015[90] found from a post-hoc exploratory multivariate analysis of the SELECT trial (first data-cut) that ECOG PS and histology (favouring FTC versus PTC) were statistically significantly associated with OS.

For PFS, all pre-specified and some post-hoc subgroup analyses (first data-cuts) have also been reported in the appendix to the primary published paper for the SELECT trial[47] and in the published paper for the DECISION trial.[48] The results for both trials showed that for all subgroups, PFS favoured lenvatinib or sorafenib versus placebo. In the majority of instances, the differences were statistically significant. Regarding PFS for pre-specified subgroup analyses, the following results are noted:

- the effect was statistically significantly in favour of lenvatinib (versus placebo) and for sorafenib (versus placebo) for patients aged ≤65 years and >65 years in the SELECT and DECISION trials
- the effect was statistically significantly in favour of lenvatinib (versus placebo) and for sorafenib (versus placebo) for males and females in the SELECT and DECISION trials
- the effect was statistically significantly in favour of lenvatinib (versus placebo) for patients with PTC, poorly differentiated carcinoma, FTC and Hürthle Cell carcinoma in the SELECT trial; the effect was statistically significantly in favour of sorafenib (versus placebo) for patients with PTC and Hürthle Cell carcinoma but not for those with FTC and poorly differentiated carcinoma in the DECISION trial

- the effect was statistically significantly in favour of lenvatinib (versus placebo) for patients classified as white and Asian in the SELECT trial; no subgroup analyses have been presented for race in the DECISION trial

- the effect was statistically significantly in favour of lenvatinib (versus placebo) for patients treated in Europe and North America (and other regions) in the SELECT trial; the effect was statistically significantly in favour of sorafenib (versus placebo) for patients treated in Europe (and Asia) but not for patients treated in North America in the DECISION trial

- the effect was statistically significantly in favour of lenvatinib (versus placebo) for those with and without lung metastases in the SELECT trial and the effect was statistically significantly in favour of sorafenib (versus placebo) for those with lung metastases *only* and for those without lung metastases *only* in the DECISION trial

- the effect was statistically significantly in favour of lenvatinib (versus placebo) and for sorafenib (versus placebo) for patients with and without bone metastases in the SELECT and DECISION trials.

It is recommended by the EMA[26] that "Before initiating treatment, physicians are recommended to carefully evaluate the prognosis in the individual patient considering maximum lesion size, symptoms related to the disease and progression rate." As reported in the appendices to the submission from Bayer 2017,[7] a post-hoc analysis of investigator assessed PFS by number of target lesions in the DECISION trial found statistically significant improvements with sorafenib compared with placebo for patients with ≥3 lesions. For patients with <3 lesions, PFS was numerically improved with sorafenib compared to placebo. It is also reported that another post-hoc subgroup analysis of investigator assessed PFS showed a treatment effect in favour of sorafenib compared with placebo for patients with maximum tumour size ≥1.5cm (HR=0.54, 95% CI: 0.41 to 0.71). A numerically lower effect was reported for patients with a maximum tumour size <1.5cm (HR=0.87, 95% CI: 0.40 to 1.89).

Aside from the caveat surrounding the use of HRs to determine statistical significance as a result of PH assumption being violated, it is important to note that subgroup analyses are not powered to detect statistical significance. Therefore, where no statistically significant differences are reported, it could be that the numbers of patients in the subgroups were not large enough to detect a difference.

4.4 Extended open-label phases of the SELECT and DECISION trials

In the extended open-label phase of the SELECT trial, the starting daily dose of lenvatinib was originally 24mg. This was later modified to 20mg and then reverted to 24mg. It is important to note that this phase of the trial only included 115 patients who crossed over from the placebo arm to lenvatinib and therefore does not present evidence from a randomised or controlled patient population. Furthermore, only placebo-treated patients who had confirmed disease progression (independent blinded review) during the randomisation phase and who met protocol-specified eligibility criteria were treated with lenvatinib. Consequently, it is noted in the EPAR[27] for lenvatinib that these patients had very advanced disease, since they had experienced two sequential, confirmed disease progressions: the first before randomisation at the time of study entry and the second during treatment with the study drug in the randomisation phase.

The extended open-label phase of the DECISION trial differed to that of the SELECT trial in that as well as including patients who crossed over from the placebo arm to receive sorafenib, it also included patients who remained on sorafenib. In total, 150 patients in the placebo arm crossed over to receive sorafenib at progression and of these, data from 137 patients were evaluable for efficacy. In addition, 55 patients randomised to the sorafenib arm continued on sorafenib treatment in the open-label extension phase, of which 46 patients were evaluable for efficacy. It is reported by Schlumberger et al 2014[121] and Paschke et al 2015[113] that patients evaluable for efficacy had poorer risk features at enrolment compared to patients who were not evaluable. Like the extended open-label phase of the SELECT trial, evidence from this patient population does not constitute evidence from a randomised or controlled patient population.

Findings from the extended open-label phase of the SELECT trial for only "…the more mature dataset of patients who started treatment at the 24mg lenvatinib dose" were reported in a conference abstract[117] describing the first data-cut (November 2013). Findings from patients who started started treatment at the 20mg lenvatinib dose and also from the second data-cut (June 2014) were reported in the EPAR[27] for lenvatinib. In the EPAR,[27] it is reported that patient characteristics, previous treatments, geographical allocation, on-study placebo exposure, lenvatinib exposure in the extended open-label phase, as well as median follow up times vary considerably for these two dose regimens. Thus, patients receiving the different dose regimens are considered by the EMA to represent different populations of patients.

In addition to conference abstracts,[113,121] the findings from the extended open-label phase of the DECISION trial have also been reported in the EPAR[51] for sorafenib. Safety data for the

extended open-label phase of the DECISION trial are reported in the submission from Bayer 2017.[7]

The efficacy and safety findings from the open-label phases of both trials are summarised in Table 24 and Table 25. OS data have not been reported. With the exception of median PFS for patients receiving sorafenib for a second time, the efficacy findings for PFS from the extended phase of the SELECT and DECISION trials 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 reported during the double-blind phase.

Table 24 Efficacy analyses from the non-randomised extended open-label phase of the SELECT and DECISION trials

Outcome	SELECT trial		DECISION trial	
	Lenvatinib 24mg dose (n=85)	Lenvatinib 20mg dose (n=30)	Sorafenib after sorafenib (n=46)	Sorafenib after placebo (n=137)
Data-cut	Second data-cut, June 2014		First data-cut, August 2012	
Overall survival	Not reported	Not reported	Not reported	Not reported
Median progression-free survival, months (95% CI)	17.5 (8.3 to NE)	NE (10.9 to NE)	6.7	9.6
Objective tumour response rate, % (95% CI)	52.9 (41.8 to 63.9)	60.0 (40.6 to 77.3)	12.2	9.5

NE=not estimable
Results are reported from start of open-label treatment
Source: European Medicines Agency,[26,27] Schlumberger et al 2014[121] and Paschke et al 2015[113]

Table 25 Safety analyses from the non-randomised extended open-label phase of the SELECT and DECISION trials

Parameter	SELECT trial	DECISION trial
	Lenvatinib 24mg dose (n=82)	Sorafenib after placebo (n=150)
Data-cut	First data-cut, November 2013	First data-cut, August 2012
Median (range) duration of treatment, months	8.9 (0 to 25)	13.1*
Median (range) dose intensity, mg	19.4 (7 to 24)	NR
Dose reductions due to adverse events, %	43.9	NR
Dose interruptions due to adverse events, %	70.7	NR
Treatment-related adverse event, %	85.4	NR
Common adverse-events, %†		
Hypertension	54	28.7
Diarrhoea	52	56.0
Decreased appetite	43	25.3
Weight loss	39	41.3
Fatigue	38	24.7
Hand-foot syndrome	NR	56.7
Alopecia	NR	56.7
Rash	NR	29.3
Common Grade ≥3 adverse-events, %†		
Hypertension	24	NR
Weight loss	9	NR
Proteinuria	7	NR
Asthenia	6	NR
Fatigue	6	NR
Treatment-related fatal adverse events, %	4.9	NR

NR=not reported
Results are reported from start of open-label treatment
*Reported as 56.9 weeks, converted to months by dividing by 4.34812141
†Adverse events are reported to be treatment-related for the SELECT trial and treatment-emergent for the DECISION trial
Source: Robinson et al 2015[117] and Bayer 2017[7]

In addition, Kappeler et al 2015[93] and Fassnacht et al 2016[82] have reported exploratory analyses of tumour growth rate in the randomised double-blind and extended open-label phases of the DECISION trial. The authors found that the tumour growth rate (mean changes per month of sum of target lesion diameters from baseline to nadir and then nadir to progression) of patients treated with sorafenib in the randomised phase was -3.9% then +2.6% and for those continuing with additional sorafenib in the open-label phase, +1.7%. In contrast, for patients in the placebo arm, the tumour growth rate was +5.0% for all placebo patients and for those who crossed-over it was +6.1%. Those who crossed over to sorafenib in the open-label phase then experienced a tumour growth rate pattern similar to patients who started on sorafenib and continued to receive it in the open-label phase: -4.4% from baseline (in the open-label phase) to nadir and then +1.8% from nadir to progression.

4.5 Associations between tumour response, progression-free survival, overall survival, safety and health-related quality of life

Gianoukakis et al 2016[85] examined the association between ORR and PFS for patients treated with lenvatinib in the SELECT trial. The analysis is based on the third data-cut (August 2015) using investigator assessed ORR (60.2%) and investigator assessed PFS (19.4 months). The authors found that the median PFS in patients who received lenvatinib and who demonstrated a tumour response was 33.1 months (95% CI: 27.8 months to not estimable). In lenvatinib-treated patients who did not show tumour response, the median PFS was 7.9 months (95% CI: 5.8 months to 10.7 months). Robinson et al 2016[116] reported that an exploratory multivariate analysis found that percentage change in tumour size at the first assessment was a marginally statistically significant positive predictor for PFS (p=0.06).

Using data from the first data-cut of the SELECT trial, Newbold et al 2015[107] analysed PFS by patients who had responded to treatment with lenvatinib at the first tumour assessment (median time to response: 1.9 months) and by those who responded later (median time to response: 3.8 months). The authors found that there was no difference in PFS between patients who achieved objective response at the time of first tumour assessment versus thereafter.

Haddad et al 2015[90] found from a multivariate analysis (first data-cut) that in the SELECT trial, all-Grade diarrhoea was statistically significantly associated with OS (median OS for lenvatinib-treated patients with diarrhoea: not reached; median OS for lenvatinib-treated patients without diarrhoea: 17.1 months). Choi et al 2015[78] reported that the results of a post-hoc analysis showed that lenvatinib-treated patients with hypertension had higher median PFS compared with those without hypertension (18.8 months versus 12.9 months, p=0.009). Haddad et al 2015[90] also reported results from multivariate analyses of associations between five other AEs (proteinuria, diarrhoea, fatigue / asthenia / malaise, rash and hand-foot syndrome) and PFS in the SELECT trial. No statistically significant associations between any of the AEs and PFS were found.

Using data from the DECISION trial, Kappeler et al 2015[94] carried out an exploratory analysis to explore the association between tumour growth rate and PFS and OS. It is reported that the data-cuts used for PFS and OS were the first data-cut (August 2012) and third data-cut (July 2015) respectively. Values of early tumour growth rate were split into quartiles (by median times derived from Kaplan-Meier [K-M] curves and from modelling with a Weibull distribution) separately by treatment arm. Better prognosis for PFS and OS with sorafenib was associated with the second and third tumour growth rate quartiles.

No other analyses have been conducted for patients treated with either lenvatinib or sorafenib in the SELECT or DECISION trials examining the relationships between any of the efficacy or safety outcomes and HRQoL. As reported earlier (Section 4.2.9), it has been speculated that AEs did affect HRQoL based on data from FACT-G and EQ-5D questionnaires but no formal analyses have been conducted in an attempt to correlate the findings.

4.6 Indirect comparison feasibility assessment

In the absence of direct clinical evidence comparing treatment with lenvatinib versus sorafenib, the AG considered whether it was appropriate to perform an indirect comparison to obtain estimates of the relative efficacy and safety of these two treatments.

The first step was to determine whether the SELECT and DECISION trials shared a common comparator. The comparator arm of both trials was placebo. As there is limited information available from Eisai 2017,[8] Bayer 2017[7] and in the published papers, describing the placebos (e.g. 'matching placebo capsules'), the AG considered that the comparator arms were likely to be similar and that a network could be constructed (see Figure 5).

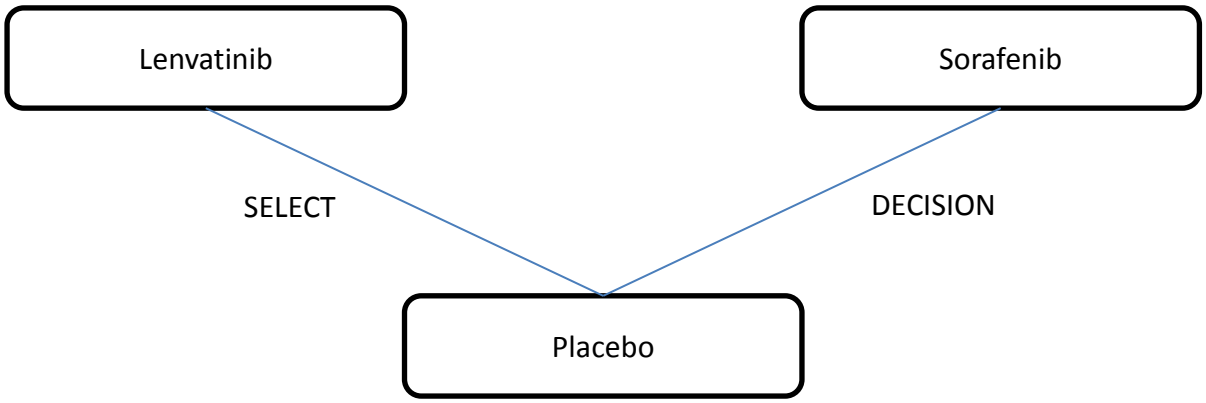

Figure 5 Indirect comparison network

The second step was to check the comparability of the participant and trial characteristics of the two trials. As described in Sections 4.2.1 and 4.2.2, the AG has noted that there are several trial design and participant differences, both within and across the SELECT and the DECISION trials. These differences raised concerns about whether data from these two trials should be included in the same network of evidence.

The final step undertaken by the AG was to examine the PFS K-M data from the placebo arms of the SELECT and DECISION trials to determine the extent to which the risk profiles of the populations in these arms of the two trials were comparable. The AG concluded that the risks were not sufficiently comparable and that these two trials should, therefore, not be included in the same network of evidence.

AG's detailed commentary on PFS K-M data from the placebo arms

An indirect comparison implicitly assumes that the randomised patients are drawn from similar populations with reference to their risk profile for the time-to-event outcomes (PFS and OS). Since investigator assessed PFS is the primary outcome specified in both clinical trials, it is important that the equivalence of the placebo arms of the two trials can be confirmed by

comparison of PFS outcomes: any significant discrepancy in progression risk would invalidate an indirect comparison between lenvatinib and sorafenib.

Figure 6 compares the K-M PFS trial results for the placebo arms of the two trials. After similar trends over the first 2 months, the curves separate markedly for more than a year before crossing over in the long-term. Visual examination is sufficient to establish that these data are not amenable to either a simple hazard ratio adjustment, or a time ratio adjustment.

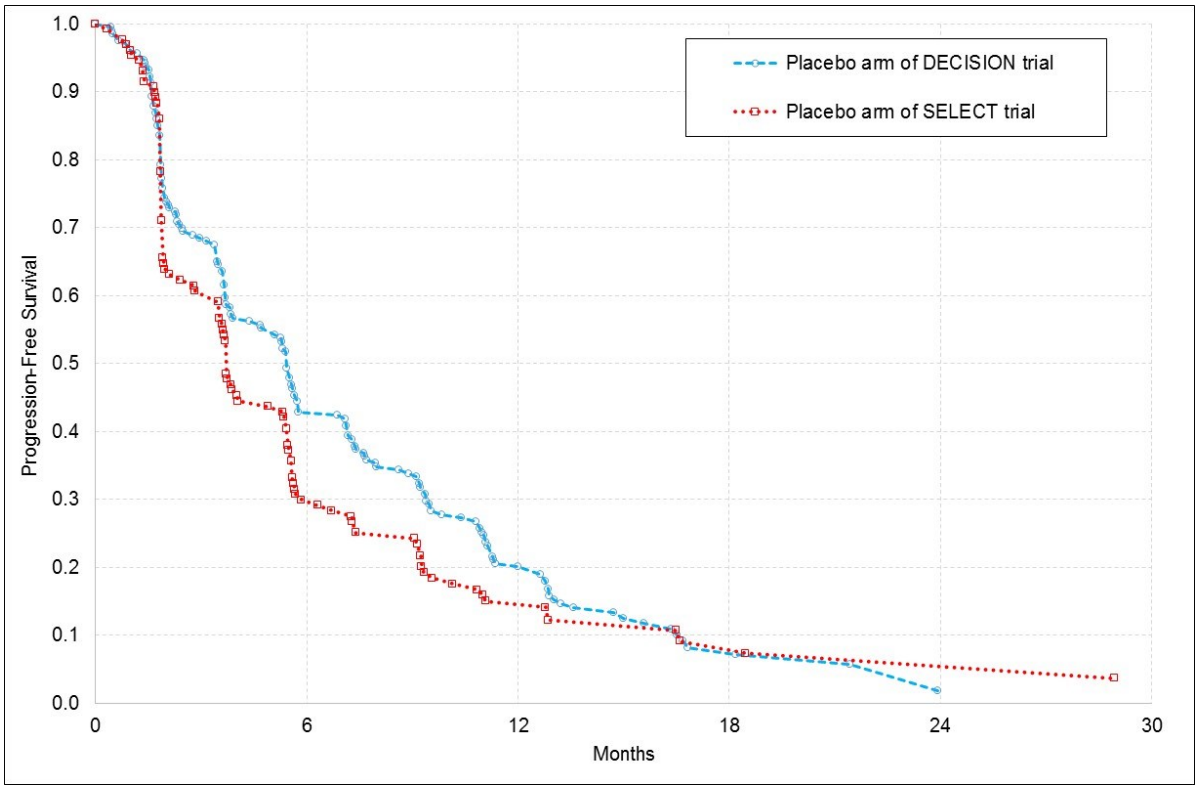

Figure 6 Comparison of progression-free survival in the placebo arms of the DECISION and SELECT clinical trials

Further exploration of these data trends through a plot of cumulative hazards in the two trial arms at common time points reveals a clear divergence from a simple linear (PH) relationship (Figure 7). The trial data indicate a higher initial risk of disease progression in the SELECT trial in the first 10 months, followed by a sharp reversal in which the risk in the SELECT trial placebo arm reduces by more than 50%.

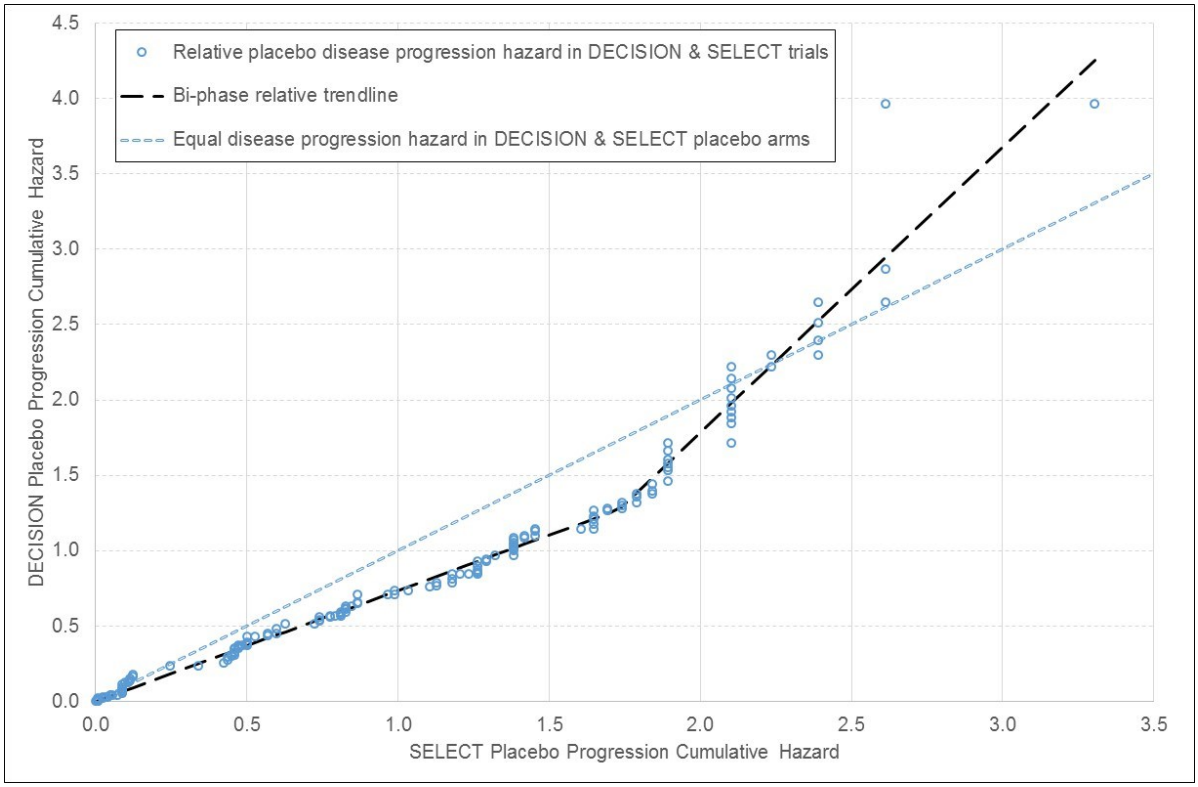

Figure 7 Comparison of progression-free survival hazard trends in the placebo arms of the DECISION and SELECT clinical trials

The AG considers that the placebo arms of the SELECT and DECISION trials exhibit unexpectedly inconsistent patterns of temporal change, not compatible with the assumption that these are similar patient groups. Consequently, patients enrolled in the two trials cannot be considered to derive from a common population and, therefore, performing an indirect comparison to obtain estimates of relative efficacy for lenvatinib and sorafenib is not appropriate.

Differences in trial and participant characteristics in the placebo arms of the trials

As reported earlier (Sections 4.2.1and 4.2.2), a number of differences in trial and participant characteristics were observed between arms within trials and across trials. Given the apparent differences in the placebo arms of the two trials, as demonstrated by differing hazard trends, the AG highlights the following differences in characteristics between the two placebo arms:

- the SELECT trial permitted the enrolment of patients who had been previously treated with a VEGFR-targeted therapy (including sorafenib) whereas the DECISION trial did not: 20.6% had received prior therapy in the placebo arm of the SELECT trial compared to no patients in the placebo arm of the DECISION trial
- palliative radiotherapy, which is commonly available as part of BSC in UK NHS clinical practice, was not permitted for patients in the placebo arm of the SELECT trial
- the proportion of patients who crossed over from the placebo arm of the SELECT trial

was 87.8% at the third data-cut compared to 75.0% in the DECISION trial

- there were proportionately more males in the placebo arm of the SELECT trial than the placebo arm of the DECISION trial (57.3% and 45.2% respectively)
- a higher proportion of patients in the placebo arm of the SELECT trial were classified as being white than similarly classified in the placebo arm of the DECISION trial (78.6% and 61.0% respectively) whereas the opposite was the case for patients classified as Asian (18.1% and 24.8% respectively)
- proportionately fewer patients in the placebo arm of the SELECT trial were from Europe (48.9%) and proportionately more were from North America (29.8%) compared to the patients in the placebo arms of the DECISION trial (59.5% and 17.1% respectively)
- a greater proportion of placebo patients in the SELECT trial had ECOG PS ≥1 than in the DECISION trial (48.1% and 31.0% respectively)
- a greater proportion of placebo patients had FTC and poorly differentiated thyroid cancer in the placebo arm of the SELECT trial (16.8% and 14.5% respectively) than in the DECISION trial (9.0% and 7.6% respectively)
- the time from diagnosis to randomisation was greater in the placebo arm of the SELECT trial (73.9 months) than in the placebo arm of the DECISION trial (66.9 months)
- a greater proportion of patients in the placebo arm of the SELECT trial had lung, bone and liver metastases (94.7%, 36.6% and 21.4% respectively) than in the DECISION trial (86.2%, 26.7% and 14.3% respectively).

Proportional hazards assumption

As discussed in Section 4.2.4, the AG concluded that the PH assumption was not valid for PFS, unadjusted OS or adjusted OS in the SELECT trial or for PFS or adjusted OS in the DECISION trial. The violation of the PH assumption, for all but unadjusted OS in the DECISION trial, means that the network of evidence is compromised for all outcomes.

AG summary statement

The AG considers that is not appropriate to perform an indirect comparison to obtain HRs for lenvatinib versus sorafenib for the outcomes of PFS, unadjusted OS and adjusted OS. This is because the risk profiles of the patients in the placebo arms of the trials are not comparable and any indirect comparison would produce results that could not be considered to be robust. This also precluded indirect comparison for subgroups of patients according to previous treatment with TKIs.

As described in the methods section (Section 3.4), in addition to trial characteristics, participant characteristics and outcome data, the AG stated it would consider the quality of the included trials when conducting its feasibility assessment. The results of the AG's risk of bias

assessment are reported in Section 4.2.3. However, given the issues already highlighted, the quality of the trials was not a factor in the AG's decision not to conduct an indirect comparison.

4.7 Systematic review evidence

The AG included 13 systematic reviews[5-8,33,56,60,92,96,103,126,137,140] in its review; these reviews included the evidence submissions reporting systematic reviews and indirect comparisons for this MTA from Eisai 2017[8] and Bayer 2017[7] and also the evidence reported in a paper by Tremblay et al 2016.[56] While Tremblay et al 2016[56] did not report the conduct of a systematic review, this paper was included as it did report results from an indirect comparison and a matched adjusted indirect comparison (MAIC) using data from the SELECT and DECISION trials.

A summary of the characteristics of the included systematic reviews is presented in Appendix 5 (Table 59). Most of the evidence was derived from observational studies of treatment with sorafenib. However, four of the reviews,[7,8,56,96] including the submissions from Eisai 2017[8] and Bayer 2017,[7] included evidence from the SELECT and DECISION trials and results from indirect comparisons, including MAICs.

The AG's assessment of the quality of the included reviews is presented in Appendix 5 (Table 60). Overall, the AG considered that the quality of nine[5-8,60,96,103,126,137 ,148] of the identified systematic reviews was good. However, only four[5-8] of the 10 reviews included a quality assessment of the included primary studies. Four[33,56,92,140] of the reviews were considered to be of poorer quality than the rest. Of these, only one[33] reported the use of an adequate search strategy. In addition, methods of cross checking during either the study selection process or the data extraction process were not reported by the authors of three reviews.[33,56,92] No quality assessment of the primary studies was reported in any of these four reviews.[33,56,92,140]

The conclusions reached by the authors of the systematic reviews are presented in Appendix 5 (Table 61). The earliest of the reviews was carried out by Anderson et al 2013[60] and was published in 2013. The authors concluded that certain treatments, notably TKIs, showed promise in phase II trials. Gruber and Colevas 2015[33] concluded that the most likely outcome of treatment with a TKI was stable disease. McFarland and Misiukiewicz 2014[103] concluded that sorafenib slowed the progression of disease in the majority of cases. For treating thyroid cancer, Ye et al 2015[140] reported that the clinical effects of sorafenib and lenvatinib outweigh the toxicities (relative risk [RR]=1.27, 95% CI: 1.05 to 1.53) and deaths (RR=15.24, 95% CI: 6.99 to 33.21). Ye et al 2015[140] concluded that lenvatinib and sorafenib were more useful for thyroid cancer compared to RR‑DTC, based on the results of the subgroup analyses that were conducted. However, the AG considers that all of the studies that included patients with DTC also included patients with RR-DTC and so the validity of this subgroup analysis the conclusions reached based on these subgroup analyses are questionable.

Jean et al 2016[92] found AEs reported for sorafenib for treating RR-DTC to be higher than for AEs reported for treating RCC or HCC. In two reviews[126,137] ORR data and AE data were pooled for sorafenib from seven observational studies[58,77,87,100,125,149,150] (five prospective and two retrospective). In the review by Shen et al 2015,[126] all of the studies [58,77,87,100,125,149,150] included patients with RR-DTC whereas the review by Thomas et al 2015[137] included five studies,[58,87,100,125,149] a retrospective study of RR-DTC[151] and a phase II study[152] of patients with medullary thyroid cancer. While the incidences of hand-foot syndrome (≥73%), diarrhoea (≥68%) and weight loss (≥50%) included in both meta-analyses were broadly similar to the incidence of the same AEs in the DECISION trial, it was noticeable that the incidences of rash (≥66%) and fatigue (≥60%) were higher than reported in the DECISION trial. Similarly, the pooled ORR (20.9% to 22%) from the two reviews[126,137] was higher than the ORR reported in the DECISION trial. The pooled median PFS (17.9 months) from the review by Thomas et al 2015[137] was also higher than median PFS reported in the DECISION trial but the pooled analysis for PFS also included patients with medullary thyroid cancer. The key results from these three reviews[92,126,137] are summarised in Appendix 5 (Table 62).

In addition, Shen et al 2015[126] noted rare but severe AEs were observed mainly due to intracranial haemorrhage, cardiac arrest, angioedema, small-cell lung cancer, carcinoma of the tongue, and Grade 5 event of sudden death. Because of the limited data, the authors did not pool these high-grade AEs. Thomas et al 2015[137] also reported that bleeding at any site occurred in 13.6% of patients, 3.8% of patients reported acute myocardial infarctions and 2.2% experienced congestive heart failure. Severe hypocalcaemia (Grade ≥3) occurred in 2.5% of patients and 8.7% patients developed cutaneous squamous cell carcinoma. It should however be cautioned that in the meta-analyses conducted by Shen et al 2015[126] and Thomas et al 2015,[137] the authors did not investigate the heterogeneity of the studies included in the meta-analyses.

For RR-DTC, all of the indirect comparison results (including results from MAICs[7,56]) showed that lenvatinib was statistically significantly superior to sorafenib in terms of PFS but not OS.[6-8,56,96] Kawalec et al 2016[96] also reported lenvatinib to result in statistically significantly less alopecia but statistically significantly more hypertension and treatment-related SAEs than sorafenib. Bayer 2017[7] found sorafenib to result in statistically [redacted] Grade ≥3 AEs and SAEs when compared with lenvatinib. However, caveats about the generalisability of the results of the indirect comparisons have been raised[6] and Kawalec et al 2016[96] stated that indirect comparison results should be interpreted with caution due to differences in trial characteristics. Of the indirect comparisons conducted, only the indirect comparison by Kawalec et al 2016[96]

was not sponsored by Eisai or Bayer. A summary of the findings from the indirect comparisons is presented in Appendix 5 (Table 63 to Table 65)

4.8 Evidence from prospective observational studies

The AG included nine prospective observational studies.[58,76,77,80,87,100,102,125,134] Five of these studies[58,77,87,100,125] were included in the meta-analyses conducted by Shen et al 2015[126] and by Thomas et al 2015.[137] Seven of the studies were included in the EPARs[26,27] for lenvatinib[76,134] and sorafenib.[58,77,87,100,125] The study and participant characteristics, and efficacy and safety findings are summarised in Appendix 6 (Table 66 to Table 73).

All studies included patients whose disease was described as being radioactive iodine refractory,[58,76,77,100,125,134] resistant to radioactive iodine[80,87] or who may have received multiple treatments of radioactive iodine.[102] Two studies[76,134] investigated the efficacy and safety of lenvatinib, six studies[58,77,87,100,102,125] assessed the efficacy and safety of sorafenib and one study[80] considered the efficacy of sorafenib. Some patients included in four of the studies[58,87,100,134] had anaplastic or medullary carcinoma. Safety data from these four studies[58,87,100,134] are, therefore, not reported for RR-DTC only. However, all nine studies[58,76,77,80,87,100,102,125,134] reported efficacy findings for patients with RR-DTC only and all efficacy data reported in this section related to patients with RR-DTC only.

Study 201[76] (lenvatinib) was conducted in the UK, France, Italy, Poland, USA and Australia and Study 208[134] (lenvatinib) was conducted in Japan. Studies of sorafenib were carried out in the UK,[58] Netherlands,[125] Italy,[102] Greece,[80] USA[100] and China.[77] The earliest study was conducted between 2004 and 2005[100] and the most recent study[134] commenced in 2012 and still ongoing. The length of study follow-up varied from a minimum of 3 months[77] to a median of 51.6 months.[27]

The number of patients included in the studies varied from nine[77] to 58.[76] In total, 109 patients were treated with lenvatinib, of whom 83 had RR-DTC; 213 patients were treated with sorafenib, of whom 186 had RR-DTC. In most studies, the majority of patients with RR-DTC had a histology of PTC,[58,76,77,87,100,125] the exception being the study by Marotta et al 2016[102] in which the ratio of patients with FTC to PTC was 2:1. The average age of participants ranged from 55 years[58] to 64 years.[100] Four studies[58,76,87,100] included a majority of males and three studies had a majority of females.[80,87,102] Two studies[77,134] did not report information on gender. The authors of only two studies[76,100] reported information on race and these included a majority of white participants. Only two studies which reported ECOG status, included patients with ECOG PS ≥2 (6.9%[76] and 35.3%[102]). The same two studies were the only two to explicitly state that patients could have received a prior TKI (11.8%[102] to 29.3%[76]). There was scant and inconsistent reporting of the sites of metastases.

Median OS was reported in five studies.[76,87,100,125,134] Median OS ranged from 31.8 months[134] to 32.3 months[76] for lenvatinib and 23 months[100] to 34.5 months[125] for sorafenib. Median PFS was reported in six studies[76,87,100,102,125,134] and ranged from 12.6 months[76] to 25.8 months[134] for lenvatinib and 12 months[102] to 22.1 months for sorafenib[87] (this latter finding was reported in a subsequent conference abstract[136]). Chen et al 2011[77] (sorafenib) reported mean PFS (9.7 months). The ORRs for patients treated with lenvatinib ranged from 50.0%[76] to 68.0%[134] and, for those treated with sorafenib, ranged from 15% (histology of PTC)[100] to 38.3%[87] (this latter finding reported in a subsequent conference abstract[136]). Median time to response and median duration of response were only reported in two studies.[76,125] For lenvatinib,[76] median time to response was 3.6 months and, for sorafenib,[125] all responses were reported to have occurred within 6 months. The median duration of response for lenvatinib was 12.7 months[76] and for sorafenib was 29.6 months.[125]

Key AEs are summarised in Table 26 to Table 28. Two studies[87,100] (sorafenib) only reported treatment-related AEs. Two of the sorafenib studies,[77,80] presented only as abstracts, reported very little information about AEs.

Incidences of the same types of AEs varied across the studies: for lenvatinib, hypertension and proteinuria were very commonly reported; for sorafenib, hand-foot syndrome, rash and alopecia were common; diarrhoea and fatigue were common with both drugs. Data on SAEs were only available from Study 201[76] (lenvatinib). Information on fatal AEs were only reported in two studies[76,134] of lenvatinib and in one study of sorafenib.[100] For patients treated with lenvatinib, 48% reported a SAE[76] and up to 8%[134] died from an AE. Only one death from AEs has been reported in one of the studies of sorafenib;[100] it is unclear if the lack of reporting of fatal AEs in the other sorafenib studies[58,77,80,87,102,125] means there were no deaths from AEs in these studies. None of the deaths from AEs in any of the three studies[76,100,134] reporting fatal AEs were described as being treatment-related.

Table 26 Range of all-Grade adverse events reported in the prospective observational studies

Event	Lenvatinib, 2 studies,[76,134] treatment-emergent (%)	Sorafenib, 4 studies,[58,77,80,125] treatment-emergent (%)	Sorafenib, 2 studies,[87,100] treatment-related (%)
All-Grade AEs	100 (2)	NR	NR
Hypertension	76 to 90 (2)	21 to 42 (3)	43 (2)
Diarrhoea	55 to 67 (2)	52 to 77 (3)	75 to 80 (2)
Decreased appetite	52 to 78 (2)	29 (1)	20 to 82 (2)
Weight loss	69 (1)	29 to 58 (2)	60 to 82 (2)
Nausea	50 (1)	10 to 27 (2)	30 to 55 (2)
Fatigue	60 to 73 (2)	59 (1)	63 to 66 (2)
Headache	43 (1)	15 (1)	16 (1)
Stomatitis/ mucositis	31 to 57 (2)	27 to 48 (3)	16 to 47 (2)
Vomiting	38 (2)	18 (1)	18 (1)
Proteinuria	61 to 64 (2)	NR	NR
Hand foot syndrome	22 to 77 (2)	71 to 79 (3)	63 to 93 (2)/ 63 to 91 (2)*
Dysphonia	43 (1)	NR	NR
Rash	24 (1)	55 to 88 (2)	79 to 80 (2)/ 79 to 85 (2)*
Alopecia	9 (1)	52 to 74 (2)	43 to 79 (2)
Other types of All-Grade AEs	Other AEs ≥25% patients in Study 201[76] (Study 208[134] only reported AEs ≥55%): Cough 45 Arthralgia 36 Dry mouth 35 Back pain 33 Pain in extremity 33 Dyspnoea 31 Musculoskeletal pain 31 Abdominal pain upper 31 Abdominal pain 28 Epistaxis 28	Other AEs ≥25% patients in any one study:[58,125] Infection 68 Hypocalcaemia 48 Abdominal cramps/pain 38 Glossitis 35 Hypophosphatemia 35 Anaemia 35 Hypoparathyroidism 32 Thrombopaenia 29 Haemorrhage 29 Hypothyroidism 26 Leukopenia 23 Myocardial infarction 10	Other treatment-related AEs ≥25% patients in Kloos et al 2009:[100] Dry skin 84 Pruritis 77 Flatulence 70 Arthralgia 61 Pain abdomen or rectal 68 Heartburn 39 Muscle cramps 36 Flushing 32 Nail changes 59

AE=adverse event; NR=not reported
*Terry et al[136] later examined treatment-related hand-foot syndrome and rash for UPCC-03305 (12192)[87] and data in the table are reported as ranges using earlier and later data-cuts, respectively
(1) AE reported by one study (2) AE reported by 2 studies (3) AE reported by 3 studies

Table 27 Range of Grade ≥3, serious and fatal adverse events reported in the prospective observational studies

Event	Lenvatinib, 2 studies,[76,134] treatment-emergent (%)	Sorafenib, 4 studies,[58,77,80,125] treatment-emergent (%)	Sorafenib, 2 studies,[87,100] treatment-related (%)
Grade ≥3 AEs	72 (2)	NR	NR
Hypertension	10 (1)	6 to 16 (2)	4 to 13 (2)
Diarrhoea	10 (1)	3 to 7 (2)	4 to 7 (2)
Decreased appetite	2 (1)	0 (1)	3 (1)
Weight loss	12 (1)	0 to 10 (2)	5 to 10 (2)
Nausea	0 (1)	0 (2)	0 (2)
Fatigue	9 (1)	9 (2)	3 to 16 (2)
Headache	2 (1)	3 (1)	0 (1)
Stomatitis/ mucositis	2 (1)	9 to 10 (2)	0 to 2
Hand foot syndrome	2 (1)	23 to 44 (2)	7 to 10 (2)/ 7 (2)*
Proteinuria	10 (1)	NR	NR
Asthenia	NR	NR	NR
Dyspnoea	0 (1)	NR	0 (1)
Dysphagia	NR	0 (1)	NR
Rash	0 (1)	6 to 16 (2)	4 to 10 (2)/ 4 to 18 (2)*
Other types of Grade ≥3 AEs	Other Grade ≥3 AEs in ≥5% of patients in Study 201 Dehydration 9 Arthralgia 5 Grade ≥3 AEs not reported in Study 208	Other Grade ≥3 AEs in ≥5% of patients in any one of the studies Myocardial infarction 10 Infection 9 Arthralgia 9 Drug hypersensitivity 9	Other Grade ≥3 treatment-related AEs in ≥5% of patients in either study: Hand or foot pain 12 Arthralgia 11 Fatigue 16 Hand-foot syndrome 7 Musculoskeletal chest pain 7 Asymptomatic hyponatremia 5 Function tests 7 Pruritus 3 Sleep disturbance/ anxiety 3
SAEs	48	NR	NR
Fatal AEs	5 to 8 (2)	1 (1)	NR
Type of SAEs	SAEs that occurred in ≥3.5% patients in Study 201: Dehydration 7 Hypotension 5 Pulmonary embolism 3 Abdominal pain 3 Hypertension 3 Cardiac failure 3	NR	NR

AE=adverse event; NR=not reported; SAE=serious adverse event
*Terry et al[136] later examined treatment-related hand-foot syndrome and rash for UPCC-03305 (12192)[87] and data in the table are reported as ranges using earlier and later data-cuts, respectively
(1) AE reported by one study (2) AE reported by 2 studies

Table 28 Range of dose modifications resulting from adverse events reported in the prospective observational studies

Event	Lenvatinib, 2 studies,[76,134] treatment-emergent (%)	Sorafenib, 4 studies,[58,77,80,125] treatment-emergent (%)	Sorafenib, 2 studies,[87,100] treatment-related (%)
AE dose interruptions	74 (1)	82 (1)	NR
AE dose reductions	66 (1)	42 to 100 (2)	47 to 52 (2)/ 47 to 55 (2)*
AE discontinued	2 to 26 (2)	23 (1)	20 (1)
Other	AEs that led to lenvatinib withdrawal and occurred in ≥3.5% patients in Study 201: Proteinuria 5 Pulmonary embolism 3 Deep vein thrombosis 3	2 out of 3 patients with a PR withdrew from the study after 5 to 7 months of treatment in one study 79% of patients required a dose reduction by one dose level to 400mg daily and a third of these patients underwent a further reduction to the lowest dose level of 400mg alternate days in one study	

AE=adverse event; NR=not reported; PR=partial response
*Terry et al[136] later examined treatment-related hand-foot syndrome and rash for UPCC-03305 (12192)[87] and data in the table are reported as ranges using earlier and later data-cuts, respectively
(1) AE reported by one study (2) AE reported by 2 studies (3) AE reported by 3 studies

4.9 Ongoing studies and studies for which there are no results

The AG identified four ongoing studies,[153-156] as summarised in Table 29. None of the study results have been published or reported as conference abstracts. Only the two studies of lenvatinib[155,156] are RCTs: NCT02702388 (Study 211)[155] is a phase II post-authorisation study which includes a randomised controlled phase, comparing two different starting doses of lenvatinib (24mg versus 18mg) with placebo; NCT02966093[156] is a phase III RCT being conducted in China comparing lenvatinib at its licensed dose of 24mg with placebo. Eisai sponsors both of these trials. The other two studies are prospective observational phase II studies of sorafenib,[153,154] a pilot study sponsored by the Royal Marsden NHS Foundation Trust[153] and post-authorisation study sponsored by Bayer.[154]

In addition, while not strictly meeting the inclusion criteria for the current MTA, the AG is aware of an ongoing global prospective non-interventional study (Radioactive Iodine reFractory asymptomatic patients [RIFTOS], NCT02303444)[157] of asymptomatic patients with RR-DTC treated with any type of MKI. The primary objective is to compare the time to symptomatic progression from study entry. Bayer sponsors this study. Planned enrolment is approximately 700 patients with an expected study end date of 1 July 2020.

Table 29 Characteristics of the ongoing studies

Parameter	NCT02702388	NCT02966093	MATiSSe	NCT02185560
Description	Post-marketing safety study of lenvatinib (Study 211)	Lenvatinib for RR-DTC in China	A pilot study evaluating the safety and efficacy of sorafenib	Post-marketing safety study of sorafenib
Sponsor	Eisai	Eisai	Royal Marsden NHS Foundation Trust	Bayer
Commencement date	28 March 2016	7 February 2017	Ethical approval, 8 January 2007	27 June 2014
Expected end date	30 October 2020	April 2020	Not reported	30 June 2021
Participants	161 patients with RR-DTC	150 patients with RR-DTC	33 patients with RR-DTC or MTC	443 patients with RR-DTC
Outcomes	• Objective tumour response rate at 6 months • Percentage of treatment-emergent Grade ≥3 AEs (up to 6 months) • PFS (up to 18 months) • PFS after next line of treatment (PFS2, up to 18 months after initiating next line of treatment) • Number of participants with treatment emergent AEs and SAEs (up to 1 months) • Time to treatment discontinuation due to an AE (up to 1 months) • Dose reductions and interruptions (up to 1 months) • AUC of lenvatinib (predose and 2 hour to 12 hour postdose) • HRQoL (up to 18 months)	• PFS (up to 12 months) • Objective tumour response rate (up to 36 months) • OS (up to 36 months) • Number of participants with treatment emergent AEs (up to 36 months)	• Proportion of patients that have achieved a response during 6 months of treatment with sorafenib • Proportion of patients achieving a response during 9 and 12 months of treatment with sorafenib • Biomarkers Toxicity outcomes at 1,3,6,9 and 12 months Progression free and overall survival	• Number of participants with adverse drug reaction (up to 9 months) • Number of participants with SAE (up to 9 months) • Number of participants with serious adverse drug reaction (up to 9 months) • 2-year survival • Time to treatment-failure (up to 9 months)

AE=adverse event; AUC=area under the concentration-time curve; HRQoL=health-related quality of life; MTC=medullary thyroid carcinoma; NR=not reported; OS=overall survival; PFS=progression-free survival; RR-DTC=radioactive iodine refractory differentiated thyroid cancer; SAE=serious adverse event

4.10 Discussion of clinical effectiveness: interpretation of results

The AG's assessment of lenvatinib and sorafenib for the treatment of patients with RR-DTC focussed on evidence from two RCTs: the SELECT trial (lenvatinib versus placebo) and the DECISION trial (sorafenib versus placebo). Supporting evidence was derived from 13 systematic reviews[5-8,33,56,60,92,96,103,126,137,140,148] (including two systematic reviews described in the submissions from Eisai 2017[8] and Bayer 2017[7]), and nine prospective observational studies.[58,76,77,80,87,100,102,125,134]

4.10.1 Clinical efficacy

Summary and interpretation of evidence: lenvatinib versus sorafenib

The primary objective of the AG's systematic review was to compare the clinical effectiveness of lenvatinib versus sorafenib. Results from the AG's literature search revealed that there have been no head to head trials comparing the effectiveness of treatment with lenvatinib versus sorafenib. However, four studies[7,8,56,96] have reported results from indirect comparisons, and two[7,56] of these also provide results from MAICs. Results from all of these analyses show that, compared with sorafenib, treatment with lenvatinib improves PFS but not OS.

The AG explored whether it was appropriate to conduct an indirect comparison. Although it was possible to construct a network, the AG identified issues that raised concerns about whether evidence from the SELECT and DECISION trials could be included in the same network. First, there were differences between trial characteristics (prior treatment with TKIs, concurrent use of palliative radiotherapy and differences in subsequent treatment received on disease progression). Second, there were differences in participant characteristics (gender, race, geographic region, ECOG PS, time from diagnosis, histology and site of metastases) both within and between trials. Third, the analysis of the PFS K-M data from the placebo arms of the SELECT and DECISION trials showed that the risk profiles of the two trial populations were not comparable. The reasons for the differences in risk are currently unknown. Fourth, the AG considered that, for the majority of patient survival hazards assessed in the two trials, PHs were violated, the exception being unadjusted OS in the DECISION trial.

The AG is unable to conclude whether treatment with lenvatinib is more effective than treatment with sorafenib for patients with RR-DTC. The AG considers that the results from the four published indirect comparisons[7,8,56,96] should be interpreted with caution. This warning also extends to the results from the MAICs.[7,56] It is unknown whether the MAIC adjustments would fully account for all of the differences in the trial populations since the AG was unable to compare the adjusted risk profiles of patients included in the MAIC.

The AG highlights that Kawalec et al 2016[96] stated that their indirect comparison results should be interpreted with caution due to differences in the characteristics of the included trials. In addition, the EMA,[27] SMC[38] and CADTH[6] all highlighted that differences in populations might have contributed to differences in results observed between the two trials. The SMC[38] also highlighted that the validity of the results from the MAIC submitted by Eisai may be limited by weaknesses including heterogeneity across the studies in inclusion criteria, assessment of disease progression and analysis of PFS. The CADTH[6] highlighted that the MAIC approach does not have the ability to control for the potential for unobserved differences such as differences in standards of care or baseline characteristics, information that has not been recorded in the t trials.

Summary and interpretation of evidence: lenvatinib and sorafenib versus best supportive care

The secondary objective of the AG's systematic review was to compare treatment with lenvatinib and sorafenib with BSC. The AG has assumed that, in both trials, treatment with lenvatinib plus BSC or sorafenib plus BSC is compared with placebo plus BSC. The unadjusted OS results from the SELECT and DECISION trials demonstrated that there was no statistically significant difference in OS between treatment with lenvatinib and treatment with sorafenib versus placebo. After adjusting OS data for treatment crossover using the RPSFTM, there was a statistically significant improvement in OS from treatment with lenvatinib compared with placebo; however, the difference in effect of sorafenib versus placebo was not statistically significant. The AG highlights that the unadjusted median OS estimates for patients treated with lenvatinib and sorafenib in the SELECT and DECISION trials are higher than those reported for patients treated with lenvatinib and sorafenib in prospective observational studies.

For PFS and ORR, the results from the SELECT and DECISION trials demonstrated that treatment with both lenvatinib and sorafenib were statistically significantly better than treatment with placebo for patients with RR-DTC. For all of the pre-specified subgroups, the results from the SELECT and DECISION trials favoured treatment with the intervention (lenvatinib or sorafenib) when compared with placebo. Median PFS and ORR for patients treated with lenvatinib in the SELECT trial were higher than the prospective, observational results from Study 201[76] and lower than the results from Study 208.[134] In contrast, median PFS and ORR results reported for patients treated with sorafenib (DECISION trial) were lower than findings from any of the prospective observational studies or the two meta-analyses.[126,137]

Patients in the DECISION trial were permitted to receive concomitant palliative radiotherapy, a common component of BSC in NHS clinical practice, whereas patients in the SELECT trial

were not; full details of the BSC provided in the two trials are not available. Whether patients in the trials received BSC that is similar to that provided by the NHS is unknown and this raises uncertainty about whether the trial results are generalisable to NHS patients. If the BSC delivered in the two trials is not comparable, then using the placebo arms to connect the two trials in an indirect comparison becomes even more challenging. However, as the rates of palliative radiotherapy administered to patients in the DECISION trial are low (10.6% of patients treated with sorafenib and 21.4% of patients treated with placebo), then perhaps this issue is not important.

There are two important issues to consider when interpreting the RCT evidence. First, a caveat to the use of the RPSFTM adjusted OS results from both trials is that the method requires the assumption that post-progression anti-cancer treatments, other than those permitted by treatment crossover, represents routine clinical practice. For patients with RR-DTC, there is currently no standard of care for patients with progressive disease. Therefore, it is unknown whether the post-study anti-cancer treatments administered to patients in the SELECT and DECISION trials reflect the treatments that would be offered to patients in the NHS. Second, the AG's examination of the PH assumption for OS (unadjusted and adjusted) and PFS in the SELECT and DECISION trials showed that the PH assumption does not hold for any of these outcomes other than unadjusted OS in the DECISION trial. This means that the majority of the HRs reported in the company submissions should be interpreted with caution. However, clinical advice to the AG is that the PFS results for the overall populations of the SELECT and DECISION trials are clinically meaningful.

4.10.2 Safety

Summary and interpretation of evidence: lenvatinib versus sorafenib

The AG did not conduct its own indirect comparison to facilitate a comparison of the effect of treatment with lenvatinib versus sorafenib for AEs. However, two other reviews[7,96] reported results from indirect comparisons of AEs. Kawalec et al 2016[96] reported that treatment with lenvatinib resulted in statistically significantly less alopecia, but statistically significantly more hypertension and treatment-related SAEs than sorafenib. Results from an analysis undertaken by Bayer 2017[7] showed that, when compared to treatment with lenvatinib, sorafenib resulted in statistically [redacted] Grade ≥3 and SAEs.

Summary and interpretation of evidence: lenvatinib and sorafenib versus best supportive care

When compared with placebo, treatment with both lenvatinib and sorafenib resulted in increased AEs. However, whilst diarrhoea was experienced by just over two-thirds of patients treated with both drugs in the SELECT and DECISION trials, there were some notable

differences in the safety profiles. Hypertension and decreased appetite were reported by over half of patients in the SELECT trial whereas in the DECISION trial the most common AEs reported by half or more of patients were hand-foot syndrome, alopecia and rash. Grade ≥3 hypertension was very common in patients treated with lenvatinib (>40%), and Grade ≥3 hand-foot syndrome was very common in patients treated with sorafenib (>20%). Hypertension was also reported to be one of the most common SAEs in the SELECT trial (3.4%). Data on the median time to onset of AEs[90,138] from the SELECT and DECISION trials suggest that AEs typically occur early with a decrease in incidence, prevalence and severity over time. In the DECISION trial, exceptions were diarrhoea that increased in prevalence over the first six cycles and weight loss which increased in severity (from Grade 1 to Grade 2) over the first nine cycles.

Overall, the safety findings from the RCTs were consistent with the findings from prospective observational studies of lenvatinib[76,134] and sorafenib[58,77,80,87,100,125] although it is noticeable that the incidence of some AEs varied quite widely in observational studies for patients treated with sorafenib. However, meta-analyses[126,137] of data from observational studies for hand-foot syndrome and diarrhoea reported incidences of all-Grade and Grade ≥3 AEs to be similar to those reported in the DECISION trial. It has, however, been found in a systematic review by Jean et al 2016[92] that the incidence of common all-Grade AEs tends to be higher for patients with RR-DTC than for patients with RCC or HCC and also for some patients with Grade ≥3 hand-foot syndrome and rash. Results from indirect comparisons conducted by the authors of four systematic reviews[7,8,56,96] found lenvatinib to result in statistically significantly less alopecia but statistically significantly more hypertension, Grade ≥3 AEs and SAEs when compared with sorafenib.

Overall, the incidence of dose interruptions was higher for patients treated with lenvatinib in the SELECT trial than with sorafenib in the DECISION trial, reflecting that it is recommended that treatment with lenvatinib is interrupted for Grade 3 hypertension.[50] Hypertension was the most common reason for dose modifications and discontinuations in the SELECT trial. In the DECISION trial, the most common reason for dose modifications and discontinuations was hand-foot syndrome. Dose reductions were frequent (>60%) for patients treated with both lenvatinib and sorafenib. Life threatening AEs from treatment with lenvatinib and sorafenib were rare. The AG considers that the AEs associated with treatment with lenvatinib and sorafenib can be managed with usual medical care and dose modifications, including treatment withdrawal. Clear guidance for managing AEs is set out in the SmPCs for lenvatinib[50] and sorafenib.[51]

4.10.3 Health-related quality of life findings

HRQoL data were not collected as part of the SELECT trial and HRQoL data from the 30 patients who participated in the open-label extension phase of the SELECT trial are not yet available. This is disappointing given that the investigators in the earlier DECISION trial had measured and reported HRQoL outcomes and highlighted that HRQoL may be negatively impacted by treatment with TKIs.[7,119] AE rates were high in the SELECT trial and it would have been informative if HRQoL data had been collected. HRQoL research is much needed as HRQoL is one of the most important outcomes to consider, both from the perspective of patients and for assessing comparative cost effectiveness.

The HRQoL data collected during the DECISION trial demonstrated that the FACT-G scores were higher for patients in the placebo arm than for patients in the sorafenib arm, indicating a higher HRQOL for patients receiving placebo. The negative impact of treatment with sorafenib on HRQoL may be linked to the high rates of AEs.[7,119] Indeed, it has been noted by Bayer 2017[7] that in response to the question on the FACT-G questionnaire 'I am bothered by side effects', the proportion of patients in the sorafenib arm who replied 'quite a bit' or 'very much' increased from 1.5% at cycle 1, to 29.6% at cycle 2 but then gradually diminished over time.

There are, however, limitations to the results from the HRQoL analyses. While the overall questionnaire completion rate during the DECISION trial was reported to be 96%,[119] the number of patients eligible to complete the questionnaires diminished with every cycle since only those who had not experienced progression were asked to complete the questionnaire. It also means that there are no HRQoL data available from patients whose disease has progressed. It is also unknown whether there is a direct correlation between HRQoL and AEs and how the different types of AEs experienced by patients treated with lenvatinib (e.g. hypertension) and sorafenib (e.g. hand-foot syndrome) affect HRQoL. Finally, to what extent a patient's HRQoL is affected by their symptom status (symptomatic versus asymptomatic) is unknown.

4.10.4 Generalisability of findings

The AG considers that the generalisability of the findings from the SELECT and DECISION trials to NHS clinical practice is questionable. This concern is driven by the fact that clinical advice to the AG is that in clinical practice there are concerns about the toxicity of TKI therapy in patients and effects on the quality of life of patients with asymptomatic disease and so treatment is more commonly given when symptomatic or clinically significant progressive disease develops. Hence BSC is a common treatment option for this group. The authors of two of the meta-analyses of sorafenib[126,137] concluded that the high incidence of AEs associated with sorafenib may affect the quality of patients' lives and most patients with

metastatic disease do not require systemic therapy. This view is supported by several clinical guidelines[4,24,25] as patients experiencing RR-DTC symptoms and/or those with rapidly progressing disease are considered to be in greatest need of systemic treatment.[31] In addition, the EMA concluded that maximum lesion size, symptoms related to the disease and progression rate should be carefully considered for each individual patient before initiating treatment.[26]

While all of the patients in the SELECT and DECISION trials had RR-DTC, it is unclear how many had symptomatic and/or rapidly progressing disease. However, it is reported in the EPAR[26] for sorafenib that results from a post-hoc subgroup analysis of data from the DECISION trial suggest that 20% of patients were likely to be symptomatic. Clinical advice to the AG is that this is probably typical of the proportion seen in clinical practice. It is, however, unclear how many patients in the SELECT trial were symptomatic and/or had progressive disease.

The post-hoc retrospective analysis of data from patients participating in the DECISION trial[112,118] categorised patients as having symptomatic disease if they had symptoms/findings that were consistent with RR-DTC reported in the medical history or pre-treatment AE dataset at baseline. Clinical advice to the AG is that there are no generally agreed definitions of 'symptomatic' or 'rapidly progressive disease' and that, in clinical practice, definition of a patient's disease status depends on individual patient characteristics.

Results from the post-hoc analysis show that median PFS was similar for all patients treated with sorafenib, irrespective of whether they were symptomatic or asymptomatic (10.7 months and 10.8 months respectively, compared with 10.8 months for all patients in the sorafenib arm of the trial). However, for patients in the placebo arm, PFS was much lower for symptomatic patients (3.6 months) than for asymptomatic patients (7.2 months), and was also lower than for all patients in the placebo arm of the trial (5.8 months).

No analyses have been undertaken to compare the effectiveness of treatment with lenvatinib in symptomatic versus asymptomatic patients. In the absence of such analyses no assumptions can be made about relative effectiveness. However, clinical advice to the AG is that, like sorafenib, only patients with symptomatic and/or progressive disease are likely to be treated in the NHS with lenvatinib.

The most recent published guidelines for treating RR-DTC, by the NCCN,[25] recommend lenvatinib or sorafenib as the treatment of choice for patients with progressive and/or

symptomatic disease. However, choice between lenvatinib and sorafenib should be based on the individual patient, taking into account the likelihood of response and comorbidities.[25]

There are further important caveats regarding the generaliseability of the findings from the SELECT and DECISION trials to NHS clinical practice.

The first caveat is that while most patients participating in the trials had a diagnosis of PTC, as would be expected in clinical practice, there were proportionately more patients with other types of DTC than would be expected in NHS clinical practice. Patients with these other types of DTC are reported to have a worse prognosis than patients with PTC.[15] However, subgroup and exploratory analyses of the SELECT trial data showed that for unadjusted OS, there was a statistically significant OS gain for patients with FTC treated with lenvatinib versus placebo[81] and that histology (favouring FTC versus PTC) was statistically significantly associated with increased OS.[90] These exploratory results warrant further investigation.

The second caveat relates to the age of patients. Thyroid cancer incidence is strongly related to age, with the highest incidence rates being in older males (aged >60 years) and the highest incidence rates in females being in younger and middle-aged women (aged 40 to 60).[1] The median age of patients was 61 years in the lenvatinib arm and 64 years in the placebo arms of the SELECT trial and 63 years in both arms of DECISION trial with approximately half of all patients in both trials being male. Given the median time from diagnosis in the trials varied from between 5.5 and 6 years, it appears that generally patients were older than may be seen in clinical practice. Moreover, the prognosis of patients tends to differ for patients aged <45 and those aged ≥45, as reflected in the staging criteria used for DTC.[4] Detailed data on the age range of included patients were not reported for either trial.

4.10.5 Other issues of relevance to clinical practice

The relative importance of ORR also warrants some discussion, particularly given the marked reported differences in effect between treatment with lenvatinib and sorafenib indicated by results from the SELECT and DECISION trials and the prospective observational studies.[58,76,77,80,87,100,102,125,134] While studies of lenvatinib[47,76,134] suggest that at least half of all patients achieve a response, meta-analyses of data from observational studies of sorafenib[126,137] suggest that no more than 22% of patients receiving this treatment respond. This finding reflects the finding from a systematic review of TKIs[33] that shows that the most likely outcome of treatment with a TKI is stable disease. Indeed, in the DECISION trial, 42% of patients in the sorafenib arm had stable disease for ≥6 months (and 12.2% had an objective tumour response) compared to 33% in the placebo arm (and 0.5% had an objective tumour response). However, given that lenvatinib and sorafenib are likely to be preferred treatment

options for patients with clinically significant progressive disease, reducing the rate of disease progression may be a more relevant outcome. The AG notes that in the submission from Bayer 2017,[7] it is reported that most patients (77%) in the sorafenib arm of the DECISION trial experienced target lesion tumour shrinkage, compared with 28% of patients in the placebo arm. The authors of a systematic review of sorafenib[103] for treating RR-DTC concluded that, although the data in the review came primarily from non-randomised phase II trials (but also included the DECISION trial), the results suggest that treatment with sorafenib slows the progression of disease in the majority of cases.

The findings from the extended open-label phases of the SELECT and DECISION trials should also be considered. These findings show that, the median PFS and ORR outcome results for patients previously randomised to the placebo arms but who crossed over to receive lenvatinib or sorafenib at the licensed doses, were similar to the median PFS and ORR reported for patients treated with lenvatinib and sorafenib in the double-blind phases of the trials. Given that patients in the placebo arm received no active systemic therapies during the double-blinded phase, these results appear to support the view that patients with progressive disease do not need to be treated immediately and can be treated when showing symptoms and/or rapidly progressing. However, the AG cautions that data on symptoms and/or whether patients were rapidly progressing are lacking, although patients were progressing to the extent that, on the basis of RECIST criteria, they were considered to have progressive disease. The AG also cautions that no OS data were available for these specific cohorts of patients.

The results from the open-label phase of the SELECT trial, which included patients who crossed over from placebo to receive treatment with two different doses of lenvatinib, suggest that PFS may be improved for those starting at the 20mg dose (median PFS not reached) as opposed to the licensed dose of 24mg (17.5 months). However, the numbers of patients in each group, particularly in the 20mg cohort, were small, and definitive conclusions could not be reached. Study 211,[155] an ongoing phase II RCT, compares two different starting doses of lenvatinib (24mg versus 18mg) with placebo. The expected end date for this trial is October 2020.

While patients treated with lenvatinib in the SELECT trial were not permitted to receive additional lenvatinib in the extended open-label phase of that trial, around a quarter of patients had received treatment with a VEGFR-targeted therapy, including sorafenib, prior to enrolment. SELECT trial subgroup PFS and ORR findings suggest that patients benefited from treatment with lenvatinib, regardless of whether they had received prior treatment with a VEGFR-targeted therapy. This result suggests that lenvatinib could be used first- or second-line for patients with RR-DTC. Further research is required to identify the effect on OS of

treating patients with lenvatinib followed by sorafenib. Furthermore, it has also been reported that SAEs were more common in the lenvatinib arm amongst patients who had received a prior VEGFR-targeted treatment (60.6%) compared with those who had not (50.8%).[104,105]

Some patients in the DECISION trial who had experienced disease progression whilst receiving sorafenib, were also eligible to receive sorafenib for a second time in the extended open-label phase of the DECISION trial. Clinical advice to the AG is that, currently in NHS practice, patients could be prescribed sorafenib post-progression as there is a view that continued treatment with sorafenib will slow the progression of disease. This expectation is supported, to some extent, by exploratory post-hoc findings.[82,93] These findings suggest that despite evidence of tumour growth or prior RECIST progression, treatment with sorafenib continued to slow tumour growth for patients who had also been treated with sorafenib during the randomised phase, when compared to tumour growth for patients treated with placebo during the randomised phase.[82,93] However, as concluded by authors of other abstracts[113,121] reporting results from the open-label extension phase of the DECISION trial, the effect of continued treatment with sorafenib after progression needs to be explored further.

Finally, there are no data for patients treated with sorafenib followed by lenvatinib. Further research is needed to identify the effect on OS and other efficacy and safety outcomes of treating patients with lenvatinib followed by sorafenib, and sorafenib followed by lenvatinib.

5 ASSESSMENT OF COST EFFECTIVENESS

The AG conducted a systematic review of the economic literature to identify the existing evidence assessing the cost effectiveness of treatment with lenvatinib and sorafenib (versus each other and versus BSC) for people with progressive, locally advanced or metastatic RR-DTC. The review focussed on the decision problem outlined in the final scope issued by NICE.[53] The economic evaluations presented in the submissions by Eisai 2017[8] and Bayer 2017[7] are discussed and critiqued separately in Section 5.3.

5.1.1 Search strategy

The AG identified cost effectiveness studies by searching Embase, MEDLINE, NHS Economic Evaluation Database via the Cochrane Library and EconLit from 1999 onwards. The starting date for all of the searches was 1999 and all databases were searched on 24 January 2017. Based on the fact that the FDA approved sorafenib for its first indication in 2005, and lenvatinib in 2015, the AG considered that this date span would allow all relevant economic evidence to be identified. The reference lists of included publications were hand-searched so too were the NICE, the SMC and the CADTH websites. The results of the searches were entered into an EndNote X7.4 library and de-duplicated.

5.1.2 Study selection and inclusion criteria

Publications were selected for inclusion in the review based on their relevance to the decision problem and the specific economic criteria displayed in Table 30. In addition to costs, quality adjusted life year (QALY), cost benefit and cost effectiveness outcomes, such as cost per PFS year, were also extracted from relevant publications.

Two reviewers (RH/NF) independently screened the titles and abstracts of all publications identified by the searches. The same two reviewers then independently retrieved and assessed (for inclusion) the full-texts of the publications that had been identified as being potentially relevant to the review. Disagreements about inclusion in the review were resolved through discussion and, in all cases, a consensus was reached; it was, therefore, not necessary to consult a third reviewer during the screening and selection process.

Table 30 AG's review of economic evidence: inclusion criteria

Criteria	Inclusion
Population	Adults with progressive, locally advanced or metastatic RR-DTC
Intervention	• Lenvatinib • Sorafenib
Comparators	• Lenvatinib • Sorafenib • Best supportive care
Costs	Direct healthcare costs
Outcomes	Incremental cost per LY gained and/or incremental cost per QALY gained
Study design	Full economic evaluations that consider both costs and consequences (cost effectiveness analysis, cost utility analysis, cost minimisation analysis and cost benefit analysis)
Date span	1999 to 24 January 2017
Language	English language only

LY=life year; QALY=quality adjusted life year; RR-DTC=radioactive iodine refractory differentiated thyroid cancer

5.1.3 Quantity of evidence

The searches for economic evidence identified 19 citations in total, 14 were obtained from the database searches, and five were identified from other sources. Once duplicates were removed, 18 publications remained and, after assessment of the titles and abstracts, ten publications[5,38,49,158-164] were retrieved and a detailed assessment of their eligibility was undertaken.

Included publications (9/10): the AG included four publications[158-160,163] that clearly met the inclusion criteria. The AG considered that the economic evidence for lenvatinib and sorafenib that had been submitted to the SMC[38,49] and CADTH[5,162] was also relevant to this review and so these four records,[5,38,49,162] one for each drug's individual submission to each regulatory agency, were included in the review. One further relevant publication[161] was identified during the citation search of the included publications; this publication only became available online after the AG's database searches had been completed.

Excluded publications (1/10): one publication[164] was a budget impact analysis and was, therefore, excluded from the review.

A flow diagram showing the process of study selection is shown in Figure 8.

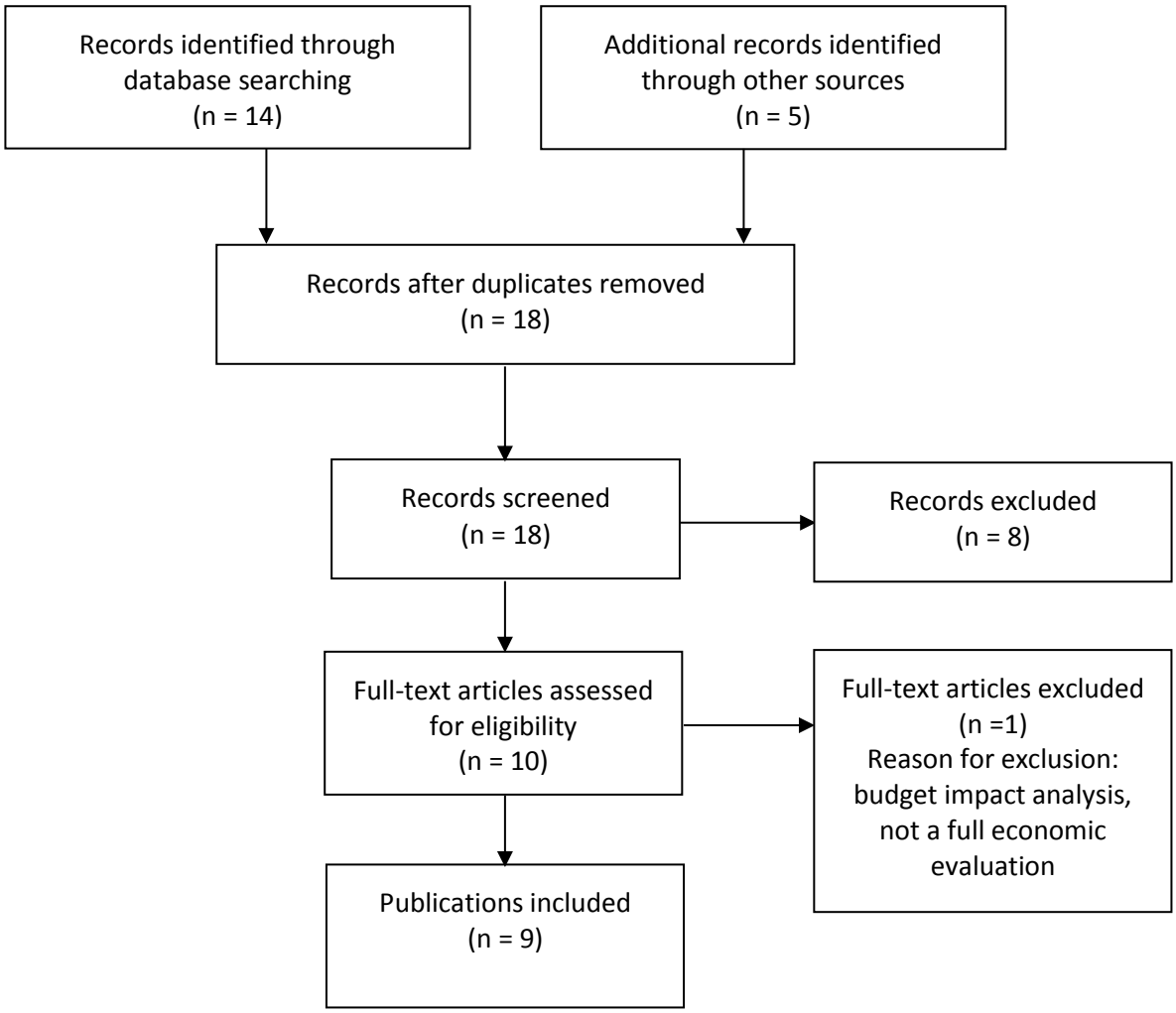

Figure 8 PRISMA flow diagram: AG economic literature review

A summary of the characteristics of the nine included publications[5,38,49,158-163] is presented in Table 31.

Table 31 Characteristics of publications included in the AG's review of economic evidence

Study	Country/ perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/ outcome source	Time horizon/cycle length/ discount rate	Cost year	Further information on publication type
Erdal et al 2015[163]	Country: Turkey Perspective: Turkish healthcare system	Sorafenib	Cost effectiveness/ utility analysis	BSC	QALYs and LYs Costs calculated in Turkish liras and converted (2.2) to US dollars	Clinical inputs from DECISION trial Resource use via expert panel	Time horizon: lifetime (max 30 years) Cycle length: 28-days Discount rate: NR	Mid-2014	Abstract only
Huang et al 2016 (a)[158]	Country: US Perspective: US health care system	Lenvatinib, sorafenib	Cost utility analysis	Placebo and each other	QALYs Costs in US dollars	Effectiveness estimates taken from DECISION and SELECT trials Costs and utilities from Redbook,[165] Healthcare Cost and Utilization Project,[166] Medicare Fee Schedule[167] and published literature (additional references NR)	Time horizon: lifetime Cycle length: bi-monthly Discount rate: 3%	2015	Abstract only

Study	Country/ perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/ outcome source	Time horizon/cycle length/ discount rate	Cost year	Further information on publication type
Huang et al 2016 (b)[159]	Country: US Perspective: US health care system	Lenvatinib, sorafenib	Expected value of perfect information analysis	Placebo and each other	ICER per QALY and EVPI per person Costs in US dollars	Effectiveness estimates taken from DECISION and SELECT trials Costs and utilities from Redbook,[165] Healthcare Cost and Utilization Project,[166] Medicare Fee Schedule[167] and published literature (additional references NR)	Time horizon: lifetime Cycle length: bi-monthly Discount rate: 3%	2015	Abstract only

Study	Country/ perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/ outcome source	Time horizon/cycle length/ discount rate	Cost year	Further information on publication type
Tremblay et al 2016[160]	Country: US Perspective: US health care system	Lenvatinib sorafenib	Cost effectiveness/ utility analysis	Each other	Costs and QALYs Cost per PFS year Cost per LYs Cost per QALY Cost per responder Costs in US dollars	IHS global pricing database,[168] CMS database[169] and published sources Kerr et al (2014)[170] as the source of EQ-5D utilities	Time horizon: 10 years (5 year horizon outcomes also reported) Cycle length: One month Discount rate: 5% (via correspondence with author)	Not fully reported but states the costs used to estimate BSC are from 2014 2014 used as cost year for currency conversion estimate	Poster only

Study	Country/ perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/ outcome source	Time horizon/cycle length/ discount rate	Cost year	Further information on publication type
Wilson et al 2017[161]	Country: US Perspective: US health care system	Lenvatinib, sorafenib	Cost utility analysis	Placebo and each other	QALYs Costs in US dollars	Effectiveness estimates taken from DECISION and SELECT trials Costs and utilities from Redbook[165], Healthcare Cost and Utilization Project[166], Medicare Fee Schedule[167] and published literature including Fordham et al (2015)[171] for utilities	Time horizon: lifetime Cycle length: bi-monthly Discount rate: 3%	2015	Peer-reviewed journal article
SMC 2015[49]	Country: Scotland Perspective: Scottish NHS	Sorafenib	Cost utility analysis	BSC	ICER per QALY Costs in pound sterling	Rates of effectiveness and resource use from the DECISION trial	Time horizon: not explicitly stated but text implies it is greater than 15 years Cycle length: NR Discount rates: NR	NR - 2015 used as cost year for currency conversion estimate	Summary of model and submission to the SMC

Study	Country/ perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/ outcome source	Time horizon/cycle length/ discount rate	Cost year	Further information on publication type
SMC 2016[38]	Country: Scotland Perspective: Scottish NHS	Lenvatinib	Cost utility analysis	BSC and sorafenib	ICER per QALY Incremental life years Costs in pound sterling	Effectiveness and resource use evidence from SELECT and DECISION trials	Time horizon: lifetime Cycle length: NR Discount rates: NR	NR - 2016 used as cost year for currency conversion estimate	Summary of model and submission to the SMC
CADTH 2015[5]	Country: Canada Perspective: Canadian health care system	Sorafenib	Cost utility analysis	BSC	ICER per QALY Incremental costs, QALYs and life years Costs in Canadian dollars	NR	Time horizon: 10 year base case horizon (re-estimated at 7 years for main results) Cycle length: NR Discount rates: NR	NR - 2015 used as cost year for currency conversion estimate	Summary of model and submission to CADTH

Study	Country/ perspective	Intervention	Study design/ purpose	Comparators	Reported measures	Cost/ outcome source	Time horizon/cycle length/ discount rate	Cost year	Further information on publication type
CADTH 2016[162]	Country: Canada Perspective: Canadian health care system	Lenvatinib	Cost utility analysis	BSC and sorafenib (results reported for BSC comparison only)	ICER per QALY Incremental costs, QALYs and life years Costs in Canadian dollars	Effectiveness data from SELECT and DECISION trials	Time horizon: 10 year base case horizon (re-estimated at 7 years for main results) Cycle length: 30.4 days Discount rate: NR	2016	Summary of model and submission to CADTH

BSC=best supportive care; CADTH=Canadian Agency for Drugs and Technologies in Health; CMS=Centers for Medicare and Medicaid Services; EVPI=expected value of perfect information; ICER=incremental cost effectiveness ratio; LYs=life years; LYS=life year saved; MAIC=matching adjusted indirect comparisons; NR=not reported; PFS=progression-free survival; QALY=quality adjusted life year; SMC=Scottish Medicines Consortium; UK=United Kingdom; US=United States

5.1.4 Quality of the included evidence

The quality of the included evidence was assessed using the NICE Reference Case checklist[172] and the Drummond checklist.[173] Summary tables of the AG's quality assessments are presented in Table 32 and Table 33. Full details of the completed checklists are presented in Appendix 7 (Table 74 to Table 81) and Appendix 8 (Table 82 to Table 89) of this report. The publications by Huang et al 2016[158,159] have been evaluated together as the same economic model was used to generate results for both publications.

Only the Wilson et al 2017[161] publication was available as a full-text paper published in a peer-reviewed journal. Three of the included publications[158,159,163] were only available as abstracts and one publication[160] was available as a poster. The submissions to the regulatory bodies in Scotland[38,49] and Canada[5,162] were only available as summary reports. As a result, only limited information was available from most of the included publications and this hindered the quality assessment of some of the methodologies described in the publications.

The authors of all of the included publications produced incremental cost effectiveness estimates enabling a single metric (an incremental cost effectiveness ratio [ICER] per QALY gained) to be used for comparative purposes. All of the publications included a discussion of the certainty associated with study results; however, full details of the sensitivity analyses and parameter values were not always available in the text.

Generally, the text describing the assumptions and data sources used to generate resource use, costs and HRQoL estimates within the economic models, was not clear. In addition, it was unclear whether the costs and benefits described in the publications were discounted appropriately. Results from analyses of the cost effectiveness of all the relevant comparators (lenvatinib, sorafenib and BSC) were only available from four of the reviewed publications.[158-161]

None of the publications considered the decision problem from the perspective of the NHS in England. However, as the Scottish NHS provides a sufficiently similar environment to the NHS in England, the AG considered that, for the purposes of this appraisal, the results from the SMC submissions[38,49] are broadly generalisable to patients in England. The characteristics of the health care systems, in terms of the way treatments are procured and used in the US,[158,159,161] Canada[5,162] and Turkey,[163] make the results from analyses based on these perspectives less useful when considering treatment options for patients in the NHS in England. However, including these studies[5,158,159,161-163] in this review allows a broad range of

cost effectiveness estimates to be considered and provides some an indication of the effect of varying assumptions such as the model timeframe and HRQoL estimates of HRQoL.

5.1.5 NICE Reference Case checklist

Table 32 NICE Reference Case checklist summary of the publications that were included in the AG's review of economic evidence

Attribute	Reference case	Erdal et al 2015[163]	Huang et al 2016[158,159]	Tremblay et al 2016[160]	Wilson et al 2017[161]	SMC 2015[49]	SMC 2016[38]	CADTH 2015[5]	CADTH 2016[162]
Decision problem	The scope developed by NICE	✓	✓	✓	✓	✓	✓	✓	✓
Comparator(s)	As listed in the scope developed by NICE	✓/✕	✓	✓	✓	✓/✕	✓	✓/✕	✓/✕
Perspective costs	NHS and PSS	✕	✕	✕	✕	✕	✕	✕	✕
Perspective benefits	All direct health effects, whether for patients or carers	✓/✕	✓/✕	✓	✓	✓	✓	✓	✓
Form of economic evaluation	Cost utility analysis with fully incremental analysis	✓	✓	✓	✓	✓	✓	✓	✓
Time horizon	Long enough to reflect all important differences in costs or outcomes	✓	✓	✓	✓	✓	✓	✓	✓
Synthesis of evidence on outcomes	Based on systematic review	✓	✓	✓	✓	✓	✓	✓	✓
Outcome measure	Health effects should be expressed in QALYs (EQ-5D preferred)	✓	NR	✓	✓	✓	✓	✓	✓
Health states for QALY	Reported directly by patients and/or carers	✓	NR	✓	✕	✓	✕	✕	✕
Benefit valuation	Time-trade off or standard gamble	✓	NR	✕	✓	✓	✓	✓	✓
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	NR	NR	✓	✕	NR	✕	NR	✕
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	NR	✕	✓	✓	NR	NR	NR	NR

✓ yes (item properly addressed) ✕ no (item not properly addressed) ✓/✕ partially (item partially addressed); NR=not reported
EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year

5.1.6 NICE Drummond checklist

Table 33 Drummond checklist summary of publications that were included in the AG's review of economic evidence

Question	Erdal et al 2015[163]	Huang et al 2016[158,159]	Tremblay et al 2016[160]	Wilson et al 2017[161]	SMC 2015[49]	SMC 2016[38]	CADTH 2015[5]	CADTH 2016[162]
Was a well-defined question posed in answerable form?	✓	✓	✓	✓	✓	✓	✓	✓
Was a comprehensive description of the competing alternatives given?	✓	✓	✓	✓	✓	✓	✓	✓
Was the effectiveness of the programme or services established?	✓	✓	✓	✓	✓	✓	✓	✓
Were all the important and relevant costs and consequences for each alternative identified?	✓	Unclear	✓	✓	✓	✓	Unclear	✓
Were costs and consequences measured accurately in appropriate physical units?	Unclear	Unclear	✓	✓	Unclear	✓	Unclear	✓
Were the cost and consequences valued credibly?	Unclear	Unclear	✓	✓ / ✗	Unclear	✓	Unclear	✓ / ✗
Were costs and consequences adjusted for differential timing?	Unclear	✓	✓	✓	Unclear	Unclear	Unclear	Unclear
Was an incremental analysis of costs and consequences of alternatives performed?	✓	✓	✓	✓	✓	✓	✓	✓
Was allowance made for uncertainty in the estimates of costs and consequences?	✓	✓	✓	✓	✓	✓	✓	✓
Did the presentation and discussion of study results include all issues of concern to users?	✓	✓	✓	✓	✓	✓	✓	✓

✓ yes (item properly addressed) ✗ no (item not properly addressed) ✓/✗ partially (item partially addressed)

5.1.7 Assessment Group economic review: overview of included publications

The AG identified nine relevant publications[5,38,49,158-163] describing the cost effectiveness of treatment with lenvatinib and sorafenib in a population of patients with RR-DTC. Where necessary, authors were contacted and asked to provide further information on methodological aspects that lacked clarity in the publications; only one lead author[160] replied and provided the discount rate used in the model.

One publication[163] considered the cost effectiveness of treatment with sorafenib compared to usual care in the Turkish setting. Four publications[158-161] compared treatment with lenvatinib versus sorafenib from a US perspective. The SMC submissions[38,49] considered resource use in the Scottish NHS and the CADTH submissions[5,162] included analyses that were undertaken from the perspective of the Canadian health care system. The results reported in the publications[5,38,49,158-162] comparing the cost effectiveness of lenvatinib versus sorafenib are based on the results of indirect comparisons. This means that the authors considered that the trial and patient characteristics of the SELECT and DECISION trials were sufficiently comparable for their data to compared using this methodology. The AG discusses the limitations of using data from the SELECT and DECISION trials in an indirect comparison in Section 4.6.

The costs, benefits and incremental results from each of the publications are presented in Table 34. All costs from 2014 have been inflated to 2015/16 prices using the hospital and community health services (HCHS) index.[174] Analyses conducted using 2015 and 2016 prices have not been inflated as the 2016/17 inflation indices are not yet available. Where the year in which the costs used within the model is not reported, the year of publication is used as a proxy. Where necessary, all cost data have been converted to UK pound sterling using the Bank of England exchange rate as of 25 May 2017.[175]

Erdal et al 2015[163]

The authors described a partition survival model that used clinical evidence from the DECISION trial, supplemented with Turkey-specific resource use and cost information, to generate estimates of the cost effectiveness of treatment with sorafenib versus BSC in a population of people with locally advanced or metastatic RR-DTC. Deterministic results were presented and the ICER per QALY gained for the comparison of treatment with sorafenib versus BSC was £23,859. The authors concluded that the results of the one-way deterministic analyses and probabilistic sensitivity analysis (PSA) were similar to the main set of deterministic results. However, as few details of the parameters and values that were used to estimate the level of uncertainty around results were reported in the publication, the AG was not able to ascertain the reliability of results generated by the sensitivity analyses. Despite not

reporting a willingness to pay threshold, the authors considered sorafenib to be a cost effective treatment compared to BSC.

Huang et al 2016 (a)[158]

The Markov model described by the authors used effectiveness evidence from the phase III SELECT and DECISION trials. Results from one-way sensitivity analyses showed that the base case model results were sensitive to changes to the costs of lenvatinib and sorafenib and the utility benefit of continuing with lenvatinib. The AG notes that the value and duration of the utility benefits were not reported. The base case ICER for the comparison of treatment with lenvatinib versus sorafenib was £61,109 per QALY gained.

Huang et al 2016 (b)[159]

The authors reported the methods and results of an expected value of perfect information (EVPI) analysis using the same model described in the abstract by Huang et al 2016 (a).[158] An ICER of £73,913 per QALY gain was reported indicating that treatment with lenvatinib offers an increase in benefit over sorafenib, but at an additional cost. At a willingness to pay threshold of approximately £77,000 per QALY gained, the probabilities of lenvatinib and sorafenib being cost effective were low (37% and 33% respectively). Due to uncertainty around the reliability of model results, the authors were not certain that treatment with lenvatinib was cost effective when compared to sorafenib and placebo.

Tremblay et al 2016[160]

The poster included results from a cost effectiveness analysis from a partition survival model designed to compare treatment with lenvatinib and sorafenib using clinical evidence from the phase III SELECT and DECISION trials. The base case ICER for the comparison of treatment with lenvatinib versus sorafenib was £81,338 per QALY gained when a 10-year time horizon was modelled, and £96,671 per QALY gained when a 5-year time horizon was modelled.

Costs per PFS year (£58,833 with a 5-year time horizon and £62,318 with a 10-year time horizon), costs per responder (£77,372 with a 5-year time horizon and £84,841 with a 10-year time horizon) and life year saved (LYS) were also reported in the publication. The authors did not set a willingness to pay threshold to determine at what level the cost per responder, for example, would offer good value for money. The authors refer to PSA in the publication but do not report the methods or the results of the analysis;

Wilson et al 2017[161]

The same set of authors who produced the abstracts by Huang et al 2016[158,159] authored a full-text paper comparing the cost effectiveness of treatment with lenvatinib versus sorafenib in which they described a Markov model that used effectiveness data from the phase III

SELECT and DECISION trials. Indirect treatment comparisons to compare the effectiveness of lenvatinib with sorafenib were made following adjustments to the placebo arms of the trials as the authors considered that the placebo arm of the SELECT trial included patients that appear to be healthier than those in the comparator arm of the DECISION trial. However, the AG does not consider the adjustments are sufficient to generate reliable estimates of the comparative effectiveness of lenvatinib and sorafenib. In addition, as discussed in Section 4.6, the AG does not consider that it is appropriate to undertake an indirect comparison of the effectiveness of lenvatinib versus sorafenib using data from the SELECT and DECISION trials.

The results of the author's cost utility analysis differ from those reported in the abstracts.[158,159] In the base case analysis, treatment with lenvatinib generated more benefits (+1.34 QALYs) than treatment with sorafenib (+0.96 QALYs), as well as more benefits than placebo (+0.71 QALYs), but at an increased cost of £7,368 versus sorafenib and £19,921 versus placebo. The base case ICER for the comparison of treatment with lenvatinib versus sorafenib was £19,522 per QALY gained. The base case ICERs for the comparison of treatment with lenvatinib versus placebo and sorafenib versus placebo were £31,566 and £49,484 per QALY gained per QALY gained respectively.

Sorafenib SMC submission 2015[49]

For the comparison of treatment with sorafenib versus BSC, the ICER was £32,083 per QALY gained; the Scottish PAS price of sorafenib was used in the analysis. These results were sensitive to the time horizon of the model and the approach used to estimate OS, with the ICER increasing with a shortened time horizon and with a change to the OS extrapolation method employed.

Lenvatinib SMC submission 2016[38]

For the comparison of treatment with lenvatinib versus sorafenib, the base case ICER was £49,525 per QALY gained; this analysis used the Scottish PAS price for lenvatinib and Eisai's estimate of the Scottish PAS discount currently in place for sorafenib. The ICERs per QALY gained were sensitive to the estimates of OS for lenvatinib (ranged from £29,000 to £96,000 per QALY gained with PAS prices) and to changing the utility rates used in the model by 20% (ranged from £41,000 to £62,000 per QALY gained with PAS prices).

Sorafenib CADTH submission 2015[5]

The company's base case cost effectiveness estimate was that, treatment with sorafenib versus BSC, resulted in an ICER of £82,080 per QALY gained. Several other ICERs per QALY gained were also presented as a result of re-analyses suggested by the Economic Guidance Panel. The re-analyses included amendments to the time horizon, the duration of treatment,

and estimates of OS. The results from the re-analyses ranged from £108,974 to £118,913 per QALY gained.

Lenvatinib CADTH submission 2016[162]

The base case analysis for the comparison of lenvatinib versus BSC, submitted by the company, generated an ICER of £72,536 per QALY gained. This increased to £101,293 per QALY gained when the amendments suggested by the Economic Guidance Panel were implemented. The reanalysis included amendments to OS estimates, time horizon, use of the intervention drug in terms of both wastage and the appropriate pack size to reach the required dosage, and the utility values used within the model.

Although the company submitted results from additional analyses comparing the cost effectiveness of lenvatinib versus sorafenib to CADTH, these results were not presented in the available CADTH guidance report.[162]

The AG notes that the SMC[38,49] and CADTH[5,162] reports highlight concerns about the clinical effectiveness data derived from the SELECT and DECISION trials. Key issues of concern related to median OS not being reached and the high rates of treatment crossover from the placebo (BSC) arms to the intervention arms (lenvatinib or sorafenib) that occurred during the trials.

5.1.8 Key results

Table 34 Results of publications that were included in the AG's review of economic evidence

Study	Interventions	Costs	LYs	QALYs	Incremental			ICER	
					Costs*	LYs	QALYs	per LY gained	per QALY gained
Erdal et al 2015[163]	BSC	NR	NR	NR					
	SOR	NR	NR	NR	£19,084	1.29	0.80	£14,754	£23,859
Huang et al 2016 (a)[158]	Placebo	£657,493	NR	NR					
	LEN	£152,448	NR	NR	-£505,045 (vs BSC) £25,491 (vs SOR)	NR	NR	NR	£61,109 (vs SOR)
	SOR	£126,957	NR	NR	-£530,536 (vs BSC)	NR	NR	NR	
Huang et al 2016 (b)[159]	LEN vs SOR	NR	NR	NR		NR	NR	NR	£73,913
Tremblay et al 2016[160] †	LEN	£217,527	2.71	1.77	£40,697	0.33	0.42	£124,843	£96,671
	SOR	£176,830	2.38	1.35					
Tremblay et al 2016[160] ††	LEN	£228,637	3.38	2.10	£44,626	0.58	0.54	£76,835	£81,338
	SOR	£184,010	2.80	1.56					
Wilson et al 2017[161]	Placebo	£107,898	NR	0.71					
	LEN	£127,819	NR	1.34	£7,368 (vs SOR) £19,921 (vs PLA)	NR	0.37 (vs SOR) 0.63 (vs PLA)	NR	£19,522 (vs SOR) £31,566 (vs PLA)
	SOR	£120,451	NR	0.96	£12,553 (vs PLA)	NR	0.25 (vs PLA)	NR	£49,484 (vs PLA)
SMC 2015[49]	SOR vs BSC	NR	NR	NR	NR	NR	NR	NR	£32,083
SMC 2016[38]	LEN vs SOR	NR	NR	NR	NR	NR	NR	NR	£49,525

Study	Interventions	Costs	LYs	QALYs	Incremental			ICER	
					Costs*	LYs	QALYs	per LY gained	per QALY gained
CADTH 2015[5]¥	SOR vs BSC	NR	NR	NR	£42,824	0.86	0.52	£49,795	£82,080
CADTH 2015[5]§	SOR vs BSC	NR	NR	NR	£45,744 to £46,054	NR	0.38-0.42	NR	£108,974 to £118,913
CADTH 2016[162]¥	LEN vs BSC	NR	NR	NR	£60,784	1.01	0.84	£60,182	£72,536
CADTH 2016[162]§	LEN vs BSC	NR	NR	NR	£84,687	1.03	0.84	£98,343	£101,293

ICER=incremental cost effectiveness ratio; NR=not reported; LYs=life years; QALYs=quality adjusted life years; UK=United Kingdom; SOR=sorafenib; PLA=placebo; LEN=lenvatinib
*All costs were inflated to 2015/16 and were converted to £
† 5 year horizon
†† 10 year horizon
¥ submitted analysis
§ Reanalysis by Economic Guidance Panel

5.1.9 AG's review of economic evidence: summary and conclusions

The published economic evidence[163] shows that the ICER of £23,859 per QALY gained for the comparison of sorafenib versus BSC (after conversion from Turkish Lira) is within the willingness to pay threshold that is considered to reflect a cost effective use of NHS resources. However, without further details of the economic model inputs, in particular the resource use and costs, the relevance of this finding to the NHS setting is unclear.

In the US setting, compared to placebo, both treatment with lenvatinib and sorafenib appear to provide additional health benefits whilst either saving resources[158] or yielding ICERs per QALY gained less than £50,000 after conversion from US dollars (£31,566 per QALY gained[161] for lenvatinib versus placebo and £49,484 per QALY gained[161] for sorafenib versus placebo). When treatment with lenvatinib is compared to sorafenib in the US setting, lenvatinib offers a health benefit over sorafenib but at an increased cost. Cost effectiveness results ranged from £19,522 per QALY gained[161] (lenvatinib versus sorafenib) to £96,671 per QALY gained[160] (lenvatinib versus sorafenib), at current UK prices. Again, it is unclear whether these results are relevant to the NHS setting.

In 2015, sorafenib became the standard of care for patients in Scotland with locally advanced or metastatic RR-DTC, provided that the company supplied the drug to the NHS at the Scottish PAS price agreed by the company with NHS Scotland.[49] The SMC sorafenib report[49] states that sorafenib generated more benefit than BSC but at an increased cost. The ICER for this comparison was £32,083 per QALY gained. In 2016, an appraisal of treatment with lenvatinib[38] versus sorafenib was submitted to the SMC; lenvatinib was considered by the SMC to be both an orphan drug and an End of Life treatment. For the comparison of treatment with lenvatinib versus sorafenib, based on survival outcome results generated using indirect comparison methods, and using the Scottish PAS price for lenvatinib, the ICER per QALY gained was estimated to be £49,525 and lenvatinib was accepted for use in NHS Scotland.

The AG notes that any discount to the list prices of the drugs agreed with the NHS in Scotland does not equate to an equivalent agreement with the NHS in England. All PAS prices are confidential and thus the applicability of the results presented within the Scottish submissions to the appraisal of lenvatinib and sorafenib for use in the NHS in England is unclear as it is not known whether the discounts agreed with the NHS in Scotland are the same as those agreed with the NHS in England.

In 2015, sorafenib was appraised by CADTH[5] and, after reanalyses suggested by the Economic Guidance Panel, estimates of the most plausible ICERs for the cost effectiveness

of treatment with sorafenib versus BSC ranged from £108,974 to £118,913 per QALY gained (after conversion from Canadian dollars). Lenvatinib was considered for use by the Canadian healthcare system in 2016. Estimates of the cost effectiveness of treatment with lenvatinib versus both BSC and sorafenib were generated but only the comparisons with BSC are reported in the CADTH report.[162] After the Economic Guidance Panel's suggested amendments were carried out, the best estimate for the comparison of treatment with lenvatinib versus BSC was £101,293 per QALY gained. Both lenvatinib and sorafenib have been recommended for use in Canada. The relevance of these results to patients in the NHS is unknown.

What is lacking from the current evidence base are any cost effectiveness analyses of direct relevance to the NHS in England. The SMC submissions[38,49] provide an insight into the costs and consequences associated with treatment with lenvatinib, sorafenib and BSC and these are likely to be similar for patients treated in England. However, the PAS prices agreed with the NHS in Scotland are confidential and this prevents the reported cost effectiveness estimates s being directly applicable to the NHS in England.

Head to head comparisons of the effectiveness of treatment with lenvatinib versus sorafenib depend on results from indirect comparisons, whether conducted in a formal statistical framework[5,38,49,160,162] or with adjustments made to the placebo arms of the phase III trials,[161] which provide estimates based on the pooling of the comparator arms within the SELECT and DECISION phase III trials. The AG considers that due to the issues discussed in Section 4.6, it is not appropriate to employ indirect comparisons of the effectiveness of lenvatinib versus sorafenib using data from the SELECT and DECISION trials.

5.2 Summary of the companies' systematic reviews of economic evidence

Both of the companies carried out SRs to identify published cost effectiveness studies that included lenvatinib and/or sorafenib. Both companies concluded that there are no cost effectiveness studies conducted in the UK from the perspective of the NHS that were relevant to decision making in England.

5.3 Summary of key features of the companies' economic models

This section includes summary details of the key features of the economic models submitted to NICE from Eisai and Bayer as part of the MTA process. All of the company data presented in this section have been taken directly from the company submissions and models.

5.3.1 Population

Both companies state that their economic evaluations focus on patients with progressive RR-DTC. However, in the submission from Eisai 2017,[8] it is highlighted that the SELECT trial definition of progressive RR-DTC was locally advanced or metastatic DTC confirmed by radiographic evidence of disease progression within the prior 13 months and that some patients participating in this trial had received prior VEGF therapy. Eisai points out that, in contrast, no patients recruited to the DECISION trial had received prior VEGF therapy and that, to be eligible for recruitment, evidence of disease progression within the 14 months prior to commencing the trial was required. The AG describes other differences in the two trial populations in Sections 4.2.1, 4.2.2 and 4.6 of this report.

5.3.2 Model structure

Key elements of the structure of the economic models submitted by Eisai and Bayer are included in Table 35. The structure of the two company models is similar and is in line with the structure of models that have previously been submitted to NICE to inform appraisals of interventions used to treat patients with cancer. The structure of both models conforms to specifications detailed in the final scope issued by NICE.[53]

Table 35 Model structure

Parameter	Eisai model (lenvatinib)	Bayer model (sorafenib)
Intervention	Lenvatinib	Sorafenib
Comparators	Sorafenib Placebo/BSC	Lenvatinib Placebo/BSC
Model structure	A four state (stable disease, response, progressive and death) partitioned survival cost utility model developed in MS Excel	A three state (progression-free, progressed and death) partitioned survival cost utility model developed in MS Excel
Cycle length	One month (30.43 days)	28 days
Model time horizon	33.35 years (5 years and 10 years are considered as scenario analyses)	30 years
Discounting	Costs and benefits were discounted at a rate of 3.5% annually in line with the NICE Reference Case[172]	
Perspective	The perspective is stated to be that of the NHS and PSS. However, no specific PSS elements are considered to be relevant to the RR-DTC population and none are included in either model	

BSC=best supportive care; MS=Microsoft; PSS=personal social services; RR-DTC=radioactive iodine refractory differentiated thyroid cancer
Source: Eisai 2017,[8] Section 5.2 and Bayer 2017,[7] Section 4.2

5.3.3 Therapies

Details about the intervention and comparators included in the company models are provided in Table 36. Both models included the therapies listed in the final scope issued by NICE.[53] The AG highlights that the lenvatinib and sorafenib doses in the models are based on average levels of use in the SELECT and DECISION trials and are lower (lenvatinib: approximately 17mg, sorafenib: 651mg) than the respective licensed doses (lenvatinib: 24mg, sorafenib: 800mg). Possible reasons include dose interruptions/reductions due to AEs and in some cases intolerance may lead to a treatment being stopped.

Table 36 Modelled therapies

Parameter	Eisai model (lenvatinib)	Bayer model (sorafenib)
Lenvatinib	**Price**: list price used in the CS; however, a completed PAS submission template was made available to the ERG during the review period **Daily dose**: 17.4mg (based on SELECT trial data, Eisai 2015) **Treatment duration**: SELECT trial TTD data	**Price**: list price **Daily dose**: 17.4mg (based on published data, estimate does not account for dose interruption) **Treatment duration**: the sorafenib TTD K-M data were adjusted to fit the SELECT trial median duration of treatment
Sorafenib	**Price**: MiMS price **Daily dose**: 651mg (based on data from the DECISION trial) **Treatment duration**: assumed until disease progression	**Price**: CMU price **Daily dose**: 651mg (based on data from the DECISION trial) **Treatment duration**: DECISION trial TTD K-M data (these data are complete and, therefore, no extrapolation was required)
Placebo/BSC	Assumption: no additional costs	BSC is defined as concurrent use of radiotherapy (10.6% in sorafenib arm, 21.4% in placebo arm of DECISION trial)
Administration cost	Deliver oral chemotherapy (SB11Z): £183.50	None
Subsequent therapies	None (assumption based on expert advice)	

CMU=Commercial Medicines Unit; K-M=Kaplan-Meier; MiMS=monthly index of medical specialities; PAS=patient access scheme; TTD=time to treatment discontinuation
Source: Eisai 2017,[8] Section 5.2 and Bayer 2017,[7] Section 4.2

5.3.4 Survival modelling

Summary details of the general approach the companies used to model patient survival (OS and PFS) are provided in Table 37 and Table 38 respectively.

Table 37 Overall survival modelling

	Lenvatinib	Sorafenib	Placebo/BSC
Eisai model	SELECT trial data from third data-cut (August 2015) extrapolated using piecewise exponential curve	Published DECISION trial OS data from first data-cut (August 2012)	SELECT trial data from third data-cut (August 2015), re-censored and RPSFTM adjusted, and extrapolated using piecewise exponential curve
Bayer model	The curve, generated to represent OS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC ([redacted] 95% CI:[redacted] to [redacted]) using data from the second data-cuts of the DECISION and SELECT trials	DECISION trial data from second data-cut (May 2013t) allowed a direct comparison. The data were extrapolated using an exponential distribution	DECISION trial adjusted ITT data from second data-cut (May 2013) allowed a direct comparison. The data were extrapolated using an exponential distribution

CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; OS=overall survival; RPSFTM=rank preserving structural failure time model
Source: Eisai 2017,[8] Section 5.3 and Bayer 2017,[7] Section 4.3

Table 38 Progression-free survival modelling

	Lenvatinib	Sorafenib	Placebo/BSC
Eisai model	SELECT trial data from first data-cut (November 2013) extrapolated using piecewise gamma curve	Published DECISION trial PFS data from first data-cut (August 2012)	Not affected by crossover – SELECT trial data from first data-cut (November 2013) extrapolated using piecewise gamma curve
Bayer model	The curve, generated to represent PFS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC ([redacted] 95% CI:[redacted] to [redacted]) using data from DECISION and SELECT trials	DECISION trial data from second data-cut (May 2013t) allowed a direct comparison. The data were extrapolated using an exponential distribution	DECISION trial data (May 2013 data-cut) allowed a direct comparison. The data from each arm were extrapolated using exponential distributions

CI=confidence interval; HR=hazard ratio; ITC=indirect treatment comparison; PFS=progression-free survival
Source: Eisai 2017,[8] Section 5.3 and Bayer 2017,[7] Section 4.3

5.3.5 Measurement and valuation of health effects

Sources of utility values

The base case utility values used in the Eisai model were the same as those used by Bayer, in their submission to the SMC for sorafenib,[49] to represent the experience of patients receiving BSC (EQ-5D values were obtained from the DECISION trial). Disutilities were then applied as a weighted proportion, based on values obtained from a vignette study carried out by Fordham et al 2015.[171]

The source of the utility values used in the Bayer model was the EQ-5D data collected during the DECISION trial. No additional utility decrements associated with AEs were included in the model.

The use of utility values derived from EQ-5D data collected during clinical trials is in line with the approach set out in the NICE Guide to the Methods of Technology Appraisal.[172]

Utility values

The utility values used in the companies' models are provided in Table 39.

Table 39 Utility values

Health State	Lenvatinib	Sorafenib	Placebo/BSC
Eisai model			
Stable disease state	0.76	0.68	0.77
Response state	0.82	0.74	0.83
Progressive state	0.64	0.64	0.64
Bayer model			
Progression-free	0.72 (SE=0.08)	0.72 (SE=0.08)	0.8 (SE=0.07)
Post-progression	0.64 (SE=0.06)	0.64 (SE=0.06)	0.64 (SE=0.06)

BSC=best supportive care; SE=standard error
Source: Eisai 2017,[8] Table 18 and Bayer 2017,[7] Table 27

5.3.6 Healthcare costs

Levels of resource use

Eisai obtained estimates of the level of healthcare utilisation inputs for the pre-progression and progressive disease states from physician surveys conducted in Europe; these estimates were then validated by four NHS England practising clinical experts. Mortality-related costs were obtained from the Nuffield Trust[176] and adjusted for inflation to 2016 values based on PSSRU[174] inflation rates for 2016.

Expert advice from oncologists was the basis for Bayer's resource use estimates. Unit costs were obtained from the NHS Reference Costs 2015-16[177] and the PSSRU report.[174] In the model it is assumed that resource use associated with treatment with lenvatinib is the same as the resource use associated with treatment with sorafenib.

The monthly routine care costs used in both company models are provided in Table 40. Eisai's routine costs included physician visits and disease associated hospitalisation days. Bayer's routine costs included inpatient stay, outpatient appointments and pharmaceutical costs.

Eisai's end of life costs (£7,450) included secondary care, local authority funded social care, district nursing and GP contacts.

Table 40 Total monthly routine care costs

Parameter	Eisai model	Bayer model
Pre-progression		
Response	£280.61	-
Stable disease	£297.98	-
Sorafenib and lenvatinib	-	[redacted]
Placebo/BSC	-	[redacted]
Progressive disease/post-progression	£1,315.56	[redacted]

BSC=best supportive care
Source: Eisai 2017,[8] Table 25 and Bayer 2017,[7] Table 28

5.3.7 Adverse event costs

The Eisai model includes the following AEs:

- lenvatinib: Grade 3 and 4 treatment-emergent AEs and AEs that required hospitalisation in the SELECT study
- sorafenib: Grade 3 and 4 treatment-emergent AEs in the DECISION trial and AEs that required hospitalisation based on proportions from the SELECT study.

The Bayer model only includes Grade 3 and 4 AEs occurring in >5% of patients in the lenvatinib arm of the SELECT trial or in the sorafenib arm of the DECISION trial.

Bayer also included AE management costs (per 28 days), see Table 29 in the CS for details.

Frequencies/rates and costs associated with AEs included in the company models are presented in Table 41. Eisai's cost sources are a mix of NHS Reference Costs[177] and PSSRU costs.[174] Bayer's cost sources are a mix of NHS Reference Costs,[178] PSSRU costs,[179] and British National Formulary (BNF) costs.[52]

Table 41 Adverse event frequencies/rates and costs

Parameter	Eisai model (lenvatinib)			Bayer model (sorafenib)				
	Frequency of Grade 3 to 4 AE hospitalisations		Hospitalisation costs	Rate of Grade 3 and 4 AEs (per 28 days)			Cost per patient per 28 days	
	Lenvatinib	Sorafenib		Lenvatinib	Sorafenib	Placebo/ BSC	Grade 3	Grade 4
Hypertension	3.5%	0.79%	£850.67	3.55%	0.76%	0.43%	£158	£65.06
Weight decrease	0.40%	0.19%	£639.83	0.67%	0.58%	0.19%	£345	-
Diarrhoea	0.40%	0.28%	£571.30	0.55%	0.55%	0.13%	£223	£102
Decreased appetite	0.40%	0.00%	£639.83	-	-	-	-	-
Hypocalcaemia	0.40%	0.69%	£615.83	0.18%	0.72%	0.30%	£9	£9
Hypokalaemia	0.00%	0.00%	£615.83	-	-	-	-	-
Asthenia	0.00%	0.00%	£658.83	-	-	-	-	-
Fatigue	0.00%	0.00%	£658.83	0.64%	0.48%	0.18%	£61	£74
Hand-foot syndrome	0.00%	1.40%	£450.35	0.23%	1.64%	-	£155	-
Proteinuria	0.40%	0.19%	£778.67	-	-	-	-	-

AE=adverse event; BSC=best supportive care
Source: Eisai 2017,[8] Table 27 and Table 28 and Bayer 2017,[7] Table 23 and Table 30

5.3.8 Cost effectiveness results

Base case cost effectiveness results

The base case cost effectiveness results from the Eisai and Bayer submitted economic models are shown in Table 42.

Table 42 Base case pairwise comparisons

Technology	Total			Incremental			ICER per QALY gained
	Costs	LYG	QALYs	Costs	LYG	QALYs	Deterministic
Eisai model results							
Lenvatinib	£107,182	4.34	3.18				
Sorafenib	£82,839	3.18	2.10	£24,342	1.16	1.08	£22,491
Placebo/BSC	£42,115	2.80	1.84	£65,067	1.54	1.34	£48,569
Bayer model results							
Placebo/BSC	[redacted]	3.49	2.35				
Sorafenib	[redacted]	4.79	3.16	[redacted]	1.30	0.81	[redacted]
Lenvatinib	[redacted]	5.92	4.04	[redacted]	1.12	0.88	[redacted]

BSC=best supportive care; ICER=incremental cost effectiveness ratio; LYG=life year gained; QALY=quality adjusted life year
Source: Eisai 2017,[8] Table 31 and Bayer 2017,[7] Table 38

Table 43 Probabilistic cost effectiveness results

Technologies	Total		Incremental		ICER/QALY gained (vs BSC)	ICER/QALY gained
	Mean costs (95% CI)	Mean QALYs (95% CI)	Costs	QALYs		
Eisai model						
Lenvatinib vs sorafenib	-	-	-	-	-	£21,578
Lenvatinib vs placebo/BSC	-		-	-	-	£48,683
Bayer model (all based on results of indirect comparison)						
BSC	[redacted]	2.41 (1.00 to 5.19)				
Sorafenib	[redacted]	3.25 (1.81 to 5.30)	[redacted]	0.84	[redacted]	[redacted]
Lenvatinib	[redacted]	4.11 (2.02 to 6.67)	[redacted]	0.86	[redacted]	[redacted]

BSC=best supportive care; CI=confidence interval; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: Eisai 2017,[8] Table 34 and Bayer 2017,[7] Table 42

Bayer also carried out cost effectiveness analyses using the adjusted MAIC HRs. The effect on the company's ICERs was small. The resultant base case ICERs for the comparison of treatment with sorafenib versus BSC and lenvatinib versus BSC are [redacted] and [redacted] per QALY gained.

Probability of being the most cost effective

Eisai model: PSA results suggest that, at a willingness to pay threshold of £50,000 per QALY gained, the probability of lenvatinib being more cost effective than sorafenib or BSC is 60%.

Bayer model: PSA results suggest that, at a willingness to pay threshold of £30,000 per QALY gained, the probability of sorafenib being cost effective was 30%, the probability of BSC being cost effective was 54% and the probability of lenvatinib being cost effective was 16%.

Sensitivity and scenario analyses

Both companies carried out a range of deterministic sensitivity analyses and scenario analyses.

In the Eisai model, for the comparison of lenvatinib versus sorafenib, the two most influential parameters in the deterministic sensitivity analysis were OS HR versus sorafenib (lenvatinib dominates) and PFS HR versus sorafenib (£5,000 to £35,000 per QALY gained). In the scenario analyses, the most influential parameters were the length of treatment duration for lenvatinib (treat to progression rather than clinical trial duration; £71,978 per QALY gained) and the cut off for OS and PFS extrapolation (20 weeks for OS and PFS; £29,874 per QALY gained).

In the Bayer model, for the comparison of sorafenib versus lenvatinib, the largest deviations from the base-case ICER were due to variation in the OS HR for lenvatinib [redacted] to £[redacted] per QALY gained and lower lenvatinib progression-free utility ([redacted] to [redacted] per QALY gained). The scenario analyses that had the biggest effects on the companies' cost effectiveness results were the time horizon (reduction to 10 years; £[redacted] per QALY gained) and lower lenvatinib progression-free utility (reduced to 0.648; £[redacted] per QALY gained).

5.4 AG independent cost effectiveness assessment

5.4.1 Model design

In common with the two companies, the AG has used a standard partitioned survival model structure, applied to the patient population specified in the final scope issued by NICE,[53] to consider the cost effectiveness of treatment with lenvatinib and sorafenib in comparison with BSC (as represented by data from the placebo arms of the SELECT and DECISION trials).

Two particular differences should be noted:

- The AG has not included a separate health state for patients who respond to treatment. On clinical advice, the AG considers that there is little merit in this addition to the standard three-state structure (in which patients begin in the progression-free health state and, following assessed disease progression, transfer to the post-progression state where they receive only BSC prior to death). For responding patients, who are mostly symptom-free, response alone is unlikely to have a measurable effect on patient-perceived quality of life/utility and has no effect on resource use.

- The AG has designed a model that allows each intervention (lenvatinib and sorafenib) 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. Though not ideal, the AG has provided an illustrative structural sensitivity analysis (Figure 9) based on applying data from the counterfactual placebo arm of both trials to illustrate the extent of uncertainty involved in comparisons between the active treatments with the currently available clinical evidence. The reason for this unusual approach is to demonstrate non-equivalence of the placebo arms of the two clinical trials, which renders indirect comparison of the two treatments via a common comparator invalid (as discussed in Section 4.6, and illustrated graphically in Figure 9).

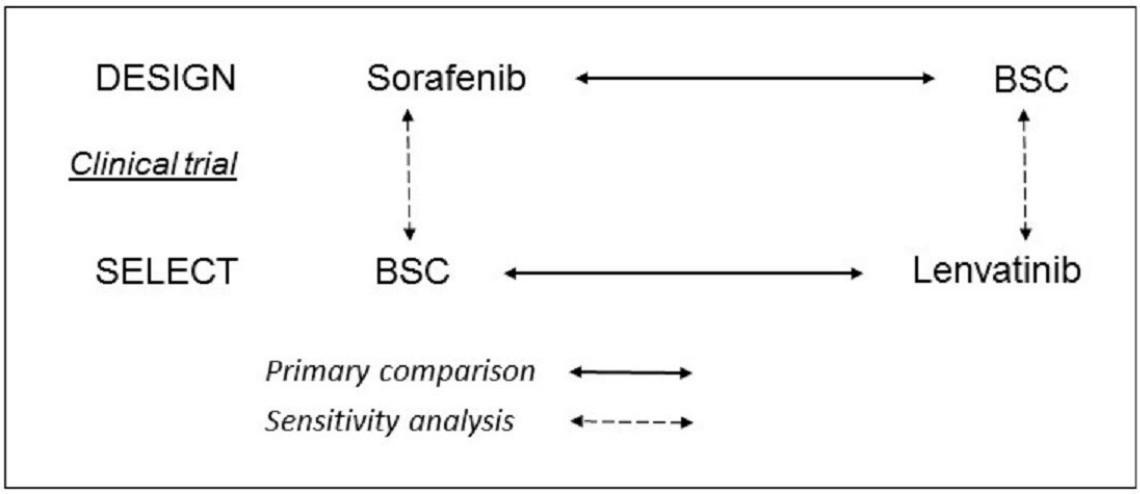

Figure 9 Model structure featuring two simple trial based comparisons, with additional cross-trial comparisons as a structural sensitivity analysis to illustrate the uncertainty associated with choice of comparator

Resource use estimation, the sources for unit costs and selection of health-related utility values used in the AG's model are presented in in this section of the AG report. Standard discount rates of 3.5% per annum are used for discounting both costs and benefits (measured as QALYs), but not for life years (survival). The AG model is structured with a maximum time horizon of 40 years.

5.4.2 Effectiveness data

Modelling long-term outcomes from trial data

Both companies have followed a conventional approach to the general problem of identifying an appropriate method by which to extrapolate time-limited follow-up trial data for PFS, OS and TTD. This involves attempting to fit a range of pre-specified statistical functions to the available evidence, and selecting one which appears to be optimal according to particular 'measures of fit' (principally Akaike information criterion [AIC] and Bayesian information criteria [BIC]).

This paradigm is wholly dependent on the limited data available and the restricted armoury of 'standard' models. In particular, it fails to take into account a wider evidence base related specifically to the natural history of the disease, and the influence of particular characteristics of both the recruited patient group and of the trial design.

The AG has investigated long-term survival trends in patients diagnosed with Stage 3 or 4 (locally advanced or metastatic) thyroid cancer in the USA and recorded on the SEER database.[180] A total of 32,818 patients (male and female) followed for 15 years yielded a persistent trend from 18 months after diagnosis. Figure 10 demonstrates the very close match

between these data and a simple linear model, indicating that the risk of death remained unchanged throughout this period indicative of a simple exponential survival process.

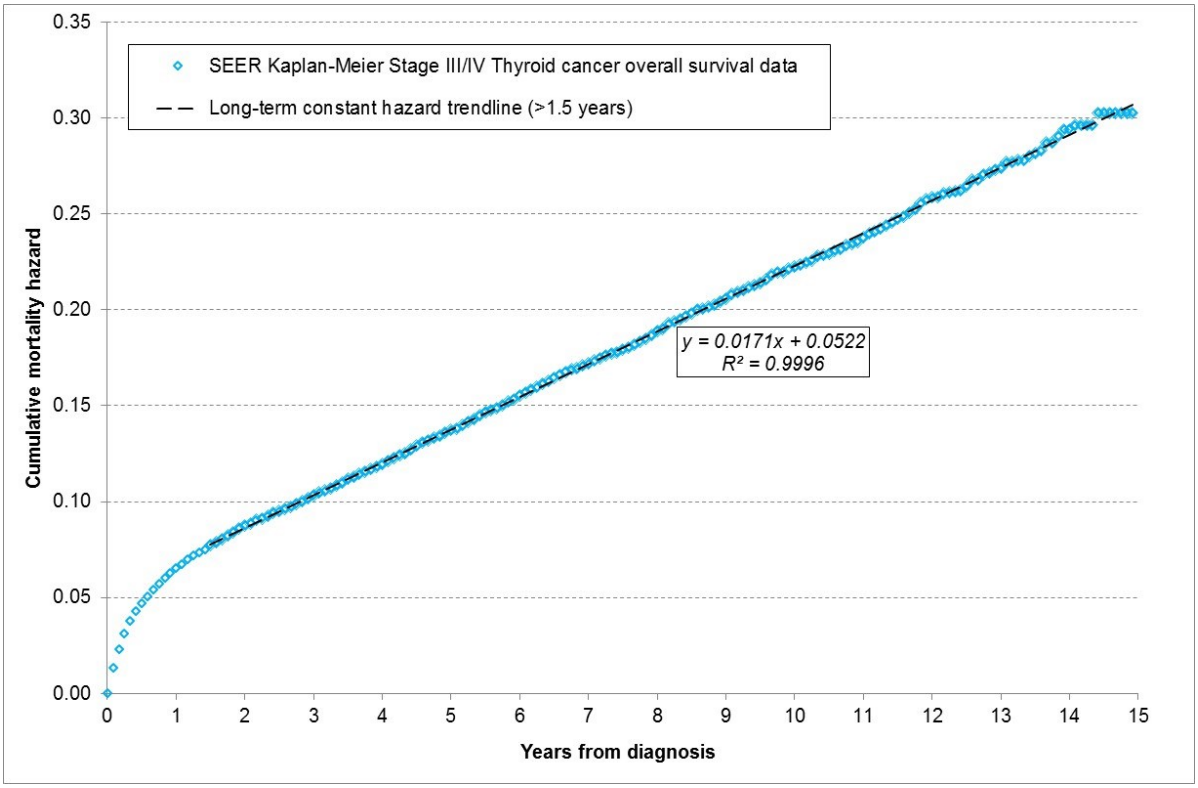

Figure 10 Cumulative hazard data from follow-up of patients diagnosed with Stage III/IV thyroid cancer for 15 years

This evidence is sufficiently compelling to give the AG confidence to employ exponential extrapolation as the default method of modelling incomplete trial data in this appraisal. The nature of clinical trials (selecting patients who have suffered a recent disease progression, and administering a novel treatment which takes time to reach full effectiveness) means that the initial period post-randomisation will give rise to temporary distortions to the underlying disease process. However, thereafter, it is likely that the natural history of the condition will be re-established, so that a long-term exponential function will reappear. The mean time since diagnosis of patients randomised in the DECISION trial was 7.24 years, suggesting that the trial cohort lies in the middle of the follow-up range shown in Figure 10. The AG is therefore confident that outcome data extrapolation should be focussed on fitting exponential models to estimate lifetime survival expectation.

Data issues

Following the initial stakeholders meeting for this appraisal (17 February 2017), the AG submitted identical requests to the two companies, asking for a set of detailed analyses of the latest data available from the two clinical trials, based on common analytical methods to allow

comparative analyses to be carried out by the AG, thus minimising the risk of methodological bias. Eisai provided the requested data relating to the SELECT trial as an appendix to their submission (Eisai 2017[8]). Unfortunately, Bayer chose not to address the AG's request. As a consequence, the AG was unable to perform some comparative analyses based on common assumptions, and the potential for bias and uncertainty in the data available to the AG remains.

The two clinical trials that provide the effectiveness evidence for this appraisal share common features, which result in interpretive complexity and uncertainty. In particular, in both trials patients were permitted to cross over from the placebo control to active treatment (lenvatinib or sorafenib) following disease progression. As a consequence, randomisation was broken in both trials and some outcome variables may not be mutually compatible, even after attempts to adjust for crossover effects.

Both companies assume that, in addition to the active treatments, a third comparator (BSC) may be represented by the placebo arms of the two trials. Moreover, it is implicitly assumed that the randomised patients are drawn from similar populations with reference to their risk profile for the various time-to-event outcomes measured (PFS, OS, post-progression survival [PPS], and time-to-treatment discontinuation). In Section 4.6, the non-equivalence of PFS data from the placebo arms of the two clinical trials has been clearly demonstrated. This is of crucial importance to attempts to employ relative effectiveness measures reliant on the proportional hazards assumption in relation to PFS, which is the only standard outcome variable reported in these trials which is free from any contamination by crossover effects (both trial protocols required confirmation of disease progression before patients were allowed to enter the open-label phase in which patients in the placebo arm were offered crossover treatment).

The problem of devising a credible approach to indirect comparison between lenvatinib and sorafenib for PFS cannot be resolved by appeal to technical argument alone. The pattern of hazard over time for disease progression in the two active arms is sufficiently similar to justify a simple HR approach. However, the placebo arms exhibit unexpectedly inconsistent patterns of temporal change, not compatible with the assumption of similarity between the patient groups not receiving active treatment. The AG, therefore, considers that the patients enrolled in the two trials cannot be considered to derive from a common population. This degree of difference precludes the use of either placebo arm as being representative of untreated patients across both trials.

The data for both placebo arms exhibit an unexpected improvement in long-term survival (reducing progression hazard) for which there is no obvious explanation. The effect of this phenomenon is to produce a varying differential in performance when comparing survival

components across the two trials without any clear confirmatory evidence. Therefore, the AG is unable to support use of a conventional indirect treatment comparison in this appraisal. The AG considers it is preferable to model the relative effectiveness and cost effectiveness of each active treatment against its own placebo comparator, and then generate results for each drug relative to the placebo of the other clinical trial as a sensitivity analysis, in order to allow assessment of the uncertainty associated with the choice of comparator.

Progression-free survival

The AG chose to use data for locally assessed PFS rather than centrally assessed PFS, as local assessment is generally more closely related to normal clinical practice.

Lifetime mean PFS for patients in the DECISION trial who received placebo may be readily estimated from trial data (for the period available) and a simple exponential curve which conforms closely to the reported trial data (Figure 11). The AG estimated lifetime mean PFS from the area under the K-M data to 16.5 months elapsed time followed by the area under the exponential function thereafter, giving a lifetime mean PFS estimate of 7.56 months. The sorafenib PFS arm of the DECISION trial exhibits a simple constant hazard (exponential) relationship (Figure 11), allowing the lifetime mean PFS to be estimated in a similar fashion, using the area under the curve (AUC) of the K-M data until 25 months, and the exponential extrapolation thereafter. This shows a lifetime mean PFS estimate of 47.18 months for patients receiving sorafenib, and a mean gain in PFS of 39.62 months compared with receiving placebo.

The SELECT trial data for PFS exhibit a more complex pattern in each arm. The cumulative hazard plots (Figure 12) reveal two distinct phases, both of which follow a constant hazard. Patients in the placebo arm who remain progression-free after 312 days experience a reduction in hazard of about 53%, which is sustained thereafter. Similarly, patients in the lenvatinib arm experience a reduction of progression hazard of about 47% at 529 days. As before, the estimated mean lifetime PFS for these patient groups were estimated as the sum of the AUC in each trial arm, followed by lifetime extrapolation using the long-term exponential hazard of progression or death. This approach yields estimates of mean lifetime PFS of 41.00 months for patients receiving lenvatinib and 6.92 months for patients in the placebo arm of the SELECT trial. Thus the estimated net lifetime gain in PFS for patients receiving lenvatinib is estimated to be 34.08 months.

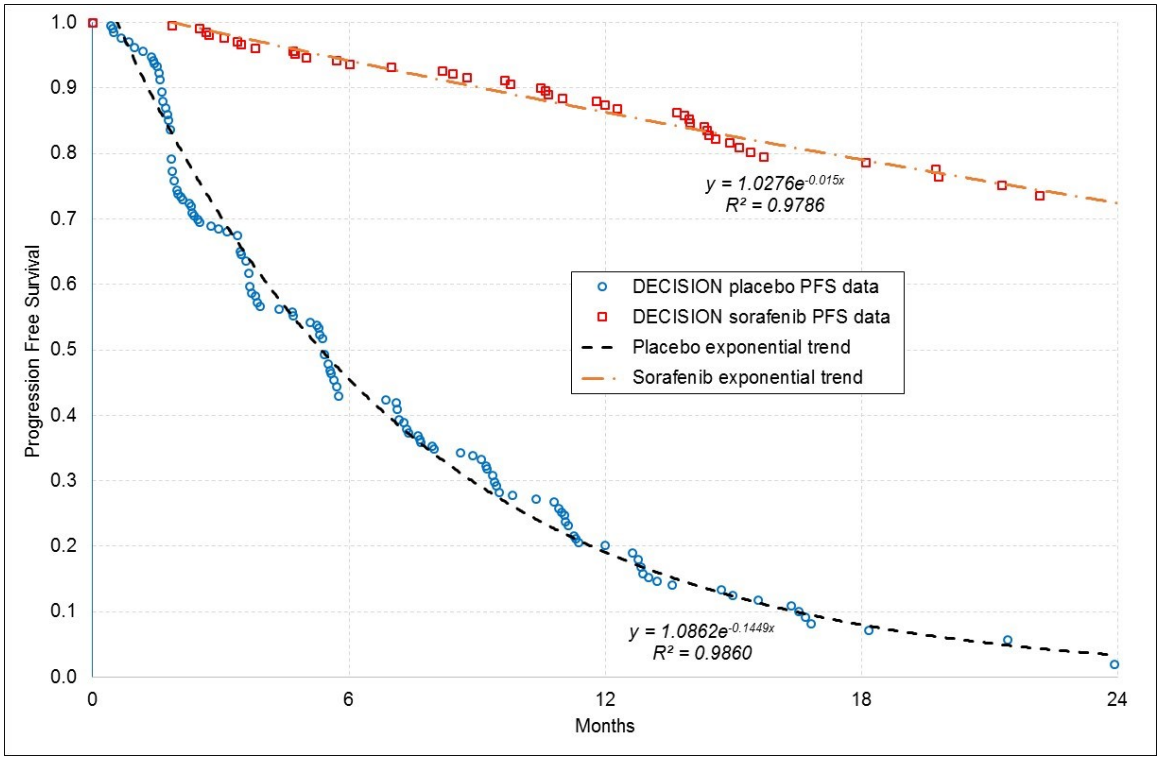

Figure 11 Progression-free survival Kaplan-Meier data from the DECISION trial modelled by an exponential function

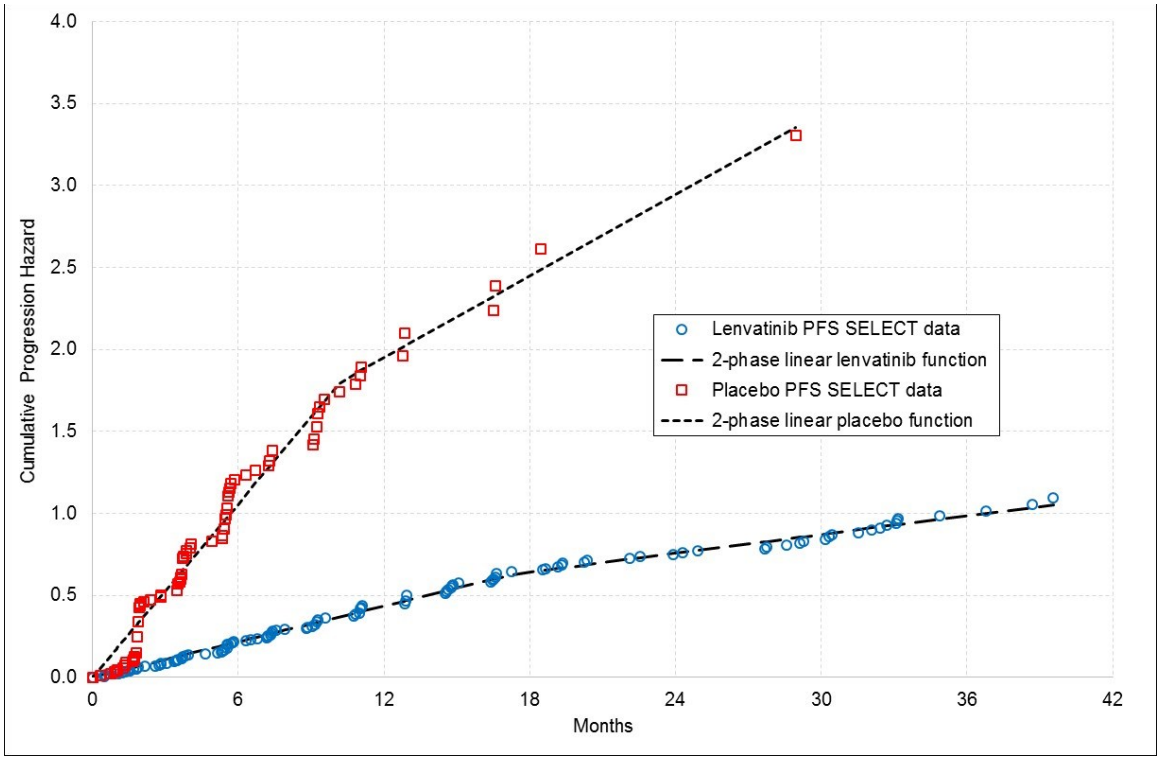

Figure 12 Cumulative hazard for disease progression for the SELECT trial, with 2-phase fitted exponential models

Time to treatment discontinuation

As illustrated in Figure 13, the SELECT trial data are virtually complete for the cycles of lenvatinib dispensed during the trial. The AG estimates mean usage of lenvatinib as 12.61 30-day cycles per patient.

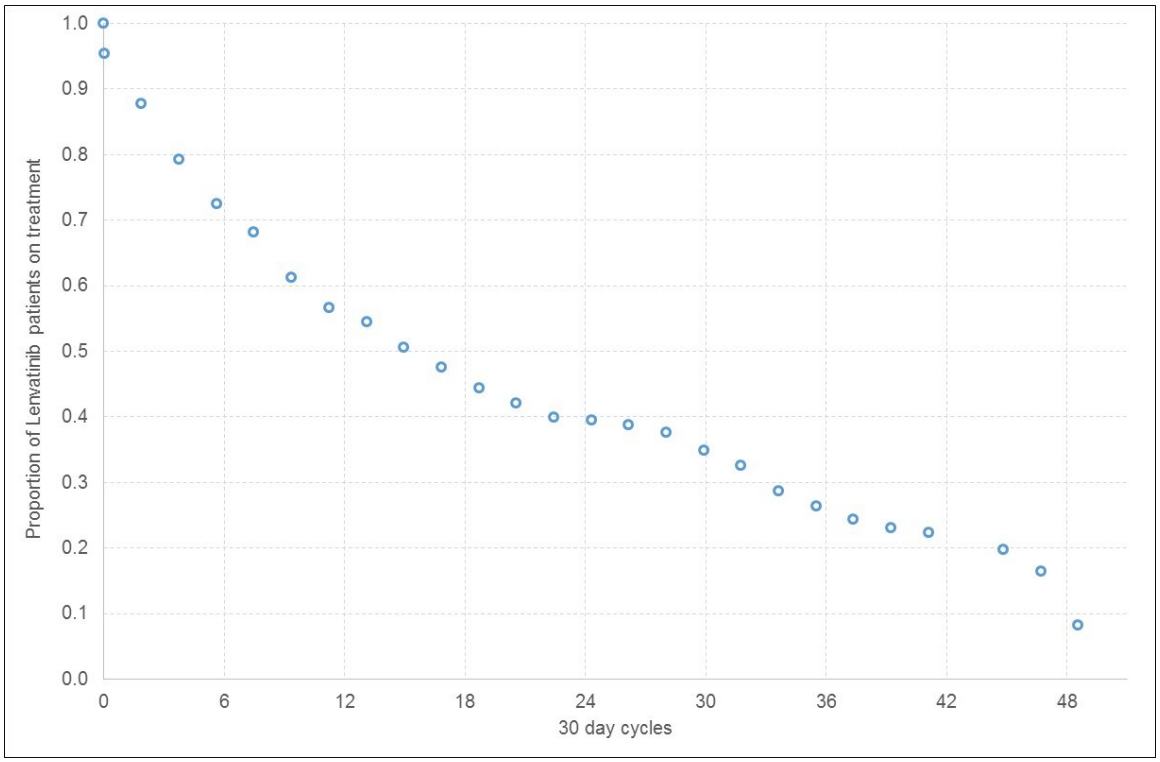

Figure 13 30-day cycles of lenvatinib dispensed in the SELECT trial

The DECISION trial data are also complete for the cycles of sorafenib dispensed during the trial, as illustrated in Figure 14. The AG estimates mean usage of sorafenib as 14.36 28-day cycles per patient.

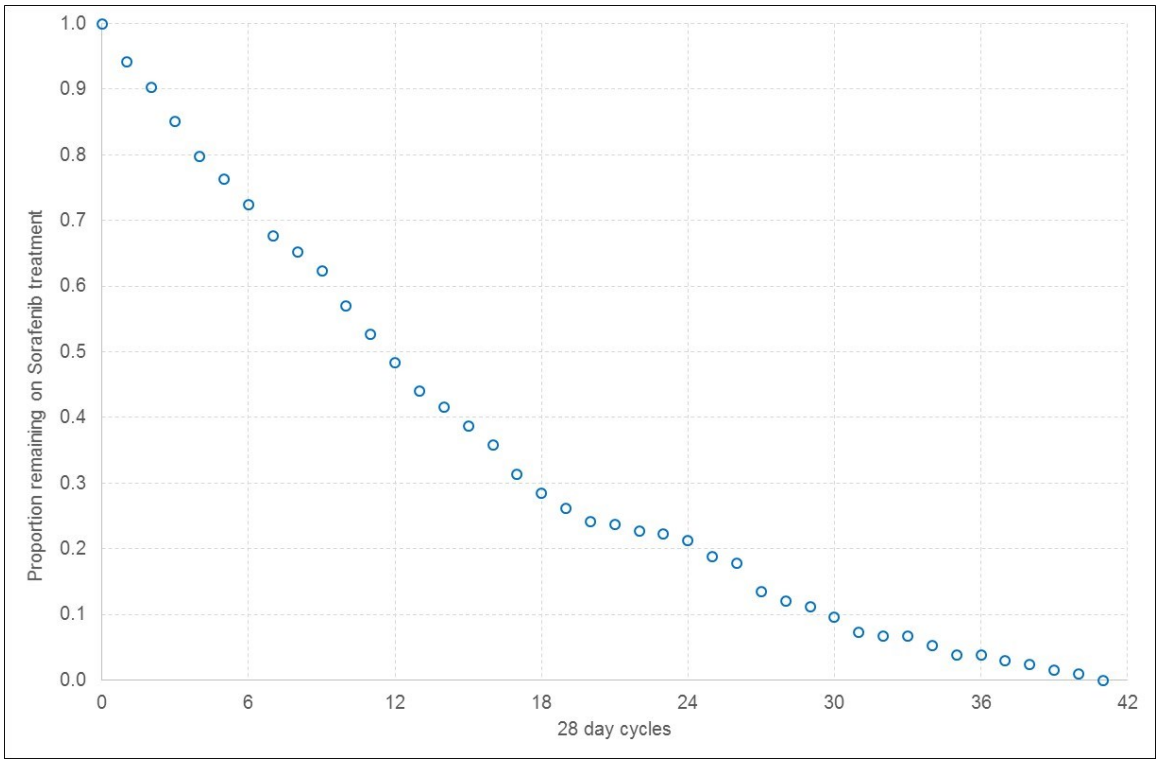

Figure 14 28-day cycles of sorafenib dispensed in the DECISION trial

Overall survival

Data provided by the company for lenvatinib treated patients in the SELECT trial (Figure 15) show a simple long-term exponential trend indicating a constant mortality risk throughout the trial period (19.6% per year). This allows the mean lifetime OS for patients treated with lenvatinib to be estimated using the AUC of the trial K-M curve until 34.7 months plus a simple exponential extrapolation thereafter, giving a total mean OS of 55.1 months.

Both companies have employed RPSFTM adjustments to data from the placebo arms of their respective clinical trials to correct for patients crossing over to the active treatment following disease progression. Adjusted OS placebo arm data from the SELECT trial are also displayed in Figure 15 and indicate that after RPSFTM adjustment, a similar long-term exponential (constant risk) trend also applies to the placebo arm beyond 6 months. Using the AUC of the adjusted K-M curve until 19.1 months plus the exponential extrapolation thereafter, yields a lifetime estimated mean OS for the corrected placebo arm of 29.9 months, and a net estimated OS gain attributable to treatment with lenvatinib of 25.3 months.

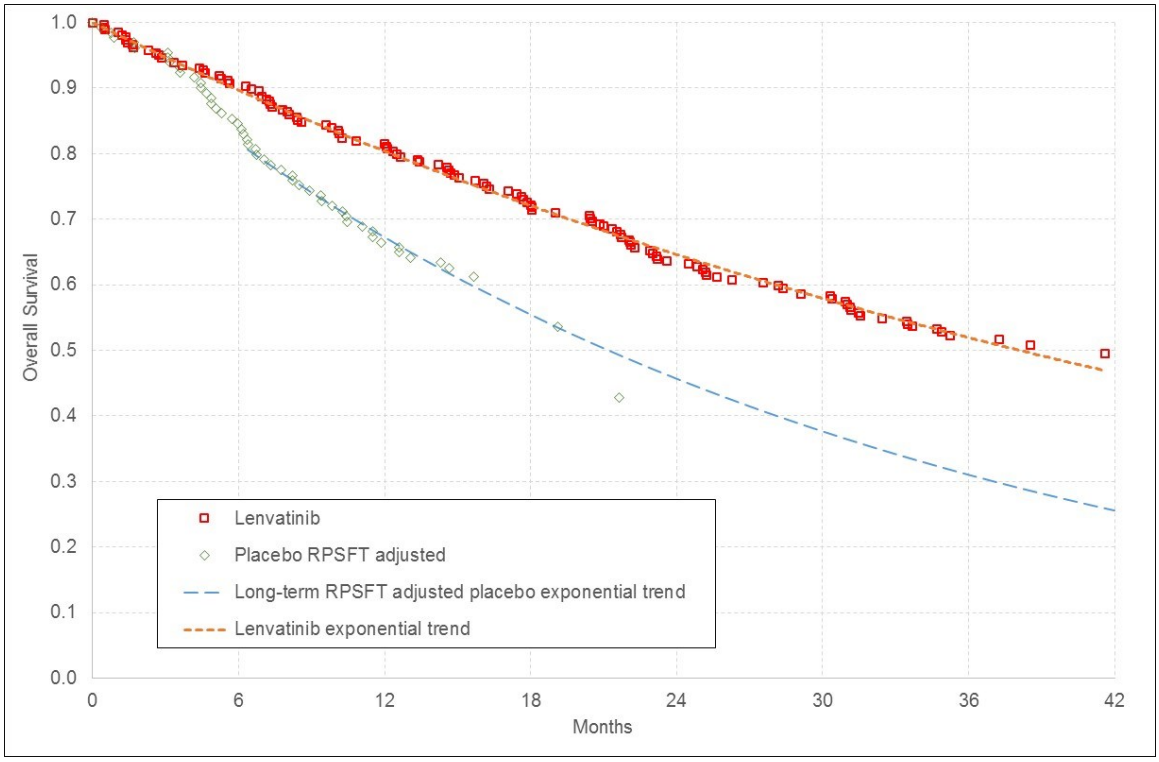

Figure 15 OS: lenvatinib treated patients in the SELECT trial, with fitted exponential model, and RPSFTM-adjusted for placebo patient crossover, with long-term exponential fitted model

Post-progression survival

Assessment of PPS may be carried out at an aggregate level by calculating the difference between model estimates of OS and PFS. However, it can also be informative to consider this outcome at the level of individual patients where it may provide useful insight into possible post-treatment long-term effects of treatments even after active treatment has ceased. The AG asked both companies to provide PPS data from their respective primary clinical trials. Unfortunately, only data from the SELECT trial have been received. As with OS, it is important to allow for the effects of crossover on PPS by using RPSFTM adjusted data.

In Figure 16, the beneficial effect of crossover to lenvatinib for patients initially randomised to the placebo arm is clearly apparent. Both trial arms exhibit a similar early pattern, albeit at different absolute levels of survival, and thereafter show similar long-term exponential trends after 15 to 18 months from the time of disease progression. When the RPSFTM adjustment is applied, the corrected placebo arm very closely follows the trajectory of the lenvatinib arm (though the effect of RPSFTM revised censoring does not allow direct comparison beyond 16 months). Nonetheless, these data suggest that, after crossover adjustment, there is probably no additional benefit to individual patients crossing from placebo to lenvatinib beyond that which would have been gained by treatment prior to disease progression.

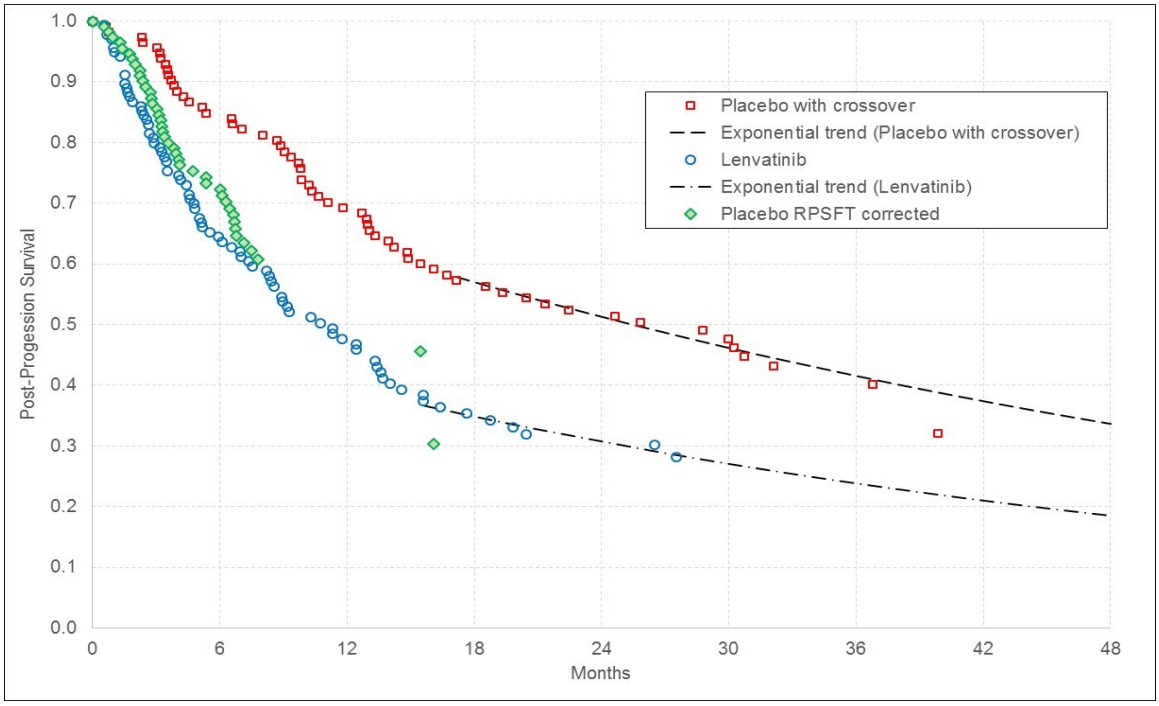

Figure 16 PPS: lenvatinib in the SELECT trial, with fitted exponential model, and RPSFTM adjusted for placebo patient crossover, with long-term exponential fitted model

Summary of time-to-event outcome data analysis

Estimates of PFS, OS and PPS and mean cycles of active treatment received in the two clinical trials are displayed in Table 44. Although the PFS results appear quite similar, those for OS and PPS suggest that treatment with lenvatinib provides superior OS gain, but inferior PPS. It is particularly noteworthy that 73% of the PFS benefit achieved in the lenvatinib treated patients was converted into OS gain. By contrast, only 24% of PFS gain experienced by patients treated with sorafenib is seen to correspond to OS gain. This discrepancy could be an artefact of different approaches to defining and registering disease progression in the two trials, but would otherwise indicate superior effectiveness of lenvatinib. The duration of active treatment in the two trials is very similar when measured in days rather than cycles, with a difference of less than 7%.

Table 44 AG estimated mean time-to-event outcome variables

Treatment group	PFS (months)	OS (months)	PPS (months)	TTD (cycles)
Lenvatinib (SELECT)	41.0	55.1	14.1	12.6 (*30 day*)
Placebo (SELECT)	6.9	30.2*	23.3	-
Gain due to lenvatinib	*+34.1*	*+24.9*	*-9.2*	-
Sorafenib (DECISION)	47.2	56.7	9.5	14.4 (*28 day*)
Placebo (DECISION)	7.6	47.2*	39.6	-
Gain due to sorafenib	*+39.6*	*+9.5*	*-30.1*	-

PFS=progression-free survival; PPS=post-progression survival; OS=overall survival; TTD=time to treatment discontinuation
*RPSFTM adjusted for crossover in placebo arms

5.4.3 Health-related utility data

The AG has considered carefully the opposing approaches used by the two companies to estimate appropriate health-related utility values to assign to health states, and to AEs. The Eisai model relies heavily on the Fordham et al 2015 vignette study[171] (which it sponsored), whereas the Bayer model draws on EQ-5D-3L data collected during the DECISION trial.

On theoretical grounds, directly collected evidence from patients with the condition (as used in the Bayer model) should always be preferred to the results of an artificial study without recourse to the views of patients either in design or calibration (as used in the Eisai model). Of particular concern is the serious over-estimation of baseline utility values in the Fordham et al 2015 study[171] when compared with UK general population values for people of a similar age. The contrary position argues that DECISION trial data include the disutility of AEs in estimates of health state utilities, and therefore are biased without any objective means of adjusting the health state estimates.

An additional cause for concern with both approaches is the absence of any model facilities to account for the duration of AE disutilities. It is generally assumed that a case of a particular problem persists in perpetuity whilst the patient is in that health state. This is an extremely pessimistic assumption regarding the ability of medicine to resolve or limit AEs both in duration and intensity.

On balance, the AG considers that the data from the DECISION trial should be used in the base case (see Table 45) with a sensitivity analysis using the Eisai model values.

Table 45 AG preferred health-related utility values

Health state	Treatment arm	Base case utility value	Standard error	Sensitivity analysis utility value	Standard error
PFS	Lenvatinib / sorafenib	0.72	0.08	0.76 / 0.68	0.08
PFS	BSC	0.80	0.07	0.80	0.019
PPS	All	0.64	0.06	0.50	0.028

BSC=best supportive care; PFS=progression-free survival; PPS=post-progression survival; BSC=best supportive care

5.4.4 Resource use and cost data used in the AG's model

Active treatments (lenvatinib and sorafenib)

The lenvatinib full acquisition cost is £4,311 per 30-day treatment (NHS Indicative Price, BNF June 2017).[52] This is reduced by the SELECT trial dose intensity factor (71.666%) so the true cost per cycle is £3,089.55.

The sorafenib full acquisition cost is £3,576.56 per 28-day treatment (NHS Indicative Price, BNF June 2017).[52] This is reduced by the DECISION trial dose intensity factor (81.40%) so the true cost per cycle is £2,911.32.

There is no administration cost associated with either drug, which can be safely taken unsupervised. The NHS Reference Cost figures quoted by both companies for administration of oral treatment relates to particular drugs which may cause serious rapid onset reactions, and so the patient must be monitored following administration. Thus, it is not appropriate to use this cost when estimating the cost of either sorafenib or lenvatinib.

Routine care costs

Table 46 summarises the schedule of itemised routine care tests, treatments and specialist visits identified by the AG's clinical advisor, in terms of use per quarter (3 months), per 28-day cycle and per 30-day cycle. These items are considered applicable to all patients irrespective

Table 46 AG estimated routine care resource use and cost

Resource item	No. per quarter	Unit cost	Standard error	Source: NHS Reference Costs 2015/16 [177]
Blood test	1	£3.10	£0.07	Ref Cost DAPS05
Coagulation test	1	£3.10	£0.07	Ref Cost DAPS05
Urine test	1	£7.63	£0.22	Ref Cost DAPS07
Liver function test	7	£1.18	£0.03	Ref Cost DAPS04
Thyroid function test	3	£1.18	£0.03	Ref Cost DAPS04
Protein test	1	£1.18	£0.03	Ref Cost DAPS04
Bone scan	1	£242.39	£7.56	Ref Cost NMOP/RN15A
MRI scan	1	£204.67	£5.07	Ref Cost IMAGOP/RD03Z
CT scan	1	£118.53	£2.92	Ref Cost IMAGOP/RD22Z
Thyroxine (4 weekly)	3.26	£4.04	-	BNF NHS indicative prices
Calcium & vitamin D	3	£7.13	-	BNF NHS indicative prices
Specialist oncology visit	1	£162.84	£4.37	Ref Cost 370/WF01A
Total per 3 months	**-**	**£789.81**	-	-
Total per 28-day cycle	**-**	**£242.19**	-	-
Total per 30-day cycle	**-**	**£259.48**	-	-

BNF=British National Formulary; CT=computed tomography; MRI=magnetic resonance imaging; Ref Cost=NHS Reference Costs

Adverse events

Four common AEs feature in the two company models for which treatment types and resource use were estimated by the AG's clinical advisor. The cost estimates shown in Table 47 are only for a single cycle (28 days or 30 days) and take no account of AE episodes which do not resolve within that time, or which subsequently recur.

Table 47 AG estimated adverse event resource use and treatment costs

Adverse event	Resource item	Unit cost	Incidence rate			
			Sorafenib	Lenvatinib	Placebo vs sorafenib	Placebo vs lenvatinib
Hand-foot syndrome	Diprobase 500g pump-pack	£10 (typical retail price)	20.29%	3.45%	0.0%	0.0%
Proteinuria	Ramipril 2.5mg x 28	£0.27 (eMIT April 2016)[181]	0.0%	3.45%	0.0%	0.0%
Hypertension	Amlodipine 10mg x 28	£0.19 (eMIT April 2016)[181]	0.0%	42.91%	1.91%	3.82%
	Ramipril 10mg x 28	£0.41 (eMIT April 2016)[181]	0.0%	42.91%	1.91%	3.82%
	2 extra oncology consultations	£162.84 per visit (NHS Reference Costs 2015/16)[177]	0.0%	42.91%	1.91%	3.82%
Total cost		**Per 28 days**	**£33.55**	**£140.37**	**£6.24**	**£12.45**
		Per 30 days	**£35.95**	**£150.40**	**£6.69**	**£13.34**

eMIT= electronic Market Information Tool

End of life care

Health care costs during the last 90 days of life were estimated using the results presented in Table 9 of the paper by Georghiou and Bardsley 2014;[176] costs were uplifted from 2010-11 to 2015-16 using the Hospital and Community Heath Services inflation index as shown in Table 48.

Table 48 AG estimated end of life (final 90 days) resource use and treatment costs

Care item	Mean cost per patient	Standard error
GP consultation	£391.78	£4.98
District nursing	£631.14	£53.77
Local authority social care	£476.57	£11.28
Emergency in-patient	£4,369.67	£6.28
Non-emergency in-patient	£1,459.78	£5.06
Out-patient attendances	£405.73	£1.10
Accident & Emergency visits	£85.87	£0.15
Total	**£7,820.54**	-

5.4.5 Cost effectiveness results

Deterministic cost utility results from the AG model using public list prices are compared with submitted results from the two companies in and Table 49 (versus Eisai model) and Table 50 (versus Bayer model). Overall, the estimates of incremental costs from the three models are not very different, but estimates of outcomes (life years and QALYs) show larger discrepancies across the three models, reflecting the different assumptions and estimation methods employed. The ICERs per QALY gained reported from the AG model are substantially greater than those obtained from the Bayer model, but the Eisai model results show a much larger ICER per QALY gained for sorafenib versus BSC than that obtained from either of the other models.

Inevitably, the relative economic performance of the treatments in all three models will change significantly when final discounted acquisition prices are applied.

Structural sensitivity analysis

The AG cross-trial ICERs per QALY gained can be readily calculated by interchanging the results shown in the two AG BSC columns of Table 50 and Table 49.

For sorafenib, this results in an incremental cost per patient of £47,993 and incremental QALYs per patient of 1.150, leading to an exploratory ICER of £41,716 per QALY gained. However, for lenvatinib the incremental cost per patient is £77,148 and the incremental QALYs are 0.591 leading to an amended ICER of £130,592 per QALY gained.

These very large changes (increase of 105% in the lenvatinib ICER per QALY gained, and decrease of 54% in the sorafenib ICER per QALY gained) serve to illustrate that the choice of BSC comparator is of major importance in this appraisal, and that the absence of a credible indirect comparison results precludes any simple resolution of this difficulty

.

Table 49 Cost effectiveness results comparing AG and Eisai models using published list prices

Source of results	Assessment Group model preferred scenario				Eisai model estimates		
	Lenvatinib	BSC	Sorafenib	BSC	Lenvatinib	Sorafenib	BSC
Drug acquisition cost	£68,217	£0	£41,281	£0	£68,061[#]	£37,267	£0
Drug administration cost	£0	£0	£0	£0	£0	£0	£0
Routine care cost	£12,742	£7,495	£13,227	£10,523	£31,022	£38,937	£35,582
Adverse events cost	£7,385	£385	£1,833	£274	£107	£21	£0
End of life care costs	£6,758	£7,314	£6,848	£7,157	£6,316	£6,615	£6,532
Total cost	**£95,102**	**£15,195**	**£63,188**	**£17,954**	**£107,182**	**£82,839**	**£42,115**
*Response (in PFS) years	-	-	-	-	0.533	0.325	0.017
*Progression-free years	3.413	0.565	1.064	0.635	3.062	0.922	0.640
*Post-progression years	1.171	1.967	3.661	3.014	1.277	2.258	2.159
***Total life years**	**4.584**	**2.532**	**4.725**	**3.649**	4.339	3.180	2.800
PFS QALYs	2.182	0.446	0.755	0.504	2.380	0.746	0.447
PPS QALYs	0.633	1.156	1.997	1.720	0.800	1.351	1.393
Total QALYs	**2.815**	**1.602**	**2.752**	**2.224**	**3.179**	**2.097**	**1.840**
Incremental cost	£79,907		£45,234		£65,067	£40,724	-
Incremental life years	2.052		1.076		1.539	0.380	-
Incremental QALYs	1.213		0.528		1.339	0.257	-
ICER per QALY vs BSC	**£65,872**		**£85,644**		**£48,569**	**£158,232**	-

BSC=best supportive care; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life years
NB: AG drug costs at list prices (no discounts)
* Life years undiscounted
[#]AG corrected half-cycle error

Table 50 Cost effectiveness estimated results comparing AG and Bayer models using published list prices

Source of results	Assessment Group preferred scenario				Bayer model estimates		
	Lenvatinib	BSC	Sorafenib	BSC	Lenvatinib	Sorafenib	BSC
Drug acquisition cost	£68,217	£0	£41,281	£0	£41,641	£33,187	£0
Drug administration cost	£0	£0	£0	£0	£0	£0	£0
Routine care cost	£12,742	£7,495	£13,227	£10,523	£46,018	£37,886	£25,695
Adverse events cost	£7,385	£385	£1,833	£274	£141	£81	£17
End of life care costs	£6,758	£7,314	£6,848	£7,157	£0	£0	£0
Total cost	**£95,102**	**£15,195**	**£63,188**	**£17,954**	**£[redacted]**	**£71,154**	**£[redacted]**
Response years	-	-	-	-	-	-	-
Progression-free years	3.413	0.565	1.064	0.635	3.767	1.342	0.808
Post-progression years	1.171	1.967	3.661	3.014	3.589	4.381	3.161
***Total life years**	**4.584**	**2.532**	**4.725**	**3.649**	**7.356**	**5.723**	**3.969**
PFS QALYs	2.182	0.446	0.755	0.504	2.394	0.920	0.628
PPS QALYs	0.633	1.156	1.997	1.720	1.645	2.237	1.724
Total QALYs	**2.815**	**1.602**	**2.752**	**2.224**	**4.039**	**3.158**	**2.352**
Incremental cost	£79,907		£45,234		£[redacted]	£45,441	-
*Incremental life years	2.052		1.076		3.487	1.754	-
Incremental QALYs	1.213		0.528		1.687	0.805	-
ICER (per QALY)	**£65,872**		**£85,644**		**£[redacted]**	**£56,417**	-

BSC=best supportive care; PFS=progression-free survival; PPS=post-progression survival; QALY=quality adjusted life years
NB: AG drug costs at list prices (no discounts)
*Life years undiscounted

5.4.6 Deterministic sensitivity analyses

Sensitivity analyses have been conducted on the cost effectiveness results obtained using the AG model and the results from these analyses are shown in Table 51,Table 53 and Table 52.

The AG identified five modelling issues, which do not involve stochastic uncertainty, and the implications, in terms of changes to the size of the estimated ICER per QALY gained in the AG model, that result from changes to these parameter values are shown in Table 51. Assuming that a change in the estimated ICER per QALY gained of less than £5,000 is not considered substantial, all but one of the five issues generated important changes in the ICER per QALY gained estimates for either sorafenib or lenvatinib (the exception being the discount rate applied to costs).

The AG identified 18 parameter values for which stochastic uncertainty could be quantified in the AG model, and the findings from adjusting these values are summarised in Table 53 and Table 52. Only three parameters (the utility values for the PFS and PPS health states estimated from EQ-5D-3L patient data in the DECISION trial, and the sorafenib OS AG extrapolation hazard) were found to lead to substantial effects on the size of the estimated ICER per QALY gained when varied between the lower and upper 95% confidence limits. In particular, the AG considers that uncertainty in specific unit costs (other than drug acquisition costs) is not an important factor when generating uncertainty in ICER per QALY gained estimates.

Table 51 Effects of non-stochastic uncertainty on estimated ICER per QALY gained

Treatment	Source of uncertainty	AG preferred scenario: cost per QALY gained	Option A: cost per QALY gained	Effect on ICER per QALY gained	Option B: cost per QALY gained	Effect on ICER per QALY gained
Lenvatinib versus BSC	Discount rate – costs: A=0%, B=5%	£65,872	£70,033	£4,161	£64,368	-£1,504
	Discount rate – outcomes: A=0%, B=5%	**£65,872**	**£53,592**	**-£12,280**	**£71,274**	**+£5,402**
	Drug use data source: A=PFS, B=least of TTD & PFS	**£65,872**	**£106,178**	**+£40,306**	**+£65,872**	**£0**
	Drug dose intensity ratio: A=not used	**£65,872**	**£87,203**	**+£21,331**	-	-
	Utility value set: A=Eisai	**£65,872**	**£54,981**	**-£10,891**	-	-
Sorafenib versus BSC	Discount rate – costs: A=0%, B=5%	£85,644	£88,747	+£3,104	£84,561	-£1,082
	Discount rate – outcomes: A= 0%, B=5%	**£85,644**	**£67,645**	**-£17,999**	**£93,751**	**+£8,108**
	Drug use data source: A= PFS, B least of TTD & PFS	£85,644	£85,814	+£170	£83,076	-£2,568
	Drug dose intensity ratio: A=not used	**£85,644**	**£103,503**	**+£17,859**	-	-
	Utility value set: A=Eisai	**£85,644**	**£105,666**	**+£20,023**		

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; TTD=time to treatment discontinuation; BSC=best supportive care
Bold text for variables modifying the estimated by more than £5,000 per QALY gained

Table 52 Effects of stochastic uncertainty on estimated lenvatinib versus BSC (ICER per QALY gained)

Source of uncertainty	AG preferred scenario: cost per QALY gained	LCL	Effect on ICER per QALY gained	UCL	Effect on ICER per QALY gained
Dose intensity ratio	£65,872	£63,892	-£1,980	£67,852	+£1,980
Blood/coagulation test cost	£65,872	£65,871	-£2	£65,874	+£2
Urine test cost	£65,872	£65,871	-£1	£65,876	+£4
Liver/thyroid/protein test cost	£65,872	£65,870	-£2	£65,877	+£5
Bone scan cost	£65,872	£65,792	-£80	£65,955	+£83
CT scan cost	£65,872	£65,842	-£30	£65,905	+£33
MRI scan cost	£65,872	£65,819	-£53	£65,928	+£56
Oncology visit cost	£65,872	£65,524	-£348	£66,223	+£351
Hand-foot syndrome incidence - lenvatinib	£65,872	£65,866	-£6	£65,888	+£15
Proteinuria incidence - lenvatinib	£65,872	£65,873	+£1	£65,874	+£2
Hypertension incidence - lenvatinib	£65,872	£65,018	-£854	£66,759	+£887
Hypertension incidence - BSC (vs lenvatinib)	£65,872	£66,074	+£202	£65,431	-£441
End of life care costs	£65,872	£65,883	+£11	£65,864	-£8
PFS utility values	**£65,872**	**£77,475**	**+£11,603**	**£42,352**	**-£23,520**
PPS utility values	**£65,872**	**£60,739**	**-£5,133**	**£71,956**	**+£6,084**
PFS lenvatinib hazard rate	£65,872	£63,127	-£2,745	£63,853	-£2,019
PFS BSC hazard rate (SELECT trial)	£65,872	£63,672	-£2,200	£63,389	-£2,483
OS lenvatinib hazard rate	£65,872	£63,231	-£2,641	£63,791	-£2,081
OS BSC hazard rate (SELECT trial)	£65,872	£68,374	+£2,502	£65,455	-£417
TTD lenvatinib hazard rate	£65,872	£65,006	-£866	£63,201	-£2,671

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; TTD=time to treatment discontinuation; LCL=lower confidence limit; UCL=upper confidence limit
Bold text for variables modifying the estimated by more than £5,000 per QALY gained

Table 53 Effects of stochastic uncertainty on estimated sorafenib versus BSC (ICER per QALY gained)

Source of uncertainty	AG preferred scenario: cost per QALY gained	LCL	Effect on ICER per QALY gained	UCL	Effect on ICER per QALY gained
Dose intensity ratio	£85,644	£83,009	-£2,635	£88,278	+£2,635
Blood/coagulation test cost	£85,644	£85,642	-£2	£85,645	+£2
Urine test cost	£85,644	£85,643	-£1	£85,648	+£5
Liver/thyroid/protein test cost	£85,644	£85,641	-£2	£85,649	+£6
Bone scan cost	£85,644	£85,549	-£94	£85,741	+£98
CT scan cost	£85,644	£85,608	-£35	£85,682	+£39
MRI scan cost	£85,644	£85,581	-£63	£85,710	+£66
Oncology visit cost	£85,644	£85,446	-£198	£85,845	+£201
Hand-foot syndrome incidence - sorafenib	£85,644	£85,592	-£51	£85,710	+£66
Hypertension incidence - sorafenib	£85,644	£84,460	-£1,184	£87,356	+£1,712
Hypertension incidence - BSC (vs sorafenib)	£85,644	£85,999	+£355	£84,782	-£862
End of life care costs	£85,644	£85,657	+£14	£85,633	-£10
PFS utility values	**£85,644**	**£97,212**	**+£11,568**	**£59,422**	**-£26,221**
PPS utility values	**£85,644**	**£95,450**	**+£9,806**	**£77,668**	**-£7,976**
PFS sorafenib hazard rate	£85,644	£85,294	-£349	£85,367	-£277
PFS BSC hazard rate (DECISION trial)	£85,644	£85,298	-£346	£85,383	-£261
OS sorafenib hazard rate	**£85,644**	**£78,853**	**-£6,790**	**£92,528**	**+£6,884**
OS BSC hazard rate (DECISION trial)	£85,644	£89,074	+£3,430	£82,063	-£3,581

AG=Assessment Group; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; TTD=time to treatment discontinuation; LCL=lower confidence limit; UCL=upper confidence limit
Bold text for variables modifying the estimated by more than £5,000 per QALY gained

5.4.7 Probabilistic sensitivity analyses

The AG carried out a PSA varying 43 model parameters subject to stochastic sampling uncertainty:

- nine routine care cost variables
- seven AE incidence rates
- seven health-related utility values
- seven end of life health and social care costs.

In most cases, probabilistic values were drawn from normal distributions around the standard error of the mean, except for incidence rates where beta distributions were employed.

Using list prices, the in-trial comparisons of lenvatinib versus BSC (Figure 17) and sorafenib versus BSC (Figure 18) yielded similar deterministic and probabilistic ICERs per QALY gained:

Lenvatinib versus BSC: deterministic ICER=£65,872 per QALY gained, probabilistic ICER=£66,038 per QALY gained.

Sorafenib versus BSC: deterministic ICER=£85,644 per QALY gained, probabilistic ICER=£83,547 per QALY gained.

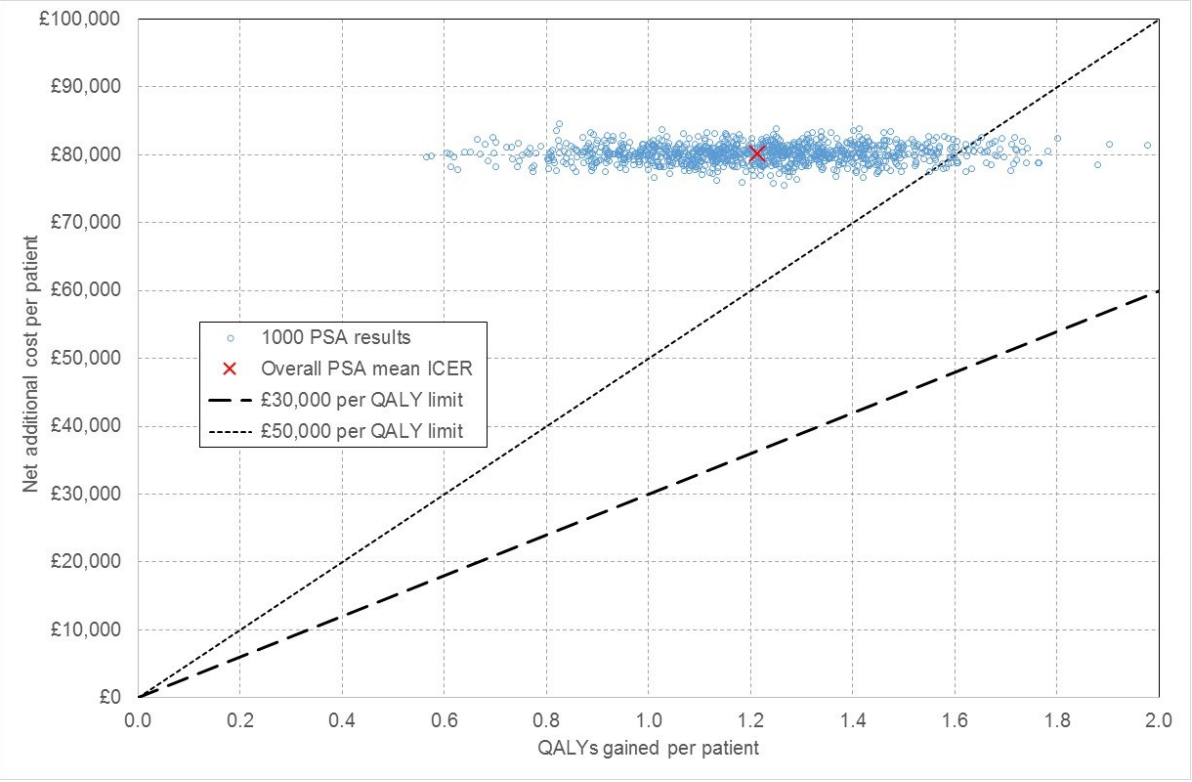

Figure 17 Probabilistic sensitivity analysis: lenvatinib vs BSC in the SELECT trial

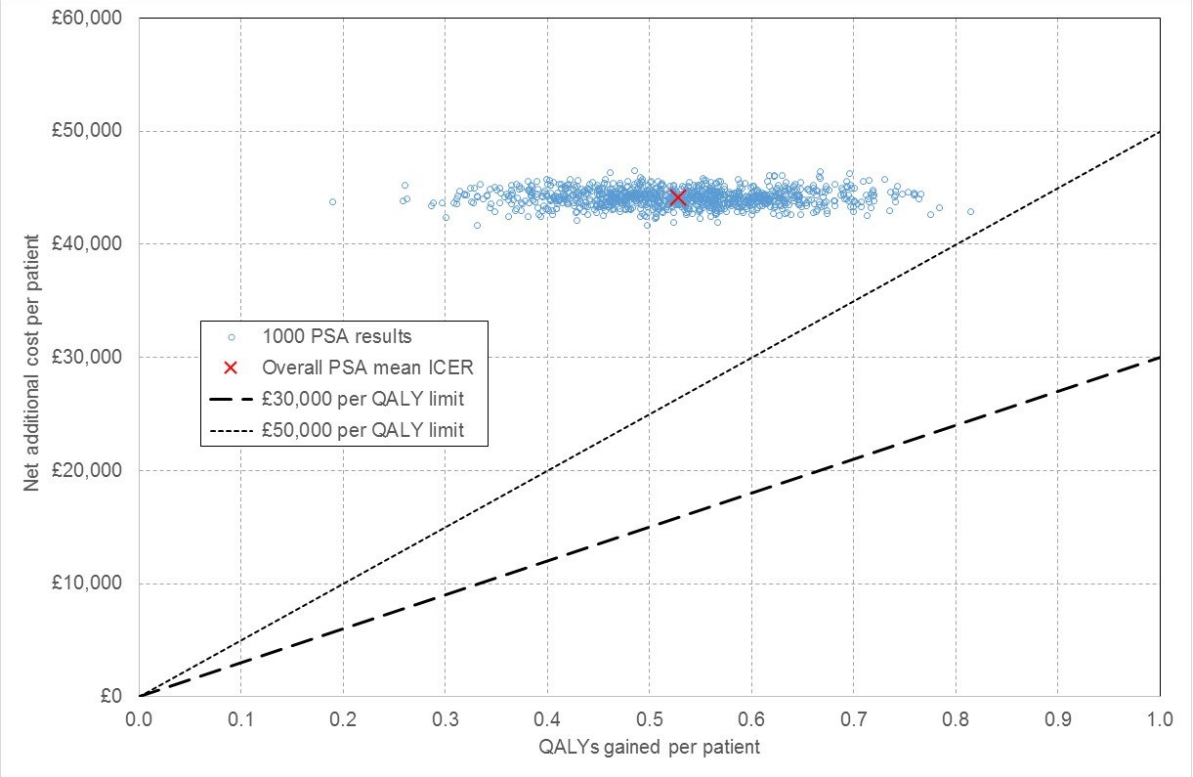

Figure 18 Probabilistic sensitivity analysis: sorafenib vs BSC in the DECISION trial

The variation in additional cost per patient is much smaller relative to the uncertainty in outcomes (QALYs) gained due to the dominance of drug acquisition costs, which constitute 85% to 90% of the incremental cost per patient when full list prices are assumed to apply.

Clearly, both treatments exhibit estimated ICERs well above £50,000 per QALY gained if list prices are applied. This is confirmed by the cost effectiveness acceptability curves (CEACs) presented in Figure 19 and Figure 20. Examination of the CEACs shows that, compared with BSC, the probability of sorafenib being cost effective at a threshold of £50,000 per QALY gained is less than 0.05% and the probability of lenvatinib being cost effective is 5.4%.

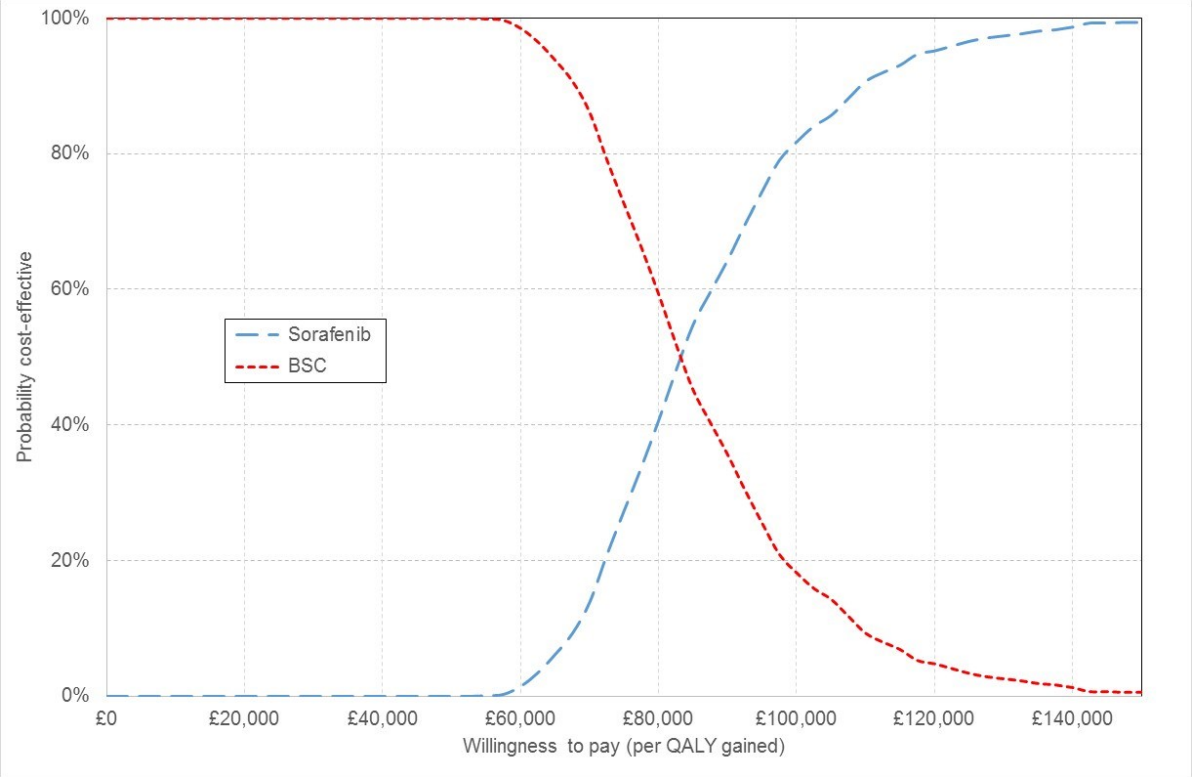

Figure 19 Cost effectiveness acceptability curves for sorafenib vs BSC (DECISION trial)

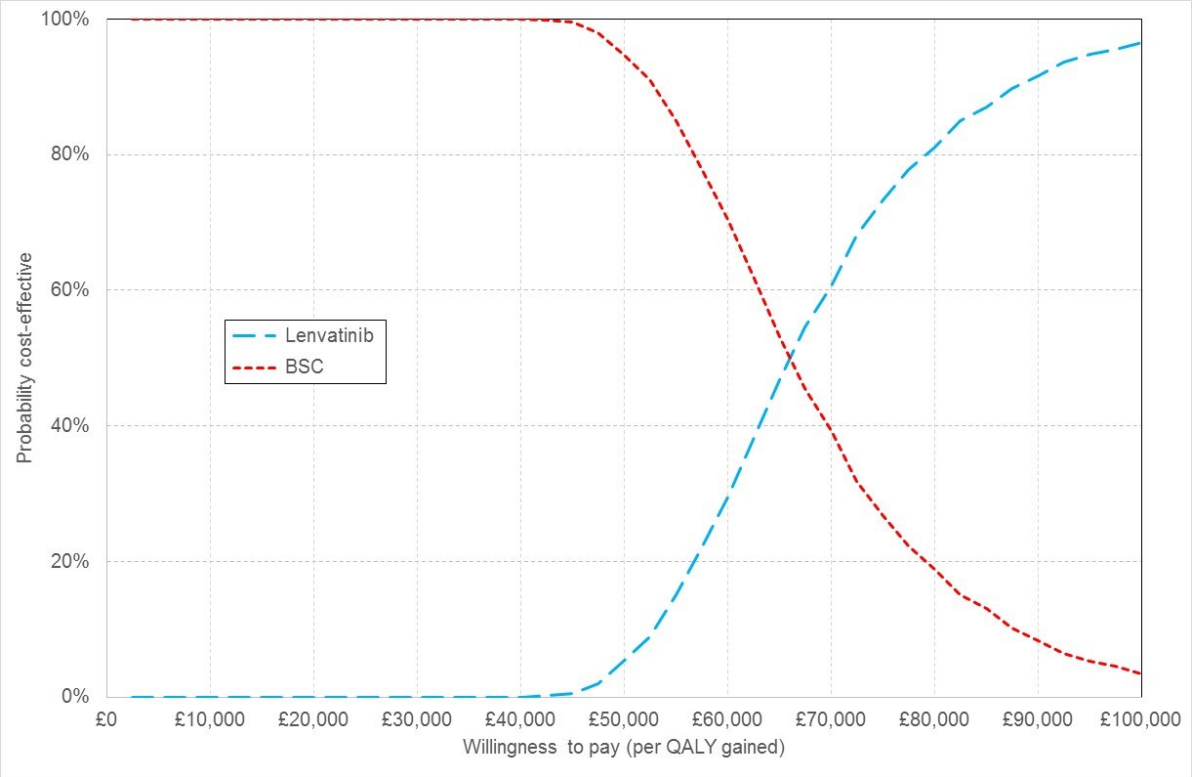

Figure 20 Cost effectiveness acceptability curves for lenvatinib vs BSC (SELECT trial)

5.4.8 Discussion and summary of cost effectiveness results

Comparison of data from the placebo arms of the SELECT and DECISION trials indicated that the experience of patients differed markedly for PFS, the principal outcome of both trials, to the extent that the PHs assumption is violated. This invalidates the derivation and application of HRs in order to model an indirect comparison to compare the effectiveness of lenvatinib with that of sorafenib. As a consequence, the AG was only able to carry out separate economic assessments of each active treatment against its trial comparator, using common methods and shared parameter values.

In order to assess the importance of the available placebo data (used to represent long-term BSC), a structural sensitivity analysis was carried out substituting the placebo arm data from each trial as the comparator for the intervention treatment. These analyses resulted in very large changes to the AG's estimated base case ICERs per QALY gained, and confirmed the suspicion that the two trial populations are not equivalent.

Using published list prices in the AG model, neither treatment was found to be cost effective at a willingness-to-pay threshold of £50,000 per QALY gained. Moreover, neither treatment meets the NICE end of life criteria for special consideration (the AG analyses show that both are indicated to have lifetime mean estimated OS of 55 to 57 months, and survival gain versus standard of care [BSC/placebo] greater than 9 months).

A comparison of the patterns of clinical effectiveness of the two treatments suggests that the proportion of the average gain in PFS, which is subsequently translated to a gain in OS, is very different between the treatments (73% for lenvatinib versus 24% for sorafenib). This suggests quite different modes of action, which may have important consequences for patients' long-term prognosis.

The estimated mean time spent in the PFS and OS health states in the AG model show little difference between the two active treatments, so that apparently different net outcome gains are mainly attributable to large differences in the experience of patients in the comparator arms of the two trials. This consistency of outcomes for the active treatments, and the apparently different modes of action, may suggest that these treatments could be used sequentially to generate additional long-term benefit.

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Lenvatinib and sorafenib are both MKIs and have been approved for use for treating RR-DTC in NHS Scotland (contingent upon the continuing availability of PAS prices). Sorafenib is currently available in NHS England via the CDF. It is not anticipated, therefore, that if recommended by NICE, the use of lenvatinib and sorafenib would have major implications for NHS service provision, particularly as the administration and AEs from both therapies are broadly in line with those of other TKIs already used to treat patients with cancer in the NHS.

7 DISCUSSION

7.1 Statement of principal findings

7.1.1 Clinical effectiveness results

The main sources of clinical effectiveness evidence were two good quality RCTs (SELECT and DECISION trials). Results from these trials show that treatment with lenvatinib and sorafenib statistically significantly improve median PFS and ORR when compared with placebo. Median OS results demonstrate that there is no statistically significant difference in effect when treatment with lenvatinib and sorafenib are compared with placebo. Treatment crossover confounds the OS results from both trials and, to adjust for this effect, OS data were modified using RPSFTM. The results from the adjusted analyses show that, when compared with placebo, treatment with lenvatinib statistically significantly improves OS but there is still no statistically significant improvement in OS from treatment with sorafenib. However, the AG considers that the assumption of PH for unadjusted OS, adjusted OS and PFS is violated in the SELECT trial and is violated for adjusted OS and PFS in the DECISION trial; therefore, these results should be interpreted with caution. Nonetheless, clinical advice to the AG is that the improvements in PFS and the benefits from active treatment do appear to be clinically meaningful.

The AG considers that the improvements in OS and PFS for patients treated with lenvatinib and sorafenib when compared to placebo are likely to reflect improvements in OS and PFS when compared to BSC, notwithstanding the possible differences in the BSC received by the patients in the two trials.

The AG highlights that differences exist between the median OS and PFS results from the observational studies and those from the SELECT and DECISION trials. Namely, OS for patients treated with lenvatinib and sorafenib in the SELECT and DECISION trial was longer than the OS reported in the observational studies. In contrast, results for PFS from the DECISION trial for patients treated with sorafenib was shorter than PFS from any of the prospective observational studies and the two meta-analyses.[126,137] Median PFS for patients treated with lenvatinib in the SELECT trial were higher than the prospective, observational results from Study 201[76] and lower than the results from Study 208.[134]

Results from indirect comparisons and MAICs[7,8,56,96] show treatment with lenvatinib leads to better PFS (but not OS) than treatment with sorafenib. The AG did not conduct an indirect comparison as preliminary analyses suggested that using data from the SELECT and DECISION trials in the same network would generate unreliable results. The AG's preliminary analyses showed that the PFS risk profiles (as demonstrated by a comparison of K-M data) of

the SELECT and DECISION trial populations receiving placebo were not comparable. In addition, results from the AG's analyses showed that, within the SELECT and DECISION trials, the PH assumption did not hold for the majority of survival outcomes. For data to be included in a network the assumption of PH should hold both across and within trials. The AG's analyses have demonstrated that this assumption is often violated. As a consequence of this violation the AG has been unable to compare lenvatinib with sorafenib. The AG considers that the relative clinical effectiveness of these two drugs cannot be currently reliably determined.

As expected, both treatment with lenvatinib and sorafenib resulted in more AEs than treatment with placebo. Both all-Grade and Grade ≥3 diarrhoea were common for patients treated with lenvatinib and those treated with sorafenib. However, the most common AE experienced by patients treated with lenvatinib was hypertension and the most common AE experienced by patients treated with sorafenib was hand-foot syndrome. Dose reductions were frequent (>60%) for patients treated with both lenvatinib and sorafenib. The results of published indirect comparisons[7,96] suggest that when treatment with sorafenib is compared with lenvatinib, the incidence of alopecia is higher but the incidence of hypertension is reduced, and those treated with sorafenib experience fewer Grade ≥3 and SAEs.

The impact of treatment with lenvatinib on HRQoL was not assessed in the SELECT trial and is, therefore, unknown; this is a limitation of the trial given the difference in the safety profiles for some of the AEs associated with lenvatinib and sorafenib. Sorafenib is reported[7,119] to have a 'mild' negative impact on patients' HRQoL possibly due to the high rates of AEs experienced by patients in the DECISION trial.

7.1.2 Cost effectiveness evidence

The two submitting companies and the AG agree that there are no published cost effectiveness studies relevant to the decision problem set out in the final scope issued by NICE.[53] The AG considered that none of the cost effectiveness studies identified via the AG's literature review were carried out from an NHS England perspective and that, where treatment with lenvatinib and sorafenib were compared, the results were based on the results of flawed indirect comparisons. In addition, the prices of the drugs reported in the studies were generally not consistent with the discounted prices that will likely be charged in the NHS in England. As a result of the absence of relevant published evidence, the AG developed a *de novo* cost effectiveness model for the specific purpose of this appraisal and carried out several cost effectiveness comparisons.

As the AG did not consider that it was appropriate to carry out an indirect comparison, the AG compared the cost effectiveness of treatment with lenvatinib versus BSC (using data from the SELECT trial) and sorafenib versus BSC (using data from the DECISION trial). The AG also compared the cost effectiveness of each of the SELECT and DECISION trial intervention drugs with BSC data from the other trial as a sensitivity analysis.

In the AG's base case analysis, using list prices only, the comparison of the cost effectiveness of treatment with lenvatinib versus BSC yields an ICER per QALY gained of £65,872 and the comparison of treatment with sorafenib versus BSC yields an ICER per QALY gained of £85,644. The base case deterministic and probabilistic results were similar for both comparisons. The AG's deterministic SA involved varying 18 parameters; the results showed that none of the variations lowered the AG's base case ICERs to below £50,000 per QALY gained.

When the AG compared the cost effectiveness of treatment with lenvatinib versus BSC (placebo data from the SELECT trial), and treatment with sorafenib versus BSC (placebo data from the DECISION trial), the ICERs per QALY gained were approximately doubled (£130,592) and halved (£41,716) respectively. These results confirm that the choice of BSC comparator is hugely influential in this appraisal.

7.2 Strengths and limitations of the assessment

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 and cost effectiveness of treatment with lenvatinib versus sorafenib in patients with RR-DTC.

The wide array of clinical results available demonstrate that treatment with lenvatinib is more effective when compared with placebo/BSC for all patients and that prior VEGFR-targeted therapy (or even a treatment delay) does not influence the potential for a patient to benefit from treatment.

Another strength of the research is the AG's detailed investigation of the PFS (and OS) risk profiles of the patients in the two main trials. The AG's analytical critique shows that the assumptions of PH underpinning the indirect comparison calculations are violated and explains why data from these two trials should not be compared in an indirect comparison. The AG's critique challenges the validity of published indirect comparison results[7,8,56,96] as well

as those from published economic evaluations[7,8,38,160,162] that have used indirect comparison results in their analyses.

The results from the AG's economic analyses demonstrate that the choice of BSC comparator has a big influence on the size of the estimated ICERs per QALY gained.

Limitations

The main limitation of this review is that the AG was unable to compare the clinical and cost effectiveness of lenvatinib versus sorafenib. The AG did not consider that it was appropriate to conduct an indirect comparison due to key differences in the intervention and placebo arms of the SELECT and DECISION trials (both within and across the trials) and because the results of AG analyses demonstrated that the risk profiles of the patients in the placebo arms were different. The AG therefore concluded that it was not possible to determine the comparative clinical and cost effectiveness of lenvatinib versus sorafenib; this is problematic as lenvatinib and sorafenib are two relatively new treatments that appear to work well versus placebo/BSC for patients with RR-DTC who have limited treatment options.

Uncertainties

While it is recommended[4,23-25] that only patients who are symptomatic and/or who have rapidly progressing disease are treated with lenvatinib or sorafenib, it is unclear how many patients in the SELECT and DECISION trials met these criteria. As there are no universally accepted objective criteria for describing patients who are symptomatic and/or rapidly progressing, it is difficult to retrospectively identify these groups of patients with any confidence.

It is therefore unclear whether the efficacy findings from the SELECT and DECISION trials differ in patients who are symptomatic and/or are rapidly progressing compared with those who are not. It is also unknown whether the frequency and type of AEs differ between these groups of patients and/or whether patient HRQoL is also influenced by symptom status.

There is considerable uncertainty around the HRQoL of patients with RR-DTC in general. While it appears that treatment with sorafenib may have a 'mild' negative impact on HRQoL, the HRQoL data collected during the DECISION trial were limited. As HRQoL data were not collected as part of the SELECT trial, the impact of treatment with lenvatinib on HRQoL, whether positive or negative, is unknown. To what extent a patient's HRQoL is affected by their symptom status (symptomatic versus asymptomatic) is also unknown.

While, for patients with RR-DTC, RCT evidence has shown clinically meaningful improvements in PFS for those treated with lenvatinib and sorafenib versus placebo, the question remains as to whether treatment with lenvatinib or sorafenib can deliver a true OS

benefit to patients. The adjusted RPSFTM OS estimates suggest this may be the case for patients treated with lenvatinib, but not for patients treated with sorafenib.

7.3 Other relevant factors

The AG considers that it is important to re-iterate that the cost utility analyses presented in this MTA report are based on list prices only. As lenvatinib has a confidential PAS price and sorafenib has a confidential Commercial Unit Access price, the cost effectiveness comparisons presented in this AG report cannot be used as the basis for decision-making. The AG has provided cost effectiveness results generated using the discounted prices for lenvatinib and sorafenib in a confidential appendix to this report.

8 CONCLUSIONS

Compared with placebo, treatment with lenvatinib or sorafenib result in an improvement in PFS, ORR, and possibly OS. However, compared with placebo, both drugs also increase the incidence of AEs, in particular hypertension, hand-foot syndrome and diarrhoea. Dose reductions with both drugs are, therefore, frequently required.

The AG considers it is not possible to compare the clinical or cost effectiveness of lenvatinib with sorafenib. Primarily, this is because the risk profiles of the patients in the placebo arms of the SELECT and DECISION trials do not appear to be comparable.

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

8.1 Implications for service provision

Clinical advice to the AG is that if NICE recommended lenvatinib and sorafenib for the treatment of patients with RR-DTC then this would not have any major implications for NHS service provision as the administration and AE profiles of both therapies are in line with those of other TKIs used to treat patients with cancer.

8.2 Suggested research priorities

In order of priority, the AG suggests the following further research priorities:

1. **Head-to-head RCT evidence**
   a) Clinical advice to the AG is that only RR-DTC patients experiencing symptoms, or those who have clinically significant progressive disease, are likely to be treated in routine clinical practice. Subgroup analyses suggest that the effects on PFS are similar for patients treated with sorafenib regardless of whether they are symptomatic or asymptomatic. However, these findings are post-hoc and include only a minority of symptomatic patients. It is unclear if other outcomes, such as OS, ORR, AEs and HRQoL, differ by symptomatic or asymptomatic disease. Future studies of patients should aim to include a greater proportion of patients with symptomatic disease and investigate possible differences. Consideration should be given to using the classification of patients as symptomatic or asymptomatic as a randomisation stratification factor.

b) It would be useful to record, and report, HRQoL outcomes from any future clinical study of lenvatinib and sorafenib. In particular, data should be collected, using the EQ-5D questionnaire, throughout the whole trial period, not only from patients whose disease has not progressed. Further research on HRQoL from treating patients who have symptomatic disease compared to those who do not is also required.

c) Currently evidence does not allow a comparison of the effectiveness of treatment with lenvatinib versus sorafenib. A head-to-head trial considering these treatments and placebo would generate results that would be valuable to decision makers.

d) It would be useful to explore how lenvatinib, sorafenib and BSC be positioned in the treatment pathway.

2. Statistical research

The AG considers 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. In addition, further statistical research is needed to develop reliable methods of undertaking indirect comparisons in cases where the PH assumptions are violated.

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10 APPENDICES

10.1 Appendix 1: Literature search strategies

Search strategies for evidence of clinical effectiveness

Embase

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	lenvatinib/
9	sorafenib/
10	6 or 7 or 8 or 9
11	5 and 10
12	limit 11 to yr="1999 -Current"

MEDLINE

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
10	limit 9 to yr="1999 -Current"

PubMed

#1	Search (((thyroid* or papillar* or follicular*))) AND ((Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))
#2	Search (DTC or FTC or PTC)
#3	Search (#1 or #2)
#4	Search (Lenvatinib or Lenvima or E7080 or Nexavar or Sorafenib or bay439006)
#5	Search (#3 and #4)
#6	Search ("2016/07/01"[Date - Entrez] : "3000"[Date - Entrez])
#7	Search (#5 and #6)

Cochrane Library (CDSR/Central/ DARE/HTA)*

#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	((thyroid* or papillar* or follicular*) near/4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))
#3	(DTC or FTC or PTC)
#4	MeSH descriptor: [Adenocarcinoma, Follicular] explode all trees
#5	MeSH descriptor: [Carcinoma, Papillary, Follicular] explode all trees
#6	MeSH descriptor: [Adenocarcinoma, Papillary] explode all trees
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	(Lenvatinib or Lenvima or E7080)
#9	(Nexavar or Sorafenib or bay439006)
#10	#8 or #9
#11	#7 and #10 Publication Year from 1999 to 2017

*CDSR=Cochrane Database of Systematic Reviews; CENTRAL=Cochrane Central Register of Controlled Trials; DARE=Database of Abstracts of Reviews of Effects; HTA=Health Technology Assessment Database

Economic filter for database search

Embase

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	lenvatinib/
9	sorafenib/
10	6 or 7 or 8 or 9
11	5 and 10
12	limit 11 to yr="1999 -Current"
13	Socioeconomics/
14	Cost benefit analysis/
15	Cost effectiveness analysis/
16	Cost of illness/
17	Cost control/
18	Economic aspect/
19	Financial management/
20	Health care cost/
21	Health care financing/
22	Health economics/
23	Hospital cost/
24	(fiscal or financial or finance or funding).tw.
25	Cost minimization analysis/
26	(cost adj estimate$).mp.
27	(cost adj variable$).mp.
28	(unit adj cost$).mp.
29	or/13-28
30	12 and 29

MEDLINE

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
10	Economics/
11	"costs and cost analysis"/
12	Cost allocation/
13	Cost-benefit analysis/
14	Cost control/
15	Cost savings/
16	Cost of illness/
17	Cost sharing/
18	"deductibles and coinsurance"/
19	Medical savings accounts/
20	Health care costs/
21	Direct service costs/
22	Drug costs/
23	Employer health costs/
24	Hospital costs/
25	Health expenditures/
26	Capital expenditures/
27	Value of life/
28	exp economics, hospital/
29	exp economics, medical/
30	Economics, nursing/
31	Economics, pharmaceutical/
32	exp "fees and charges"/
33	exp budgets/
34	(low adj cost).mp.
35	(high adj cost).mp.
36	(health?care adj cost$).mp.
37	(fiscal or funding or financial or finance).tw.
38	(cost adj estimate$).mp.
39	(cost adj variable).mp.
40	(unit adj cost$).mp.
41	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.
42	or/10-41
43	9 and 42

Cochrane Library (NHS EED)

#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	(thyroid* near/4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))
#3	DTC or FTC or PTC
#4	#1 or #2 or #3
#5	(Lenvatinib or Lenvima or E7080 or Nexavar or Sorafenib or bay439006)
#6	#4 and #5

NHS EED=NHS Economic Evaluation Database

EconLit

(thyroid* N4 (Neoplasm* or Cancer* or Carcinoma* or Adenocarcinom* or Tumour* or Tumor* or Malignan* or Lump* or adenoma*))

10.2 Appendix 2: Table of excluded studies with rationale

The studies excluded by the AG at screening stage 2 are summarised in Table 54.

Table 54 References excluded at screening stage 2 (full text stage)

Reference	Reason for exclusion
Abbadessa et al 2016[182]	Wrong study design
Alonso-Gordoa et al 2015[183]	Wrong study design
Andrews 2013[184]	Wrong study design
Anonymous 2013[185]	Wrong study design
Anonymous 2013[186]	Wrong study design
Anonymous 2014[187]	Wrong study design
Anonymous 2015[188]	Wrong study design
Anonymous 2015[189]	Wrong study design
Anonymous 2016[190]	Wrong study design
Anonymous 2016[191]	Wrong study design
Antonelli 2014[192]	Wrong study design
Baudin et al 2005[193]	Wrong study design
Belum et al 2015[194]	Wrong population
Benvenga et al 2011[195]	Wrong study design
Bernet and Smallridge 2014[196]	Wrong study design
Bible 2012[197]	Wrong study design
Bikas et al 2016[198]	Wrong study design
Blair and Plosker 2015[199]	Wrong study design
Boudou-Rouquette 2015[200]	Wrong study design
Bradford Carter et al 2011[201]	Wrong study design
Brose 2009[202]	Wrong study design
Brose et al 2015[157]	Wrong study design
Butler 2015[203]	Wrong study design
Cabanillas and Habra 2016[204]	Wrong study design
Cabanillas et al 2011[205]	Wrong study design
Capdevila 2010[206]	Wrong study design
Cappagli et al 2011[207]	Wrong study design
Clayman 2015[208]	Wrong study design
Cooper et al 2009[209]	Wrong study design
Corrado et al 2017[210]	Wrong study design
Costa et al 2016[211]	Wrong study design
Covell and Ganti AK 2015[42]	Wrong study design
Cully 2015[212]	Wrong study design
De La Fouchardier et al 2013[213]	Wrong study design
De Lartigue 2015[214]	Wrong study design
Deshpande et al 2008[215]	Wrong study design
Dezso 2015[216]	Wrong study design
Droz et al 2010[217]	Wrong study design
Duntas and Bernardini 2010[218]	Wrong study design
Fala 2015[219]	Wrong study design
Fallahi et al 2013[220]	Wrong study design

Reference	Reason for exclusion
Feliz and Tsimberidou 2013[221]	Wrong population
Funakoshi 2013[222]	Wrong population
Gadaleta-Caldarola et al 2015[223]	Wrong study design
Ghatalia et al 2016[224]	Wrong population
Ghatalia et al 2015 [225]	Wrong population
Giuffrida et al 2012[226]	Wrong population
Gyawali et al 2016[227]	Wrong population
Haddad 2014[228]	Wrong study design
Hannallah et al 2013[229]	Wrong study design
Haraldsdottir and Shah 2014[230]	Wrong study design
Hasskarl 2014[231]	Wrong study design
Haugen et al 2016[24]	Wrong study design
Hesselink 2014[232]	Wrong population
Hewett et al 2016[233]	Wrong study design
Ho and Sherman 2011[195]	Wrong study design
Hodak and Carty 2009[234]	Wrong study design
Hoftijzer et al 2011[235]	Wrong study design
Hong et al 2010[236]	Wrong population
Hong et al 2014[237]	Wrong population
Ibrahim et al 2012[238]	Wrong study design
Ito et al 2016[239]	Wrong study design
Iwasaki et al 2015[240]	Wrong study design
Iwasaki et al 2016[241]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Iyer et al 2010[242]	Wrong study design
Kapiteijn et al 2012[243]	Wrong population (too broad)
Killock 2015[244]	Wrong study design
Klein Hesselink et al 205[245]	Wrong population (too broad)
Kojic et al 2012[246]	Wrong study design
Krajewska and Jarzab 2014[247]	Wrong study design
Krajewska et al 2015[248]	Wrong study design
Krajewska et al 2016[249]	Wrong study design
Krajewska et al. 2015[250]	Wrong study design
Launay-Vacher et al 2015[251]	Wrong study design
Lerch and Richter 2012[252]	Wrong population (too broad)
Liu et al 2011[253]	Wrong population (too broad)
Liu et al 2014[254]	Wrong study design
Lorusso and Newbold 2015[255]	Wrong study design
Lorusso et al 2016[256]	Wrong study design
Ma 2015[257]	Wrong population
Majethia et al 2016[258]	Wrong study design
Marotta et al 2013[150]	Wrong study design
Mayor 2015[259]	Wrong study design
Moreo et al 2016[260]	Wrong population
Nair et al 2015[261]	Wrong study design
Nixon et al 2013[262]	Wrong study design

Reference	Reason for exclusion
Okamoto et al 2015 [263]	Wrong study design
Pacini et al 2009[264]	Wrong study design
Pall 2013[265]	Wrong study design
Pall 2014[266]	Wrong study design
Pfister and Fagin 2008[267]	Wrong study design
Puxeddu et al 2011[268]	Wrong study design
Qi et al 2013[269]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Qi et al 2013[270]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Qi et al 2014[271]	Wrong intervention (no data for lenvatinib or sorafenib alone)
Ramadan et al 2012[272]	Wrong study design
Sacks and Braunstein 2014[273]	Wrong study design
Safavi 2012[274]	Wrong population
Saiyed et al 2015[275]	Wrong population
Schlumberger 2010[276]	Wrong study design
Schlumberger 2011[277]	Wrong study design
Schutt and Eberhardt 2010[278]	Wrong population
Sherman 2008[279]	Wrong study design
Sherman 2009[280]	Wrong study design
Sherman et al 2012[281]	Wrong intervention (not sorafenib monotherapy
Sherman et al 2013[282]	Wrong intervention (not sorafenib monotherapy
Sherman et al 2015[283]	Wrong intervention (not sorafenib monotherapy
Shojaei 2012[284]	Wrong study design
Smit et al 2016[285]	Wrong study design
Takahashi 2014[286]	Wrong study design
Terada et al 2015[287]	Wrong study design
Thanigaimani et al 2011[288]	Wrong study design
Tracy and Roman 2016[289]	Wrong study design
Tremblay et al 2015[290]	Wrong study design (reports the findings from a matched indirect treatment comparison but no reporting of a systematic review)
Tremblay et al 2015[291]	Wrong study design (reports the findings [number needed to treat] from an indirect treatment comparison but no reporting of a systematic review)
Tremblay et al 2015 [292]	Wrong study design (reports the findings from a matched indirect treatment comparison but no reporting of a systematic review)
Tremblay et al 2016	Wrong study design (cost effectiveness methods paper)
Tsimberidou et al 2009[293].	Wrong interventions
Tu et al 2016[294]	Wrong study design
Tuttle and Leboeuf 2007[295]	Wrong study design
Tuttle et al 2014[296]	Wrong study design
Vetter 2014[297]	Wrong study design
Wagner et al 2015[298]	Wrong study design
Warpakowski 2014[299]	In German
Wendling 2013[300]	Wrong study design
Wirth 2015[301]	Wrong study design

Reference	Reason for exclusion
Wong and Lang 2012[302]	Wrong study design
Worcester 2015[303]	Wrong study design
Yang et al 2015[304]	Wrong population
Yang et al 2017[305]	Wrong population
Yeung and Cohen 2015[306]	Wrong study design
Yimaer et al 2016[307]	Wrong population
Zhu C et al 2016[308]	Wrong population
Zygulska et al 2013[309]	Wrong study design

10.3 Appendix 3: Proportional hazards assumption

The AG assessed the validity of the PH assumptions in the DECISION and SELECT trials.

The H-H plot for PFS by investigator assessment from the SELECT trial (final data-cut) is provided in Figure 21. The estimated constant for a linear relationship is statistically significantly different from zero (-0.0589, 95% CI: -0.075 to -0.043, p=6.73 E-12). Comparison by ANOVA of the linear trend with a quadratic trend shows an improved fit (F(146,1)=252.3, p=1.25 E-33), indicating that the assumption of PH does not hold for investigator assessed PFS data from the SELECT trial.

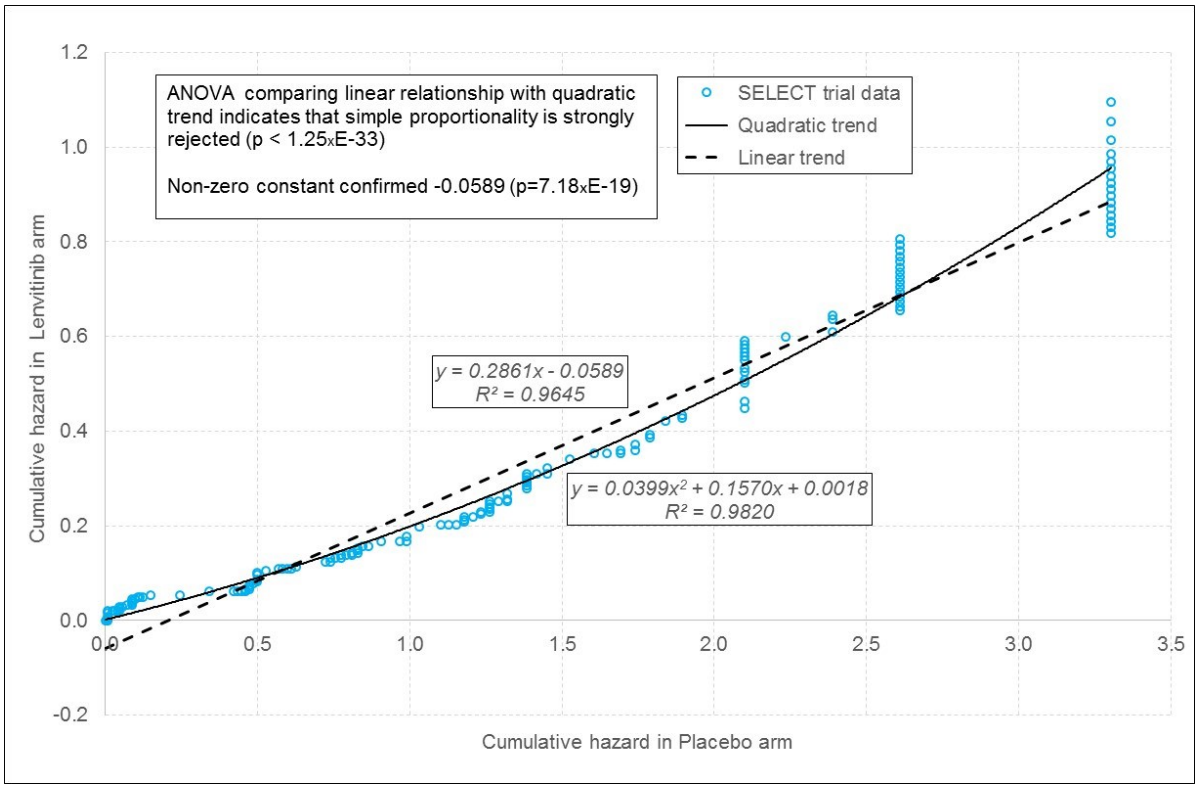

Figure 21 H-H plot for progression-free survival data from the SELECT trial

The H-H plot for OS unadjusted for treatment crossover from the SELECT trial (final data-cut) is provided in Figure 22. The estimated constant for a linear relationship is statistically significantly different from zero (-0.0103, 95% CI: -0.0200 to -0.00005, p=0.039). Comparison by ANOVA of the linear trend with a quadratic trend shows a significantly improved fit for the quadratic relationship (F(146,1)=63.6, p=1.86 E-13), indicating that the assumption of PH does not hold for unadjusted OS data from the SELECT trial.

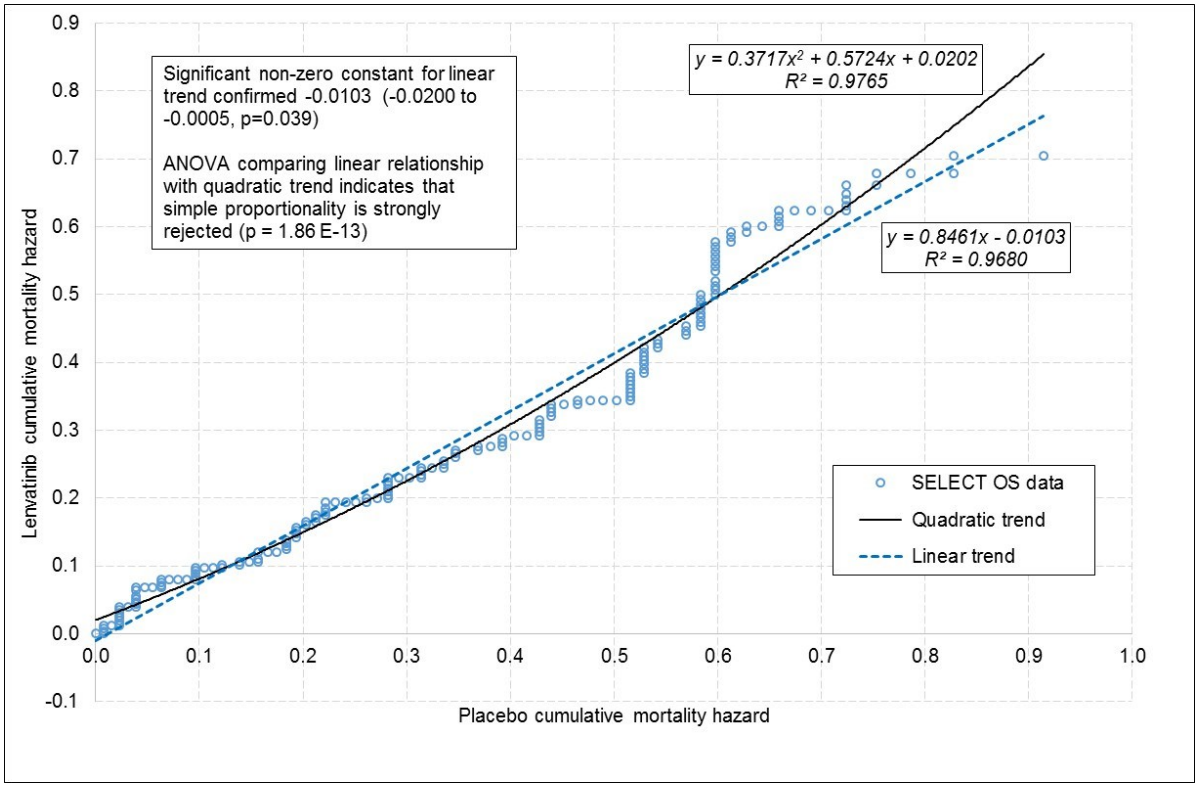

Figure 22 H-H plot for unadjusted overall survival data from the SELECT trial

The H-H plot for OS adjusted by the RPSFTM for treatment crossover using data from the SELECT trial (final data-cut) is provided in Figure 23. In this case, the estimated constant for the fitted linear trend does not show a significant deviation from zero (-0.0041, 95% CI: -0.0166 to +0.0084, p=0.52). However, a comparison by ANOVA of the linear trend with a fitted quadratic trend shows an improved fit for the quadratic relationship (F(166,1)=12.03, p=0.000665), indicating that the assumption of PH is questionable on the basis of evidence of non-linearity in the relationship between the two arms of the trial following adjustment for crossover.

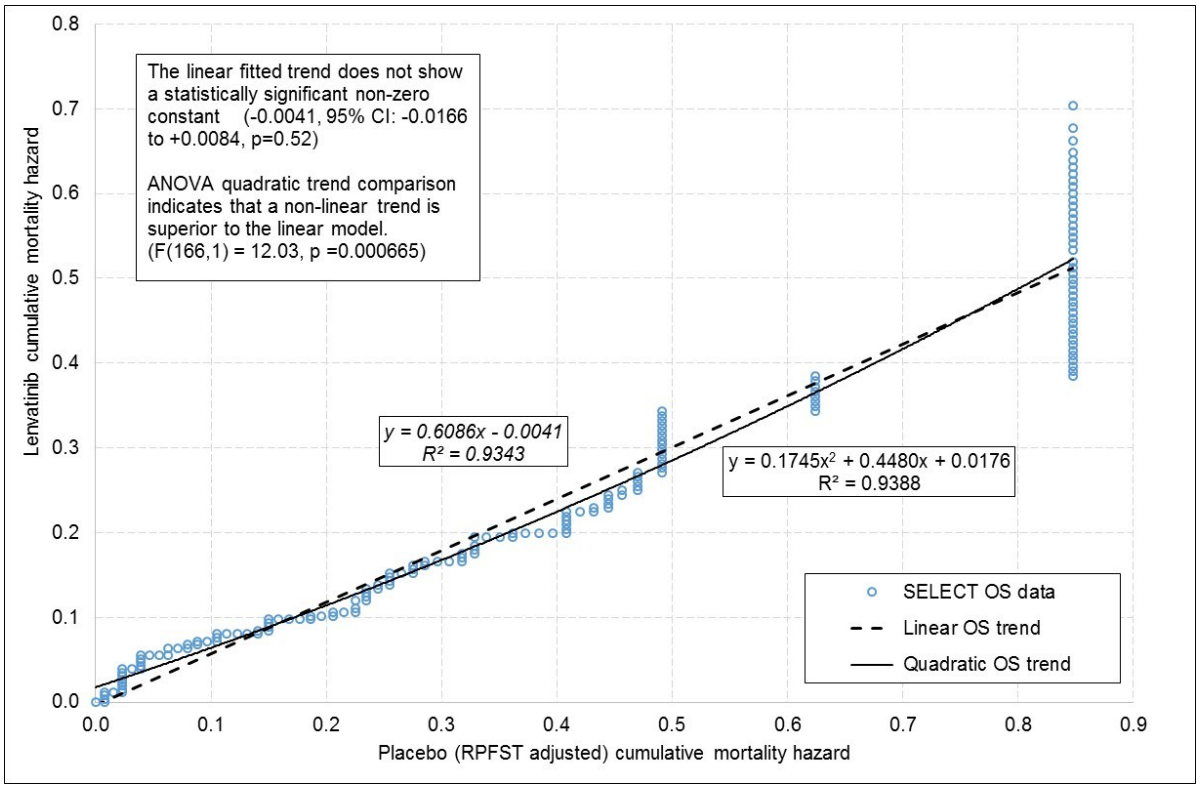

Figure 23 H-H plot for overall survival data adjusted by RPSFT for treatment crossover from the SELECT trial

The linear trend fitted to the PFS DECISION trial data (final data-cut) in Figure 24, shows a statistically significant non-zero constant of -0.1263 (95% CI: -0.1635 to -0.0892, p=2.59 E-10). In addition, the ANOVA test for non-linearity indicates a statistically significant deviation from linearity (F(177,1)=6.722, p=0.0103). On both criteria the PH assumption is called into question.

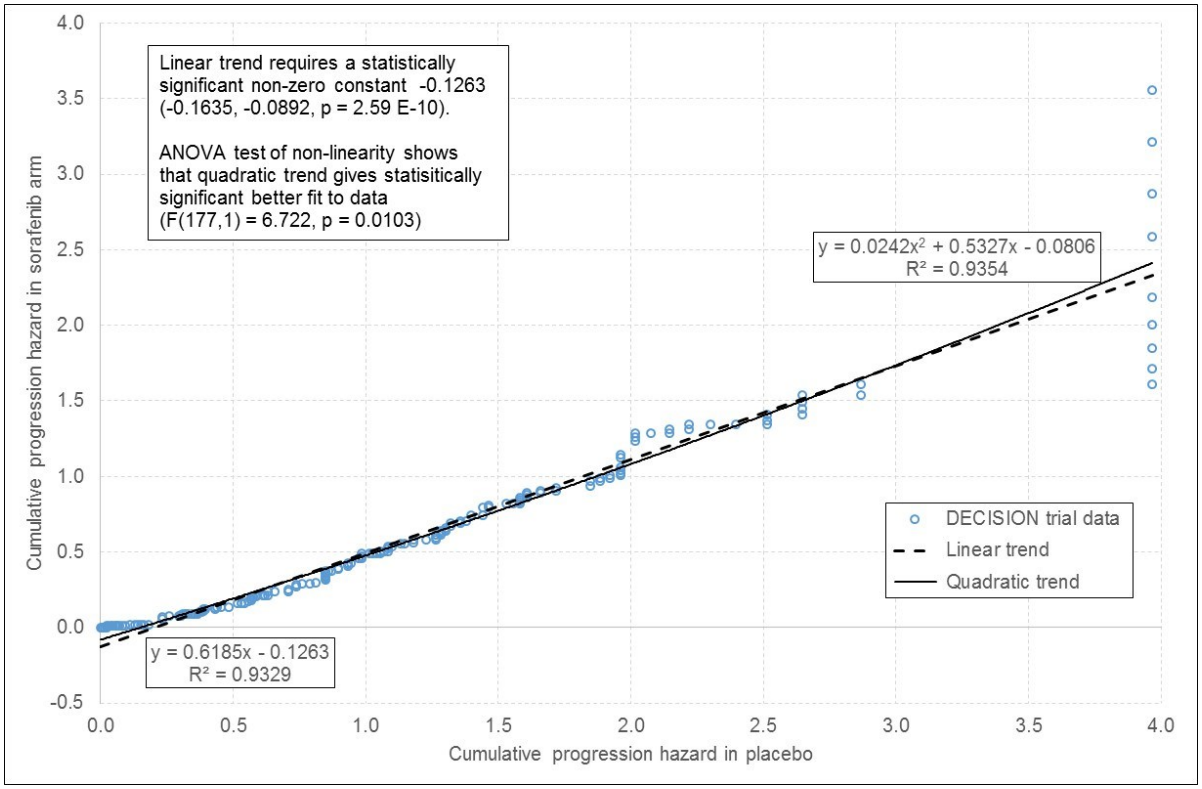

Figure 24 H-H plot for progression-free survival from the DECISION trial

The linear trend fitted to the unadjusted OS data from the DECISION trial (final data-cut) shows a very small constant of 0.0018 (95% CI: -0.0036 to +0.0073, p=0.505) consistent with the PH requirement for a zero constant. In addition, the ANOVA test for non-linearity indicates no statistically significant deviation from linearity (F(89,1)=0.0675, p=0.796). On both criteria the PH assumption is supported for unadjusted OS trial data.

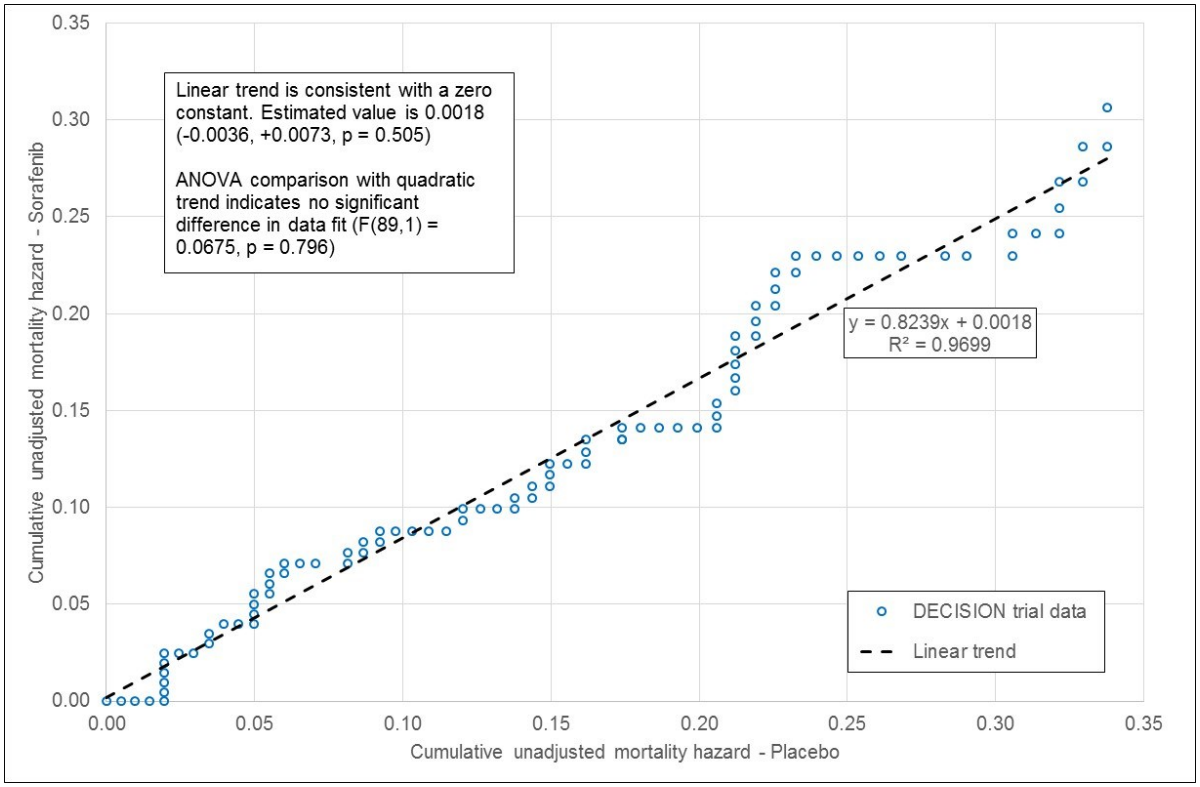

Figure 25 H-H plot for unadjusted overall survival data from the DECISION trial

Figure 26 shows the linear trend fitted to the RPFST-adjusted OS DECISION trial data (final data-cut), which shows a statistically significant non-zero constant of 0.0115 (95% CI: 0.0026 to 0.0204, p=0.0117). In addition, the ANOVA test for non-linearity indicates a statistically significant deviation from linearity (F(122,1)= 56.915, p= 9.03 E-12). On both criteria the PH assumption is questionable.

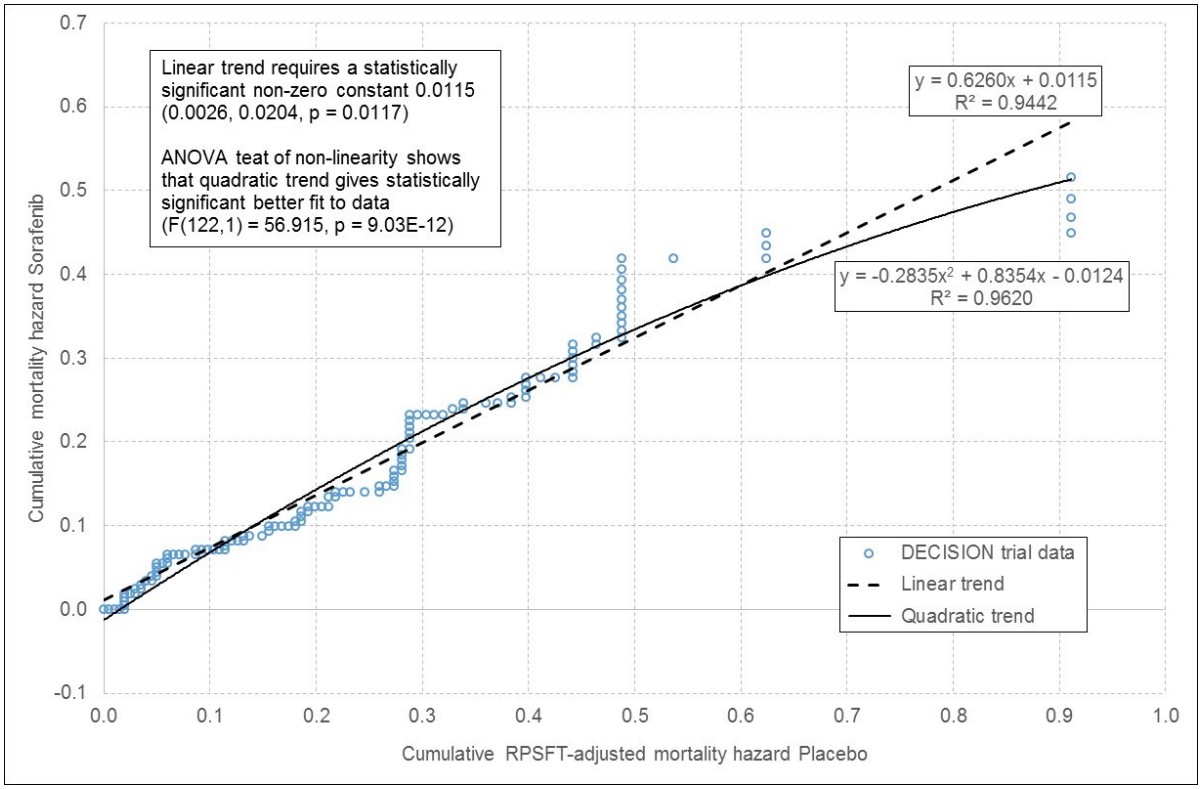

Figure 26 H-H plot for RPFST-adjusted overall survival from the DECISION trial

10.4 Appendix 4: Data extraction tables not presented in the main body of the report

Table 55 Subgroup analyses conducted in the SELECT and DECISION trials

SELECT trial	DECISION trial
Pre-specified subgroup analyses	
Age (≤65 years, >65 years) Geographic region (Europe, North America, Other) Prior VEGF targeted therapy (0, 1) Gender (male, female) Race (white, non-white) Histology (PTC, FTC) TSH (≤ 0.5, >0.5 to 2.0, >2.0 to 5.5; >5.5 µU/mL)	Age (<60 years, ≥60 years) Geographical region (North America, Europe, Asia) Gender (male, female) Histology (PTC, FTC: Hürthle cell, FTC: other subtypes, poorly differentiated) Site of metastasis (bone (yes, no] and lung only [yes, no] 2-[18F] fluoro-2-deoxy-D-glucose -positronemission tomography (FDG-PET) uptake (negative, positive) Prior radioactive iodine cumulative dosing (<600 mCi (22.2 GBq), ≥ 600 mCi (22.2 GBq) Tumour burden as measured by number of target or non-target lesions (< median, ≥ median) Tumour burden as measured by sum of target diameters (< median, ≥ median)
Post-hoc subgroup analyses	
Number of sites of metastasis (1, 2, 3, ≥4) * Site of metastasis (brain, bone, liver, lung, lymph node) * Site of metastasis (bone (yes, no] and lung [yes, no] Target tumour size (≤35mm, 36 to 60mm, 91 to 92mm, ≥92mm) BRAF status (wild type or mutant) RAS status (wild type or mutant) TSH levels (≤0.5, 0.5 to 2.0, >2,0) Pharmacodynamic biomarkers (TG and CAF levels (Ang2, VEGF, sTie2, and FGF23) * Body mass index (under- and normal weight [<25kg/m2], overweight [25 kg/m2 to 29.99kg/m2] and obese [≥30 kg/m2]) * With or without treatment emergent hypertension *	BRAF status (wild type or mutant) * RAS status (wild type or mutant) * TSH levels (< median 449.4ng/mL, ≥ median 449.4ng/m)* Maximum tumour size (<1.5cm, ≥1.5cm) Category of lesion size (<1.5cm, ≥1.5cm, <2cm, ≥2cm, <3cm, ≥3cm, <4cm, ≥4cm) Lesion category: number of target lesions (<3, ≥3, <4, ≥4, <5, ≥5) † Symptomatic or asymptomatic at baseline † ¥ Subgroup analyses on safety parameters by region, body mass index, gender, and age (full details not reported) § Subgroup analyses of baseline factors predictive of health-related quality of life (full details not reported) §

All the analyses were reported in the primary published papers except

*Reported in conference abstracts [70,83,89,111,131-133,310]

† Bayer 2017,[7] appendix 7.3

¥EPAR for sorefanib[26]

§ Bayer 2017[7]

Table 56 Overall survival findings from the SELECT and DECISION trials, including information on treatment crossover and subsequent treatment received

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
Received anti-cancer treatment following progression	41 (15.7)	16 (12.2)	42 (20.3	18 (8.6)
Overall survival – First data-cut	November 2013		August 2012	
Number (%) of patients who crossed-over: First data-cut	n/a	109 (83.2)	55 (26.6)	150 (71.4)
Number of deaths (%)	71 (27.2)	47 (35.9)	45 (21.7)	54 (25.7)
Median OS in months (95% CI)	NE (22.0 to NE)	NE (14.3 to NE)	NE	NE
Unadjusted HR (95% CI) p value	0.73 (0.50 to 1.07) p=0.1032		0.80 (0.54 to 1.19) p=0.14	
RPSFTM adjusted HR (95% CI) p value (Bootstrapping 95% CI)	0.62 p=0.0510 (0.40 to 1.00)		0.61 (0.40 to 0.94) p=0.0125 (0.18 to 2.16)	
IPE adjusted HR (95% CI) p value (Bootstrapping 95% CI)	n/a		0.70 (0.47 to 1.04) p=0.0388 (0.40 to 1.38)	
Overall survival – Second data-cut	June 2014		May 2013	
Number (%) of patients who crossed-over: Second data-cut	n/a	115 (87.8)	NR	157 (74.8)
Number of deaths (%)	93 (35.6)	55 (42.0)	66 (31.9)	72 (34.3)
Median OS in months (95% CI)	NE (30.9 to NE)	19.1 (21.7 to NE)	NE	36.5 (32.2 to NE)
Unadjusted HR (95% CI) p value	0.80 (0.57 to 1.12) nominal p=0.1993		0.88 (0.63 to 1.24) p=0.24	
RPSFTM adjusted HR (95% CI) p value (Bootstrapping 95% CI)	0.53 nominal p=0.0051 (0.34 to 0.82)		0.69 (0.49 to 0.99) NR (0.33 to 1.65)	
IPE adjusted HR (95% CI) p value (Bootstrapping 95% CI)	n/a		0.79 (0.57 to 1.11) NR (0.46 to 1.61)	
Overall survival – Third data-cut	August 2015		July 2015	
Number (%) of patients who crossed-over: Third data-cut	n/a	115 (87.8)	NR	158 (75.0)
Number of deaths (%)	121 (46.4)	70 (53.4)	103 (49.8)	109 (51.9)
Median OS in months (95% CI)	41.6 (31.2 to NE)	34.5 (21.7 to NE	39.4 (32.7 to 51.4)	42.8 (34.7 to 52.6)
Unadjusted HR (95% CI) p value	0.84 (0.62 to 1.13) nominal p=0.2475		0.92 (0.71 to 1.21) one-sided p=0.28	
RPSFTM adjusted HR (95% CI) p value (Bootstrapping 95% CI)	0.54 nominal p=0.0025 (0.36 to 0.80)		0.77 (0.58 to 1.02) NR (0.42 to 1.79)	
IPE adjusted HR (95% CI) p value (Bootstrapping 95% CI)	n/a		0.80 (0.61 to 1.05) NR (0.48 to 1.71)	

HR=hazard ratio; n/a=not applicable; NE=not estimable; NR=not reported; RPSFTM=Rank Preserving Structural Failure Time Method

Source: Eisai 2017,[8] Table 8, Eisai Data on File,[311] Table 14.2.2.1.1a and Table 14.2.2.1.2a and Bayer 2017,[7] Table 7 and text on pages 29 to 30

Table 57 Progression-free survival findings (by blinded review) from the SELECT and DECISION trials*

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
PFS by blinded review – First data-cut	November 2013		August 2012	
Number of events (%)	93 (35.6)	109 (83.2)	113 (54.6)	137 (65.2)
Died before progression	14 (5.4)	4 (3.1)	NR	NR
Median PFS in months (95% CI)	18.3 (15.1 to NE)	3.6 (2.2 to 3.7)	10.8	5.8
Stratified HR (95% CI) p value	0.21 (0.14 to 0.31) p<0.001		0.59 (0.45 to 0.76) p<0.0001	

n/a=not applicable; NE=not estimable; NR=not reported
*Only investigator assessed PFS has been reported for subsequent data-cuts – see Table 58
Source: Schlumberger et al 2015[47] and Brose et al 2014[48]

Table 58 Progression-free survival findings (by investigator assessment) from the SELECT and DECISION trials

Characteristic	SELECT		DECISION	
	Lenvatinib N=261	Placebo N=131	Sorafenib N=207	Placebo N=210
PFS by investigator – First data-cut	November 2013		August 2012	
Number of events (%)	91 (34.9)	104 (79.4)	140 (67.6)	184 (87.6)
Died before progression	16 (6.1)	6 (4.6)	NR	NR
Median PFS in months (95% CI)	16.6 (4.8 to NE)	3.7 (3.5 to NE)	10.8	5.4
Stratified HR (95% CI) p value	0.24 (0.16 to 0.35) p<0.001		0..49 (0.39 to 0.61) P<0,0001	
PFS by investigator – Second data-cut	June 2014		May 2013	
Number of events (%)	n/a	n/a	n/a	n/a
Died before progression	n/a	n/a	n/a	n/a
Median PFS in months (95% CI)	n/a	n/a	n/a	n/a
Stratified HR (95% CI) p value	n/a		n/a	
PFS by investigator – Third data-cut	August 2015		July 2015	
Number of events (%)	121 (46.4)	107 (81.7)	n/a	n/a
Died before progression	19 (7.3)	6 (4.6)	n/a	n/a
Median PFS in months (95% CI)	19.4 (14.8 to 29.3)	3.7 (3.5 to 5.4)	n/a	n/a
Stratified HR (95% CI) p value	0.24 (0.17 to 0.35) p<0.001		n/a	

n/a=not applicable; NE=not estimable; NR=not reported
Source: Schlumberger et al 2015,[47] Eisai Data on File,[311] Table 14.2.2.1.5a and Brose et al 2014[48]

10.5 Appendix 5: Evidence from systematic reviews

Table 59 Summary of the characteristics of the systematic review evidence included

			Number of studies							
Study	**Cancer type**	**Intervention**	**All**	**RR-DTC**	**Lenvatinib**	**Sorafenib**	**RCT**	**Non-RCT (prospective)**	**Non-RCT (retrospective**	**Note**
Anderson et al et al 2013[60]	RR-DTC	Potential treatment options for RR-DTC	45	45	1	3	1	44	0	SLR
Gruber and Colevas 2015[33]	RR-DTC	Tyrosine kinase inhibitors	18	18	2	6	2	16	0	SLR
Jean et al 2016[92]	DTC versus other cancer	Sorafenib	9	4	0	4	4*	5	0	SLR (PubMed only)
Kawalec et al 2016[96]	RR-DTC	Lenvatinib and sorafenib	2	2	1	1	2	0	0	SR and ITC
McFarland and Misiukiewicz 2014[103]	RR-DTC	Sorafenib (single or in combination)	18	18	0	18	1	12	5	SLR
Shen et al 2014[126]	RR-DTC	Sorafenib	7	7	0	7	0	5	2	SLR
Thomas et al 2014[137]	Metastatic thyroid cancer	Sorafenib	7	6	0	7	0	6	1	SLR
Tremblay et al 2016[56]	RR-DTC	Lenvatinib versus sorafenib	2	2	1	1	2	0	0	Does not report SLR or SR methodology but reports ITC and MAIC results
Ye et al 2015[140]	Thyroid cancer	Lenvatinib and sorafenib	10	9	2	8	2	8	0	SR and meta-analysis
CADTH lenvatinib 2016[6]	RR-DTC	Lenvatinib	2	2	1	1	2	0	0	Includes only SELECT trial but reports on ITC from Eisai
CADTH sorafenib 2015[5]	RR-DTC	Sorafenib	1	1	0	1	1	0	0	Includes only DECISION trial
Eisai 2017[8]	RR-DTC	Lenvatinib	2	2	1	1	2	0	0	Includes ITC
Bayer 2017[7]	RR-DTC	Sorafenib	2	2	1	1	2	0	0	Includes ITC

DTC=differentiated thyroid cancer; ITC=indirect treatment comparison; MAIC=matched adjusted indirect comparison; RR-DTC= radioactive iodine refractory differentiated thyroid cancer; SLR=systematic literature review; SR=systematic review

Table 60 Quality assessment of systematic review evidence included

Assessment criterion	Anderson et al 2013[60]	Gruber & Colevas 2015[33]	Jean et al 2016[92]	Kawalec et al 2016[96]	McFarland & Misiukiewicz 2014[103]	Shen et al 2014[126]	Thomas et al 2014[137]	Trembaly et al 2016[56]	Ye et al 2015[140]	CADTH lenvatinib 2016[6]	CADTH sorafenib 2015[5]	Eisai 2017[8]	Bayer 2017[7]
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	✓	✓/✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the search strategy adequate and appropriate?	✓	✓	✗a	✓	✓	✓	✓	NR	✓	✓	✓	✓	✓
Were preventative steps taken to minimise bias and errors in the study selection process?	✓	NR	NR	✓	✓	✓	NR	NR	✓	✓	✓	✓	✓
Were appropriate criteria used to assess the quality of the primary studies, and were preventative steps taken to minimise bias and errors in the quality assessment process	NR	NR	NR	✗b	NR	✗	✗	NR	NR	✓c	✓c	✓	✓d
Were preventative steps taken to minimise bias and errors in the data extraction process?	✓	NR	NR	✓	✓	✓	✓	NR	✓	NR	NR	NR	✓
Were adequate details presented for each of the primary studies?	✓	✓/✗	✓	✓	✓	✓	✓/✗	✓	✓	✓	✓	✓	✓
Were appropriate methods used for data synthesis?	✓	✓	✓	✓	✓	✓/✗e	✓/✗e	✓	✓/✗f	✓	✓	✓	✓
Do the authors' conclusions accurately reflect the evidence that was reviewed?	✓	✓	✓	✓	✓	✓	✓	✓	✓/✗f	✓	✓	✓	✓
Was the review published in peer reviewed journal?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗
Was the review sponsored by pharmaceutical company?	✓1	✗	✗	✗	✗	✗	✓/✗1	✓/✗2	✗	✗	✗	✓2	✓1

✓ yes (item properly addressed) ✗ no (item not properly addressed) ✓/✗ partially (item partially addressed); NR=not reported
a Only PubMed was searched
b Used the Jadad scale (not an appropriate assessment tool)
c Results of the assessment were not presented
d Only the DECISION trial was assessed
e No investigation of heterogeneity of studies included in meta-analysis
f Subgroup analyses were conducted based on patients with and without RR-DTC, however the AG considers all studies of patients with DTC included a majority, if not all, of patients with RR-DTC
1=Bayer; 2=Eisai

Table 61 Overall findings / conclusions receded by the authors of the included systematic review evidence

Study	Analysis	Overall findings / conclusions
Anderson et al et al 2013[60]	Descriptive analysis	Certain treatments, notably TKIs, have shown promise in Phase II trials, and two Phase III randomised placebo controlled trials [the SELECT and DECISION trials] are ongoing
Gruber and Colevas 2015[33]	Descriptive analysis	The most likely outcome of treatment with a TKI is stable disease. Lenvatinib appears to be the most active agent but is not yet available, with a PFS versus placebo triple that of sorafenib and a RECIST response rate five times that of sorafenib in the phase III setting
Jean et al 2016[92]	Descriptive analysis	There is a distinct increase in the rate of occurrence of AEs of sorafenib when used in DTC compared with RCC and HCC. While many theoretical explanations have been proposed, the exact mechanism for this differential in toxic effects remains unclear
Kawalec et al 2016[96]	Indirect comparison (Bucher)	Lenvatinib and sorafenib are drugs with strong evidence on efficacy in treatment of RR-DTC. Based on the currently available clinical data lenvatinib occurred more efficacious then sorafenib in RR-DTC therapy. Safety profile of the drugs was acceptable and comparative. Indirect comparison results should be interpreted with caution due to differences in trial characteristics
McFarland and Misiukiewicz 2014[103]	Descriptive analysis	Although the data are based primarily on nonrandomised Phase II trials and on only one randomised Phase III trial, it has been shown convincingly that sorafenib slows the progression of disease in the majority of cases
Shen et al 2014[126]	Descriptive analysis and meta-analysis	As far as PR and AEs are concerned, the results of this meta-analysis indicate that sorafenib has a modest effect in patients with radioiodine-refractory differentiated thyroid cancer and the high incidence of AEs associated with this agent may affect the quality of patients' lives. Though the use of sorafenib in the treatment of RR-DTC is considered promising by most physicians working in this field, more effective agents with less toxicity and cost are still needed
Thomas et al 2014[137]	Descriptive analysis and meta-analysis	ORR from meta-analysis is higher than recently reported in the DECISION trial. The differences between the meta-analysis results and this phase III trial could be explained by the study design and the challenges that arise from using RECIST criteria. The targeted therapy agents are associated with significant incidence of adverse events and a small risk of death. Although there is evidence of efficacy with TKIs, these drugs may diminish quality of life because of significant toxicities; therefore, it is important to assess the need for treatment. Most patients with metastatic disease do not require systemic therapy
Tremblay et al 2016[56]	Indirect comparison (Bucher) and MAIC	After adjusting for observed differences between the SELECT and DECISION trials in patients with RR-DTC, lenvatinib was associated with statistically significantly longer PFS compared with sorafenib based on an MAIC of individual patient data from the SELECT trial and aggregate data from the DECISION trial. Some limitations of this analysis should be considered. Only patient characteristics common to both trials and reported in the DECISION trial were matched; other unobserved factors may therefore have influenced the results. The exclusion from this analysis of patients previously treated with VEGFR-targeted therapies limits our conclusions to patients who have not received prior treatment with these agents
Ye et al 2015[140]	Descriptive analysis and meta-analysis and meta-analysis	Lenvatinib and sorafenib are useful in the treatment of TC. Although, their toxicities remain high (57.4%) in the patients, the death rate is controlled (4.1%). Lenvatinib and sorafenib are more useful for thyroid cancer compared to RR‐DTC

Study	Analysis	Overall findings / conclusions
CADTH lenvatinib 2016[6]	Descriptive analysis*	The Endocrine Clinical Guidance Panel concluded that there is a net overall clinical benefit of lenvatinib in the treatment of RR-DTC. In making this conclusion the Clinical Guidance Panel also noted: OS was a secondary endpoint and confounded by crossover; HRQoL was not studied but AE profiles were similar to AEs seen with sorafenib in the DECISION trial. Hypertension was more common with lenvatinib but hand-foot syndrome and drug discontinuation due to AEs was more common with sorafenib
CADTH sorafenib 2015[5]	Descriptive analysis	The Endocrine Clinical Guidance Panel concluded that there is a net overall clinical benefit of sorafenib compared to placebo in patients with clinically progressive RR-DTC. Toxicity was increased with sorafenib compared both to placebo and to other trials studying sorafenib in cancer, and there may be an increased risk of squamous cell cancers of the skin during sorafenib use. As HRQoL was reduced by sorafenib, the decision to initiate and monitoring of treatment should be done by a clinician experienced in the use of targeted agents and in the treatment of thyroid cancer
Eisai 2017[8]	Descriptive analysis and indirect comparison (Bucher)	Lenvatinib was shown to be of superior efficacy to placebo in the SELECT trial (crossover adjusted OS, PFS and ORR) and to sorafenib (PFS) from an indirect treatment comparison. Comparative safety information with sorafenib has shown that sorafenib and lenvatinib share many of their AEs, although their safety profiles are not identical and lenvatinib is associated with lower rates of some AEs that have been shown to impact patients' daily lives
Bayer 2017[7]	Descriptive analysis and indirect comparison (Bucher) and MAIC	Crossover makes it difficult to detect and attribute improvements in OS in the DECISION trial. While there were no statistical statistically significant differences between arms, analyses of OS, at 9 months and 36 months after the original data-cut, showed a consistent separation of the K-M curves in favour of sorafenib. Results from the indirect comparison show sorafenib to have a statistically superior safety profile to lenvatinib in respect to AEs. Overall, AEs in the DECISION trial were consistent with the known safety profile of sorafenib in other indications, and effectively managed by supportive care, pharmacological treatment, dose interruption or dose reduction. Additionally sorafenib was shown to be associated with a lower risk of treatment discontinuation due to AEs. Sorafenib is an efficacious treatment option, especially for patients presenting with co-morbidities or in circumstances where managing and maintaining quality-of-life is a primary treatment objective. The results of the DECISION trial are directly relevant to the progressive RR-DTC patients within routine clinical practice in England. The safety results from the indirect comparison support sorafenib as a tolerable treatment option. This may be important in patients with co-morbidities where managing and maintaining quality of-life is a primary treatment objective

AE= adverse event; DTC=differentiated thyroid cancer; HCC=hepatocellular carcinoma; HRQoL=health-related quality of life; K-M=Kaplan Meier; MAIC=matched adjusted indirect comparison; ORR=objective tumour response rate; OS=overall survival; PFS=progression-free survival ; PR=partial response; RCC=renal cell carcinoma ; RECIST=response evaluation criteria in solid tumours; RR-DTC=radioactive iodine refractory differentiated thyroid cancer; TKI=tyrosine kinase inhibitor; VEGFR=vascular endothelial growth factor receptor

Table 62 Results from three systematic reviews of sorafenib

Outcome	Jean et al 2016[92]			Shen et al 2015[126]	Thomas et al 2015[137]
	TARGET trial (RCC)	SHARP trial (HCC) 312312312153152	DECISION trial	Meta-analysis*	Meta-analysis*
Efficacy					
PFS, months (95% CI)	5.5†	5.5†§	10.8	-	17.9 (17.9 to 18.0)¥
ORR, % (95% CI)	1.6†	0.7†	12.2†	22 (15 to 28)	20.9 (14.3 to 27.5)¥
All-Grade adverse events, % (95% CI)					
Hand-foot syndrome	30†	21†	76†	80 (68 to 91	73.5 (64 to 83)
Rash	40†	16†	50†	66 (50 to 82)	66.7 (51.7 to 81.7
Diarrhoea	43†	39†	69†	68 (59 to 77)	70.3 (62.3 to 78.3)
Hypertension	17†	5†	41†	52 (33 to 72)	36.1 (26.6 to 45.6
Fatigue	37†	22†	50†	67 (57 to 78)	60.6 (44.8 to 76.4)
Weight loss	10†	9†	51†	52 (33 to 72)	56.8 (38.8 to 74.8)
Muscositis	NR	NR	36†	-	35.4 (23.1 to 47.7)
Grade ≥3 adverse events, % (95% CI)					
Hand-foot syndrome	6	8	20	-	19.4 (8.3 to 30.5)
Rash	1	1	5	-	6.8 (2.7 to 10.9)
Diarrhoea	2	8	6	-	6.8 (3.3 to 10.3)
Hypertension	4	2	10	-	7.3 (2.5 to 12.1)
Fatigue	5	4	6	-	10.3 (4.4 to 16.2)
Weight loss	<1†	2†	12†	-	5.2 (1.2 to 9 0.2
Muscositis	NR	NR	4†	-	3.9 (0.6 to 7.2)
Dose modifications due to adverse events					
Dose reductions	13†	26†	64†	62 (36 to 89)	56 (43.4 to 69.3)
Discontinued	10†	38†	19†	-	16 (8.6 to 23.4)

CI=confidence interval; NR=not reported, ORR-objective tumour response rate; PFS=progression-free survival
*The meta-analyses in both reviews included 7 studies (6 studies for RR-DTC only in the review by Thomas et al 2015[137])
†Data not reported in the review by Jean et al 2016[92] or did not match the data reported in the source papers and so data were extracted by the AG from source papers[48,312,313]
§The SHARP trial[312] reports time to symptomatic progression (median 4.1 months) and time to radiological progression (5.5 months), the latter is reported here

¥ PFS includes patients with medullary thyroid cancer. From all studies, including the study of patients with medullary thyroid cancer, median ORR was 20.7% (95% CI: 13.0% to 28.0%)

Table 63 Efficacy results from indirect comparisons: lenvatinib versus sorafenib

Outcome	Relative effectiveness	Source
OS (RPSFTM adjusted)	HR=0.78 (95% CI: 0.42 to 1.42)	Kawalec et al 2016[96]
OS (RPSFTM adjusted)	HR=0.77 (95% CI: 0.44 to 1.35)	Tremblay et al 2016[291]
OS (RPSFTM adjusted)	[redacted]	Eisai 2017[8]
OS (MAIC and RPSFTM adjusted)	HR=0.73 (95% CI: 0.40 to 1.35)	Tremblay et al 2016[291]
PFS	HR=0.36 (95% CI: 0.22 to 0.57)	Kawalec et al 2016[96]
PFS	HR=0.36 (95% CI: 0.22 to 0.57)	Tremblay et al 2016[291]
PFS	[redacted]	Eisai 2017[8]
PFS (MAIC adjusted)	HR=0.33 (95% CI: 0.22 to 0.57)	Tremblay et al 2016[291]

CI=confidence interval; HR=hazard ratio; MAIC= Matching-Adjusted Indirect Comparison; NA=not applicable; ORR=objectiveOS=overall survival; PFS=progression-free survival; RPSFTM=rank-preserving structural failure time model; RR=relative risk

Table 64 Efficacy results from indirect comparisons: sorafenib versus lenvatinib

Outcome	Relative effectiveness	Source
OS (MAIC and RPSFTM adjusted)	[redacted]	Tremblay et al 2016[291] *
OS (MAIC and RPSFTM adjusted)	[redacted]	Bayer 2017[7]
PFS (MAIC adjusted)	[redacted]	Tremblay et al 2016[291] *
PFS (MAIC adjusted)	[redacted]	Bayer 2017[7]

CI=confidence interval; HR=hazard ratio; MAIC= Matching-Adjusted Indirect Comparison; NR=not areported; OS=overall survival; PFS=progression-free survival; RPSFTM=rank-preserving structural failure time model
*Direction of analysis inverted from publication, as reported in Bayer 2017,[7] Table 19

Table 65 Safety results from indirect comparisons*

Outcome	Lenvatinib versus sorafenib (Kawalec et al 2016[96]), HR (95% CI)	Sorafenib versus lenvatinib (Bayer 2017[7]), HR (95% CI)
Grade ≥3 adverse event	Not reported	[redacted]
Serious adverse event (SAE)	1.54 (0.99 to 2.40)	[redacted]
Treatment-related SAE	4.02 (1.69 to 9.60)	Not reported
Discontinuation due to adverse event	1.26 (0.32 to 4.96)	[redacted]

CI=confidence interval; HR=hazard ratio; MAIC= Matching-Adjusted Indirect Comparison; NR=not areported; OS=overall survival; PFS=progression-free survival; RPSFTM=rank-preserving structural failure time model
*Data are also reported for 17 specific types of adverse events by Kawalec et al 2016,[96] the difference between lenvatinib and sorafenib was statistically significant for hypertension (HR=2.31, 95% CI: 1.18 to 4.53) and alopecia (HR=0.33, 95% CI: 0.12 to 0.94)

10.6 Appendix 6: Evidence from observational studies

Table 66 Study characteristics of observational studies

Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen et al	Duntas et al	Kloos et al	Study 12791	Marotta et al
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31	RR-DTC: 17
Primary source	Cabanillas et al 2015[76]	Takahashi et al (abstract)[134]	Ahmed et al 2011[58]	Gupta-Abramson et al [87]	Chen et al (abstract)[77]	Duntas et al (abstract)[80]	Kloos et al 2009[100]	Schneider et al[125]	Marotta et al[102]
Other sources	2 abstracts[127,128] Lenvatinib EPAR[27]	1 other abstract[135] and Lenvatinib EPAR[27]	1 other abstract[59] and Lenvatinib EPAR[27]	5 abstracts[74,75,79,97,136]	None	None	Lenvatinib EPAR[27]	1 abstract[124] and 1 other study[91]	None
Country	USA, Italy, UK, Australia, Poland and France	Japan	UK	USA	China	Greece	USA	Netherlands	Italy
Recruitment period	October 2008 to February 2010	03 September 2012 to 09 July 2015 latest cut-off date (still ongoing)†	Patient accrual commenced in May 2007	February 2006 to August 2009[97]	NR	NR	October 2004 and August 2005	October 2007 and February 2011	NR
Length of follow up, months	September 2013 Median 16.1 (range: 15.0 to 16.6) June 2014 Median: 51.6	Safety: 2 years Secondary outcomes: 40 months†	Median 19 months	Median 9*[74]	Minimum 3*	4 to 9	NR	Median 25 (range 3.5 to 39)	Median 17

NR=nor reported; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer
*Converted from weeks into months by dividing by 4.34812141
†Data taken from lenvatinib EPAR[27]

Table 67 Participant characteristics of observational studies

Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen et al	Duntas et al	Kloos et al	Study 12791	Marotta et al
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31	RR-DTC: 17
Median age, years (range)	63 (34 to 77)	NR	All: 55 (21 to 78)	Initial 30 patients: 63 (31 to 89)	NR	NR	PTC / no prior chemotherapy (n=19): 67 (33 to 90) PTC / prior chemotherapy (n=22): 56 (27 to 75)	Median 64 (53 to 82)	58
% male	59	NR	All: 55.9	All: 49.0[74]	NR	36.4	All: 55.4 PTC (n=41): 51.2	61.2	23.5
Ethnicity, %	White=86	NR	NR	NR	NR	NR	White All: 83.9 PTC (n=41): 87.8	NR	NR
ECOG PS ≥2, %	6.9	NR	All: 0	Initial 30 patients: 0	NR	NR	NR	NR	35.3
PTC, %	74.1	NR	All: 23.5	All: 52.7	100	NR	73.2	41.9	35.3
FTC, %	25.9 +	NR	All: 14.7	32.7 +	0	NR	19.6 +	48.4	64.7
Lung metastases, n (%)	93	NR	NR	NR	NR	NR	NR	Lung only: 25.8	NR
Bone metastases, n (%)	45	NR	NR	NR	NR	NR	NR	Lung and bone only: 25.8	23.5
Prior TKI	29.3	NR	NR	NR	NR	NR	NR	0	11.8

ATC=anaplastic thyroid carcinoma; ECOG PS= Eastern Cooperative Oncology Group performance status; FTC=follicularcarcinoma; MTC=medullary thyroid carcinoma; NR=nor reported; PTC= Papillary carcinoma; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer; TKI=Tyrosine kinase inhibitor
+ Explicitly stated that FTC also includes Hurthle Cell carcinoma

Table 68 Efficacy findings from observational studies

Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen et al	Duntas et al	Kloos et al	Study 12791	Marotta et al
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31	RR-DTC: 17
Median OS, months (95% CI)	September 2013: 27.7 (27.7 to NE)† June 2014: 32.3 (23.3 to 35.8)†	RR-DTC only: 31.8 (31.8 to NE)	For RR-DTC only: Median not met	RR-DTC 32.4 (21.6 to NE)*	NR	NR	23 (18 to 43)¥	34.5 (19 to 50) (n=26)	No patient died during follow-up
Median PFS, months (95% CI)	12.6 (9.9 to 16.1)	RR-DTC only: 25.8 (18.4 to NE)	RR-DTC only: Median not met	RR-DTC only: 22.1 (17.3 to 31.1)*	Mean: 9.7 (6.8 to 12.4) *	NR	All PTC (n=41): 15 (10 to 27.5)	18 (7 to 29) (n=26)	12
ORR, % (95% CI)	50.0 (36.6 to 63.4)	RR-DTC only: 68.0	21¥	RR-DTC only: 38.3	33.3	27.3	All PTC (n=41): 15¥	30.8 (n=26)	35.3
Median time to response, months	3.6 (95% CI: 1.8 to 3.7)	NR	NR	NR	NR	NR	NR	All responses achieved in the first 6 months of treatment (n=26)	NR
Duration of response, months	12.7 (8.8 to NE) (n=29)	NR	NR	NR	NR	NR	NR for all PTC patients	29.6 (range: 3 to 33) (n=26)	NR

ATC=anaplastic thyroid carcinoma; MTC=medullary thyroid carcinoma; NE=not estimable; NR=nor reported; PTC= Papillary carcinoma; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer
*Converted from weeks into months by dividing by 4.34812141
†Data taken from lenvatinib EPAR[27]
¥Data taken from sorafenib EPAR[26]
Note: ORR=complete response + partial response; there were no patients with a complete response in any of the studies

Table 69 Incidence of all-Grade adverse events reported from observational studies, n (%)

Parameter	Study 201	Study 208	Study 12636	UPCC-03305*	Chen et al	Duntas et al	Kloos et al*	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
All-Grade AEs	58 (100)	51 (100)	NR	NR	NR	NR	NR	NR
Hypertension	44 (76)	46 (90)	7 (21)	13 (43)	NR	3 (27)	24 (43)	13 (42)
Diarrhoea	39 (67)	28 (55)	26 (77)	24 (80)	NR	“one of the most frequent AEs”	42 (75)	16 (52)
Decreased appetite / anorexia	30 (52)	40 (78)	10 (29)	6 (20)	NR	NR	46 (82)	NR
Weight loss	40 (69)	NR	10 (29)	18 (60)	NR	NR	46 (82)	18 (58)
Nausea	29 (50)	NR	9 (27)	9 (30)	NR	NR	31 (55)	3 (10)
Fatigue	35 (60)	37 (73)	20 (59)	19 (63)	NR	“one of the most frequent AEs”	37 (66)	NR
Headache	25 (43)	NR	5 (15)	NR	NR	NR	9 (16)	NR
Stomatitis/ mucositis	18 (31)	29 (57)	9 (27)	14 (47)	NR	NR	9 (16)	15 (48)
Vomiting	22 (38)	NR	6 (18)	Included with nausea	NR	NR	10 (18)	NR
Proteinuria	37 (64)	31 (61)	NR	NR	NR	NR	NR	NR
Hand-foot syndrome	13 (22)	39 (77)	27 (79)	28 (93)	NR	“one of the most frequent AEs”	35 (63)	22 (71)
Dysphonia	25 (43)	NR	NR	NR	NR	NR	NR	NR
Rash	14 (24)	NR	Dermatology (other) = 30 (88)	24 (80)	NR	NR	44 (79)	17 (55)
Alopecia	5 (9)	NR	25 (74)	13 (43)	NR	NR	44 (79)	16 (52)

Parameter	Study 201	Study 208	Study 12636	UPCC-03305*	Chen et al	Duntas et al	Kloos et al*	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Other types of All-Grade AEs	Other AEs ≥25% Cough=26 (45) Arthralgia 21 (36) Dry mouth 20 (35) Back pain 19 (33) Pain in extremity 19 (33) Dyspnea 18 (31) Musculoskeletal pain 18 (31) Abdominal pain upper 18 (31)) Abdominal pain 16 (28) Epistaxis 16 (28)	None Note, abstract only reports AEs reported by ≥55% patients	Other AEs ≥25% Infection 23 (68) Abdominal cramps/pain 13 (38) Glossitis 12 (35) Haemorrhage 10 (29)	Terry et al later examined treatment-related hand-foot syndrome and rash. AE data for all 55 patients not RR-DTC only (n=47) Hand-foot syndrome 50 (91) Rash 49 (85)	NR	NR	Other AEs ≥25% Pain abdomen or rectal 35 (63) Heartburn 22 (39) Flatulence 39 (70) Arthralgia 34 (61) Muscle cramps 20 (36) Flushing 64 Dry skin 47 Pruritis 43 Nail changes 33	Hypocalcemia 15 (48) Hypophosphatemia 11 (35) Anemia 11 (35) Hypoparathyroidism 10 (32) Thrombopenia 9 (29) Hypothyroidism 8 (26) Leukopenia 7 (23) Myocardial infarction 3 (10)

*Treatment-related
AE=adverse event; ATC=anaplastic thyroid carcinoma; MTC=medullary thyroid carcinoma; NR=not reported; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer

Table 70 Incidence of Grade ≥3 adverse events reported from observational studies, n (%)

Parameter	Study 201	Study 208	Study 12636	UPCC-03305*	Chen et al	Duntas et al	Kloos et al*	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
Grade ≥3 AEs	42 (72)	RR-DTC 12 (72)	NR	NR	NR – see 'other'	NR	NR	NR
Hypertension	6 (10)	NR	2 (6)	4 (13)	NR	NR	2 (4)	5 (16)
Diarrhoea	6 (10)	NR	1 (3)	2 (7)	NR	NR	2 (4)	2 (7)
Decreased appetite	1 (2)	NR	0	1 (3)	NR	NR	0	NR
Weight loss	7 (12)	NR	0	3 (10)	NR	NR	3 (5)	3 (10)
Nausea	0	NR	0	0	NR	NR	0	0
Fatigue	5 (9)	NR	3 (9)	1 (3)	NR	NR	9 (16)	NR
Headache	1 (2)	NR	1 (3)	NR	NR	NR	0	NR
Stomatitis/ mucositis	1 (2)	NR	3 (9)	0	NR	NR	1 (2)	3 (10)
Hand-foot syndrome	1 (2)	NR	14 (44)	3 (10)	NR	NR	4 (7)	7 (23)
Proteinuria	6 (10)	NR	NR	NR	NR	NR	NR	NR
Asthenia	NR	NR	NR	NR	NR	NR	NR	NR
Dyspnoea	0	NR	NR	NR	NR	NR	0	NR
Dysphagia	NR	NR	0	NR	NR	NR	NR	NR
Rash	0	NR	Dermatology (other) = 2 (6)	3 (10)	NR	NR	2 (4)	5 (16)

Parameter	Study 201	Study 208	Study 12636	UPCC-03305*	Chen et al	Duntas et al	Kloos et al*	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Other types of Grade ≥3 AEs	Other Grade ≥3 AEs in ≥5% of patients Dehydration 5 (9) Arthralgia 3 (5)	NR	Other Grade ≥3 AEs reported: Infection 3 (9) Arthralgia 3 (9) Drug hypersensitivity 3 (9) Constipation 1 (3) Muscle cramps 1 (3) Anaemia 1 (3) Fever 1 (3)	Elevated liver function tests 2 (7) Pruritus 1 (3) Sleep disturbance/ anxiety 1 (3) Terry et al later examined hand-foot syndrome and rash. AE data for all 55 patients not RR-DTC only (n=47) Treatment-related Hand-foot syndrome 4 (7) Rash 9 (18)	"Although the types of toxicities were consistent with other sorafenib trials, their severity was relatively mild"	NR	Grade ≥3 AEs reported: in text: most common (≥5% frequency) Grade 3 AEs included: hand or foot pain (12) arthralgia (11) fatigue (16) hand-foot syndrome (7) musculoskeletal chest pain (7) asymptomatic hyponatremia (5)	Grade 3 AEs: Congestive heart disease 1 Deep venous thrombose 1 Grade 4 AEs: Myocardial infarction 3 (10) Small-cell lung cancer 1 (3)

*Treatment-related
AE=adverse event; ATC=anaplastic thyroid carcinoma; MTC=medullary thyroid carcinoma; NR=not reported; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer

Table 71 Incidence of serious adverse events and fatal adverse events reported from observational studies

Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen et al	Duntas et al	Kloos et al	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
SAEs	28 (48%)	NR	NR	NR	NR	NR	NR	NR
Types of SAEs	SAEs that occurred in at least 2 patients: dehydration (7%) hypotension (5% pulmonary embolism (3%) lower abdominal pain (3%) hypertension (3%) cardiac failure (3%)	NR	NR	NR	NR	NR	NR	NR
Fatal AEs	Deaths due to AEs 3 (5%): progressive disease arterial haemorrhage cardiac arrest	4 deaths, all unrelated to study drug	NR	NR	NR	NR	1 (not considered treatment-related)	NR

AE=adverse event; ATC=anaplastic thyroid carcinoma; MTC=medullary thyroid carcinoma; NR=not reported; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer; SAE=serious adverse event

Table 72 Dose modifications reported from observational studies, n (%)

Parameter	Study 201	Study 208	Study 12636	UPCC-03305*	Chen et al	Duntas et al	Kloos et al*	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
AE dose interruptions	43 (74)	NR	28 (82)	NR	NR	NR	NR	NR
AE dose reductions	38 (66)	NR	NR	14 (47)	0	11 (100)	29 (52)	3 months: 13 (42) 6 months: 15 (52) 12 months: 18 (58)
AE discontinued	15 (26)	1	NR	6 (20)	NR	NR	NR	7(23)
Other	AEs that led to lenvatinib withdrawal and occurred in at least 2 patients were: Proteinuria (5%) Pulmonary embolism (3%) Deep vein thrombosis (3%)		79% of patients required a dose reduction by one dose level to 400mg daily and a third of these patients underwent a further reduction to the lowest dose level of 400mg alternate days	Terry et al 2013[136] later reported 30 (55) dose reductions (n=55)		2/3 with a PR withdrew from the study after 5 to 7 months of treatment		

*Treatment-related
AE=adverse event; ATC=anaplastic thyroid carcinoma; MTC=medullary thyroid carcinoma; NR=not reported; PR=partial response; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer

Table 73 Other adverse event information reported from observational studies

Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen et al	Duntas et al	Kloos et al	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
Laboratory AEs	Clinically important changes in mean vital signs from baseline to the endpoints at various visits were observed. Blood pressure changes occurred and were reported as AEs if deemed clinically important by the investigator. Lenvatinib treatment was correlated with an increase in blood pressure		Liver abnormalities were common (32% of patients experiencing a Grade 1/2 transaminitis; 15% of patients developed Grade 3 amylasaemia) but no patients developed acute pancreatitis Lipase levels were found to be raised in 22% of patients half of which were Grade ≥3 12% of patients developed an elevated TSH. As all patients were on thyroxine (T4) replacement therapy and asymptomatic, this was interpreted as subclinical hypothyroidism corrected by increasing the T4 dose		There was a marked and rapid change in the serum thyroglobulin level after start of treatment with a mean decrease of 60% within 12 weeks, consistent with radiographic findings	Tg level was variably decreased by up to 85%	Although dramatic sustained decreases in serum Tg levels were observed in some patients with PRs and stable disease, neither baseline Tg nor Tg response consistently correlated with degree or duration of objective response	Tg response reflected the radiological response -, patients with a PR had a median decrease in their serum Tg levels. Patients with stable or progressive disease showed an increase in their serum Tg levels.

Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen et al	Duntas et al	Kloos et al	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
Timing of AEs	Most of the increases in blood pressure occurred during the first cycle. After the increase, downward trends in both systolic and diastolic blood pressure were observed, primarily due to treatment with antihypertensive medications and/or dose interruption or reduction.			From Terry et al 2013 (n=55): The severity of skin toxicity peaked by cycle 1 for rash and cycle 2 for HFSR. The severity improved dramatically for rash by cycle 3 and for HFSR by cycle 6. Our data support the close supervision of skin-related AEs in the first six cycles of treatment with sorafenib. However, the sustained high prevalence of rash and HFSR requires all patients receive ongoing skin care for the duration of therapy				The majority of AEs were seen in the first year of treatment and were controllable with dose reduction, medication, or supporting measures (i.e. dietary consultation and additional feeding)

Parameter	Study 201	Study 208	Study 12636	UPCC-03305	Chen et al	Duntas et al	Kloos et al	Study 12791
Intervention	Lenvatinib	Lenvatinib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib	Sorafenib
Number of patients	RR-DTC: 58	All: 51 RR-DTC:25	All: 34 RR-DTC: 19	All:55 RR-DTC: 47	RR-DTC: 9	RR-DTC: 11	All: 56 RR-DTC: 52	RR-DTC: 31
Other	Authors concluded: In this study, lenvatinib had an acceptable safety profile for subjects with refractory thyroid cancer. No new safety concerns were observed.	Authors state: Toxicities were manageable with dose modifications	Authors state: This study demonstrates that sorafenib is tolerable at reduced doses over prolonged periods of time in patients with thyroid cancer. Sorafenib leads to radiological and biochemical stabilisation of disease in the majority of these patients despite dose reductions	Terry et al 2013 state: Our data support the close supervision of skin-related AEs in the first six cycles of treatment with sorafenib. However, the sustained high prevalence of rash and hand-foot syndrome requires all patients receive ongoing skin care for the duration of therapy	Prospective controlled randomized studies with more patients and longer observation times are greatly needed.	Authors state: However, the aggressive-ness of disease in some patients implies that targeted therapy should take into account biomarkers and consider combinations with other TKIs or with mTOR inhibitors, adapting the dose, to enhance tolerability and response.	Authors state: Sorafenib is reasonably well-tolerated therapy with clinical and biologic antitumor activity in metastatic PTC	Authors concluded: Toxicity was consistent with other sorafenib trials

AE=adverse event; ATC=anaplastic thyroid carcinoma; MTC=medullary thyroid carcinoma; mTOR=mammalian target of rapamycin; NR=not reported; PTC= Papillary carcinoma; RR=DTC=Radioactive iodine refractory differentiated thyroid cancer; Tg=Thyroglobulin; TKI= Tyrosine kinase inhibitor; TSH=Thyroid stimulating hormone; VEGF= Vascular endothelial growth factor receptor

10.7 Appendix 7: NICE Reference Case checklists in full

Table 74 NICE Reference Case checklist completed by AG – Erdal et al 2015

Attribute	**Reference case**	**Does the economic evaluation match the reference case?** **Erdal et al 2015**[163]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – sorafenib is compared to BSC but not to lenvatinib
Perspective costs	NHS and PSS	Turkish payer's perspective taken
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial - patient related direct health effects were considered
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – lifetime horizon
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily taken from the DECISION trial
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs and based on EQ-5D data collected in the DECISION trial
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in the DECISION trial
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Does not state in abstract which valuation set is used for the EQ-5D estimates of utility
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Sensitivity analysis was conducted but no details of the methods used were reported

BSC=best supportive care; EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year

Table 75 NICE Reference Case checklist completed by AG – Huang et al 2016 (a & b)

Attribute	Reference case	Does the economic evaluation match the reference case? Huang et al 2016 (a & b)[158,159]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes- lenvatinib versus sorafenib and both drugs versus placebo. The placebo evidence is derived from the phase III trials; the AG assumes placebo and BSC are equivalent comparators
Perspective costs	NHS and PSS	US perspective. The authors states that direct medical costs were used but some costs were sourced from Medicare Fee Schedule which reflects tariffs rather than direct costs.
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial - patient related direct health effects were considered although source and values not reported in abstract
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – lifetime horizon
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from the DECISION and SELECT trials
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Authors state the utility values were taken from published sources but it is unclear which measurement tools were used as the published sources were not referenced
Health states for QALY	Reported directly by patients and/or carers	Unclear
Benefit valuation	Time-trade off or standard gamble	Unclear
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Unclear but unlikely to be representative of UK population as the study is set in the US
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes - 3% used
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Sensitivity analysis was conducted but no details of the methods used were reported

EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year

Table 76 NICE Reference Case checklist completed by AG – Tremblay et al 2016

Attribute	Reference case	Does the economic evaluation match the reference case? Tremblay et al 2016[160]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes- lenvatinib versus sorafenib
Perspective costs	NHS and PSS	US perspective
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 5 year and 10 year results reported
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from the DECISION and SELECT trials
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	QALYs – not EQ-5D
Health states for QALY	Reported directly by patients and/or carers	UK general population
Benefit valuation	Time-trade off or standard gamble	Neither
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes – 5% (details provided by lead author)
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Sensitivity analysis was conducted but no details of the methods used were reported

EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=personal social services; QALY=quality adjusted life year; US=United States

Table 77 NICE Reference Case checklist completed by AG – Wilson 2017

Attribute	Reference case	Does the economic evaluation match the reference case? Wilson 2017[161]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective costs	NHS and PSS	US health care perspective
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – lifetime
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from the SELECT and DECISION trials
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	No – utility is estimated from a vignette study generated from a sample of the general UK population in which participants were asked to value health state scenarios they were presented with.
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	No
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Yes - 3%
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	Yes

EQ-5D=EuroQol-5 dimension; HRQoL=health related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year; US=United States

Table 78 NICE Reference Case checklist completed by AG – SMC 2015

Attribute	Reference case	Does the economic evaluation match the reference case? SMC 2015[49]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – sorafenib is compared to BSC but not to lenvatinib
Perspective costs	NHS and PSS	NHS Scotland
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – time horizon up to 10 years
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily taken from the DECISION trial
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs and taken from EQ-5D data collected in DECISION trial
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in the DECISION trial
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Does not state which valuation set is used for the EQ-5D estimates of utility
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis conducted but no mention of probabilistic sensitivity analysis

BSC=best supportive care; EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=personal social services; QALY=quality adjusted life year

Table 79 NICE Reference Case checklist completed by AG – SMC 2016

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case?** **SMC 2016**[38]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective costs	NHS and PSS	NHS Scotland
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – time horizon up to lifetime
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from the DECISION and SELECT trials
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	No – utility is estimated from a vignette study generated from a sample of the general UK population in which participants were asked to value health state scenarios they were presented with.
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Not applicable
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis was conducted but there was no mention of probabilistic sensitivity analysis in the publication

EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year

Table 80 NICE Reference Case checklist completed by AG – CADTH 2015

Attribute	Reference case	Does the economic evaluation match the reference case? CADTH 2015[5]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – sorafenib is compared to BSC but not to lenvatinib
Perspective costs	NHS and PSS	Canadian health care perspective
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – up to 10 years
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from the DECISION trial
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs and based on the EQ-5D data collected in the DECISION trial
Health states for QALY	Reported directly by patients and/or carers	Yes – reported directly by patients in the DECISION trial
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Does not state in the abstract which valuation set is used for the EQ-5D estimates of utility
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis was conducted but there is no mention of probabilistic sensitivity analysis in the publication

BSC=best supportive care; EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year

Table 81 NICE Reference Case checklist completed by AG – CADTH 2016

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case?** **CADTH 2016**[162]
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Partial – lenvatinib is compared to BSC but not to sorafenib
Perspective costs	NHS and PSS	Canadian health care perspective
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – up to 10 years
Synthesis of evidence on outcomes	Based on systematic review	Data have been primarily derived from the SELECT trial
Outcome measure	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes – health effects were expressed in QALYs
Health states for QALY	Reported directly by patients and/or carers	No – utility is estimated from a vignette study generated from a sample of the general UK population in which participants were asked to value health state scenarios they were presented with.
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	No
Discount rate	The same annual rate for both costs and effects (currently 3.5%)	Not stated
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes - all QALYs estimated by the economic model have the same weight
Sensitivity analysis	The scope developed by NICE	One-way parameter sensitivity analysis was conducted but there is no mention of probabilistic sensitivity analysis in the publication

BSC=best supportive care; EQ-5D=EuroQol-5 dimension; HRQoL=health-related quality of life; PSS=Personal Social Services; QALY=quality adjusted life year

10.8 Appendix 7: Drummond checklists in full

Table 82 Critical appraisal checklist for the economic analysis completed by the AG – Erdal et al 2015

Erdal et al 2015[163] **Question**	**Critical appraisal**	**AG comment**
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from the DECISION trial
Were all the important and relevant costs and consequences for each alternative identified?	Yes	Resource use estimates generated from an expert panel
Were costs and consequences measured accurately in appropriate physical units?	Unclear	Sources of cost evidence described but no details of what was measured were reported
Were the cost and consequences valued credibly?	Unclear	Not reported
Were costs and consequences adjusted for differential timing?	Unclear	Not reported
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were calculated accurately
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	One-way and probabilistic sensitivity analysis were undertaken but details of the methods and parameters varied were not reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs=incremental cost effectiveness ratios; AG=Assessment Group

Table 83 Critical appraisal checklist for the economic analysis completed by the AG – Huang et al 2016 (a & b)

Huang et al 2016 (a & b)[158,159] Question	Critical appraisal	AG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from the DECISION and SELECT trials
Were all the important and relevant costs and consequences for each alternative identified?	Unclear	Based on the phase III trials but does not report resource use or costs used within the model
Were costs and consequences measured accurately in appropriate physical units?	Unclear	Sources of cost evidence described but no details of what was measured were reported
Were the cost and consequences valued credibly?	Unclear	Details of resource use estimates were not reported
Were costs and consequences adjusted for differential timing?	Yes	3% discount rate used
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	One-way and probabilistic sensitivity analyses were undertaken but details of the methods and parameters that were varied were not reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs=incremental cost effectiveness ratios; AG=Assessment Group

Table 84 Critical appraisal checklist for the economic analysis completed by the AG – Tremblay et al 2016

Tremblay et al 2016[160] Question	**Critical appraisal**	**AG comment**
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from the DECISION and SELECT trials
Were all the important and relevant costs and consequences for each alternative identified?	Partially unclear	Based on data from the phase III trials, time-trade off utility values that were taken from the Kerr et al (2014)[170] abstract (details provided via correspondence by lead author of paper). Details of resource use and costs were presented in the abstract. Details of discount rates were provided via correspondence by lead author (5%)
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	% discount rate used for both costs and outcomes obtained through correspondence with lead author
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Probabilistic sensitivity analysis was mentioned in the conclusion but no results or methods were reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs=incremental cost effectiveness ratios; AG=Assessment Group

Table 85 Critical appraisal checklist for the economic analysis completed by the AG – Wilson 2017

Wilson 2017[161] **Question**	**Critical appraisal**	**AG comment**
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from data collected in the DECISION and SELECT trials
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partially	Utility estimates were from a published study rather than directly from the trial population
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost, QALYS, LYs and ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Parameter and probabilistic sensitivity analyses were conducted
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs =incremental cost effectiveness ratios; QALYs=quality adjusted life years; LYs=life years; AG=Assessment Group

Table 86 Critical appraisal checklist for the economic analysis completed by the AG – SMC 2015

SMC 2015[49] **Question**	**Critical appraisal**	**AG comment**
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from the DECISION trial
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Unclear	
Were the cost and consequences valued credibly?	Unclear	
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Results of multiple parameter sensitivity analysis were reported
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs=incremental cost effectiveness ratios; AG=Assessment Group

Table 87 Critical appraisal checklist for the economic analysis completed by the AG – SMC 2016

SMC 2016[38] **Question**	**Critical appraisal**	**AG comment**
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from the DECISION and SELECT trials
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Scenario and sensitivity analysis was completed
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs=incremental cost effectiveness ratios; AG=Assessment Group

Table 88 Critical appraisal checklist for the economic analysis completed by the AG – CADTH 2015

CADTH 2015[5] **Question**	**Critical appraisal**	**AG comment**
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Not detailed in the report but effectiveness data were derived from the DECISION trial
Were all the important and relevant costs and consequences for each alternative identified?	Unclear	Not reported
Were costs and consequences measured accurately in appropriate physical units?	Unclear	
Were the cost and consequences valued credibly?	Unclear	
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost effectiveness ratios (ICERs) were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Results of several sensitivity analyses were presented
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs=incremental cost effectiveness ratios; AG=Assessment Group

Table 89 Critical appraisal checklist for the economic analysis completed by the AG – CADTH 2016

CADTH 2016[162] **Question**	**Critical appraisal**	**ERG comment**
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	Outcomes from data collected in the DECISION and SELECT trials
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Partially	From a published study[171] rather than directly from the trial population
Were costs and consequences adjusted for differential timing?	Unclear	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Incremental cost, QALYS, LYs and ICERs were reported
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Parameter sensitivity analysis was conducted
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

ICERs=incremental cost effectiveness ratios; QALYs=quality adjusted life years; LYs=life years