NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

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

Committee papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

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

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

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

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Assessment Group (AG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the AG before the company has checked the AG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues: clinical effectiveness

- Are trials generalisable to clinical practice?
  - Both DECISION and SELECT included patients with RR-DTC with PS 0-2 but unclear how many had symptomatic and/or rapidly progressing disease.
  - Palliative radiotherapy (commonly available in current practice) not allowed in SELECT. Trials do not report details of treatments used as part of BSC.
  - Both trials use post-progression anti cancer treatments
- Is RPSFTM adjustment appropriate (assumes post-progression treatments represents routine clinical practice)
  - Trials allowed cross over from placebo to active treatment
- Are there clinical reasons for the differences in comparator arms in trials? Is an indirect comparison appropriate?
  - AG: indirect comparison not appropriate because placebo arms in both trials not comparable (trial, population and data issues)
- Is there a difference in clinical effectiveness of lenvatinib and sorafenib?
- In clinical practice, can lenvatinib and sorafenib be used sequentially?
  - In SELECT 24% had prior VEGFR (including sorafenib)

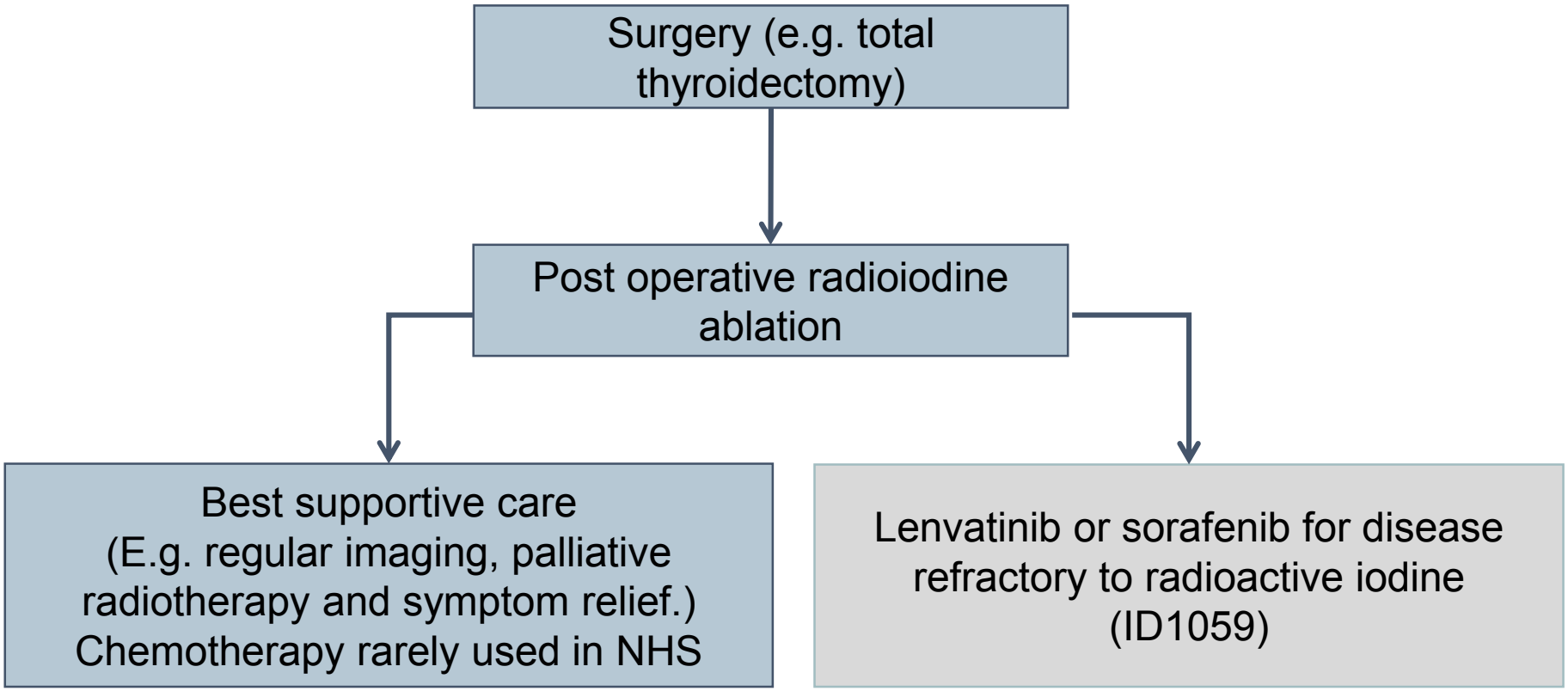
Key issues: cost-effectiveness

- Which model is most appropriate for decision making?
  - AG model does not include separate state responding to treatment
  - AG base case does not include indirect comparison because BSC arms not comparable (choice of BSC comparator has large impact on ICER)
  - All models use utility values from EQ-5D-3L data in DECISION. Eisai use data from Bayer's SMC submission and apply disutilties as weighted proportion based on vignette study. AG and Bayer do not include utility decrements
  - AG use exponential extrapolation for overall survival (SEER database)
  - AG use locally assessed PFS (closer to clinical practice) and longer time horizon (40 years)
- Most plausible ICER
- Are end of life criteria met?
- Are lenvatinib and sorafenib innovative?
- Are there any potential equalities issues?

Thyroid cancer

- Rare cancer representing only 1% of all malignancies
- Thyroid cancer can be differentiated' or 'undifferentiated
- 'Differentiated' thyroid cancer cells still retain appearance of normal thyroid cells and do not spread as rapidly.
- Differentiated thyroid cancer (DTC) accounts for most thyroid cancers (94%), in particular papillary, follicular and Hürthle cell types
- 10-year survival for people with DTC is around 90%.
- Surgery most common treatment; radioactive iodine ablation can be given afterwards to destroy remaining cancer cells. External beam radiotherapy and chemotherapy used for palliative care
- Only around 225 new cases of DTC that does not respond to radioactive iodine diagnosed each year in England and Wales
- Sorafenib currently available through CDF for
  - Papillary or follicular thyroid cancer
  - Inoperable or metastatic disease, refractory to radioiodine

Treatment pathway for thyroid cancer



Recreated using section 1 in assessment report

*** Clinical advice to the AG - In clinical practice, BSC often preferred treatment option for RR-DTC (at least until symptoms occur) ***

Impact on patients and carers (1)
Patient and professional submissions

- Received submissions from 3 organisations (NCRI/RCP/RCR/ACP, Butterfly thyroid cancer trust, The British Thyroid Foundation)
- Rare cancer: good patient information and dedicated clinical nurse specialists often not available
- Patients often experience systemic complications
  - For example breathing difficulties from lung metastases, pain, bone fractures, swallowing difficulties
- Low mood, fatigue, anxiety and depression commonly reported
- Poor quality of life

Impact on patients and carers (2)
Lenvatinib and sorafenib

- No alternative treatments (best supportive care may include palliative radiotherapy, locally ablative therapies, analgesia, bisphosphonates and/or denosumab) – not likely to impact survival
- Currently sorafenib available through CDF and lenvatinib (progressed on or intolerance to sorafenib) through compassionate access programme
- Treatment can help control symptoms and manage pain-allowing return to work and improved quality of life
- Psychological benefits of treatment-increased optimism and emotional wellbeing
- Side effects of lenvatinib (gastrointestinal) and sorafenib (hand and foot syndrome) manageable
- Lenvatinib oral-no need to attend hospital and easy to take

Decision problem

	NICE scope	Assessment group
Population	Adults with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine	As NICE scope
Interventions	• Lenvatinib • Sorafenib	
Comparators	• The interventions listed above will be compared with each other • Best supportive care (BSC)	AG model compares interventions vs placebo + BSC: • No direct evidence comparing lenvatinib with sorafenib • Indirect comparison not appropriate as risk profiles in placebo + BSC arms of 2 main trials not comparable*
Outcomes	Overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life	

*Both company's reported indirect treatment comparisons

The technologies

Lenvatinib	Sorafenib
• Lenvima (Eisai) 4mg & 10mg capsules • inhibits multiple receptor tyrosine kinases including vascular endothelial growth factor (VEGF) receptors 1-3, • recommended daily dose 24mg • continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs • £1,437 for 4 and 10mg (BNF Dec 2016) • Cost per year: £52,307(assuming max starting dose, source: AR) • Confidential PAS available	• Nexavar (Bayer) 200mg tablets • inhibits multiple receptor tyrosine kinases including VEGF receptors 2-3 • recommended daily dose 800 mg • continue treatment as long as clinical benefit is observed or until unacceptable toxicity occurs • £3,576.56 for 112 x 200mg tablets (BNF Dec 2016) • Cost per year: £38,746 (assuming max starting dose, source: AR) • Confidential CAA available
Marketing authorisation	Marketing authorisation
treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.

SELECT and DECISION trials

	SELECT	DECISION
Design	phase 3 multi-centre double-blind randomised controlled trial	
Population	• histologically/cytologically confirmed diagnosis of radioactive iodine-refractory (RR-DTC) showing progression within 12 months • **0 or 1 prior VEGF/VEGFR therapy** • ECOG 0-2	• locally advanced or metastatic RR-DTC (papillary, follicular [including Hürthle cell], and **poorly differentiated**) • progression in past 14 months • at least 1 measurable lesion by CT or MRI • ECOG 0-2
Intervention	Lenvatinib 24 mg	Sorafenib 800 mg
Comparator	Placebo	
Concomitant drugs	Allowed thyroid hormone suppressive therapy (other anti-tumour therapies not allowed)	Allowed thyroid hormone replacement, bisphosphonate, narrow therapeutic index medication e.g. warfarin etc.
Duration and location	Median treatment: 13.8 months, 117 sites (including Europe)	Median treatment: 10.6 months, 18 countries (including Europe)

Baseline characteristics

Characteristic	SELECT		DECISION	
	Lenvatinib (n=261)	Placebo (n=131)	Sorafenib (n=207)	Placebo (n=210)
Papillary carcinoma	169 (64.8)	90 (68.7)	118 (57.0%)	119 (56.7%)
Follicular	92 (35.2)	41 (31.3)	NR	NR
Follicular (Hürthle cell)	48 (18.4)	22 (16.8)	37 (17.9%)	37 (17.6%)
Follicular non-Hürthle cell	53 (20.3)	22 (16.8)	13 (6.3%)	19 (9.0%)
Poorly differentiated	28 (10.7)	19 (14.5)	24 (11.6%)	16 (7.6%)
Median time from diagnosis 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)
Prior VEGFR therapy	66 (25.3)	27 (20.6)	NR	NR
Previous anticancer therapy	NR	NR	7 (3.4%)	6 (2.9%)
All data are proportions unless otherwise stated.				

Source: Table 4 in Bayer submission and table 6 in Eisai submission

Cross over

- OS immature at primary analysis for SELECT and DECISION.
- Cross over from placebo to active treatment after progression in both trials (OS data needs adjustment)
- Both companies and AG prefer rank preserving structural failure time (RPSFT) model to correct cross over

	SELECT		DECISION	
Data cut	Lenvatinib	BSC	Sorafenib	BSC
1	N/A	83.2	26.6*	71.4
2	N/A	87.8	NR	74.8
3	N/A	87.8	NR	75.0
All data are proportions crossing over. Abbreviations: NR not reported. *permitted to receive additional sorafenib				

Treatment post progression

- Some patients received subsequent anti-cancer treatments after disease progression, not part of the trial protocols
- **AG caveat:** RPSFTM adjustment assumes post-progression anti-cancer treatments, other than those permitted by treatment crossover, represents routine clinical practice

Treatment	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)

† includes pazopanb and sorafanib in SELECT, but not reported for DECISION
*Various includes the following categories: other therapeutic radiopharmaceuticals; all other therapeutic products; diagnostic agents; diagnostic radiopharmaceuticals

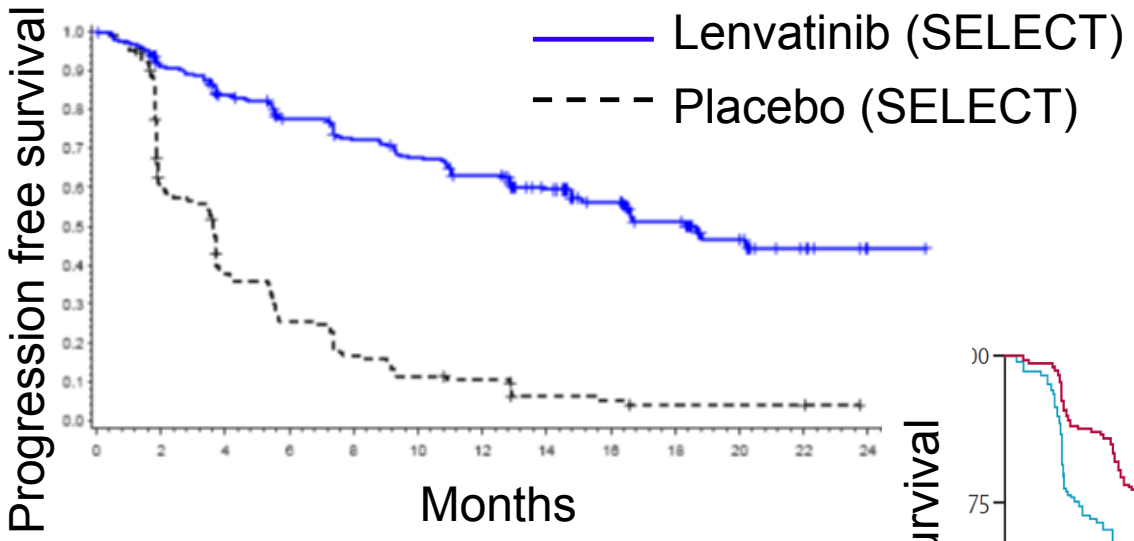
Source: Table 10 in AR

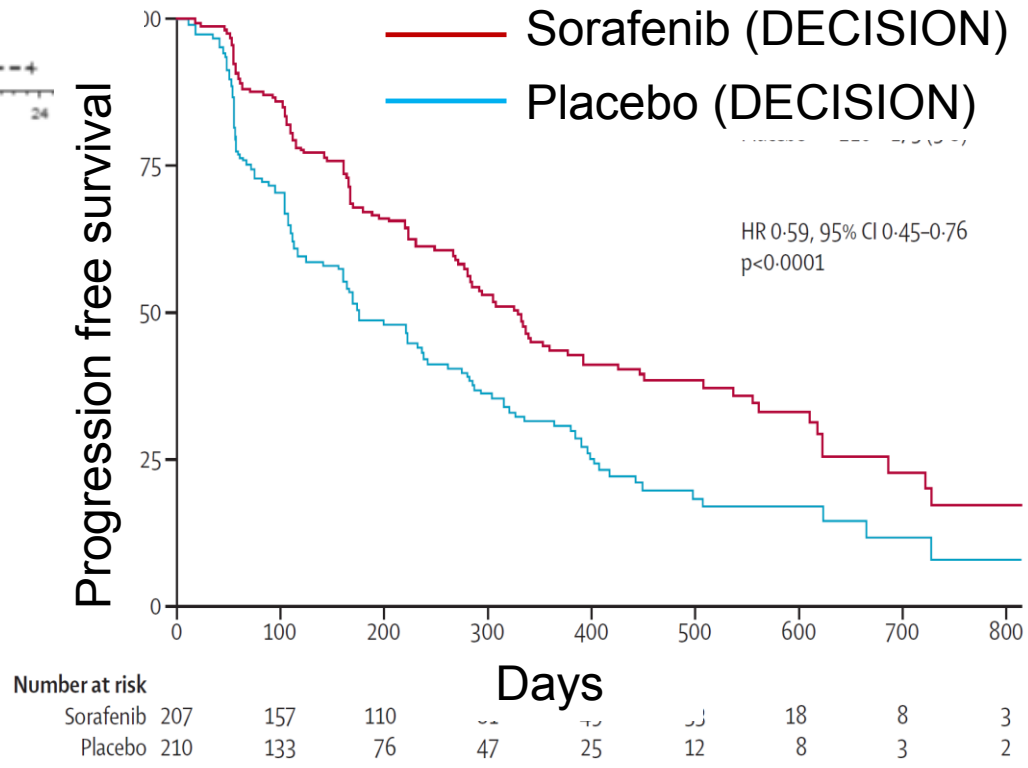
Summary of clinical effectiveness (1)

Outcome	Data cut	Lenvatinib vs. placebo (SELECT)	Sorafenib vs. placebo (DECISION)
Median PFS-independent review (months)	1.	Lenvatinib: 18.3 (15.1 to NE) Placebo: 3.6 (2.2 to 3.7)	Sorafenib: 10.8 (NR) Placebo: 5.8 (NR)
PFS (independent review)	1.	HR 0.21 (95% CI 0.14 to 0.31)*	HR 0.59 (0.45 to 0.76)*
Median PFS-investigator (months)	1.	Lenvatinib: 16.6 (4.8 to NE) Placebo: 3.7 (3.5 to NE)	Sorafenib: 10.8 (NR) Placebo: 5.8 (NR)
PFS (investigator)	1.	HR 0.24 (0.16 to 0.35)*	NR

Abbreviations: CI confidence interval; HR hazard ratio; OS overall survival; PFS progression free survival;
*stratified HR, SELECT: age (≤65 years or >65 years), geographical region (Europe, North America, Other) and prior VEGFR-targeted therapy (0, 1). DECISION: age (<60 years or ≥60 years) and geographical region (North America, Europe, Asia)

Progression free survival





Summary of clinical effectiveness (2)

Outcome	Data cut	Lenvatinib vs. placebo (SELECT)	Sorafenib vs. placebo (DECISION)
OS	3.	HR 0.84 (0.62 to 1.13)	HR 0.92 (0.71 to 1.21)
Median OS (months)	3.	Lenvatinib: 41.6 (31.2 to NE) Placebo: 34.5 (21.7 to NE)	Sorafenib: 39.4 (32.7 to 51.4) Placebo: 42.8 (34.7 to 52.6)
OS (RPSFTM)	3.	HR 0.54 (0.36 to 0.80)†	HR 0.77 (0.58 to 1.02)
ORR (%)	NR	Lenvatinib: 64.8 (59.0 to 70.5) Placebo: 1.5 (0.0 to 3.6)	Sorafenib:12.2 (8.0 to 17.7) Placebo: 0.5 (0.0 to 2.7)
Median time to response (months)	NR	Lenvatinib: 2.0 (1.9 to 3.5) Placebo: 5.6 (1.8 to 9.4)	Sorafenib: NR Placebo: NR
Progressive disease (%)	NR	Lenvatinib: 18 (6.9) Placebo: 52 (39.7)	Sorafenib: 20 (10.2) Placebo: 46 (22.9)
EQ-5D	NR	NR	Did not reach clinical minimal important difference

Abbreviations: ORR, objective tumour response rate. † 95% confidence interval from bootstrapping (reported in AR) and assumes that proportional hazards applies

Subgroup results

Prior TKI treatment

- No patients in DECISION had received prior treatment with a TKI

SELECT subgroup	Median PFS
Prior VEGFR-targeted therapy	HR 0.22 (0.12 to 0.41)
No prior VEGFR-targeted therapy	HR 0.20 (0.14 to 0.27)

Symptomatic disease

- Subgroup analyses based on symptomatic disease not carried out in SELECT

DECISION subgroup	Median PFS
Symptomatic (approx. 20%)	HR 0.386 (0.207 to 0.720)
Asymptomatic (approx. 80%)	HR 0.602 (0.448 to 0.807)

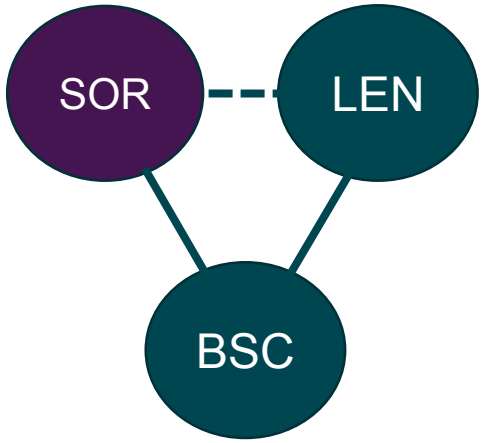
Summary of adverse events

- Most common Grade ≥3 AEs were hypertension and hand-foot syndrome for patients treated with lenvatinib (>40%) and sorafenib (>20%) respectively

Outcome, n (%)	SELECT		DECISION	
	Lenvatinib (N=261)	Placebo (N=131)	Sorafenib (N=207)	Placebo (N=209)
Any AE*	260 (99.6)	118 (90.1)	204 (98.6)	183 (87.6)
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)
SAEs	133 (51.0)	31 (23.7)	77 (37.2)	55 (26.3)
Dose interruptions from AE	215 (82.4)	24 (18.3)	137 (66.2)	54 (25.8)
Discontinuation due to AE	43 (16.5)	6 (4.6)	39 (18.8)	8 (3.8)

Abbreviations: AE adverse events; SAE serious adverse event
*All-Grade adverse events reported by ≥30% of patients in any arm of the SELECT and DECISION trials

Indirect treatment comparison (ITC)



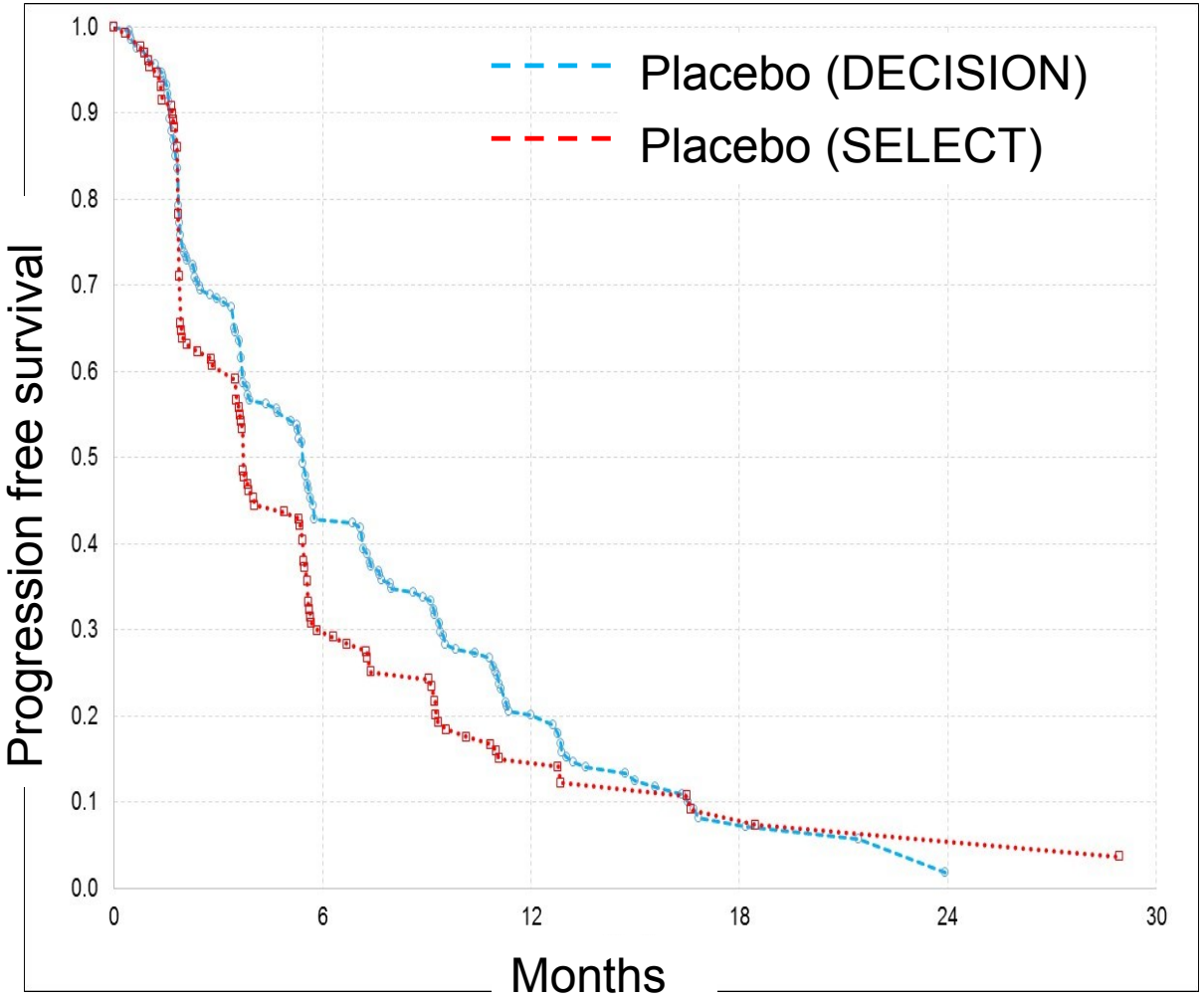
- No direct evidence for lenvatinib vs. sorafenib
- Both companies use indirect treatment comparison
- AG: ITC not appropriate because BSC arms in 2 trials not comparable

Trial characteristics	• Previously treated with VEGFR targeted therapy allowed in SELECT but not DECISION • Palliative radiotherapy not allowed in SELECT • Post progression treatment differed
Population characteristics	• Higher cross over in SELECT • Gender, race, geographic region, ECOG PS, time from diagnosis, histology and site of metastases differed within and between trials
Data	• PFS KM data for placebo arms: risk profiles not comparable • Proportional hazards assumption only met for unadjusted OS HR in DECISION

Summary of companies' ITC results

Outcome	Eisai (lenvatinib)	Bayer (sorafenib)
Lenvatinib vs. sorafenib (indirect)		
PFS	RR [redacted]	RR [redacted]
OS	RR [redacted]	HR [redacted]
Grade 3 or 4 AE	Not reported	HR [redacted]
Serious AE	Not reported	HR [redacted]
Discontinuation due to AE	Not reported	HR [redacted]
Abbreviations: AE adverse events; OS overall survival; PFS progression free survival; Analysis for PFS is unadjusted and OS is adjusted using RPSFTM * Bayer ITC is for sorafenib vs. lenvatinib		

PFS data in placebo arms



- PFS in placebo arms of both trials should be similar
- KM plots (placebo arms) for PFS similar for 1st 2 months but curves separate markedly after
- higher initial risk of progression in 1st 10 months in SELECT, then risk in placebo arm reduces by more than 50%
- Inconsistent pattern of temporal change and implies placebo arms not from similar patient groups

Assessment Group comments

Trials	• Both trials relevant, good quality but relevance to NHS questionable (TKI toxicity concerns so treat when symptomatic or clinically significant progression)
Lenvatinib vs. sorafenib	• Indirect comparison not appropriate because risk profiles of placebo arms across 2 trials not comparable • AG: results from other indirect comparisons should be interpreted with caution
Comparison with BSC	• PFS and ORR: significant improvements with both lenvatinib and sorafenib • OS: significant improvement with lenvatinib but not sorafenib (RPSFTM) • Unadjusted OS estimates in trials higher compared with observational studies
Other issues	• Concomitant palliative radiotherapy allowed in DECISION but not SELECT and full details of BSC not reported • Proportional hazards assumption only holds for unadjusted OS (DECISION) so caution with all other HR results

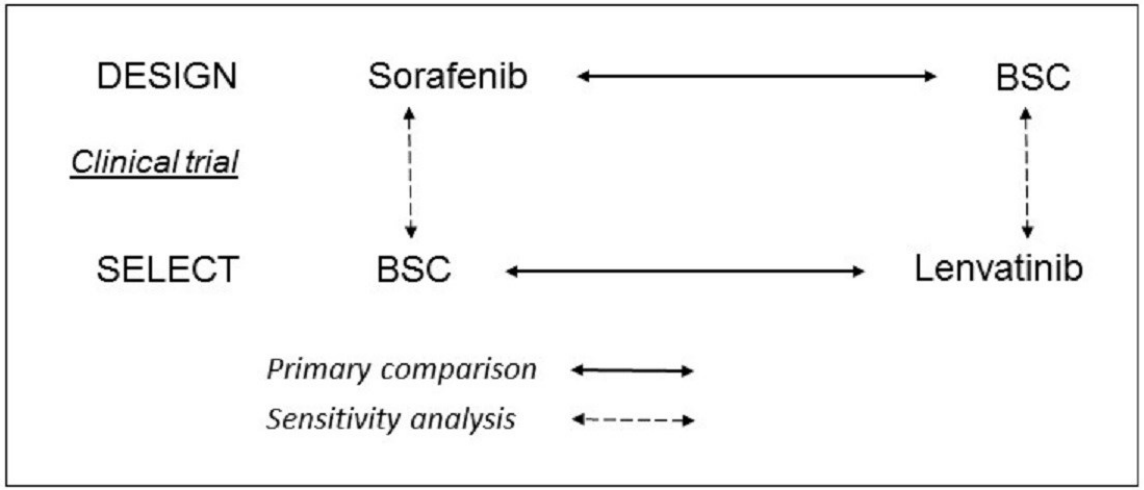
Key issues: clinical effectiveness

- Are trials generalisable to clinical practice?
  - Both DECISION and SELECT included patients with RR-DTC with PS 0-2 but unclear how many had symptomatic and/or rapidly progressing disease.
  - Palliative radiotherapy (commonly available in current practice) not allowed in SELECT. Trials do not report details of treatments used as part of BSC.
  - Both trials use post-progression anti cancer treatments
- Is RPSFTM adjustment appropriate (assumes post-progression treatments represents routine clinical practice)
  - Trials allowed cross over from placebo to active treatment
- Are there clinical reasons for the differences in comparator arms in trials? Is an indirect comparison appropriate?
  - AG: indirect comparison not appropriate because placebo arms in both trials not comparable (trial, population and data issues)
- Is there a difference in clinical effectiveness of lenvatinib and sorafenib?
- In clinical practice, can lenvatinib and sorafenib be used sequentially?
  - In SELECT 24% had prior VEGFR (including sorafenib)

Companies' models

	Eisai (lenvatinib)	Bayer (sorafenib)
Model	Partitioned survival model (informed by trial data)	
Number of health states	4 (stable disease, response, progressive and death)	3 (progression-free, progressed and death)
Treatment duration	Informed by trial data	
BSC arm	Not associated with additional costs	
Cycle	1 month cycle (treatment cycle for both lenvatinib and sorafenib 28 days)	
Time horizon	33 years (scenarios: 5 and 10 year)	30 years
Discount	3.5% and half cycle correction	

AG model structure



1.
   - No separate health state for people responding to treatment
   - clinical input suggests no additional merit for separate state
2.
   - Each treatment represented in natural time metric (lenvatinib 30 day and sorafenib 28 day cycles)
   - Can demonstrate non-equivalence of 2 placebo +BSC arms
3.
   - Maximum time horizon: 40 years

Source: Figure 9 in AR

Summary of base case

Model	Eisai	Bayer	AG approach
Survival data	Indirect comparison with RPSFT adjustment		Indirect comparison not appropriate. Compare each drug against own BSC arm (scenario: other BSC arm)
Extrapolation	PFS: Piecewise gamma, OS: Piecewise exponential	PFS and OS: Exponential	PFS: Locally assessed (closer to clinical practice). Exponential OS: Exponential
Treatment duration	LEN: trial SOR: treat to progression	From trials	From trials (lenvatinib mean 12.61 cycles, sorafenib 14.36 cycles per patient)
PPS	No treatment	Treat until progression¥	Exponential
Utilities	From trial*	From trial	Trial (scenario: Eisai data)

Abbreviations: LEN; lenvatinib, SOR; sorafenib, PFS; progression free survival, OS; overall survival. *utilities from DECISION and disutilities applied as weighted proportion from vignette (Fordham et al 2015). ¥or until treatment discontinuation

Extrapolations

- Companies use extrapolation based on measures of fit
- AG: companies approach doesn't take into account wider evidence base on natural history of disease
  - AG investigate long term survival trends for locally advanced or metastatic thyroid cancer in USA (SEER database n=32,818 people over 15 years)
  - Close match between data from SEER database and simple linear model indicates risk of death unchanged throughout time period (simple exponential survival process)
  - Fit exponential models to estimate lifetime survival

Outcome	Eisai	Bayer	AG
PFS	Gamma	Exponential	Exponential
OS	Exponential	Exponential	Exponential

Abbreviations: OS overall survival; PFS progression free survival

Model estimates

Outcome	AG estimate	LEN gain	SOR gain
PFS	Lenvatinib: 41.0, Placebo: 6.9 Sorafenib: 47.2, Placebo: 7.6	*+34.1*	*+39.6*
OS (RPSFT)	Lenvatinib: 55.1, Placebo: 30.2 Sorafenib: 56.7, Placebo: 47.2	*+24.9*	*+9.5*
PPS	Lenvatinib: 14.1, Placebo: 23.3 Sorafenib: 9.5, Placebo: 39.6	*-9.2*	*-30.1*

Abbreviations: OS overall survival; PFS progression free survival; PPS post progression survival

Assessment group:

- PFS results appear similar but for lenvatinib 73% PFS gain translated to OS gain compared with 24% for sorafenib
- Lenvatinib shows improved OS and worse PPS

Health related quality of life

- No utility data from SELECT for lenvatinib. Both companies use EQ-5D data from DECISION for sorafenib and exclude adverse events from base case (effect of adverse events captured in EQ-5D response from DECISION)
- Eisai: disutilities applied as weighted proportion from vignette Fordham et al 2015
- AG: concerned that models do not account for duration of AE disutilities but use same values as Bayer (scenario: Eisai values)

State	Eisai (lenvatinib)	Bayer (sorafenib)	AG
Stable disease	Lenvatinib: 0.76, Sorafenib: 0.68, BSC: 0.77	N/A	N/A
Response	Lenvatinib: 0.76, Sorafenib: 0.68, BSC: 0.7	N/A	N/A
Progression free	N/A	Lenvatinib: 0.72 Sorafenib: 0.72 BSC 0.80	
Post progression	Lenvatinib: 0.76, sorafenib: 0.68, BSC: 0.77	0.64	

Source: Tables 18 and 27 in Eisai and Bayer submission

List price cost effectiveness results

Base case	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER per QALY gained
Eisai model results					
Lenvatinib	3.18	£107,182	-	-	**-**
Sorafenib	2.10	£82,839	1.08	£24,342	**£22,491 (LEN vs SOR)**
BSC	1.84	£42,115	1.34	£65,067	**£48,569 (LEN vs BSC)**
Bayer model results					
BSC	2.35	25,712	-	-	-
Sorafenib	3.16	71,154	0.81	45,441	**£56,417 (SOR vs BSC)**
Lenvatinib	4.04	87,800	1.687	62,088	**£36,802 (LEN vs BSC)**
AG model results					
Lenvatinib	2.82	£95,102	1.21	£79,907	**£65,872 (LEN vs BSC)**
BSC	1.60	£15,195	-	-	-
Sorafenib	2.75	£63,188	0.53	£45,234	**£85,644 (SOR vs BSC)**
BSC	2.22	£17,954	-	-	-

- AG probabilistic ICERs lenvatinib vs. BSC: £66,038 per QALY gained and sorafenib vs. BSC £83,547 per QALY gained

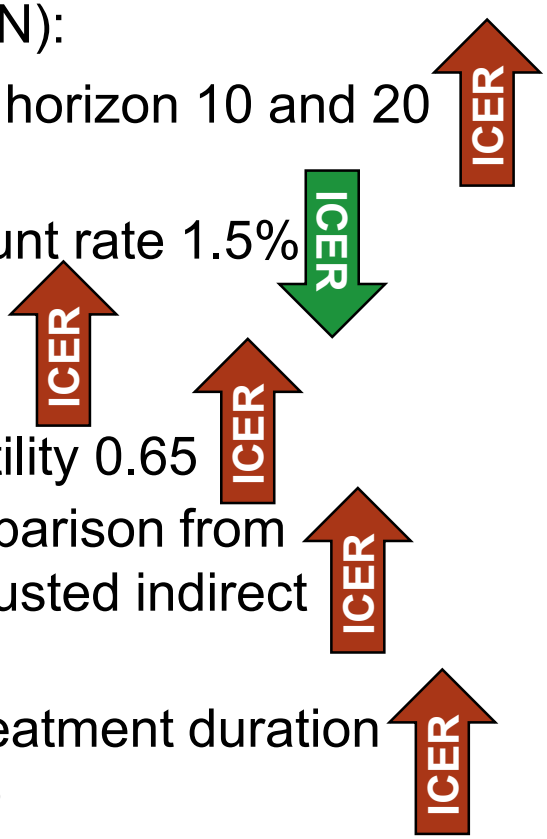
Note: list price ICERs for Bayer are from table 50 in the AR (Bayer report PAS analyses only)
Confidentiality marking has been updated before publication

Companies' scenario analyses

Scenario (Eisai)	ICER	
	LEN vs. BSC	LEN vs. SOR
Base case	**NR**	**£22,491**
1.5% discount	NR	£20,765
Medical cost ± 20%	NR	£21,403 to £23,578
Mortality cost ± 20%	NR	£22,436 to £22,546
Higher utility (vignette)	NR	£19,953
Change PFS & OS extrapolations	NR	£20,015 to £29,115
20 wk extrapolation	NR	£29,874
LEN treat to progression	NR	£71,978
Exclude AE disutility	NR	£22,084

Bayer also carry out scenario analyses (direction of effect on ICER for SOR vs. LEN):

- Shorter time horizon 10 and 20 years
- Lower discount rate 1.5%
- Weibull PFS
- Weibull OS
- Lenvatinib utility 0.65
- Indirect comparison from matched adjusted indirect comparison
- Increased treatment duration for lenvatinib



Largest impact:10 year time horizon, lower LEN utility and longer LEN treatment duration

AG scenario analyses

- Substitute placebo arm data from each trial to assess importance of available comparator data
- Results show large changes in AG base case ICER
  - increase of 105% for lenvatinib vs. BSC
  - decrease of 54% for sorafenib vs. BSC
- Confirm trial populations not equivalent (indirect comparison not appropriate)
- BSC comparator - key factor in cost effectiveness results

Base case	Lenvatinib vs. BSC	Sorafenib vs. BSC
AG base case	£65,872	£85,644
Cross trial placebo arm	**£130,592**	**£41,716**

End of life criteria

- AG: neither treatment meet end of life criteria
- No active treatment option available in England & Wales (best supportive care only alternative)

End of life criteria	Life expectancy (median OS)	Life extension
Eisai (Lenvatinib)	SELECT placebo: 34.5 months Model: Not reported	No details reported in submission
Bayer (Sorafenib)	DECISION placebo: 42.8 months Model: Not reported	Median OS extended by 8.54 months vs. BSC
AG	SELECT placebo 30.2*, DECISION placebo 47.2* Model: lifetime mean lenvatinib 55.1 months and sorafenib 56.7 months	survival gain compared with BSC >9 months for both
*RPSFT adjusted		

Innovation and equality

- Potential equality issues not raised by companies or other stakeholders

Innovation: lenvatinib

- Company consider lenvatinib innovative as it is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode
- Unlike sorafenib, shown that fibroblast growth factor FGF23 is significantly upregulated with lenvatinib and this was associated with longer PFS
- Lenvatinib has reduced tumour size in the majority of patients (65% in the SELECT trial, including 4 complete responses)

Innovation: sorafenib

- Company consider first licensed MKI treatment for radioactive iodine-refractory advanced and progressive differentiated thyroid cancer.
- treatment could allow patients to return to normal daily activities such as caring for their children or returning to work and contribute to family life.

Key issues: cost-effectiveness

- Which model is most appropriate for decision making?
  - AG model does not include separate state responding to treatment
  - AG base case does not include indirect comparison because BSC arms not comparable (choice of BSC comparator has large impact on ICER)
  - All models use utility values from EQ-5D-3L data in DECISION. Eisai use data from Bayer's SMC submission and apply disutilties as weighted proportion based on vignette study. AG and Bayer do not include utility decrements
  - AG use exponential extrapolation for overall survival (SEER database)
  - AG use locally assessed PFS (closer to clinical practice) and longer time horizon (40 years)
- Most plausible ICER
- Are end of life criteria met?
- Are lenvatinib and sorafenib innovative?
- Are there any potential equalities issues?

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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

This report was commissioned by the NIHR HTA Programme as project number 16/51/20

24 July 2017

Contains academic in confidence and commercial in confidence information

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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None.

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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.

In addition, Eisai Ltd 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 following data reported in the clinical study report for the DECISION trial was previously marked as commercial in confidence but which Bayer Healthcare agreed could be cited in this report without confidentiality restrictions:

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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Rider on responsibility for report
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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Nigel Fleeman	Reviewer of evidence for clinical effectiveness including study selection, data extraction, synthesis and interpretation; study selection for inclusion into cost effectiveness review, editorial input
Rachel Houten	Reviewer of evidence for cost effectiveness including study selection, data extraction, synthesis and interpretation; study selection for inclusion into clinical effectiveness review. Development of cost models for routine treatment and adverse events
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Angela Boland	Interpretation of clinical and cost effectiveness evidence, editorial input
Yenal Dundar	Data extraction and quality assessment of studies included in the clinical effectiveness review
Janette Greenhalgh	Data extraction and quality assessment of studies included in the clinical effectiveness review
Juliet Hounsome	Protocol development and selection of studies for inclusion into clinical effectiveness review
Rui Duarte	Editorial input
Aditya Shenoy	Clinical advice on all aspects of the review

All authors contributed to the writing of the report

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

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]

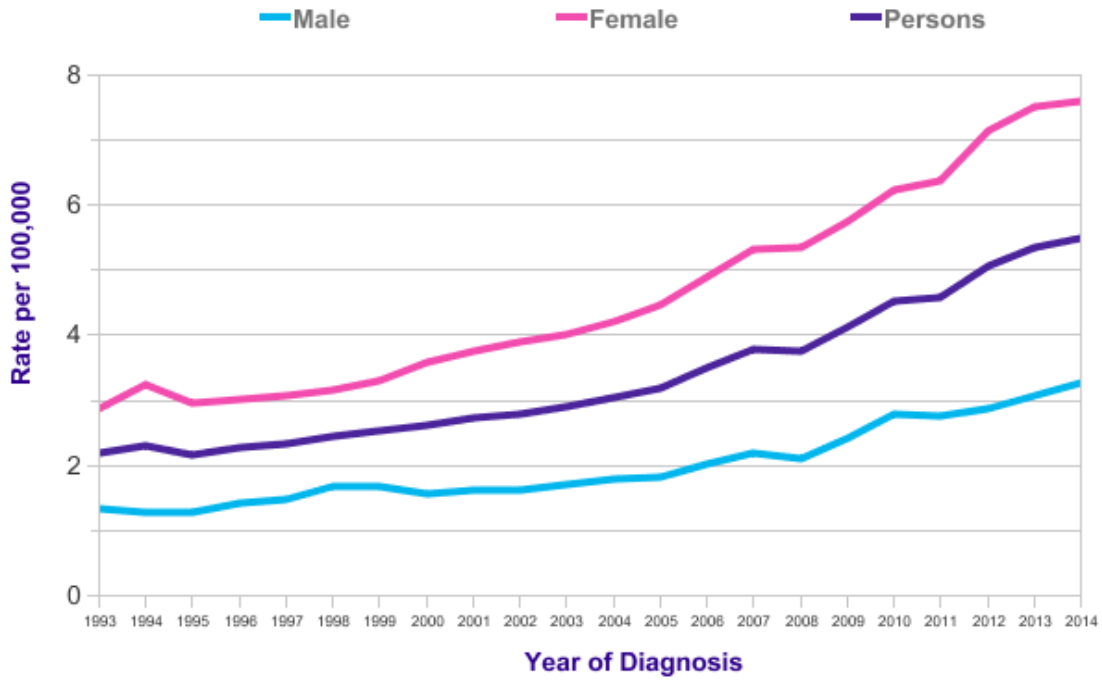

Figure 1 Average number of new cases per year per 100,000 population, UK

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).

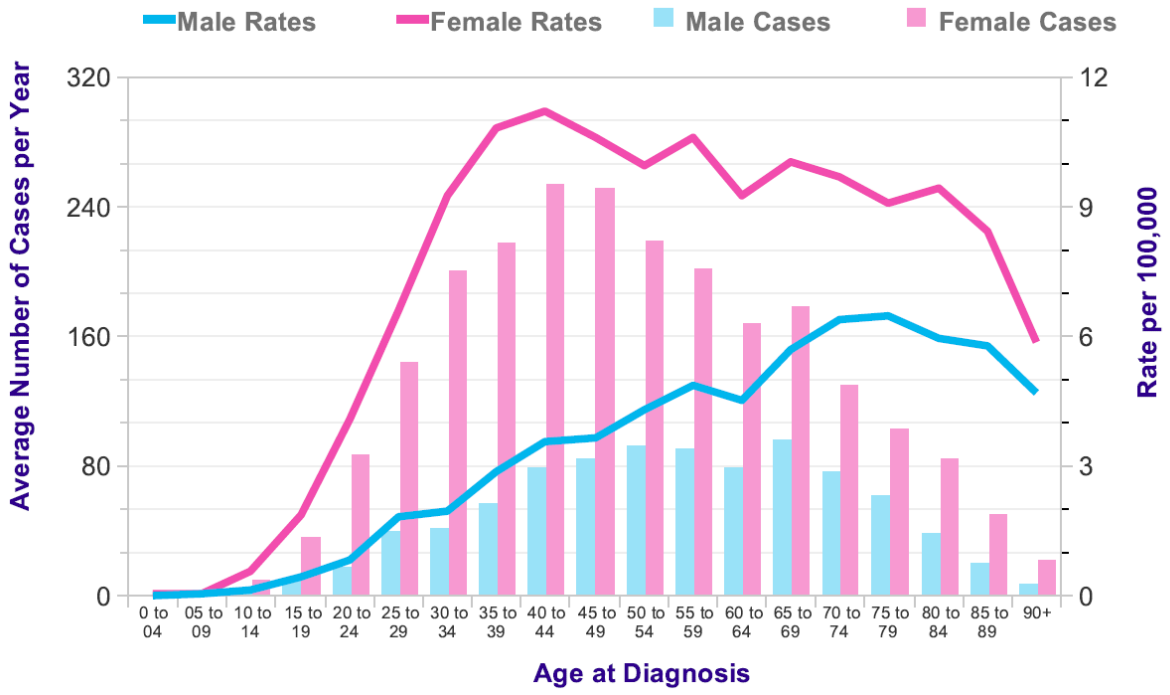

Figure 2 Age-specific incidence rates per 100,000 population, UK

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]

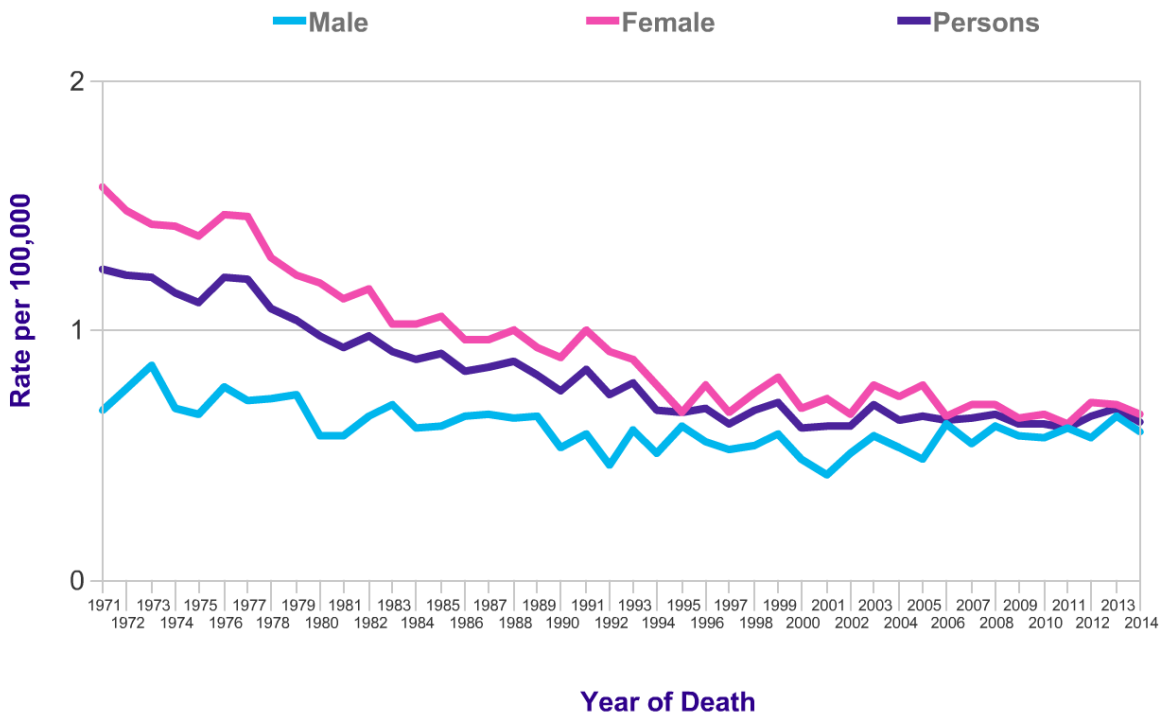

Figure 3 Thyroid Cancer, European Age-Standardised Mortality Rates, UK, 1971-2014

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[7] 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]

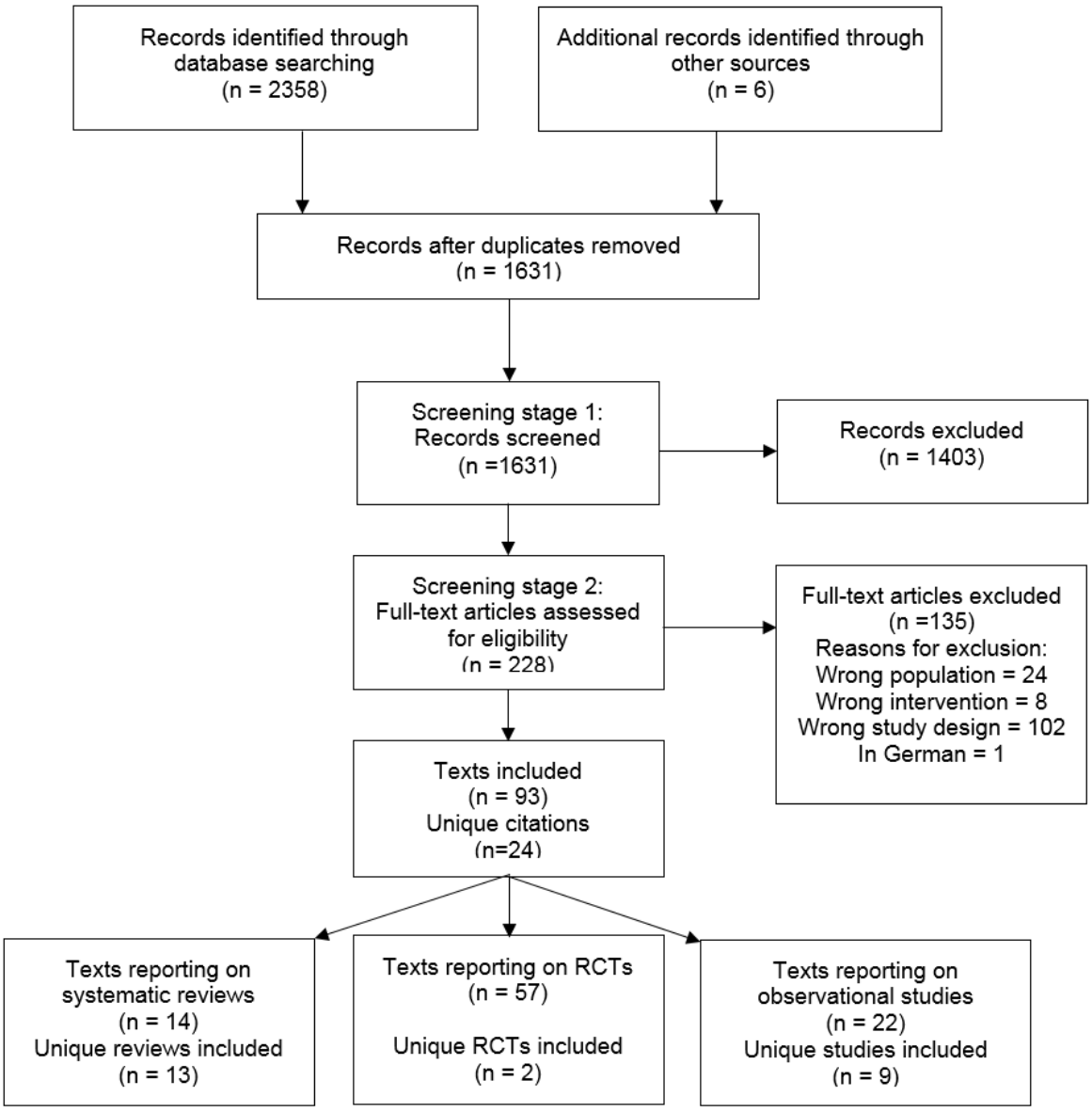

Figure 4 PRISMA flow diagram: studies included in AG's systematic review

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 (22.1 to 24.5)	24.1 (23.1 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)	37.0 (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	135 (51.9)	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).

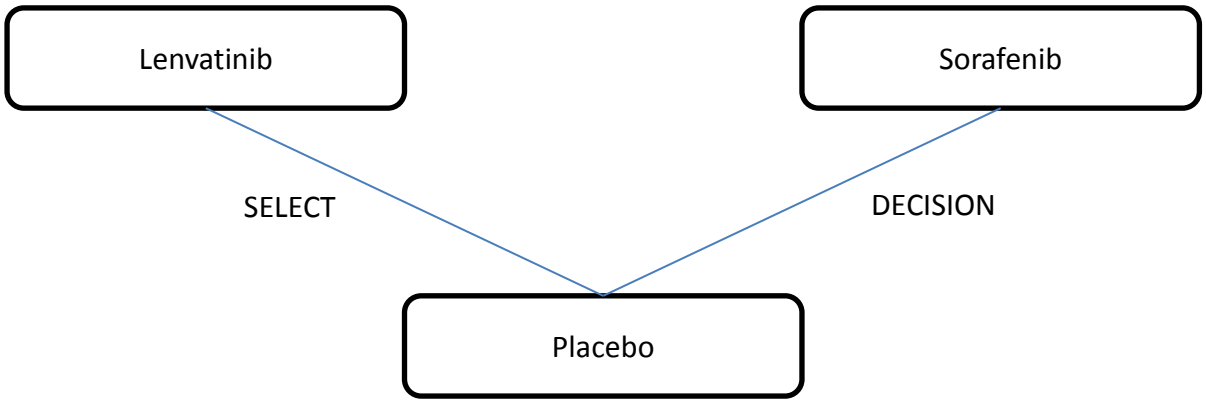

Figure 5 Indirect comparison network

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.

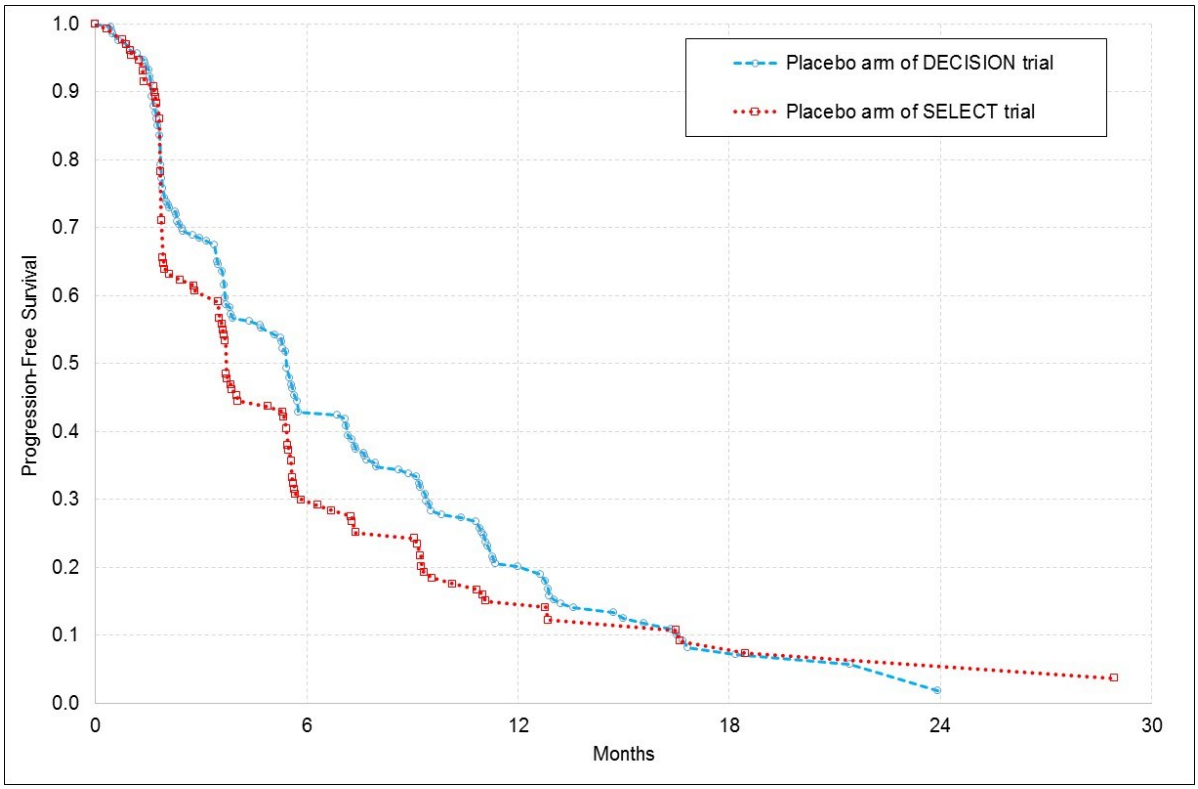

Figure 6 Comparison of progression-free survival in the placebo arms of the DECISION and SELECT clinical trials

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%.

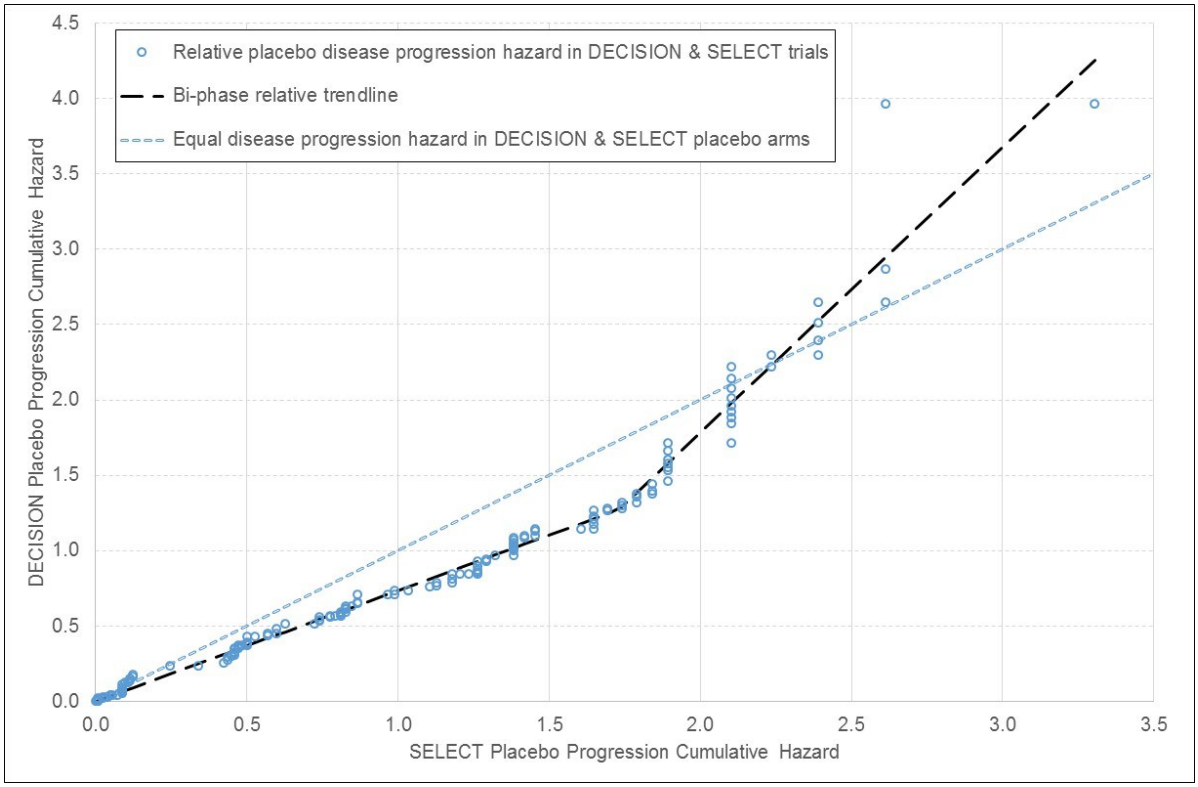

Figure 7 Comparison of progression-free survival hazard trends in the placebo arms of the DECISION and SELECT clinical trials

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[12,13] 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.

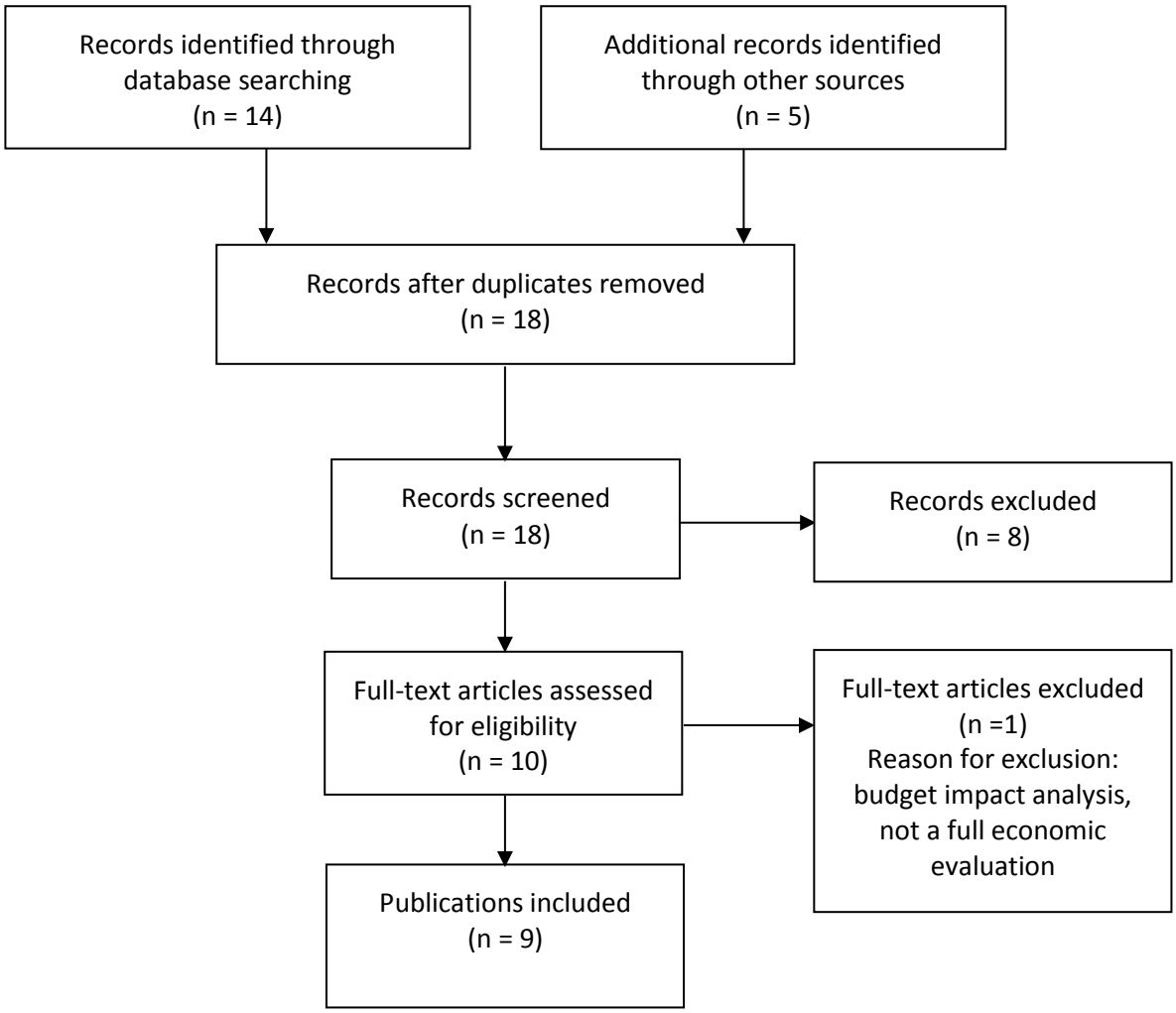

Figure 8 PRISMA flow diagram: AG economic literature review

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	£25,712	3.49	2.35				
Sorafenib	[redacted]	4.79	3.16	[redacted]	1.30	0.81	[redacted]
Lenvatinib	£87,800	5.92	4.04	[redacted]	1.12	0.88	£36,802

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	£26,612 (£1,429 to £60,687)	2.41 (1.00 to 5.19)				
Sorafenib	[redacted]	3.25 (1.81 to 5.30)	[redacted]	0.84	[redacted]	[redacted]
Lenvatinib	£90,448 (£60,133 to £128,193)	4.11 (2.02 to 6.67)	[redacted]	0.86	£37,483	[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 £38,064 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).

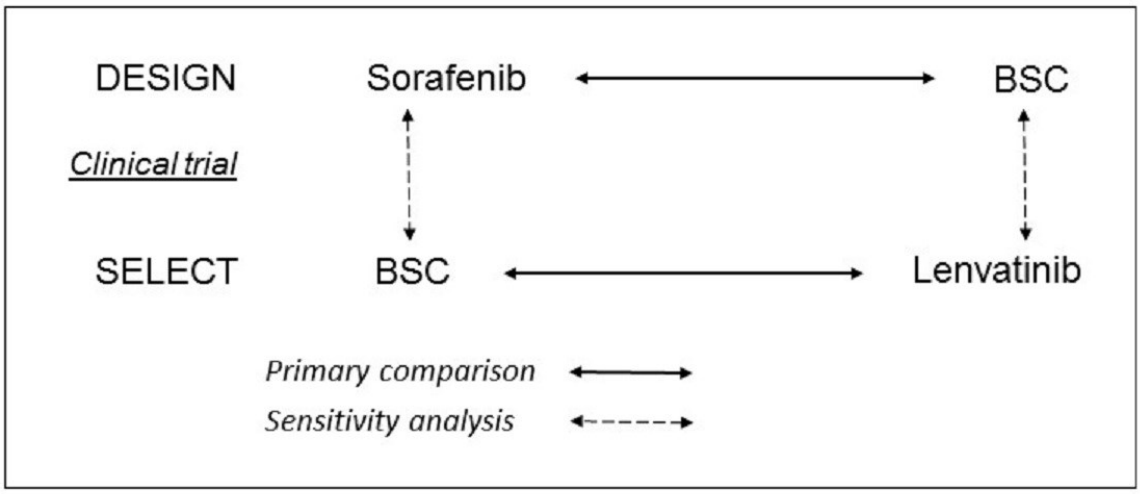

Figure 9 Model structure featuring two simple trial based comparisons, with additional cross-trial comparisons as a structural sensitivity analysis to illustrate the uncertainty associated with choice of comparator

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.

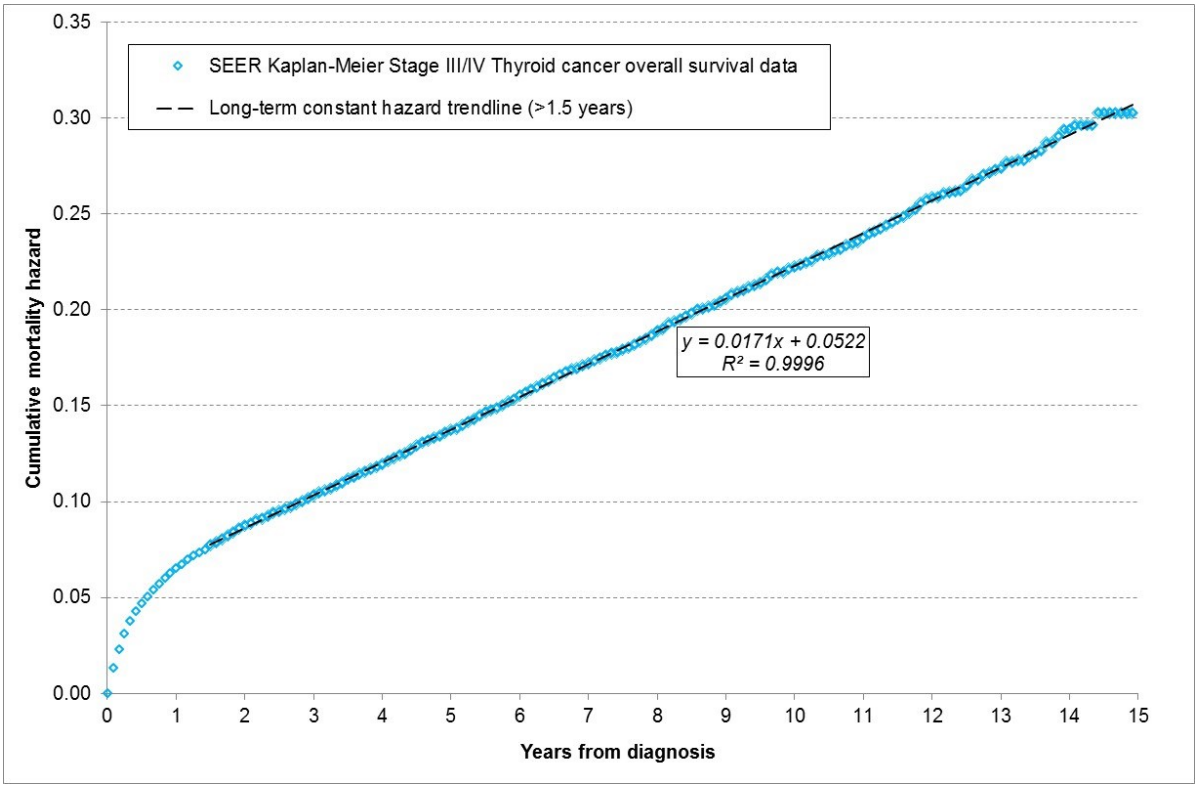

Figure 10 Cumulative hazard data from follow-up of patients diagnosed with Stage III/IV thyroid cancer for 15 years

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.

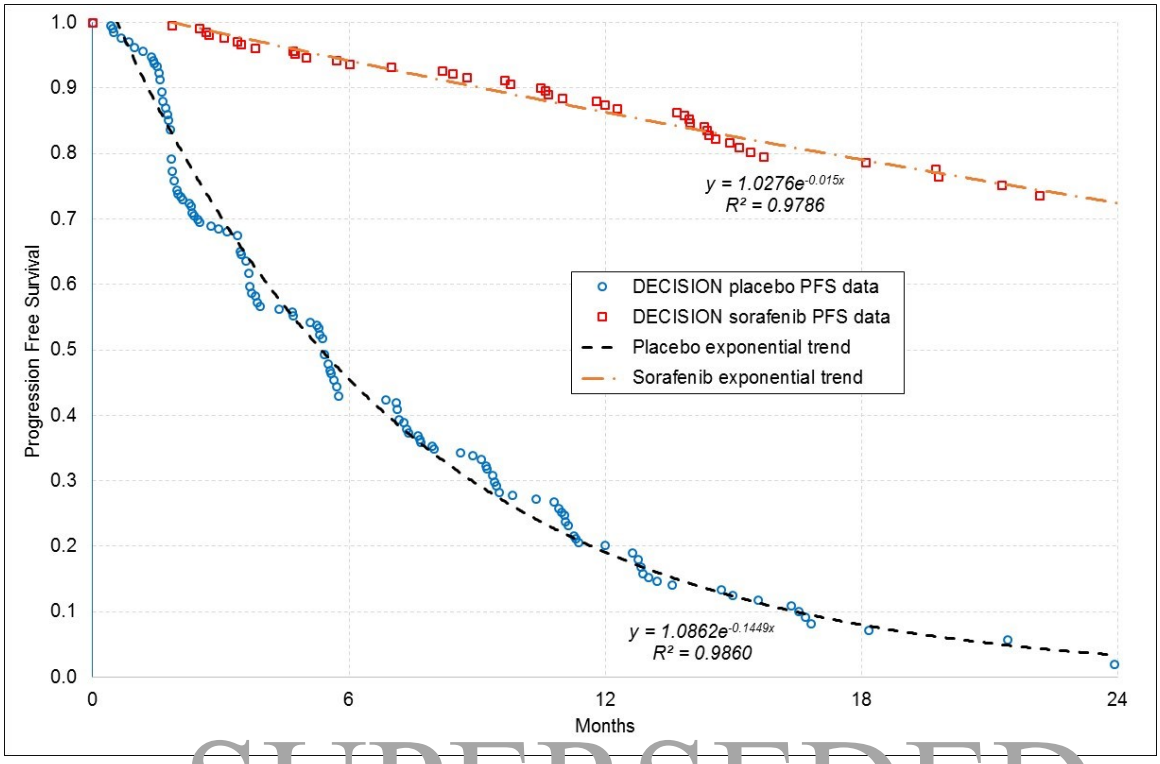

Figure 11 Progression-free survival Kaplan-Meier data from the DECISION trial modelled by an exponential function

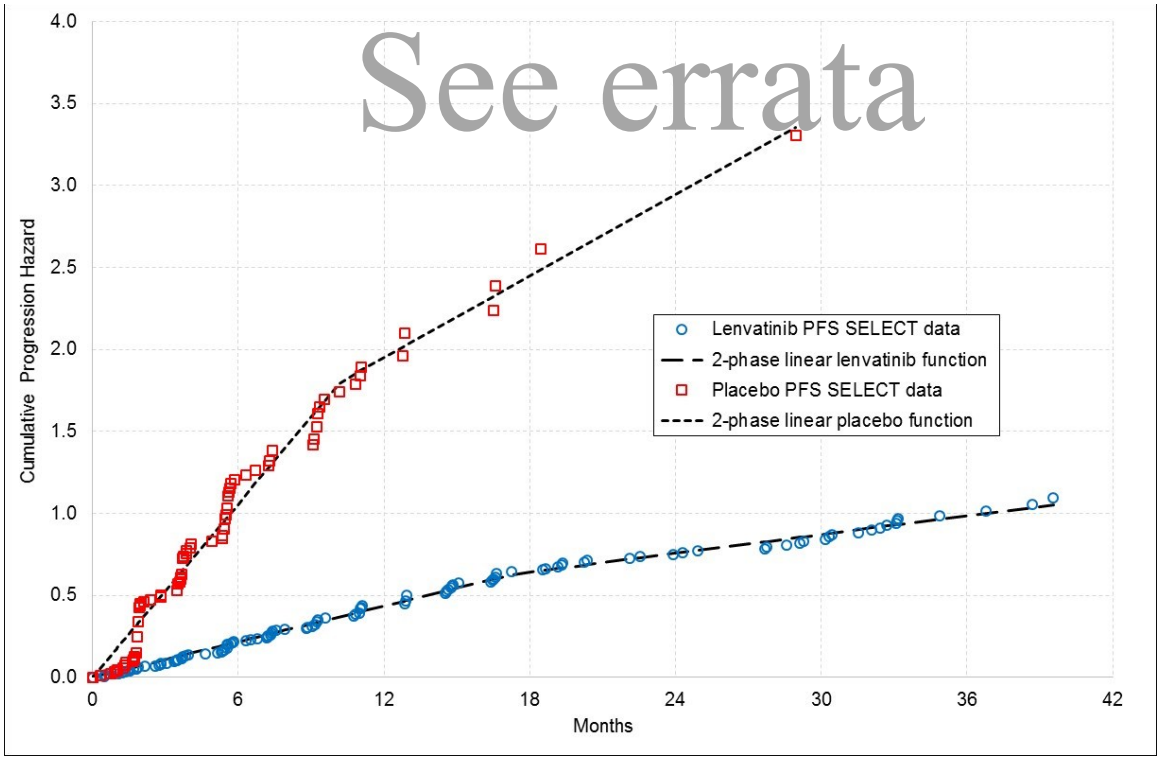

Figure 12 Cumulative hazard for disease progression for the SELECT trial, with 2-phase fitted exponential models

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.

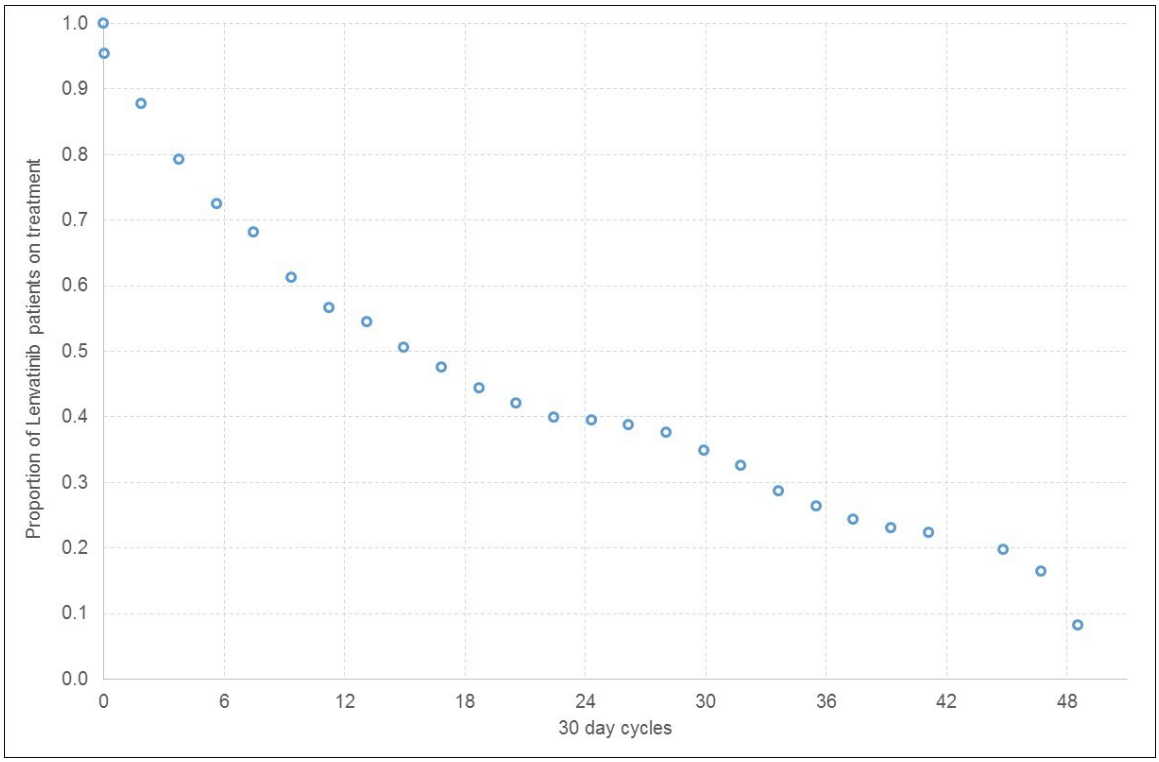

Figure 13 30-day cycles of lenvatinib dispensed in the SELECT trial

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.

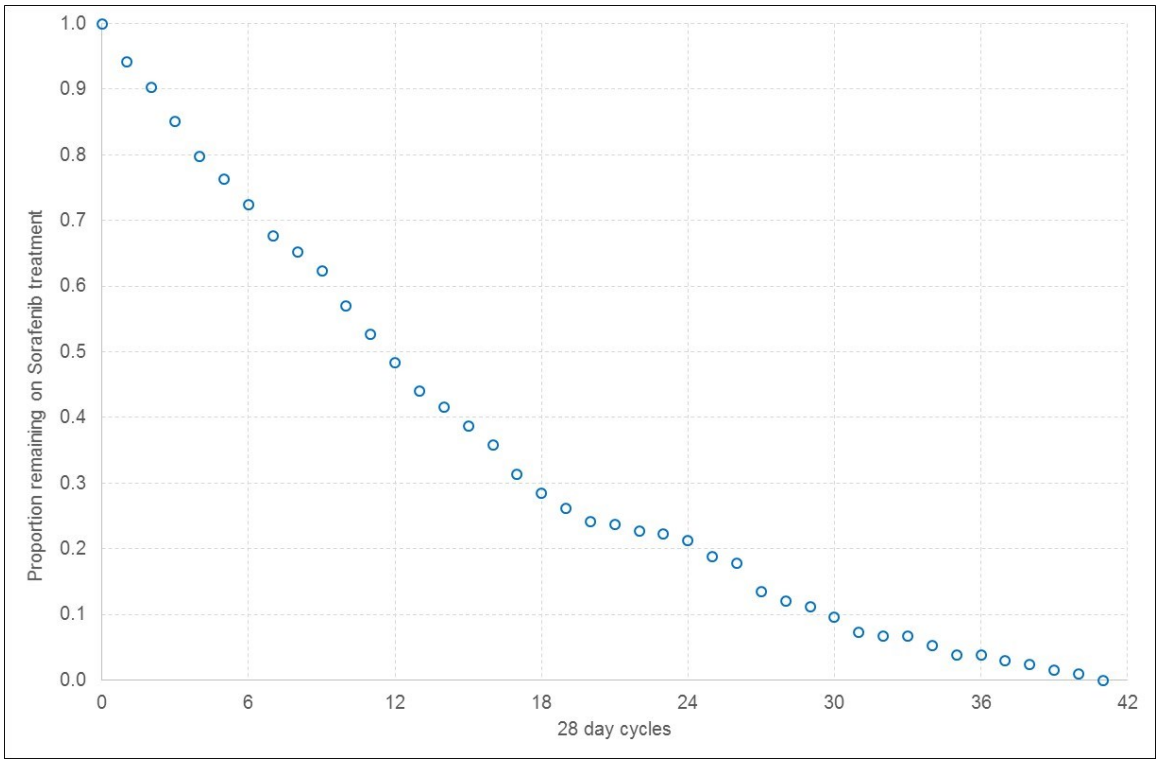

Figure 14 28-day cycles of sorafenib dispensed in the DECISION trial

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.

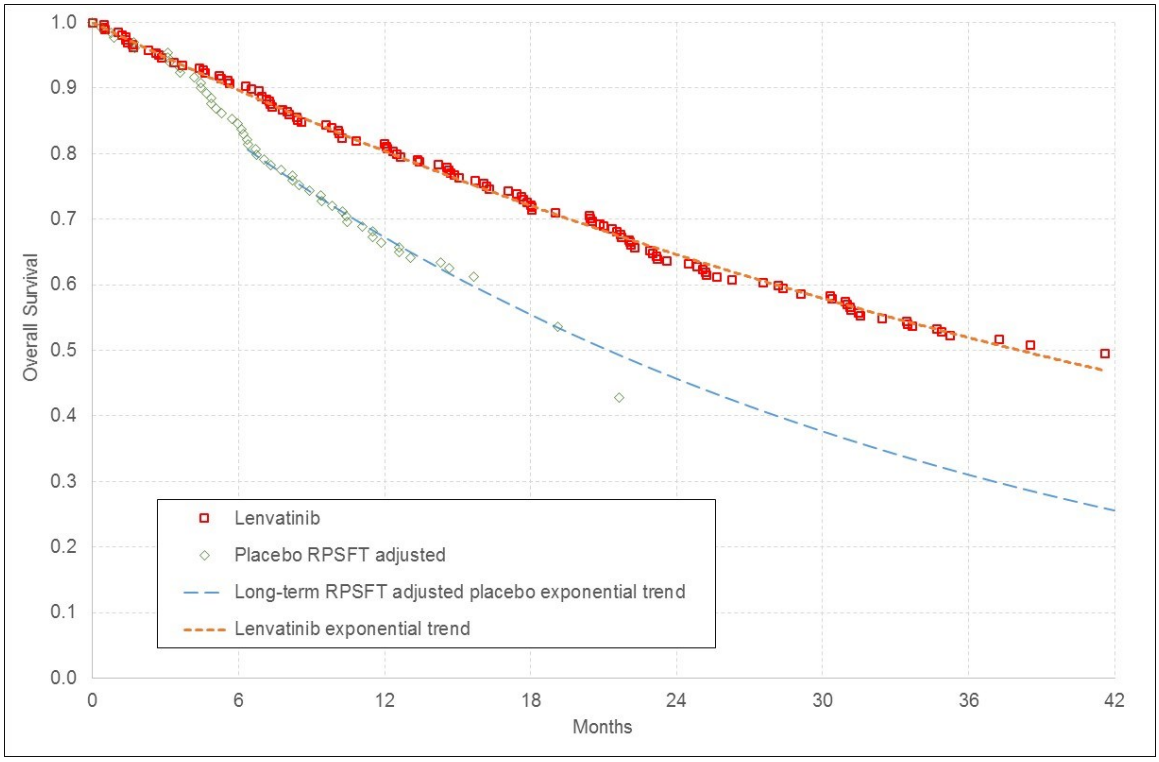

Figure 15 OS: lenvatinib treated patients in the SELECT trial, with fitted exponential model, and RPSFTM-adjusted for placebo patient crossover, with long-term exponential fitted model

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.

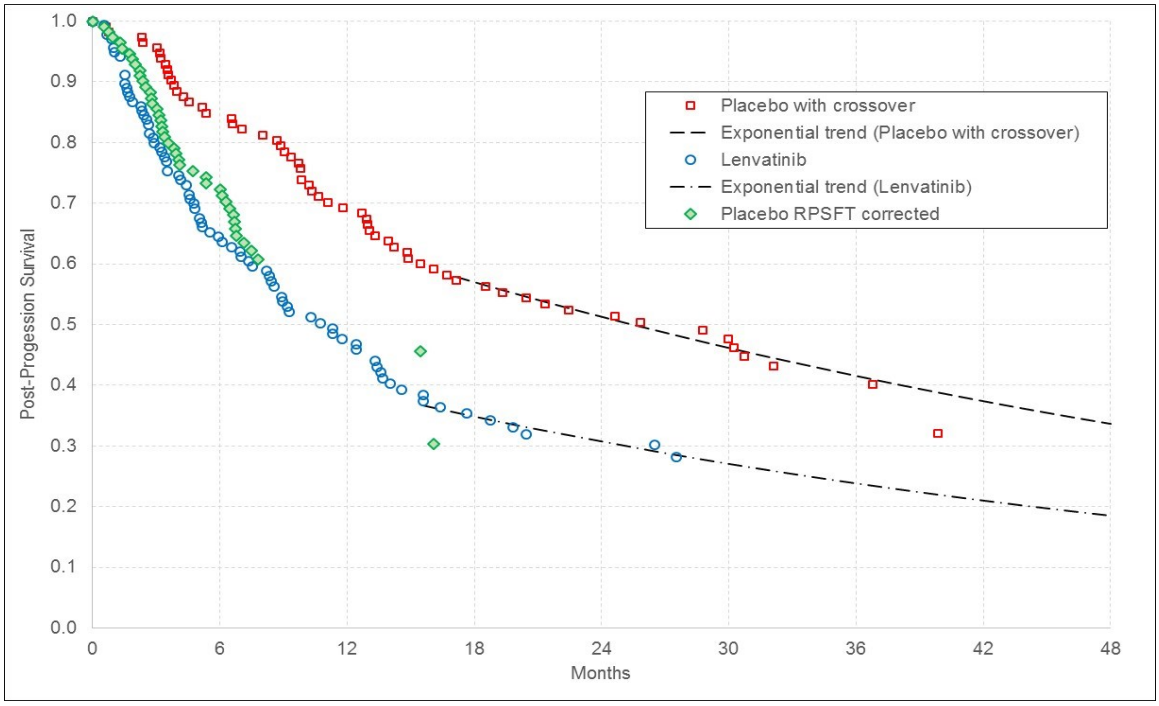

Figure 16 PPS: lenvatinib in the SELECT trial, with fitted exponential model, and RPSFTM adjusted for placebo patient crossover, with long-term exponential fitted model

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	5[illegible].1	14.[illegible]	12.6 (*30 day*)
Placebo (SELECT)	6.9	[illegible].2*	23.[illegible]	-
Gain due to lenvatinib	*+34.1*	*+24.9*	*-9.2*	-
Sorafenib (DECISION)	47.2	56.7	9.5	14.4 (*28 day*)
Placebo (DECISION)	[illegible]	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

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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	£6,843	£7,157	£0	£0	£0
Total cost	**£95,102**	**£15,195**	**£63,188**	**£17,954**	**£87,800**	**£71,154**	**£25,712**
Response years	-	-	-	-	-	-	-
Progression-free years	3.413	0.565	1.004	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		£62,088	£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**		**£36,802**	**£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=£85,372 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.

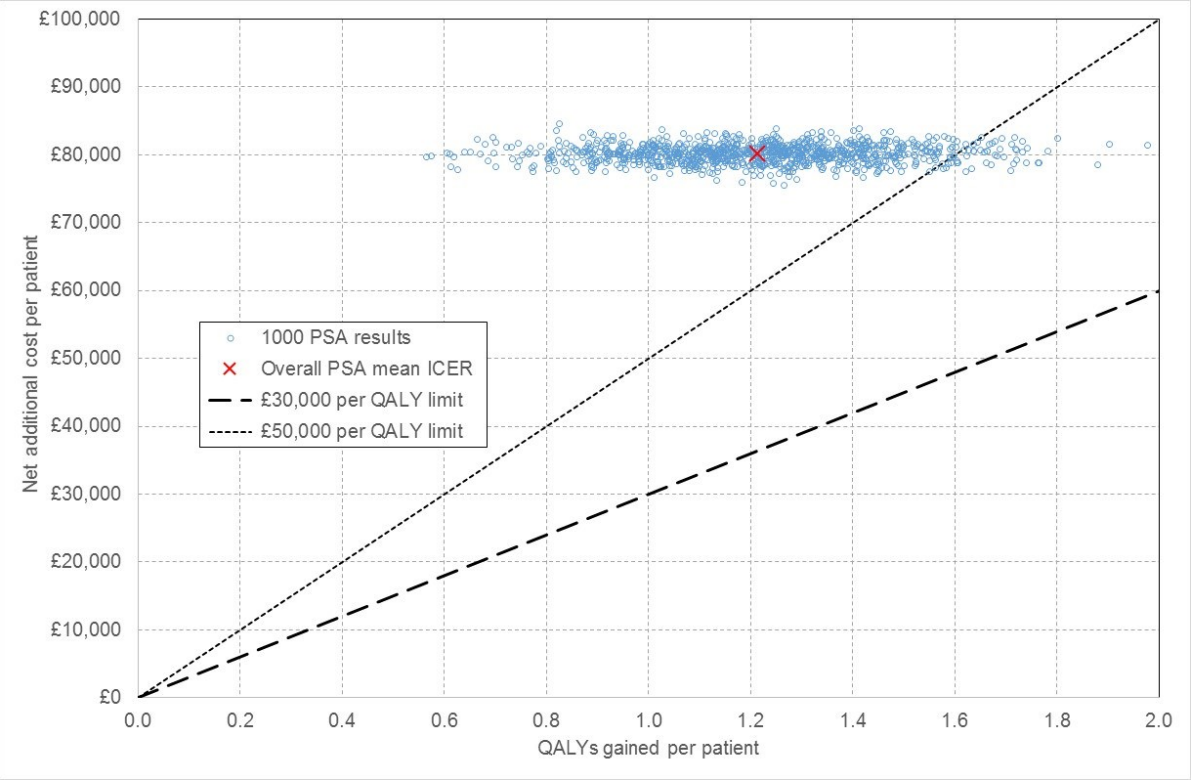

Figure 17 Probabilistic sensitivity analysis: lenvatinib vs BSC in the SELECT trial

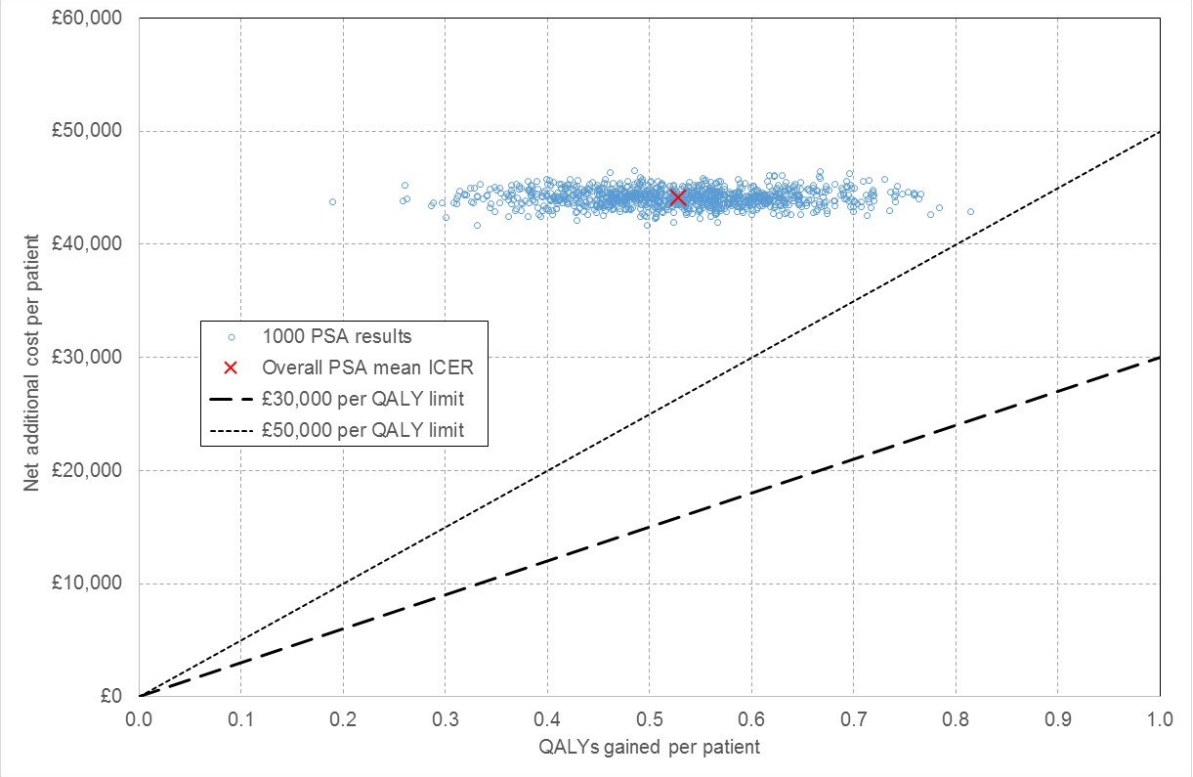

Figure 18 Probabilistic sensitivity analysis: sorafenib vs BSC in the DECISION trial

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%.

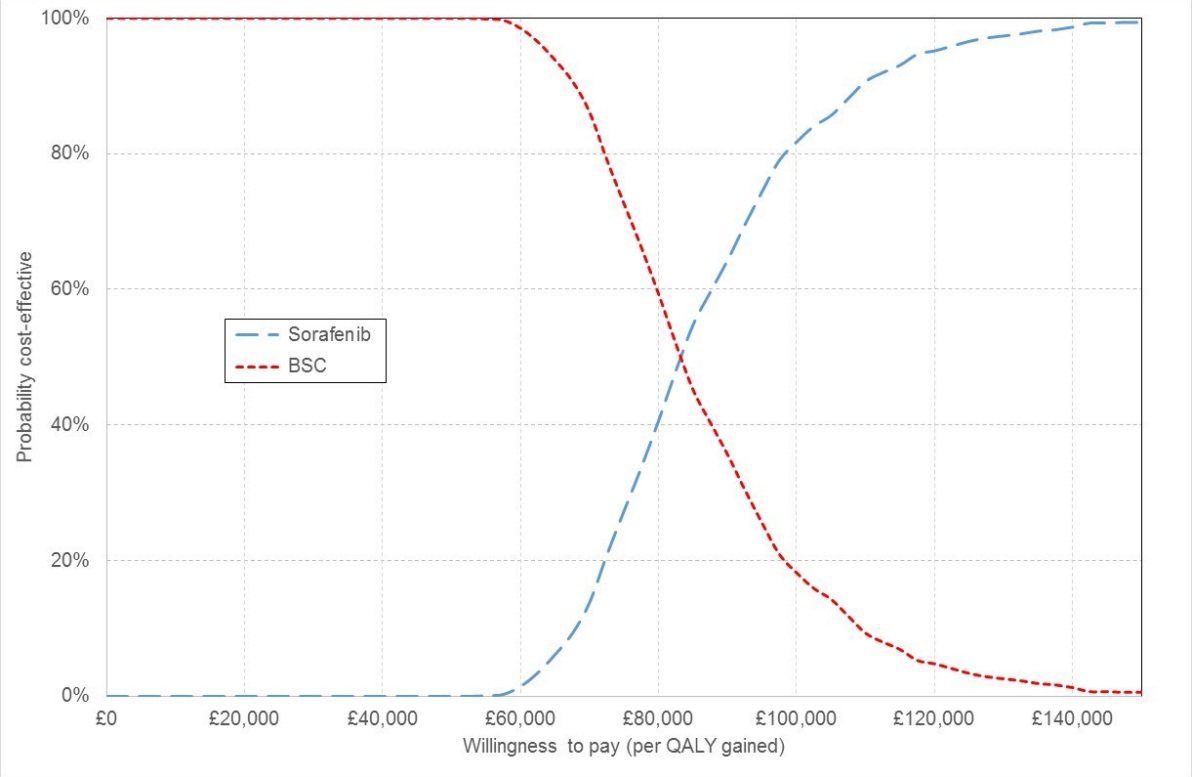

Figure 19 Cost effectiveness acceptability curves for sorafenib vs BSC (DECISION trial)

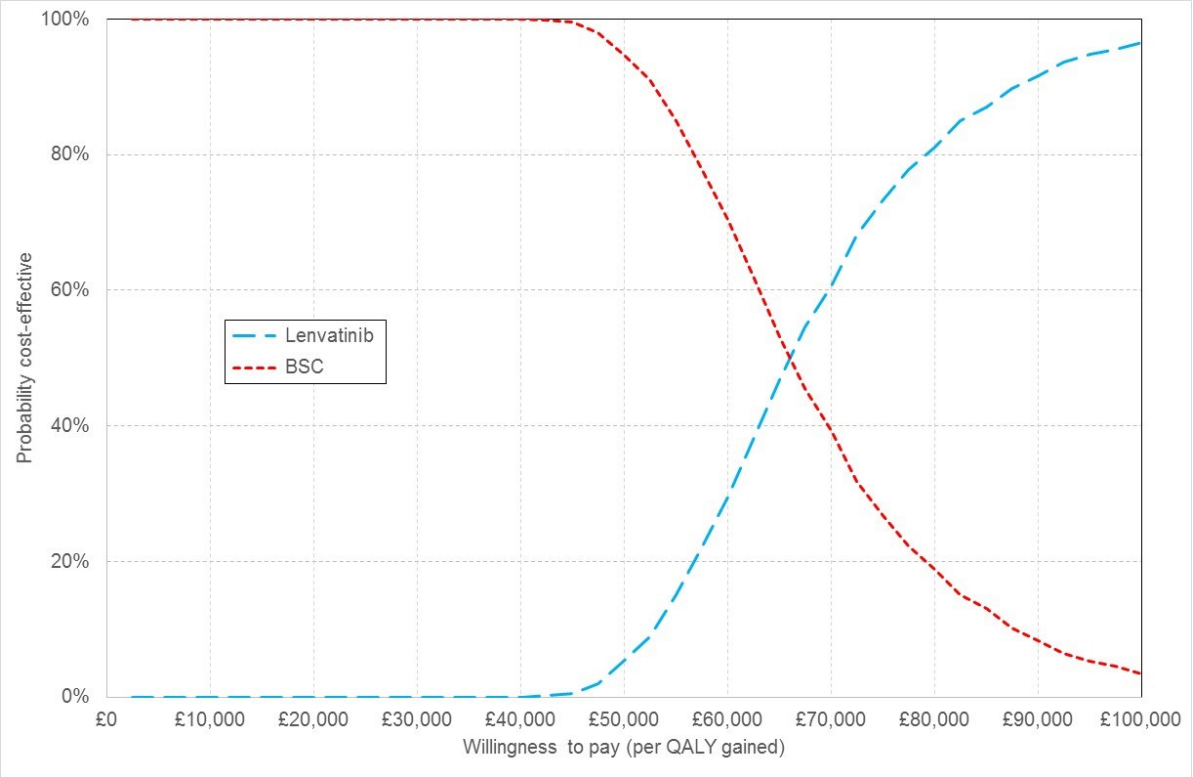

Figure 20 Cost effectiveness acceptability curves for lenvatinib vs BSC (SELECT trial)

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.

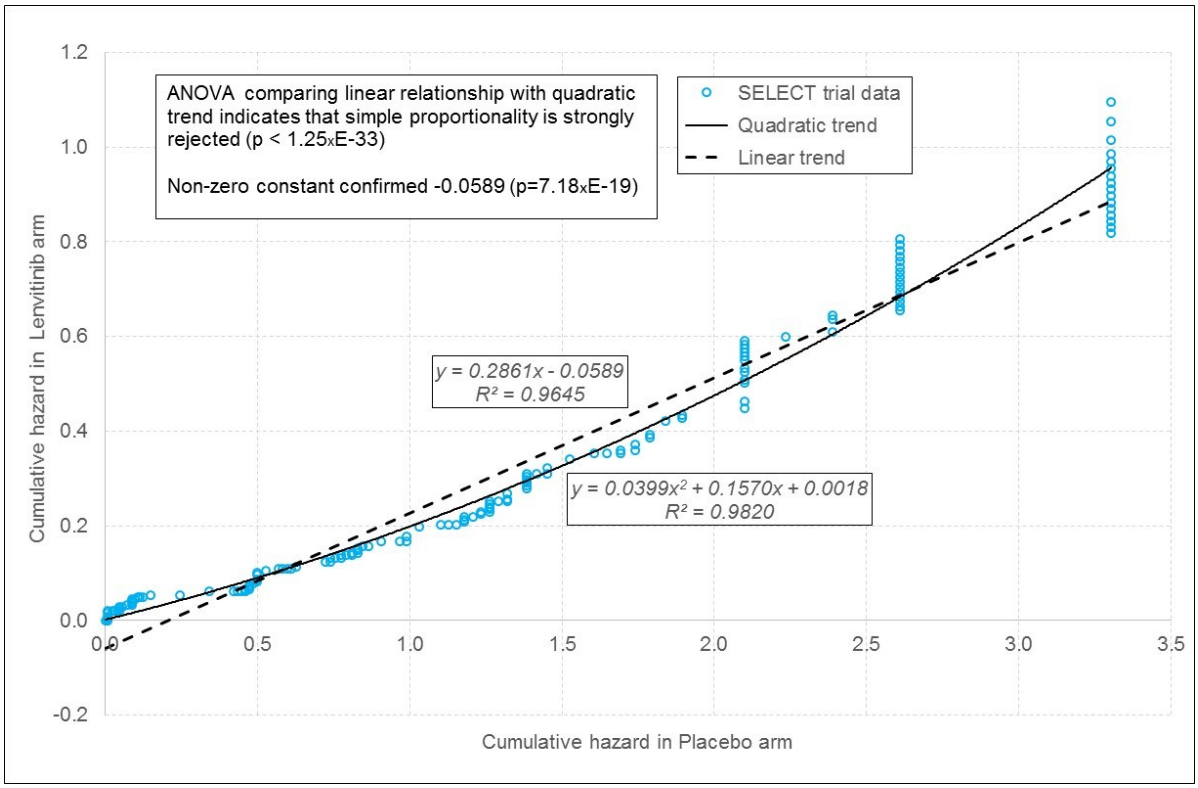

Figure 21 H-H plot for progression-free survival data from the SELECT trial

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.

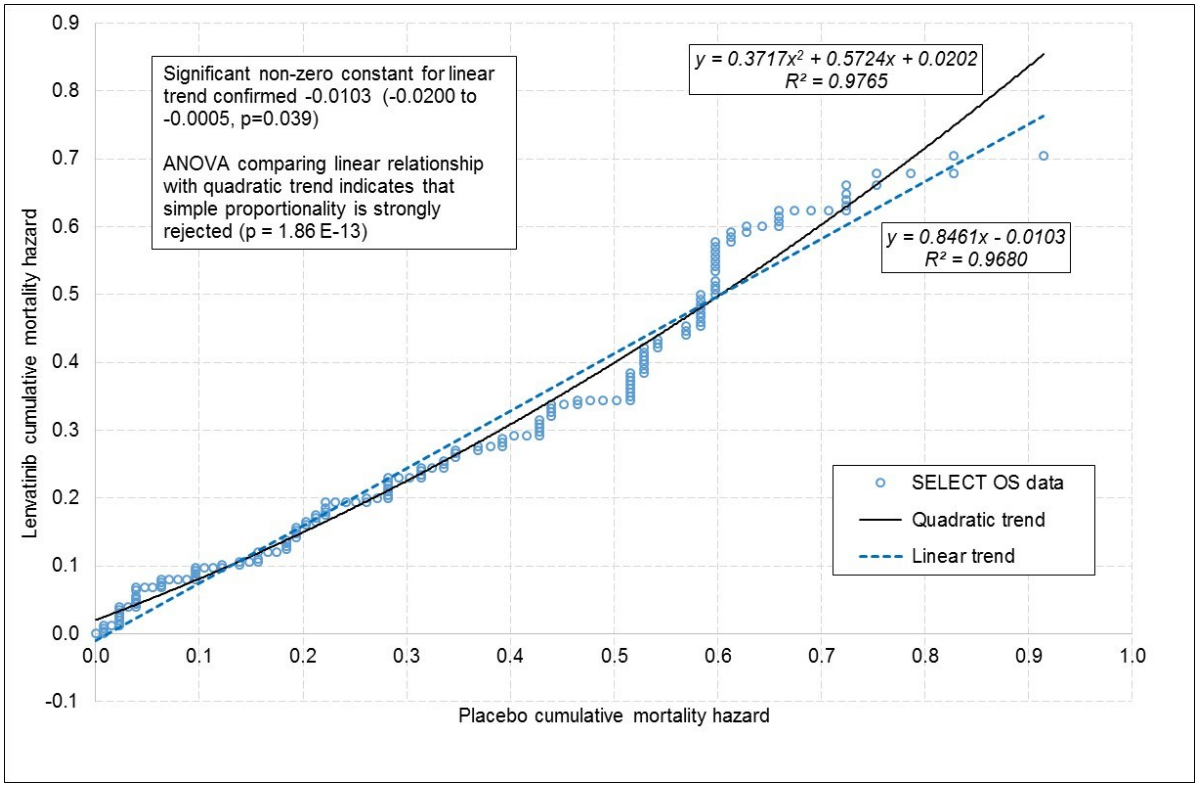

Figure 22 H-H plot for unadjusted overall survival data from the SELECT trial

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.

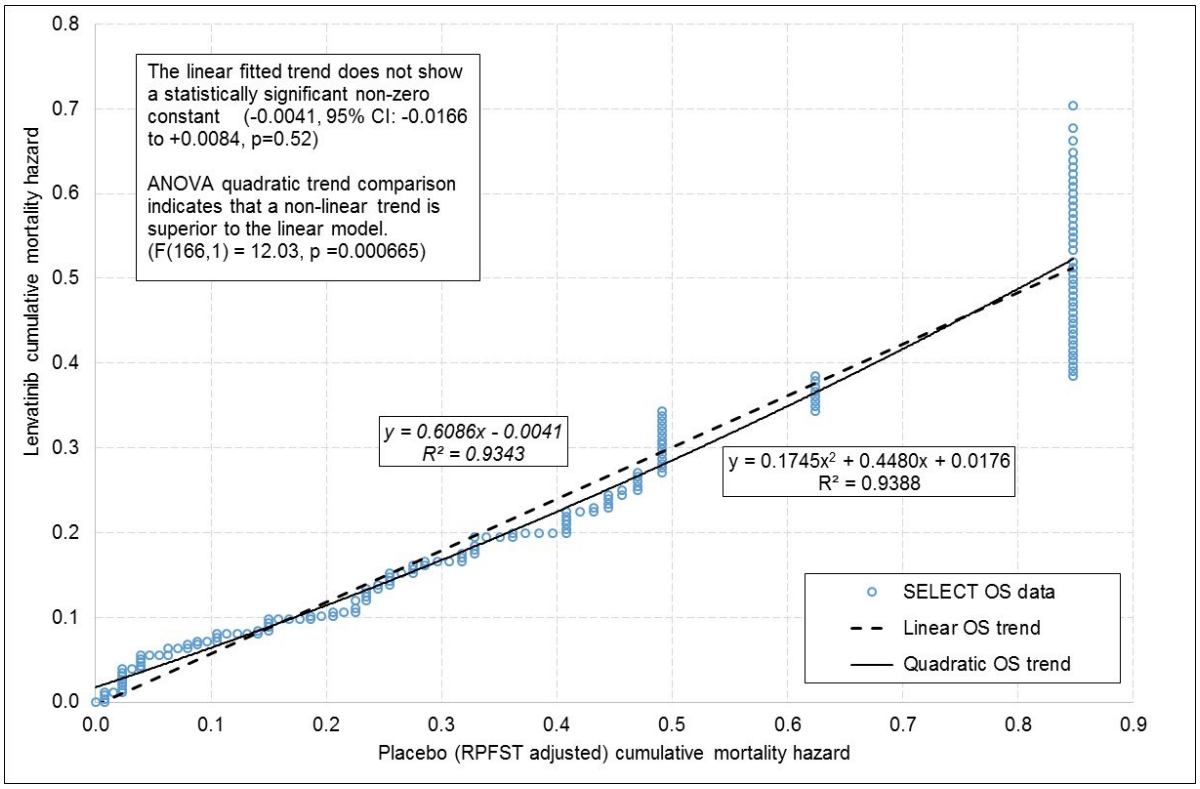

Figure 23 H-H plot for overall survival data adjusted by RPSFT for treatment crossover from the SELECT trial

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.

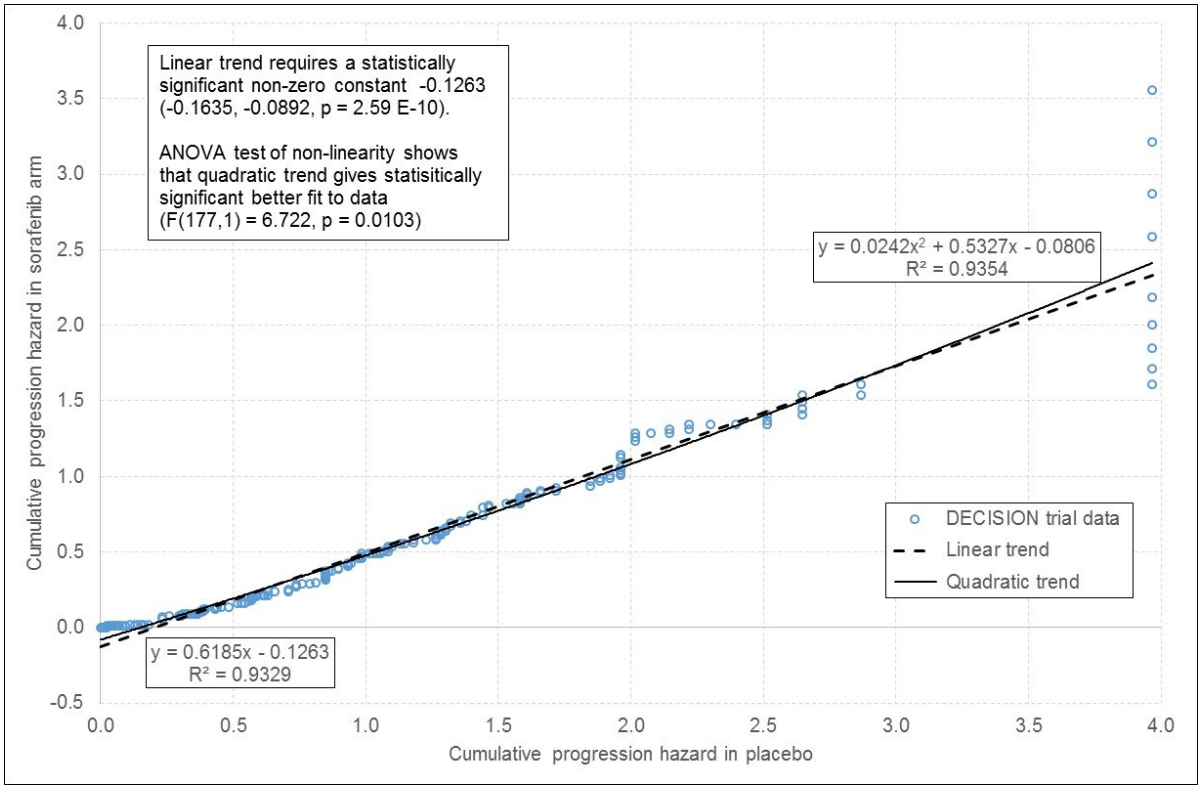

Figure 24 H-H plot for progression-free survival from the DECISION trial

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.

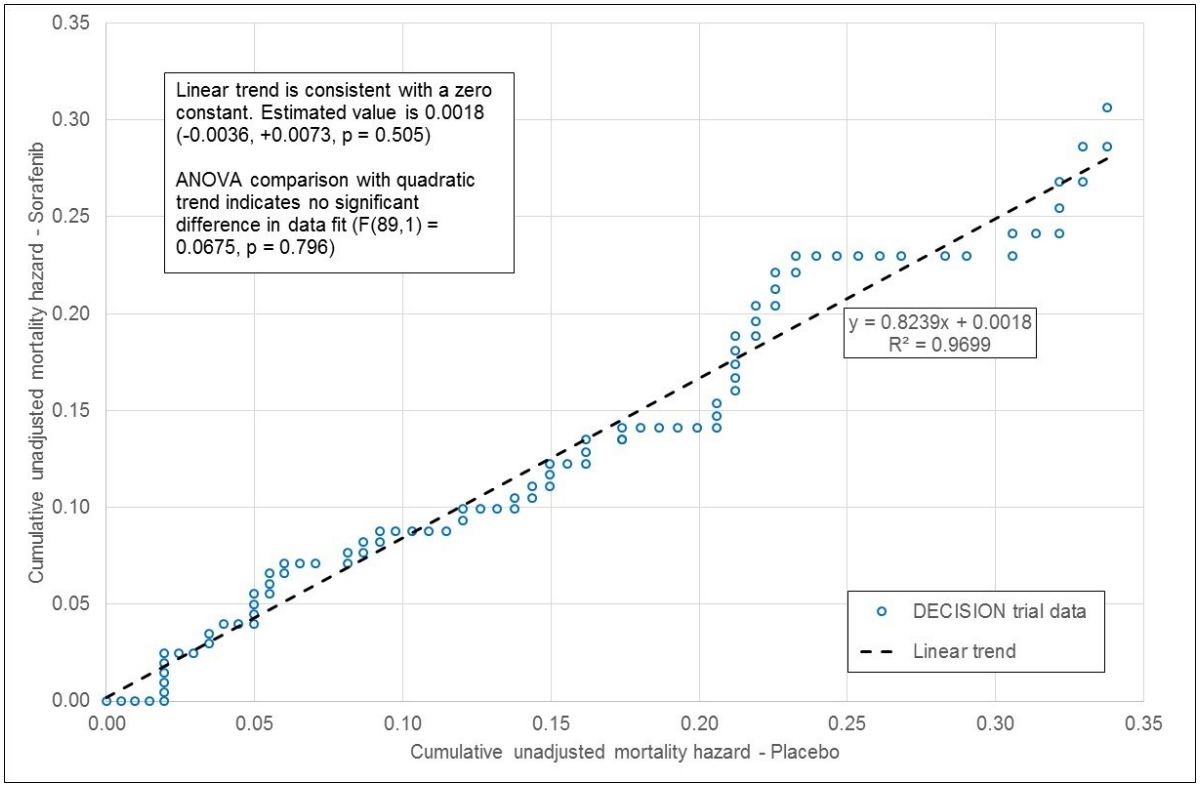

Figure 25 H-H plot for unadjusted overall survival data from the DECISION trial

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.

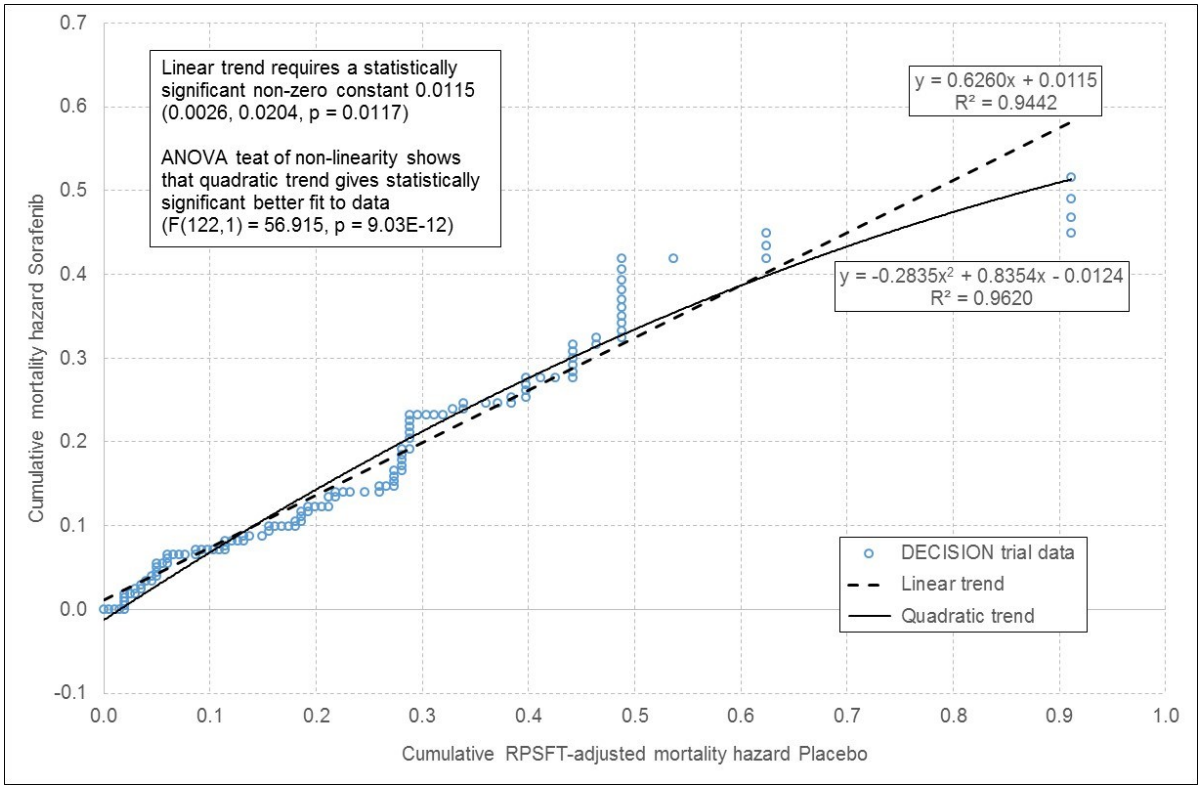

Figure 26 H-H plot for RPFST-adjusted overall survival from the DECISION trial

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

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Kate Moore
Technology Appraisals Project Manager - Committee D
National Institute for Health and Care Excellence
Level 1A, City Tower, Piccadilly Plaza
Manchester
M1 4BT

23rd August 2017

Dear Kate,

Re: Multiple Technology Appraisal. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [ID1059]

Please find the Assessment Group (AG) response to Bayer's query regarding how the AG extrapolated the time to event (TTE) data in the model.

Analysis of TTE data (where necessary) was carried out on the Kaplan-Meier (K-M) data sets provided by the respective companies (Eisai as an appendix to their company submission in response to the AG pre-submission request, Bayer using data contained in the submitted decision model, subsequently amended after correspondence with the AG via NICE).

In each case, the outcome data (overall survival [OS] or progression-free survival [PFS]) was converted to cumulative hazard using the transformation

Cumulative hazard(H) = - Ln (OS or PFS)

Each H plot was examined to determine whether the full data set conformed to a simple linear trend. If so, then a simple exponential model was fitted to all K-M event-times by least-squares minimisation. Some H plots showed strong evidence of clear changes in the hazard rate at particular times, switching from an early linear trend to a long-term trend. This pattern was modelled using 3 numeric parameters (early hazard rate, switching time, and long-term hazard rate). The model was fitted to the data by minimizing the residual sum of squares between the observed cumulative hazard at each event time and the estimated cumulative hazard at the same times. This was carried out using a Generalised Reduced Gradient (GRG) nonlinear algorithm to estimate the 3 parameters simultaneously without any imposed constraints.

The application of the extrapolation within the AG decision model involves applying the general principle that where the model for an intervention or comparator is to be populated from results of a single clinical trial, the observed K-M data should have primacy over any estimates from parametric modelling until the K-M data are no longer available, or are too unstable (due to small numbers of patients at risk and/or events), when parametric functions can be applied for extrapolation. We have employed this criterion wherever K-M trial data was incomplete, generally selecting the maximum limit for direct K-M data use to coincide as far as possible with an event time where the difference between the K-M value and the modelled estimate is minimized. Thereafter all subsequent estimates of the outcome variable were based solely on the model values without any further adjustment.

This approach minimizes the risk of arbitrary uncertainty arising from the selection of a (possibly inappropriate) parametric function, so that uncertainty is restricted to sampling error within the trial and abides by the principle of parsimony in model fitting for the purpose of extrapolation (as opposed to overriding the unique evidence set by supplanting the whole of the observed dataset with a preselected functional form).

Best wishes,
[redacted]

ERATUM

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erratum:

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

This report was commissioned by the NIHR HTA Programme as project number 16/51/20

Date of erratum: 23 August 2017

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Following a query from Bayer, the Assessment Group (AG) would like to notify the appraisal committee of two amendments in its report for the appraisal of lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Please see below for details of the amendments.

Correction to Figure 11

An incorrect Figure 11 on page 129 of the AG report had been inserted in error. This erratum includes the corrected Figure 11. The text relating to Figure 11 in the original report (page 128) was correct and remains unaltered, as does Figure 12 (also reproduced here).

Additional text and figure for the DECISION trial (overall survival)

Section 5.4.2 of the AG report erroneously only included an examination of the overall survival (OS) data from the SELECT trial (text on page 132 and Figure 15). This erratum includes the AG's examination of OS data from the DECISION trial.

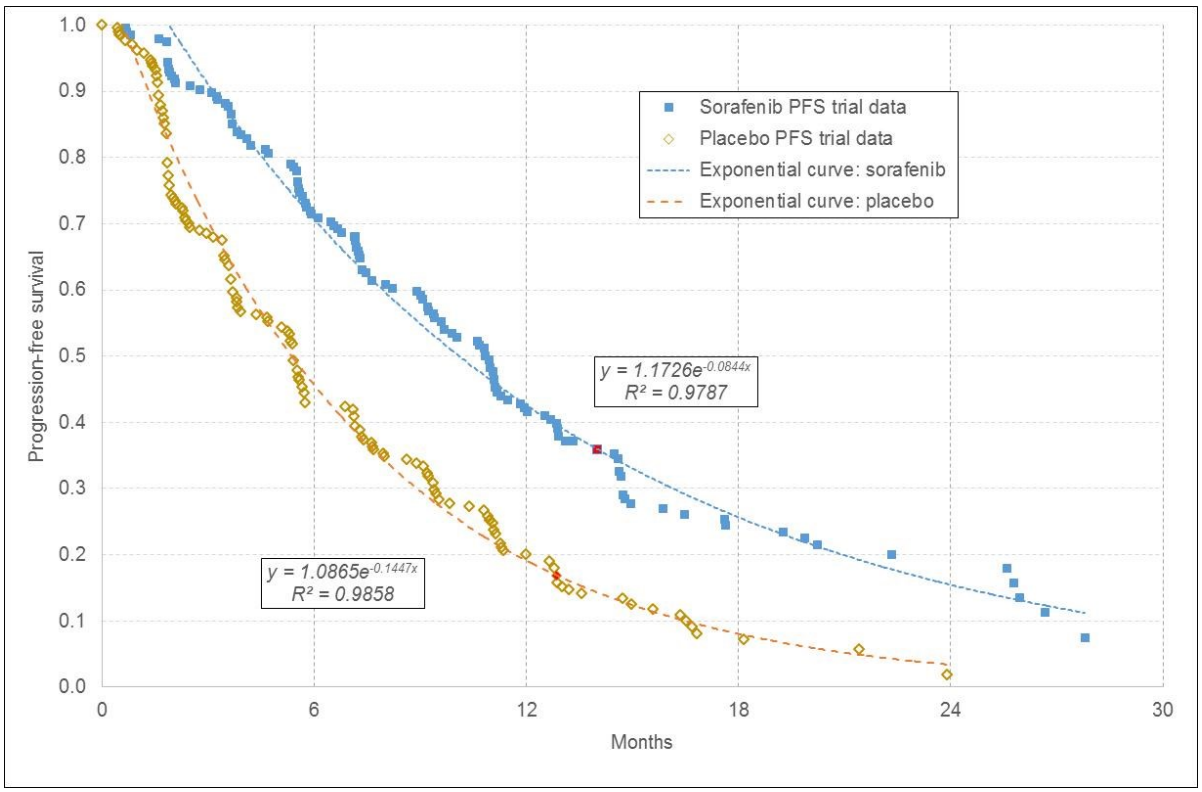


Figure 11 Progression-free survival Kaplan-Meier data from the DECISION trial modelled by an exponential function

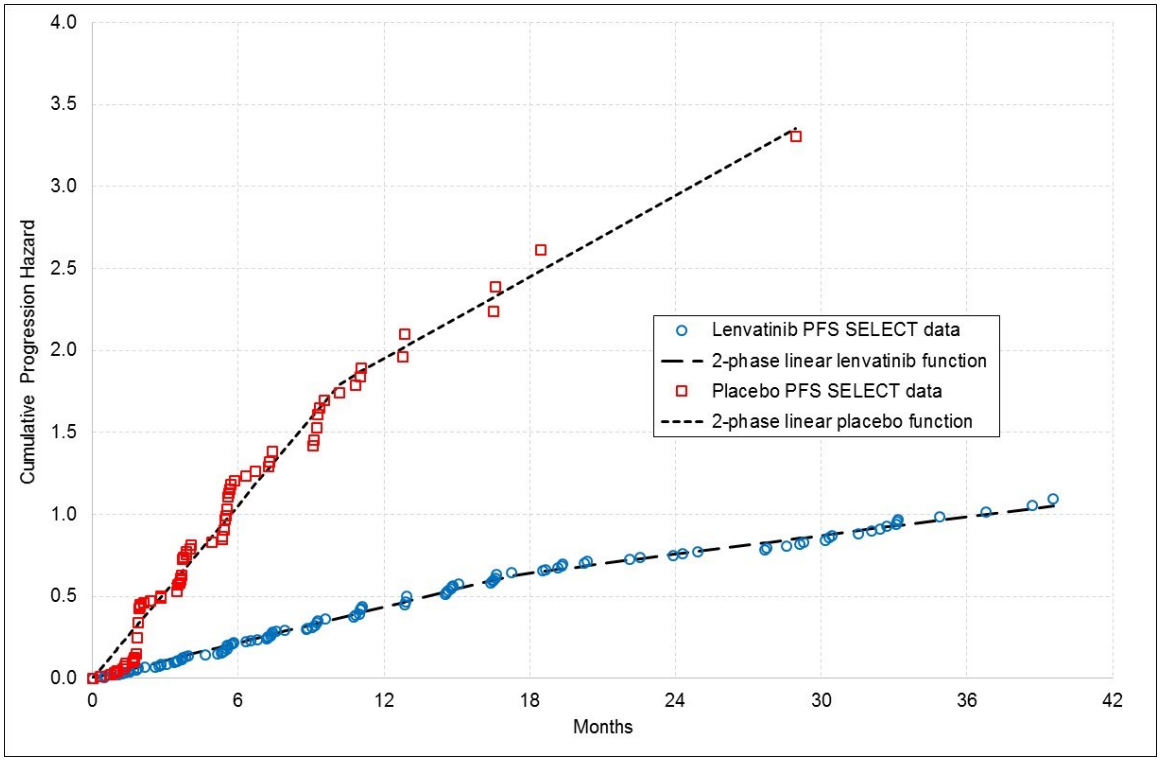


Figure 12 Cumulative hazard for disease progression for the SELECT trial, with 2-phase fitted exponential models

Examination of the OS data from the DECISION trial (Figure A) indicates that both patients in both treatment arms were subject to a period of relatively low mortality hazard, followed by transition to a higher constant risk of death. This transition occurred after 11.2 months for sorafenib patients and 6.4 months for placebo patients.

Using the area under the curve (AUC) of the rank preserving structural failure time method (RPSFTM)-adjusted Kaplan-Meier curve for the placebo arm until 6.4 months plus the AUC of the exponential extrapolation thereafter, yields a lifetime estimated mean OS for the placebo arm of 47.18 months. Similarly, combining the AUC of the sorafenib arm to 11.96 months added to the exponential trend thereafter yields an estimated lifetime mean OS of 56.66 months. Thus, the net mean OS gain attributable to sorafenib is 9.48 months.

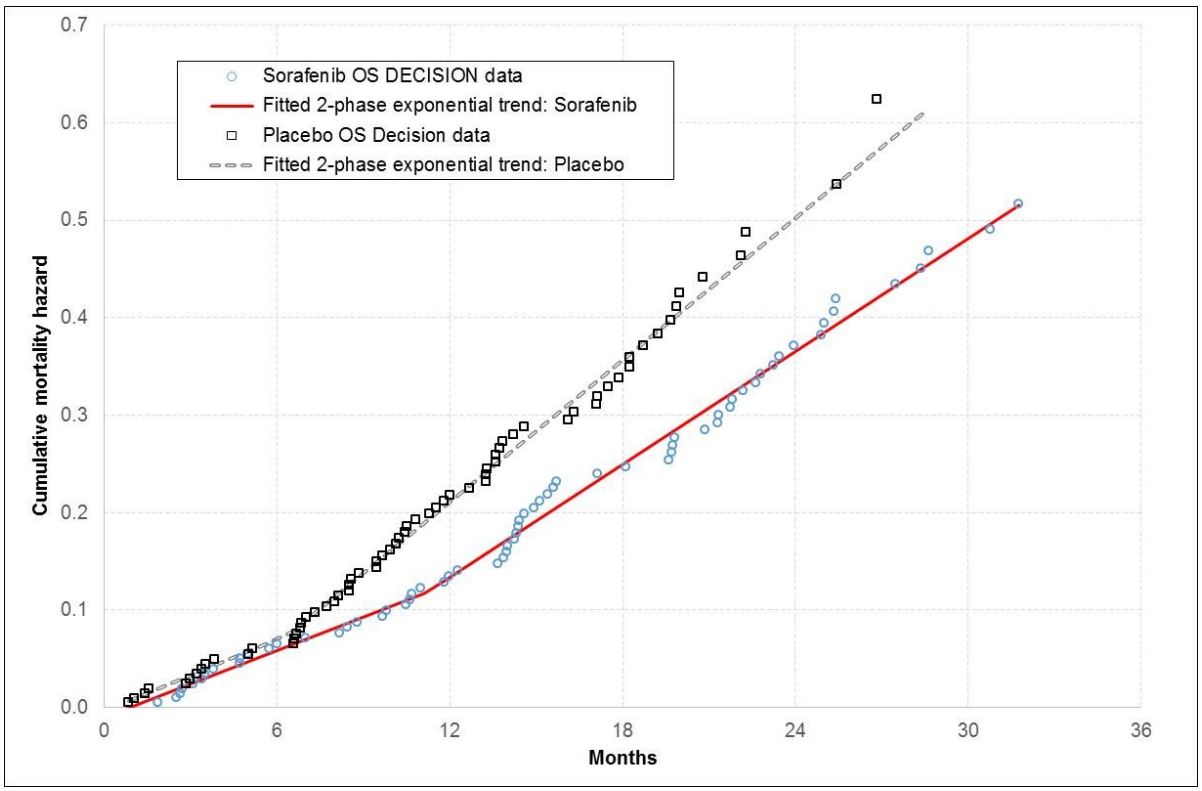


Figure A: Cumulative mortality hazard for sorafenib treated patients in the DECISION trial, with fitted 2-phase exponential model, and for RPSFTM-adjusted placebo patients, with fitted 2-phase exponential model.

MTA report Erratum 2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erratum 2:

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

This report was commissioned by the NIHR HTA Programme as project number 16/51/20

Date of Erratum 2: 25 September 2017

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Following comments on the Assessment Group (AG) report made by Eisai and Bayer, the AG has made minor modifications to the AG report. The pages of the report affected are presented here.

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 (24 January 2017) 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 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 confounding 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 dose reductions were frequently required (>60%). 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.

Limitations

We consider it is not possible to compare the clinical or cost effectiveness of lenvatinib with sorafenib.

Conclusions

Compared with placebo, treatment with lenvatinib and sorafenib result in an improvement in PFS, ORR and possibly OS. Both treatments exhibit estimated ICERs >£50,000 per QALY gained.

Future work

Further research should include examination of the effects of lenvatinib, sorafenib and BSC (including HRQoL) for both symptomatic and asymptomatic patients, and the positioning of treatments in the treatment pathway.

Study registration

PROSPERO CRD42017055516

Funding

The National Institute for Health Research Health Technology Assessment programme

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. 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.

Study registration

This review is registered as PROSPERO CRD42017055516

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 based on a response rate of 65% for lenvatinib when compared with 12% sorafenib, although these agents have not been directly compared. However, 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 via the Cancer Drugs Fund (CDF) since prior to the launch of the indication in April 2014. Where the treating specialist has established treatment with sorafenib may be beneficial, it is currently funded for all patients with RR-DTC. According to Bayer, based on its analysis of notification data from July 2013 to June 2016, sorafenib has now became the standard of care for patients where systemic treatment is appropriate.[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 potentially 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. Estimates provided by the companies are reflective of the population defined by the agreed final scope of this Appraisal. However, 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. 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. Therefore, it is difficult to further segment the population.

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 alpha, 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 and assume a patient receives the full dose. However, in clinical practice, most patients will not receive the full dose throughout the course of their treatment. Based on clinical trials, median dose intensity has been reported to be approximately 70% for lenvatinib and approximately 80% for sorafenib.

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 2011 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]

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	16.5	NR	651.2mg	793.6mg
Dose intensity (% of maximum dose)	68.8%	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 as data were not collected on the specific agents used during the trial follow-up for the DECISION 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

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)	1 (0.5)	0
Hypertension	9 (3.4)	0	0	0
Dehydration	7 (2.7)	0	0	2 (1.3)
General physical health deterioration	6 (2.3)	0	2 (1.0)	0
Dysphagia	3 (1.1)	3 (2.3)	2 (1.0)	1 (0.7)
Dyspnoea	3 (1.1)	5 (3.8)	7 (3.4)	6 (2.9)
Haemoptysis	0	3 (2.3)	0	2 (1.3)
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] Brose et al 2014[48] and communication from Bayer (7 September 2017)

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.

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 and 1.1% of patients discontinued due to asthenia. 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%).

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] After diarrhoea, hypertension was the most common reason for dose modifications as well as being the most common reason for discontinuations (alongside asthenia) 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]

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	The curve, generated to represent OS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC using data from the third data-cuts of the DECISION and SELECT trials (July 2015 and August 2015, respectively)	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 using data from the second data-cuts of the SELECT and DECISION trials (June 2014 and May 2013 respectively)	DECISION trial data from second data-cut (May 2013) 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	The curve, generated to represent PFS for patients receiving sorafenib, was adjusted using the HR generated by the company's ITC using data from the third data-cuts of the DECISION and SELECT trials (July 2015 and August 2015, respectively)	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 using data from SELECT and DECISION 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 stated to taken from EQ-5D values for sorafenib 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 AG notes that only the utility values used in the progressive state were the same as the utility values derived from the DECISION trial.

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. The main difference occurs in the PFS results where lenvatinib provides substantially greater benefit than sorafenib (34 additional months before progression compared to only 6 months). However, the estimated OS results are very similar (55 vs 57 months), and consequently estimated PPS is reduced with lenvatinib treatment but increased for sorafenib treatment). Thus, it appears that lenvatinib shows effect more strongly in initially delaying progression, but does not offer additional benefit over sorafenib in terms of long-term survival. 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)	13.8	56.8	42.9	14.4 (*28 day*)
Placebo (DECISION)	7.6	43.8*	36.2	-
Gain due to sorafenib	+6.3	+13.0	+6.7	-

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.

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

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 (72.5%) 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 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**	**£87,800**	**£71,154**	**£25,712**
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		£62,088	£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**		**£36,802**	**£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

5.4.7 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:

Unfortunately, information relating to the key outcome variables (PFS, OS and TTD) was not provided to the AG by one of the companies in the form requested, and information on uncertainty in the estimated treatment dose intensity was not included by the other company in their submission or their model. Without these key data items, it was not possible to incorporate these important components of the normal PSA on this occasion. Therefore, the results presented below should be treated with caution.

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.

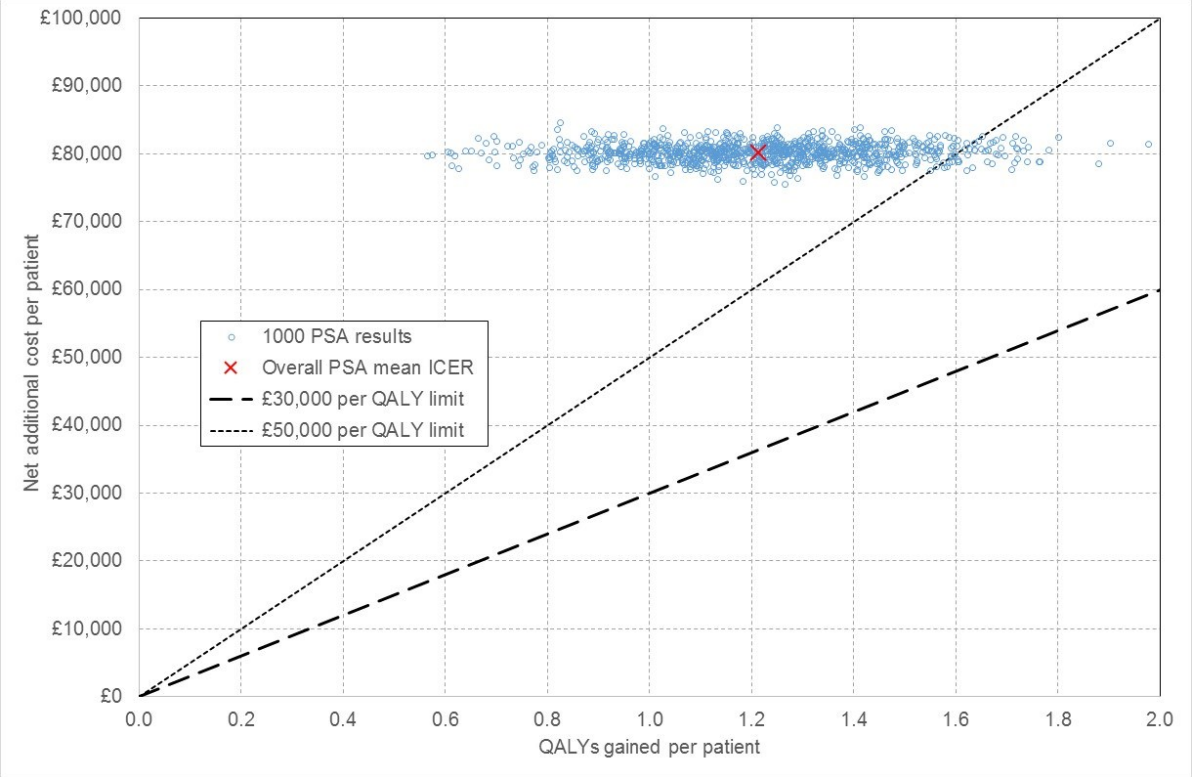


Figure 17 Probabilistic sensitivity analysis: lenvatinib vs BSC in the SELECT trial

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.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

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

Response by Bayer

Date of response: 6th September 2017

Contains confidential information

AIC: Academic in confidence is marked in yellow

CIC: Commercial in confidence is marked in blue

Overview

The Assessment Group report outlines the majority of challenges associated with the appraisal of sorafenib and lenvatinib for patients with differentiated thyroid cancer after radioactive iodine (RR-DTC). The response from Bayer discusses some of the key conclusions drawn in the report that we believe are of particular importance for decision makers. These points are briefly summarised in the first instance, and described further in turn throughout the document. Tables 6 and 9 found at the back of the document provide a consolidated list of comments on the report.

1. **Current evidence does not allow a comparative assessment of sorafenib and lenvatinib**
   - Differences in trial populations, study design, BSC arms, prior/post study treatments, in addition to the proportion of crossover in the DECISION and SELECT trials, prevent a robust comparison of sorafenib and lenvatinib, even in the event that non-proportional hazards are accounted for.
   - Previous attempts to adjust patient characteristics have failed to align BSC arms of the DECISION and SELECT trials, indicating population adjustment alone cannot facilitate a robust comparative assessment.
   - The trial based assessment of sorafenib versus BSC provides the most robust economic evaluation, as all key inputs for both arms are taken from the randomised DECISION trial.

2. **The relevant population for this appraisal should not be restricted to patients who are symptomatic and/or have rapidly progressing disease**
   - Clinical benefit was observed in both symptomatic and asymptomatic patients treated with sorafenib in the DECISION trial.
   - The available data is insufficient to restrict the patient population.
   - The Assessment Group conclude there is “no objective criteria for assessing patients who are symptomatic and/or rapidly progressing” with disease status dependent “on individual patient characteristics”.
   - Specialists consider multiple factors when making a treatment decision, any restriction may be harmful to selected asymptomatic patients likely to tolerate and respond to treatment

3. **Issues identified with extrapolation of variables in the AG model**
   - Issues were identified with the extrapolation of time to event estimates in the AG model:
     i. Decision on the choice of approach is not sufficiently supported.
     ii. Implementation of the extrapolated curves lacks face validity and underestimates values.
     iii. Treatment duration is overestimated for sorafenib and underestimated for lenvatinib.
     iv. As a result drug costs associated with lenvatinib are underestimated while drug costs associated with sorafenib are overestimated.

4. **EQ-5D utilities collected in the DECISION trial are inappropriate for application to the SELECT trial due to differences in the trial populations and safety profile of treatments**

5. **Sorafenib and lenvatinib should both be considered end of life treatments**
   - RR-DTC is a terminal condition with no alternative treatment options for patients in the absence of sorafenib or lenvatinib.
   - Sorafenib and lenvatinib provide a large extension of life, greatly exceeding the 3 month requirement for end-of-life consideration.
   - The overall survival of patients with RR-DTC is not well documented, though a midpoint of median survival from the SELECT and DECISION trials estimates it to be 26.7 months. Other estimates identified find median OS to range from 8 to 26 months.

6. **Important differences in safety profiles are acknowledged by the Assessment Group**
   - Treatment with lenvatinib was found to result in significantly more grade ≥3 adverse events and serious adverse events than treatment with sorafenib
   - A choice of treatment options would allow clinicians to account for patient co-morbidities and patient preference in line with the recent NCCN guidelines which suggest choice of lenvatinib or sorafenib be based on the individual patient.

7. **Sequencing of sorafenib and lenvatinib treatments**
   - The potential for sequencing treatment of sorafenib and lenvatinib was highlighted by the Assessment Group, citing differences in mechanism of action and safety profile
   - There is no evidence on the efficacy of sorafenib, following treatment with lenvatinib.
   - The tables and text used in this discussion contain multiple errors and should be corrected.

8. **Updated Cost-effectiveness results**
   - **Using the AG's preferred assumptions, after revision of the model to reflect the key issues cited in this document, the list price ICER for sorafenib versus BSC decreased from £85,644 to £57,706 per QALY.**
   - **Using the PAS price the updated base case ICER is [redacted] per QALY.**

1. Current evidence does not allow a comparative assessment of sorafenib and lenvatinib

The company supports the Assessment Group's (AG) conclusion that the lenvatinib and sorafenib populations in the SELECT and DECISION trials are not comparable, mainly "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" (page 74).

However, in providing research priorities, the AG conclude by suggesting that *"further statistical research is needed to develop reliable methods of undertaking indirect comparisons in cases where the proportional hazard assumptions are violated" (page 158)*. Though, as acknowledged throughout the report, due to the many underlying differences in patient populations, study design, BSC arms, prior and post study treatment, in addition to the differences in percentages of patients that crossover, in this case cross-trial differences

cannot be fully adjusted for, and could not be addressed by methods that do not require the proportional hazards assumption.

Bayer has previously explored adjustment of the DECISION trial population when assessing the feasibility of conducting a matched-adjusted indirect comparison. The objective was to align treatment effect modifiers that differed between the DECISION and SELECT trial populations in order to facilitate a robust comparison.

After adjustment and matching of the lenvatinib and sorafenib treatment arms it was not possible to align the best-supportive care arms. Effect modifiers including age, histology, lymph metastases and tumour size could not be balanced, a requirement for an unbiased indirect comparison. However had this approach been successful it would have introduced other limitations, reducing the population size for comparison, breaking randomisation and producing comparative effectiveness estimates with high levels of uncertainty.

Our conclusion is that the trial based comparison of sorafenib vs. best-supportive care provides the most robust assessment, as all key inputs are taken from the randomised DECISION trial.

Given the differences in populations between trials, uncertainty is best demonstrated by the Assessment Group's sensitivity analyses. **When the sorafenib arm from DECISION is compared against the SELECT placebo arm, the ICER for sorafenib halved to £41,716 per QALY. When the lenvatinib arm of SELECT was compared against the DECISION placebo arm the ICER for lenvatinib doubled to £130,592 per QALY.**

2. The relevant population for this appraisal should not be restricted to patients who are symptomatic and/or have rapidly progressing disease

The selection of patients who are symptomatic and/or have rapidly progressing disease, while an interesting suggestion, is problematic, as:

- Available data is insufficient to support this assumption
- Definition of patients who are symptomatic and/or have rapidly progressing disease is unclear
- Exclusion of patients likely to tolerate and respond to treatment

Clinical advice provided to the Assessment Group was that treatment for RR-DTC patients tended to be given to patients who are *'symptomatic'* or when *'clinically significant progressive disease develops'.*

The statement was supported by a post-hoc analysis conducted in the DECISION trial that showed sorafenib provided a clinical benefit in both symptomatic and asymptomatic patients, with a greater incremental benefit seen in symptomatic patients. However the results of this post-hoc analysis should be interpreted with caution, as the trial was not designed or powered to consider this small subgroup of patients.

"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)" Pg. 14.

The company believe that whilst this statement may be of relevance for helping inform treatment decisions, other factors such as age, comorbidities and patient preference must also be accounted for.

Whilst the Assessment Group do not suggest formally restricting treatment to patients with 'symptomatic' and/or 'rapidly progressing disease' it is worth noting the AG's conclusion that there is currently *"no universally accepted objective criteria for assessing patients who are symptomatic and/or rapidly progressing"* and *"no generally agreed definitions of 'symptomatic' or 'rapidly progressive disease'*, with a *"patient's disease status being dependant on individual patient characteristics".*

In addition for asymptomatic patients likely to tolerate and respond to treatment, it would result in the loss of a much needed treatment option, in a population where sorafenib has been demonstrated to be efficacious.

It is hoped that any recommendation does not restrict treatment from those currently eligible and benefiting from sorafenib in UK clinical practice via the Cancer Drugs Fund.

3. Issues identified with extrapolation of variables in the AG model

Within the AG report insufficient detail is provided on the method of extrapolating the time-to-event data. In the model the calculation of parameters are hard-coded so it is not possible to test the method used to generate the model parameters. Upon request from Bayer the AG provided some additional explanation of the method employed, however after investigation of the additional information, certain aspects of the extrapolation are still unclear.

Our comments relate to the following:

- Decision on the choice of approach is not sufficiently supported
- Implementation of the extrapolated curves lacks face validity and underestimates values
- Treatment duration is overestimated for sorafenib and underestimated for lenvatinib.

Decision on the choice of extrapolation approach

The AG considered only exponential or segmented exponential fits. The AG report only uses the SEER database to justify the choice of exponential, not to assess other potential distributions. Due to the assessment of temporal changes in some time to event data the AG states that a segmented exponential should be used.

It is not clear from the report or the AG response which curves are used in the model. While for OS, the AG report suggests a two-phase exponential model with transitions at 11.2 months for sorafenib patients and at 6.4 months for placebo patients, with only the second

phase used in the model to extrapolate beyond the Kaplan-Meier curve. The extrapolation point (split point) is given in the model as 31.8 months and 25.4 months. For PFS, it is not clear from the Erratum, which approach was used.

Implementation of the extrapolated curves

Despite the additional information provided by the AG *("generally selecting the maximum limit for direct K-M data use to coincide as far as possible with an event time where the difference between the K-M value and the modelled estimate is minimized"*) it is still unclear how and from what time point the segmented exponential curves are implemented. In addition the selected time for splicing a piece-wise model should be justified both statistically and using clinical plausibility.

One of the key aspects of DSU guidance for selecting a suitable extrapolation is visual inspection of the curves. However visual inspection of the fits generated by the AG suggests that in certain key instances the segmented exponential extrapolation using the current implementation underestimates long-term outcomes. The most striking example is for lenvatinib treatment duration (Figure 2), and sorafenib PFS (Figure 1). While not certain, the AG model appears to have followed an unorthodox approach of projecting survival curves by attaching the exponential distribution to the last Kaplan-Meier estimate, which does not necessarily correspond to the estimated survival probability from the 2-phase exponential curves at that point. In cases where there is a sharp decrease in the Kaplan-Meier curve at the last estimate due to a few events (e.g. for PFS and treatment duration), this approach not only lacks face validity, but also underestimates the cycle estimates. It is not clear if the same approach has been used for OS.

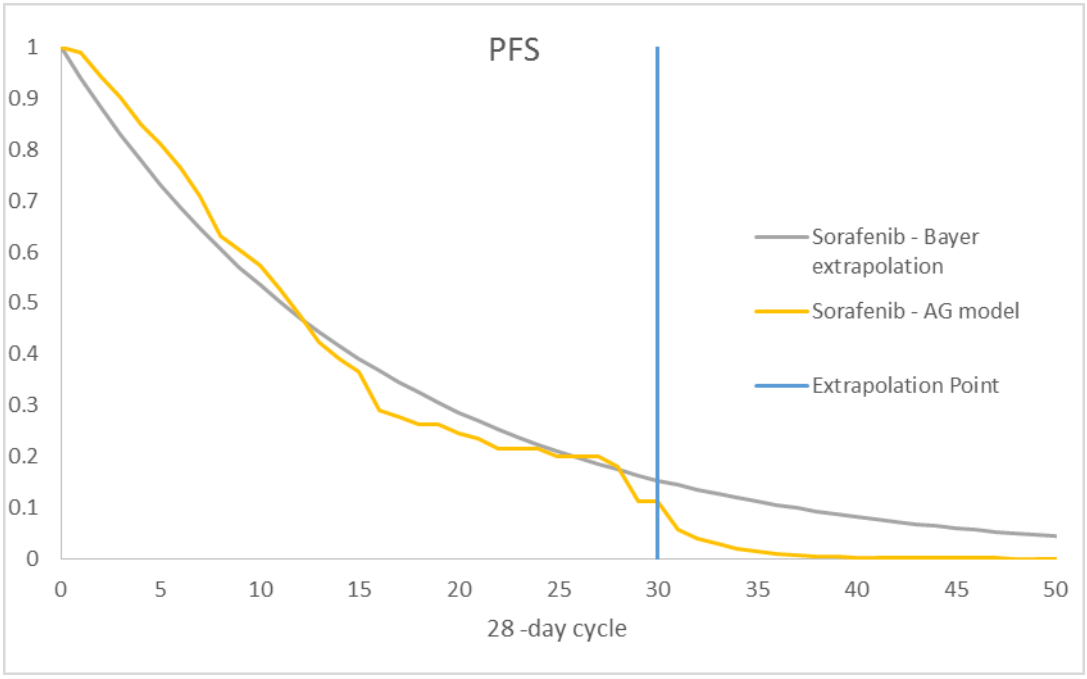
For PFS, the exponential distribution submitted by Bayer follows the Kaplan-Meier curve used in the AG model, however from the point the AG model curve switches to the extrapolated portion, there is an unexplained drop in the curve, which appears to underestimate the PFS (Figure 1).

The DSU guidance, which clearly defines a set of standard methods for conducting survival analysis, recommends a different approach. This states that all possible distributions (exponential, Weibull, Gompertz, Log-logistic and log normal) should be fitted to trial data. The DSU then recommends a range of methods to be used to assess each potential fit; log-cumulative hazard plots, AIC/BIC, visual inspection, clinical validity and external data. AIC/BIC test results were not provided in the AG report, nor was clinical validity taken into account. Bayer has submitted log-cumulative hazard plots, AIC/BIC, visual inspection, and clinical validity in the form of clinical expert interviews and data from the literature.

While Bayer agrees in the choice of exponential distribution for the DECISION trial, basing the choice of distribution on the SEER data assumes, that the population in the database (patients diagnosed with Stage 3 or 4 (locally advanced or metastatic) thyroid cancer in the USA and recorded on the SEER database) matches the population in the DECISION trial. However there are clear differences, e.g. the SEER data is not restricted to iodine refractory patients. Alternatively, it assumes that the pattern of survival is not dependent on the differences between populations within stage 3/4 thyroid cancer. However the different pattern seen in the DECISION and SELECT trials suggests otherwise. Additionally in

selecting the distribution, and method for implementation, the AG assume that the same approach must fit both sorafenib and lenvatinib trial data. However, this might not be the case, since the KM curves are visibly different.

Figure 1: Comparison of AG and Bayer extrapolation for sorafenib PFS



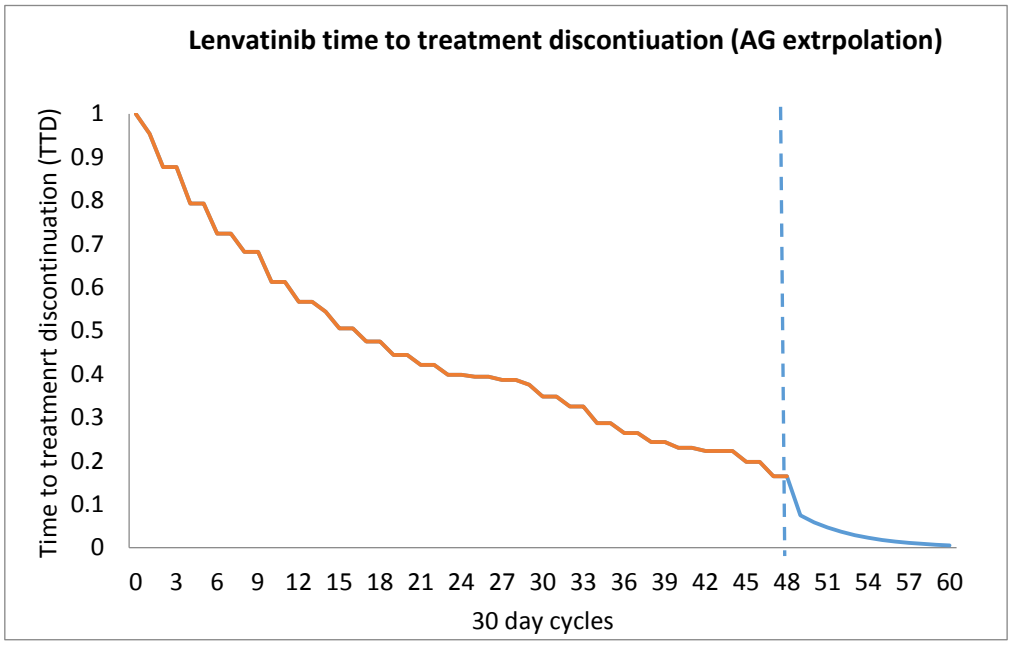
Lenvatinib time to treatment duration

The same can be seen for the treatment discontinuation curve for lenvatinib. The Assessment Group reported the treatment discontinuation curve from the SELECT trial to be "virtually complete". Upon inspection of the AG model at cycle 48 (the last cycle of which there is data) [redacted] of patients remained on treatment with lenvatinib the extrapolation (as per the AG basecase) is presented in Figure 2.

From cycle 48 the percentage of patients on treatment with lenvatinib drops by over half ([redacted]) from [redacted]% to [redacted]% in the course of a one month cycle. This is not in keeping with the previous 10 months (cycles 38-48) where the number of patients receiving treatment drops by a total of [redacted]%.

The sharp drop after cycle 48 is likely to significantly underestimate the treatment cost of lenvatinib.

Figure 2: Lenvatinib time to treatment discontinuation (TTD): SELECT trial



Treatment duration is overestimated for sorafenib and underestimated for lenvatinib

In addition to the underestimation of the lenvatinib costs due to the method of implementing the extrapolation, additional concerns are noted below.

The SELECT trial did not allow patients to continue treatment with lenvatinib outside of the double-blind period. The Assessment Group conducted a sensitivity analysis demonstrating that when lenvatinib is used until progression as anticipated in clinical practice, it results in an ICER of £106,000 per QALY (a 60% increase) (pg.122).

In the DECISION trial sorafenib patients could continue treatment past progression.

Whilst it can be argued that lenvatinib patients did not receive the clinical benefit from continuing lenvatinib treatment past progression, some lenvatinib patients in the SELECT trial did continue treatment with other TKIs (sorafenib and pazopanib), these were not costed into the economic evaluation. TKIs taken after lenvatinib would have been likely to have a similar effect as continuing sorafenib past progression. The current base case of the AG model assumes, that while sorafenib patients will continue after progression with TKI treatment, lenvatinib patients will not receive any TKI treatment post-progression. This is inconsistent. The differences in the trial design of allowing patients to continue with the same TKI (DECISION trial) or allowing patients to switch to another TKI (SELECT) is potentially due to the timing of the trials. When the DECISION trial was conducted, no other TKI was available for this patient population, while when the SELECT trial was conducted, patients could, and did receive sorafenib after progression.

If, based on the assumption used for lenvatinib, patients will not receive TKI treatment post-progression in clinical practice, the time to treatment discontinuation curve used in the base

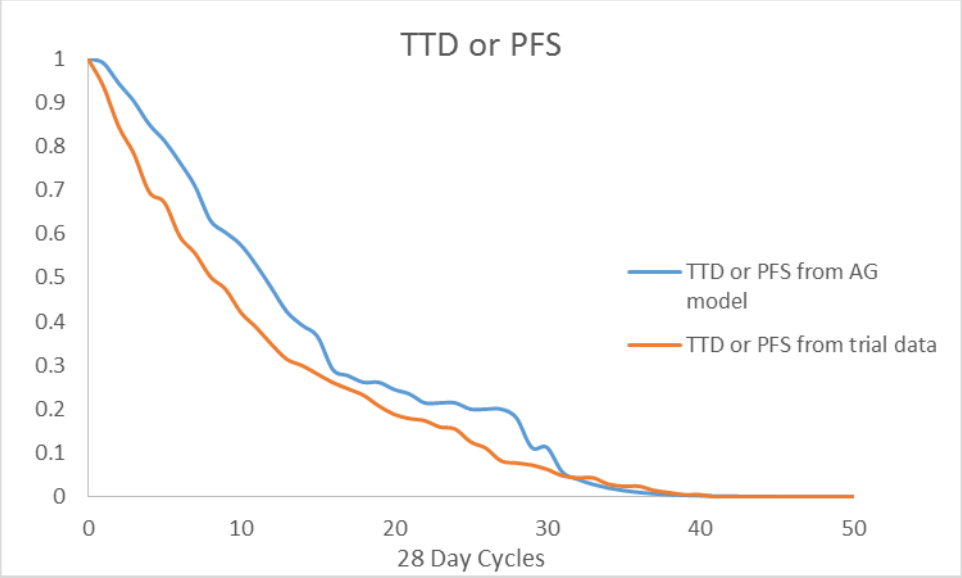
case for the Bayer submission should be used for sorafenib. This assumes that sorafenib patients will also stop TKI treatment at progression and is reflective of UK clinical practice.

The AG model has also attempted to include this scenario as a sensitivity analysis (pg. 144). However the implementation is incorrect. Bayer has provided data for this scenario, based on the patient level data from the DECISION trial, where every patient stops treatment at the latest at disease progression. The AG model instead of this data, looks at the average discontinuation of the whole cohort and compares it to the average PFS of the cohort to make sure the average time to treatment discontinuation is not greater than the average PFS, i.e. that the curves do not cross. However since some patients stop treatment early before progression, while others stop after progression, in average, the time to treatment discontinuation is similar to PFS as seen in Table 1. This leads to the AG model overestimating the proportion of patients on treatment (Figure 3) and thus the drug costs, when assuming patients stop at progression. The Bayer submission has provided the correct data to implement. (Submission model: TTD Detail sheet Column W for central assessment and column AC for investigator assessment, Submission document Appendix 7.9 for central assessment).

Table 1: ICERs based on treatment assumption used in the model

Treatment	Treatment based on TTD	Treatment based on PFS
Sorafenib	£85,644	£85,814
Lenvatinib	£65,872	£106,178

Figure 3: Time to treatment discontinuation curves for sorafenib from the AG model and Bayer submission assuming patients stop treatment at progression



4. Utility data from DECISION is inappropriate for application to the SELECT trial

EQ-5D utilities from the DECISION trial are robust when used to estimate the quality-of-life of sorafenib and BSC patients treated within the DECISION trial. These utilities also allow consistency in the source of efficacy, costs, safety profile and quality of life inputs. However the appropriateness of using these values for lenvatinib treated patients in the SELECT trial is highly uncertain.

1. The SELECT trial was conducted in a more severe population. The expectation here would be that on average patients in SELECT would be associated with a poorer quality-of-life and subsequently lower EQ-5D valuations. Using EQ-5D values from DECISION for lenvatinib will likely overestimate total QALYs gained for lenvatinib in the SELECT trial, and is inappropriate given the AG's assessment of the comparability of the trial populations.

2. The AG note that EQ-5D data from the DECISION trial *"include the disutility of AEs in estimates of health state utilities, and are therefore biased without any objective means of adjusting the health state". (*AG report, pg. *136)*

   The pre-progression utilities from DECISION reflect the quality of life of patients on treatment with sorafenib. Utility decrements due to adverse events are reflected in these estimates making these valuations treatment specific. Whilst this is appropriate for the 'in-trial analysis' of sorafenib and best supportive care, these values cannot be directly applied to the SELECT trial. Given the differences in the safety profile identified by the AG, including significantly more SAEs and ≥grade 3 AEs the use of sorafenib treatment utilities from the DECISION trial for lenvatinib is likely to overestimate the utilities for lenvatinib pre-progression.

3. Using EQ-5D utilities from DECISION and incorporating additional adverse events (as per the Eisai basecase) is also problematic as it introduces double counting, as AE utility decrements from the DECISION trials are already accounted for in the EQ-5D valuations, as the AG note this cannot be objectively adjusted for.

To reflect these uncertainties, it is suggested that health related quality-of-life of the 30 patients who participated in the open-label extension phase of SELECT (AG report, pg. 60) be used to validate the appropriateness of use of EQ-5D utilities from the DECISION trial for lenvatinib.

As a scenario analysis Bayer investigated reducing the PFS utility for lenvatinib by 10% resulting in a utility value of 0.646. This generated an ICER for lenvatinib versus BSC based on the SELECT trial of £80,320 compared to £65,872 when using the same value as sorafenib.

5. Sorafenib and lenvatinib are both end-of-life treatments

The Assessment Group note that neither treatment meets the criteria for the NICE appraisal of end-of-life treatments. However as the AG economic evaluation used a £50,000 willingness-to-pay threshold it is assumed these results are of relevance to the Committee.

The NICE end-of-life criteria consider that based on societal valuation QALYs gained towards the later stages of terminal diseases may be given greater weight. To reflect this NICE developed the following criteria used to assess whether a treatment can be considered end-of-life.

The first statement relates to the individual treatments:

> 1: A treatment must offer an extension of life of at least three months.

In this respect both treatments provide a sufficient extension to life to meet the criteria. Using results of the AG model lenvatinib and sorafenib offer an incremental extension of life of 2.05 and 1.07 years.

> 2: The treatment is indicated for patients with a short life expectancy, **normally** less than 24 months

The second point relates to the condition and is not treatment specific.

RR-DTC is a terminal condition with no alternative treatment options for patients in the absence of sorafenib or lenvatinib other than best-supportive/palliative care.

The AG present mean BSC overall survival to demonstrate that patient survival with falls between 55-57 months. Whilst this is a very narrow estimate, considering the differences in populations, it is also questionable whether mean survival, which is influenced by extreme values, accounts for a patient's expectation of survival and subsequent valuation of life extension.

The median, which is not influenced by extreme values, is perhaps a better way to assess a patient's expectations of survival. The median suggests that for the patient population median OS is significantly shorter at 19.1 months (SELECT) and 34.26 months (DECISION). A simple average of these gives a median survival of 26.7 months, though this estimate is uncertain given both best-supportive care arms have been adjusted for crossover.

The overall survival in patients with RR-DTC is not well documented. Given this uncertainty the Committee is urged to take into consideration the total extension of life provided and a further consideration as to whether end-of-life the criteria allows for variation in prognosis between different cancers. Table 2 considers data from studies reporting the overall survival of patients with RR-DTC.

Whilst the end-of-life criteria no longer includes a population size restriction, it is worth noting that RR-DTC has ultra-orphan designation.

Table 2: Previous studies in RR-DTC population

Author	Treatment arm	Population	Estimated median overall survival
Pennell et al 2008 (1)	Gefitinib	Radioiodine-refractory, locally advanced, or metastatic thyroid cancer	17.5 months
Argiris 2008 (2)	Doxorubicin	Locally recurrent or metastatic, radioiodine-refractory thyroid cancer, excluding medullary carcinoma	26.4 months
Shimaoka 1985 (3)	Doxorubicin/ doxorubicin + cisplatin	Progressive disease that was resistant to radioiodine therapy	8-9 months (estimate from KM)

6. Differences in safety profile of treatments acknowledged by the Assessment Group

The Assessment Group made important observations when comparing the safety profiles of sorafenib and lenvatinib.

Treatment with lenvatinib was found to result in significantly more grade ≥ 3 adverse events and serious adverse events (SAEs), than with sorafenib. Importantly for patients the types of adverse events experienced differed between treatments.

A choice of treatments would allow clinicians to account for patient comorbidities when making treatment decisions. Matching treatments to patients individual needs would likely reduce the impact of adverse events seen across the RR-DTC treated population. This is reflected in the 2017 NCCN guidelines which state “the choice between lenvatinib and sorafenib should be based on the individual patient, taking into account the likelihood of response and comorbidities”(4).

7. Sequencing of sorafenib and lenvatinib treatment

The Assessment Group report provides support for further investigation into the treatment sequencing of sorafenib and lenvatinib. This is supported through evidence cited in the AG report of differences in the mechanism of action, safety profiles of treatments and evidence of the efficacy of lenvatinib following progression with sorafenib treatment.

Whilst the company support recommendations for both sorafenib and lenvatinib as treatment options there is no evidence on the efficacy or safety of sorafenib following treatment with lenvatinib. Any recommendation on treatment sequencing must be supported by the relevant clinical evidence.

One of the main sources of evidence described by the AG report for the sequencing is based on table 44 and the results described there as:

“*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" (AG report, pg. 134)

However the table used, and the evidence cited in the table is incorrect, and as a result the conclusions drawn are also incorrect and should be deleted from the report. The revised and corrected estimates using the AG model can be seen below in Table 4. The mean PFS estimate should be 12.8 months rather than 47.2 months, leading to a PPS of 43.9 instead of 9.5.months. Revised values are based on the AG model calculations and are more aligned with the median PFS of 10.8 month seen in the DECISION trial. Similarly, the mean OS for BSC in the DECISION trial is 43.8 months, instead of 47.2 months, leading to an increase of 12.0 months instead of 9.5 months. The time to treatment discontinuation estimate for lenvatinib has also been corrected to 21.8 from 12.6 months. The difference with the revised numbers would also require changes to the conclusion in the AG report, since while for lenvatinib the OS benefit is 73% of the PFS benefit (PFS benefit: +34.1, OS benefit: +24.6), with the shorter post-progression survival offsetting some of the PFS benefit, for sorafenib the OS benefit is 248% of the PFS benefit (PFS benefit: +5.2, OS benefit: +12.9).

In addition the conclusion, that the proportion of gain from PFS converting into OS benefit could indicate superiority for lenvatinib is misleading, since PFS is not perfectly indicative of OS. Benefits of treatment are often, and in the case of sorafenib here, seen in both pre and post-progression periods, which also needs to be taken into account. Should this conclusion hold, it could be reversed to indicate the superiority of sorafenib.

Table 3: Mean time to event estimates from the AG report

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*	-

Table 4: Corrected mean time to event estimates

Table 44 AG estimated mean time-to-event outcome variables **Treatment group**	**PFS (months)**	**OS (months)**	**PPS (months)**	**TTD (months)**
Lenvatinib (SELECT)	41.0	55.1	14.1	21.8
Placebo (SELECT)	6.8	30.4	23.6	-
Gain due to lenvatinib	*+34.1*	*+24.6*	*-9.5*	-
Sorafenib (DECISION)	12.8	56.7	43.9	12.8
Placebo (DECISION)	7.6	43.8	36.2	-
Gain due to sorafenib	*+5.2*	*+12.9*	*+7.8*	-

8. Updated cost-effectiveness results

Bayer updated the model with the following assumptions to reflect an update base case based on the discussion of the topics above. Please see section 3 for full details of changes made:

1. PFS – separate exponential extrapolations to sorafenib and BSC to take into account the AG's assessment of non-proportionality
2. OS – separate exponential extrapolation to sorafenib and BSC fitted to RPSFT adjusted KM data using 2015 trial cut off to take into account the AG's view of non-proportionality and the updated data
3. TTD or PFS – direct from the trial data

Using these settings the list price ICER for sorafenib versus BSC decreased from £85,644 to £57,706 per QALY. Using the PAS price the ICER with updated base case is [redacted].

Table 5: Updated cost-effectiveness results using AG preferred assumptions and Bayer's updated assumptions

	Total LYs-BSC*	Total LYs – Sorafenib*	Total QALYs – BSC	Total QALYs - sorafenib	Incremental costs	ICER sorafenib versus BSC
Original AG base case	3.65	4.72	2.22	2.75	[redacted]	£85,644
AG model using proposed PFS	3.65	4.72	2.22	2.76	[redacted]	£83,911
AG model using proposed OS	4.33	5.75	2.55	3.20	[redacted]	£70,302
AG model using proposed TTD	3.65	4.72	2.22	2.75	[redacted]	£71,213
AG model using proposed PFS/OS	4.33	5.75	2.55	3.21	[redacted]	£69,150
AG model using proposed PFS/OS and TTD **NEW base case**	4.33	5.75	2.55	3.21	[redacted]	£57,706
NEW base case with PAS price	4.33	5.75	2.55	3.21	[redacted]	[redacted]

Table 6: Bayer proposed alterations to report

Page	AG comment in report	Bayer comment/ description of proposed amendment
30	The AG report states: *"authors of the NCCN guidelines 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"*	The NCCN guidelines state that lenvatinib is preferred "based on a response rate of 65% for lenvatinib when compared with 12% sorafenib, although these agents have not been directly compared" (4) This preference is based on a naive comparison between the DECISION and SELECT trials which the AG consider to be inappropriate due to differences in the trial populations. Please consider the use of "preferred" as this is potentially misleading given that the basis for the NCCN panel decision is not explained and this preference is not aligned with the AG's assessment, which could not conclude "whether the effectiveness of treatment with lenvatinib and sorafenib are similar, or different" (Page 18).
31	The AG report states: *"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"*	Sorafenib has been available via the Cancer Drugs Fund (CDF) since prior to the launch of the indication in April 2014, and is currently funded for all patients with RR-DTC, where the treating specialist has established treatment with sorafenib may be beneficial. Between July 2013 and June 2016, there were [redacted] notifications for DTC patients to commence treatment with sorafenib. It is on this basis the company stated that for patients where systemic treatment is appropriate sorafenib has replaced BSC as the standard of care.
57	The AG report states: *"The following AEs are reported as <2% due to a lack of information provided in source documents"*	Table 18 presents a comparison of all serious adverse events reported by ≥2% of patients in any arm of the SELECT and DECISION trials. Many of the sorafenib AEs are presented as <2% due to these events not being included in the source documents. Please find an updated table reflecting treatment related AEs from the DECISION trial. These are in the CSR supplied with the submission.

<table>
<tr><td></td><td></td><td>
<table>
<tr><th rowspan="2">Outcome, n (%)</th><th colspan="2">DECISION trial</th></tr>
<tr><th>Sorafenib N=207</th><th>Placebo N=209</th></tr>
<tr><td>SAEs</td><td>77 (37.2)</td><td>55 (26.3)</td></tr>
<tr><td>Pneumonia</td><td>1 (0.5)</td><td>0</td></tr>
<tr><td>Hypertension</td><td>0</td><td>0</td></tr>
<tr><td>Dehydration</td><td>0</td><td>2 (1.3)</td></tr>
<tr><td>General physical health deterioration</td><td>2 (1)</td><td>0</td></tr>
<tr><td>Dysphagia</td><td>2 (1)</td><td>1 (0.7)</td></tr>
<tr><td>Dyspnoea</td><td>6 (2.9)</td><td>7 (3.3)</td></tr>
<tr><td>Haemoptysis</td><td>0</td><td>2 (1.3)</td></tr>
<tr><td>Secondary Malignancy</td><td>9 (4.3)</td><td>4 (1.9)</td></tr>
<tr><td>Pleural effusion</td><td>6 (2.9)</td><td>4 (1.9)</td></tr>
</table>
</td></tr>
<tr><td>118</td><td>The AG report states:

“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, to represent the experience of patients receiving BSC (EQ-5D values were obtained from the DECISION trial).”</td><td>Please consider revising this statement:

1. Utility values used by Bayer in the submission to the SMC are the same as those used in this submission, as described in the following SMC guidance, “EQ-5D data were collected in the DECISION study and were used to estimate utility values for the model. The weighted average of all EQ-5D scores per cycle while patients were on treatment was assumed to represent the pre-progression utility value for each treatment arm. This resulted in utility values of 0.72 and 0.8 for the sorafenib and BSC arms respectively.” (5)

2. Utilities used in the Eisai model for lenvatinib, sorafenib, and BSC in the stable or response disease states are not aligned to valuations derived from the DECISION trial or previously submitted by Bayer to the SMC. Only the progressive health state utility is taken from the DECISION trial in the</td></tr>
</table>

<table>
<tr><td></td><td></td><td>Eisai model.

3. Use of utility values from the DECISION trial for lenvatinib patients is highly uncertain due to the differences highlighted by the AG in the trial populations and safety profiles of treatments. This was not mentioned when reporting on appropriateness of selected utilities for each treatment.</td></tr>
<tr><td>119</td><td>The AG report states:

“no additional utility decrements associated with AEs were included in the (Bayer) model”</td><td>Please consider revising this statement.

EQ-5D responses collected in the DECISION trial were averaged across all patients in a given health state and reflect utility decrements associated with adverse events. To further account for these with additional utility decrements would result in double counting.</td></tr>
<tr><td>134</td><td>Table 44 does not correspond with results from the AG model.</td><td>Please update table 44 with correct values and amend any text or conclusions in the report citing this data.

Table 7: Mean time to event estimates from the AG report
<table>
<tr><td>Table 44 AG estimated mean time-to-event outcome variables
Treatment group</td><td>PFS (months)</td><td>OS (months)</td><td>PPS (months)</td><td>TTD (cycles)</td></tr>
<tr><td>Lenvatinib (SELECT)</td><td>41.0</td><td>55.1</td><td>14.1</td><td>12.6 (30 day)</td></tr>
<tr><td>Placebo (SELECT)</td><td>6.9</td><td>30.2*</td><td>23.3</td><td>-</td></tr>
<tr><td>Gain due to lenvatinib</td><td>+34.1</td><td>+24.9</td><td>-9.2</td><td>-</td></tr>
<tr><td>Sorafenib (DECISION)</td><td>47.2</td><td>56.7</td><td>9.5</td><td>14.4 (28 day)</td></tr>
<tr><td>Placebo (DECISION)</td><td>7.6</td><td>47.2*</td><td>39.6</td><td>-</td></tr>
<tr><td>Gain due to sorafenib</td><td>+39.6</td><td>+9.5</td><td>-30.1</td><td>-</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td></td><td>Table 8: Corrected mean time to event estimates
<table>
<tr><th>Table 44 AG estimated mean time-to-event outcome variables
Treatment group</th><th>PFS (months)</th><th>OS (months)</th><th>PPS (months)</th><th>TTD (months)</th></tr>
<tr><td>Lenvatinib (SELECT)</td><td>41.0</td><td>55.1</td><td>14.1</td><td>21.8</td></tr>
<tr><td>Placebo (SELECT)</td><td>6.8</td><td>30.4</td><td>23.6</td><td>-</td></tr>
<tr><td>Gain due to lenvatinib</td><td>+34.1</td><td>+24.6</td><td>-9.5</td><td>-</td></tr>
<tr><td>Sorafenib (DECISION)</td><td>12.8</td><td>56.7</td><td>43.9</td><td>12.8</td></tr>
<tr><td>Placebo (DECISION)</td><td>7.6</td><td>43.8</td><td>36.2</td><td>-</td></tr>
<tr><td>Gain due to sorafenib</td><td>+5.2</td><td>+12.9</td><td>+7.8</td><td>-</td></tr>
</table></td></tr>
<tr><td>134</td><td>The AG report states:

“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.”</td><td>This conclusion is based upon incorrect data in table 44 (noted above).

Updated values change the direction of the final conclusions made here.

Although benefits of treatment are often, and in the case of sorafenib here, can be seen in both pre and in the post progression period, which also needs to be taken into account. Should this conclusion hold, it could be reversed to indicate the superiority of sorafenib.

For more information see Section 7 of this response.</td></tr>
<tr><td>135</td><td>The AG report states:

“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”</td><td>EQ-5D data was collected in DECISION at each follow-up appointment. For the economic model all valuations collected were averaged across all patients in the given health state.

The AG conclude that this approach assumes that AE disutilities persist in perpetuity whilst the patient is in that health state. This is not correct, as EQ-5D values reflect the average patient’s utility including experiences of, and recovery from adverse events.</td></tr>
<tr><td>142</td><td>Commercial in confidence markings have been applied to the BSC costs instead of the sorafenib costs</td><td>Please update the commercial in confidence markings.</td></tr>
</table>

144	Implementation of the “least of TTD and PFS” treatment assumption for sorafenib	The implementation of this scenario in the model is incorrect. Bayer has provided data for this scenario, based on the patient level data from the DECISION trial, where every patient stops treatment at the latest at disease progression. The AG model instead of this data, looks at the average discontinuation of the whole cohort and compares it to the average PFS of the cohort to make sure the average time to treatment discontinuation is not greater than the average PFS, i.e. that the curves do not cross. However since some patients stop treatment early before progression, while others stop after progression, in average, the time to treatment discontinuation is similar to PFS as seen in (Table 1 of main response). This leads to the AG model overestimating the proportion of patients on treatment (Figure 3 of main response) and thus the drug costs, when assuming patients stop at progression.
147	The AG report states: *“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.”*	The probabilistic sensitivity analysis (PSA) described in the AG report and included in the AG model appear to be limited. To better represent the uncertainty, the PSA should include all parameters with parameter uncertainty. However the PSA provided, excludes the efficacy parameters, TTD and the dose intensity from the analyses, which are all influential parameters. In addition, while the use of normal distribution for most parameters can be appropriate sufficient care needs to be taken that the normal distribution, where needed, is limited ta realistic range.
150	The AG report states: “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).”	Please update this data and conclusions in line with errors identified in Table 44. Please ensure that any other references to this are updated.

If any additional information is required to implement changes please contact the company via NICE.

Table 9: Bayer response to AG questions in the report

Page	AG comment in report	Bayer response
31	The AG report states: *"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"*	Estimates provided by the company are reflective of the agreed final scope of this Appraisal. The AG acknowledged there is "no universally accepted objective criteria for assessing patients who are symptomatic and/or rapidly progressing" and on this basis it is difficult to further segment the population. CDF notifications for sorafenib (approximately [redacted] per year) are less than population based estimates, and reflect clinical judgement currently exercised by specialists.
46	The AG report states: *"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)."*	Bayer did not collect data on the specific agents used during the trial follow-up. In the DECISION trial sorafenib patients could continue treatment past progression. In the SELECT trial did not allow patients to continue treatment with lenvatinib outside of the double-blind period. Whilst it can be argued that lenvatinib patients did not receive the clinical benefit from continuing lenvatinib treatment past progression, some lenvatinib patients in the SELECT trial did continue treatment with other TKIs (sorafenib and pazopanib), these were not costed into the economic evaluation. TKIs taken after lenvatinib would have been likely to have a similar effect as continuing sorafenib past progression. The current base case of the AG model assumes, that while sorafenib patients will continue after progression with TKI treatment, lenvatinib patients will not receive any TKI treatment post-progression. This is inconsistent. The differences in the trial design of allowing patients continuing with the same TKI (DECISION trial) or allowing patients to switch to other TKI (SELECT) is potentially due to the timing of the trials. When the DECISION trial was conducted, no other TKI was available for this patient population, while when the SELECT trial was conducted, patients could receive, and have received sorafenib after progression. If, based on the assumption used for lenvatinib, patients will not receive TKI treatment post-progression in clinical practice, the time to treatment discontinuation curve used in the base case for the Bayer submission should be used for sorafenib. This assumes that sorafenib patients will also stop TKI treatment at progression. This is reflective of UK clinical practice

125	The AG report states: *"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."*	While Bayer agrees in the choice of exponential distribution for the DECISION trial, basing the choice of distribution on the SEER data assumes, that the population in the database (patients diagnosed with Stage 3 or 4 (locally advanced or metastatic) thyroid cancer in the USA and recorded on the SEER database) matches the population in the DECISION trial. However there are clear differences, e.g. the SEER data is not restricted to iodine refractory patients. Alternatively, it assumes that the pattern of survival is not dependent on the differences between populations within stage 3/4 thyroid cancer. However the different pattern seen in the DECISION and SELECT trials suggests otherwise. The company recommends tests for statistical, visual and clinical plausibility should conducted as outlined in the NICE DSU technical support document.

References

1. Pennell NA, Daniels GH, Haddad RI, Ross DS, Evans T, Wirth LJ, et al. A phase II study of gefitinib in patients with advanced thyroid cancer. Thyroid. 2008;18(3):317-23.
2. Argiris A, Agarwala SS, Karamouzis MV, Burmeister LA, Carty SE. A phase II trial of doxorubicin and interferon alpha 2b in advanced, non-medullary thyroid cancer. Investigational new drugs. 2008;26(2):183-8.
3. Shimaoka K, Schoenfeld DA, Dewys WD, Creech RH, Deconti R. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer. 1985;56(9):2155-60.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma March 31, 2017. [August 2017]. http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.].
5. Scottish Medicines Consortium (SMC). Detailed advice on the assessment of sorafenib (Nexavar) for the treatment of patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, rafractory to radioactive iodine. 2015 5th June 2015. Report No.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

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

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by Kleijnen Reviews. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

August 2017

Issue 1 TTD or PFS implementation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Method for calculating option 3 for treatment discontinuation (TTD or PFS) takes the average TTD of the whole cohort and compares it to the average PFS of the cohort to make sure the average time to treatment discontinuation is not greater than the average PFS, i.e. that the curves do not cross. However since some patients stop treatment early before progression, while others stop after progression, on average, the time to treatment discontinuation is similar to PFS. This leads to the AG model overestimating the proportion of patients on treatment and thus the drug costs. See full discussion in Bayer response document (issue 3).	Use TTD or PFS KM curve supplied in the Bayer submission model (TTD detail tab cells W6-389 for central assessment and cells AC6-389 for investigator assessment) and in the submission document (Appendix 7.9 for central assessment).	The KM curve for TTD or PFS from trial data falls below the minimum of PFS and TTD curves (see Bayer response document figure 3) therefore treatment duration for sorafenib will be shorter with this option. Reducing treatment duration will reduce drug costs and hence the ICER for sorafenib versus BSC.

Issue 2 Confidence intervals for lenvatinib PFS utility

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Calculation of upper and lower confidence bound for sorafenib/lenvatinib PFS utility uses the untreated utility not the PFS utility	Cells G and H51 in parameters sheet should read “EQ_PFS_Sor-1.96*F51” and not “EQ_PFS_BSC-1.96*F51”	Results in a wider CI around treatment utilities used in the PSA and therefore will produce higher uncertainty

Issue 3 Dose intensity value for sorafenib

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Dose intensity for sorafenib used has been rounded. The value should be 81.375% and not 81.4%	Use unrounded value in cell C9 in parameters tab	Minor decrease in drug acquisition cost for sorafenib

Issue 4 Method of extrapolation

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Method of extrapolating long-term TTE outcomes underestimates PFS, OS for sorafenib and TTD for lenvatinib. See full discussion in Bayer response document (issue 3).	We recommend revising the calculations, so that the extrapolation is in line with the observed data. Since calculations are not provided in the model, only hardcoded numbers, the exact revision of the formulas could not be provided.	As a proxy, using the OS and PFS extrapolations with single exponential distribution from our submitted model in the AG model the ICER for sorafenib versus BSC falls from £85,644 to £69,150. See full discussion in Bayer response document. For lenvatinib, due to the underestimation of TTD, time on treatment and subsequently the drug costs would increase, resulting in a higher ICER.

Issue 5 Incidence for AEs for DECISION BSC

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Incidence of AEs for BSC from the DECISION trial are incorrect.	Value for hypertension hard coded in the incidence calculation for BSC (cell K37-39) is 4/207 whereas for it should be 5/209	Very minimal impact

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

Eisai Response to the Assessment Report

September 2017

Eisai provides the following comments on the Assessment Report and the conclusions:

1. **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."**

As per the company submission, Eisai believe that despite the differences in the baseline characteristics of the SELECT and DECISION study populations, the trials are indeed similar enough to allow indirect comparison. As such, we feel that the assessment group (AG) should re-consider undertaking this analysis.

In our submission, Eisai highlighted that indirect treatment comparison (ITC) approaches are limited by differences in the studies being compared, such as study design and patient characteristics, which can bias the results. These limitations are especially pronounced when the number of studies is small. Matching-adjusted indirect comparison (MAIC) is a technique that has been developed to allow for the comparison of two studies, while controlling for baseline characteristics, when individual patient data are available for only one study.

In this approach, the population with individual patient data (lenvatinib in this case) is adjusted and reweighted to match the population with summary statistical data. By doing this, treatment outcomes can then be compared between the two groups. This approach has been used to provide comparative evidence in advance of the publication of randomised comparative studies in several settings, including chronic myeloid leukemia, attention-deficit hyperactivity disorder, diabetes, and psoriatic arthritis (1).

Both an ITC and MAIC were performed for the second data cut results of lenvatinib and sorafenib and the results of the MAIC were published (1).This publication has also been identified by the AG in their systematic review.

For this MAIC analysis, since no prior VEGF/VEGFR-targeted therapy patients were permitted in the DECISION trial, all VEGF/VEGFR treated patients in the SELECT study (66 lenvatinib, 27 placebo) were removed from the analysis. In addition, the brain metastases covariate was excluded from the analysis since it was not recorded in the DECISION study and 16 additional patients from SELECT (9, lenvatinib; 7, placebo) were removed. This was done in order to avoid an imbalance in disease severity between both studies, since patients with brain metastasis tend to be more severe than the overall RAI-refractory DTC population.

Balance in patient characteristics between the trials was achieved by the application of weights to patients in the SELECT trial. Weights were generated by using a logistic regression model on the patient-level data from SELECT, with age, sex, race, ECOG performance status, region, histology, metastasis and common sites of metastasis

included as predictors of enrolment in the trials. Weight for a patient was defined as the inverse odds of enrolment in the SELECT versus DECISION trials.

The result of this MAIC show slightly better results for both overall survival (OS) and progression-free survival (PFS) in favour of lenvatinib versus sorafenib. The hazard ratio (HR) for PFS for lenvatinib vs. sorafenib was 0.36 (95% CI: 0.22, 0.57) for the unadjusted clinical trial and 0.33 (95% CI: 0.20, 0.53) after MAIC. Indirect treatment comparison of the crossover-corrected OS data for lenvatinib compared to sorafenib resulted in an HR of 0.77 (95% CI: 0.44-1.35) for the clinical trial data and in an HR of 0.73 (95% CI: 0.40-1.35) when MAIC is applied.

The MAIC is therefore showing a trend in favour of lenvatinib, indicating that even after adjusting for baseline characteristics, lenvatinib is still statistically significantly superior to sorafenib for PFS and has an non-significant absolute risk reduction of 27% for OS (23% without MAIC adjustment).

As highlighted above, the results from the MAIC and ITC using the efficacy data from the second data cut were very similar. As an ITC is simpler and requires fewer assumptions, it can be considered as more robust and introduces less uncertainty. Therefore, Eisai decided to perform an ITC only on the third data cut results to inform the base case of the cost effectiveness model.

2. **"The generalisability of the SELECT trial 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."**

Eisai disagrees with these conclusions. There is excellent awareness around the side effect profile of TKIs and how these can be managed. Eisai does not believe that this translates into concerns around using TKIs. We feel that this represents a cautious and responsible approach in prescribing TKIs by evaluating the risk benefit ratio for each patient.

As indicated in the company submission, the SELECT trial included seven investigational sites in the UK, five of them in England and so the findings include UK patients. Since an agreement was reached with NHSE to provide lenvatinib on compassionate grounds, around 40 requests have been received to date from clinicians for their patients in England. This reinforces the generalisability of the SELECT trial findings to NHS clinical practice.

As stated in the AG report, the SELECT trial only included patients who had measurable disease and who had progressed within the last 13 months (including screening window) (2). Therefore, the SELECT trial population only included patients with progressive disease and this is reflected in the licensed indication which is "for the treatment of adult patients with **progressive**, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)." (3)

In addition a large proportion of patients in the SELECT trial had metastatic disease (40%). Feedback provided to Eisai by UK clinical experts in RAI-refractory DTC, and highlighted in the company submission, is that metastatic RAI-refractory DTC can cause problematic disease-related symptoms which are experienced for a long time and can severely impact on quality of life.

Therefore the results of the SELECT trial reflect use in UK patients with progressive disease and/or symptomatic disease and are therefore representative of current NHS clinical practice.

It is also important to note that lenvatinib adverse events are manageable with dose interruption/reduction and conventional medical care. A dose modification table is prominently displayed within section 4.2 of the Lenvima Summary of Product Characteristics (SPC) so clinicians will be aware of this.

The SELECT trial used an algorithm to manage treatment interruption due to adverse events (AEs) and subsequent reintroduction at a lower dose. As a result, the majority of patients were able to continue therapy in the SELECT trial with adverse events leading to study drug withdrawal in only 16.5% of patients receiving lenvatinib.

The median duration of treatment in study SELECT was more than 3 times longer in patients treated with lenvatinib than in those who received placebo (13.8 vs. 3.9 months, respectively). Therefore, the rate of adverse events should be considered in the light of this relatively long treatment duration and exposure for lenvatinib versus placebo.

The company submission highlighted that the comparative safety information with sorafenib has shown that lenvatinib has a different safety profile from sorafenib.

The most frequent AEs for sorafenib in the DECISION trial (4), hand-foot skin reaction (76.3%) and alopecia (67.1%), which are known to greatly impact patients' daily lives, were reported much less frequently (32.2% and 12.3%, respectively) for lenvatinib patients in the SELECT trial.

In summary, 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.

3. **"There are further important caveats regarding the generalisability of the findings from the SELECT trials to NHS clinical practice":**

    a. **"…while most patients participating in the trials had a diagnosis of PTC, as would be expected in clinical practice there more proportionally more patients with other types of DTC than would be expected in NHS clinical practice and patients with these other types of DTC are reported to have a worse prognosis."**

Eisai do not believe that this is a valid conclusion for the SELECT study.

As stated in the AG report, 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 and that histology (favouring FTC versus PTC) was statistically significantly associated with increased OS.

Therefore, it can be assumed that the SELECT study results would be consistent irrespective of type of DTC and therefore generalisable to NHS clinical practice.

    b. **"…it appears that generally patients were older than may be seen in clinical practice."**

Eisai do not believe that this is a valid conclusion for the SELECT study. The majority of patients (60.2%) in the study were aged less than 65 years.

In addition, it is important to note that, as highlighted in the AG report, results of a subgroup analyses have shown that there was no statistically significant difference in overall survival (OS) between older (≥65 years) and younger (<65 years) lenvatinib-treated patients (HR=0.78, 95% CI: 0.49-1.26, p=0.30) (5).

Therefore, it can be assumed that the SELECT study results would be consistent irrespective of age and therefore generalisable to NHS clinical practice.

4. "The AG has not included a separate health state for patients who responded to treatment"

The AG report quotes that "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."

Eisai disagree with this conservative assumption as it contradicts published evidence (6) and advice from UK clinical experts. It is important for the cost effectiveness analysis to reflect that there is a group of patients who will respond to treatment and as a result have a better HRQoL, as described in the Eisai company submission.

5. **Implementation of HRQoL in the AG's model**

In the AG's base case, it is assumed that disutility due to treatment-emergent adverse events is sufficiently captured by the utility values obtained from DECISION, and that these are equal for both lenvatinib and sorafenib. While this may be a reasonable assumption for sorafenib, Eisai feel that this is highly conservative for lenvatinib. The difference in the impact on health-related quality of life (HRQoL) of both treatments is highlighted by the two most common AEs for each treatment: hypertension (lenvatinib) and hand-foot syndrome (sorafenib).

Given that the majority of cases of hypertension were asymptomatic, it would be expected that hypertension would have little impact on HRQoL. This is further supported by advice received from UK clinical experts, who stated that hypertension is manageable and does not impact on patients' daily activities. However, the same cannot be said for hand-foot syndrome which is considered by the clinical experts as difficult to manage and having a significant impact on HRQoL.

Therefore, it is reasonable to assume that the utility values for lenvatinib should be higher than those of sorafenib. In addition, it is important to highlight that patients who respond to treatment have a higher health state utility value than those with stable disease, as supported by published evidence (6) and validated by UK clinical experts.

6. **Resource use data used in the AG model**

Eisai have concerns about the data used by the AG to estimate resource use in the model. In particular, Eisai feel that it is not clinically plausible to assume the same level of resource use and cost for the pre and post-progression states, an assumption which directly contradicts the expert clinical advice received by Eisai and published evidence.

In addition, Eisai also feel that the estimates of resource use in the company model are more robust than the estimates used in the AG model, given that the Eisai estimates were obtained from a published study in a relevant population (7) and were then validated further by 4 UK clinical experts experienced in treating RAI-refractory - DTC, as opposed to the estimates in the AG model which were obtained from one clinical expert.

In a scenario exploring resource use in the AG model; using the AG resource use estimates for pre-progression and then adding in the Eisai estimates for hospitalisations to post-progression, the ICER for lenvatinib vs BSC decreases from £65,872 to £56,602 per QALY and the ICER for sorafenib vs BSC increases from £85,644 to £96,909 per QALY. Eisai feel this scenario is far more plausible than the AG base case.

7. Methodology of calculating adverse event costs in the AG model

On page 138 of the AG report it is stated:

"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."

It is not clear from this description that the executable model and economic evaluation assume that:

1. All adverse events are assumed to be incident in the first cycle of the model, and
2. All adverse events are assumed to persist indefinitely, even after cessation of treatment, until death
    a. This issue is also detailed in Issue 1 of the pro-forma response for the executable model

We do not believe that assuming treatment-emergent AEs are unresolvable and persist indefinitely beyond the cessation of treatment are clinically plausible assumptions. We would propose that assumptions for a more clinically plausible approach and therefore one which reflects UK clinical practice may include:

1. Application of the costs of treatment-emergent adverse events while subjects receive treatment only
2. Modelling of the incidence rate and duration of adverse events, to account for the observation that some adverse events may resolve before patients stop treatment.

We also note in Table 47 of the AG report that an incidence rate of 3.45% for proteinuria for lenvatinib is reported. It is not clear how this estimate has been derived, and may represent a copy/paste error from the above hand-foot syndrome data within the same table. Based on the incidence of Grade ≥ 3 treatment-emergent adverse events (as per Table 17 on page 56 of the report), the incidence rate for proteinuria in the report and in the model should be 10.0% for lenvatinib.

In addition, the table lists an incidence rate of 0% for hypertension for sorafenib. This is inconsistent with the model which reports an incidence rate of 9.7% which is consistent with Table 17 on page 56 of the report. These data as presented in the current report may therefore represent a factual inaccuracy.

8. **Finally, Eisai would like to highlight the following factual inaccuracies in the report:**
   a. **Page 12, "Lenvatinib and sorafenib also increased the incidence of adverse events (AEs)":**
      Eisai would like to clarify that lenvatinib is associated with increased AEs versus placebo.
   b. **Page 32, Table 1, Lenvima cost per year:**
      Eisai would like to highlight that the estimated cost per year of Lenvima is £40,236, as per the company submission
   c. **Page 33, "Mechanism of action: Targets VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, PDGFR beta, RET and KIT"**
      Eisai would like to highlight that lenvatinib targets both PDGFR beta and PDGFR alpha.
   d. **Page 41, "Recruitment period: 5 August 2012 to 4 October 2012"**
      Eisai would like to highlight that, as per the company submission, the recruitment period for the SELECT study was from 5 August 2011 to 4 October 2012
   e. **Page 45, Table 8, Average dose**
      Eisai have identified an error in the average dose reported in the company submission and as a result in the AG report. The average dose 17.4mg is from the first datacut (November 2013). The updated correct average dose for the August 2015 datacut is 16.3mg.
   f. **Page 89,** "**Hypertension was the most common reason for dose modifications or discontinuations in the SELECT trial."**
      Diarrheoa was the most common reason for dose interruption or reduction. 1.1% of patients discontinued treatment due to hypertension.
   g. **Page 118, Table 37- It is stated that for OS modelling for sorafenib, "Published DECISION trial OS data from first data-cut (August 2012)" was used.**
      This is incorrect as, similarly to lenvatinib in the Bayer model, the OS curve for sorafenib was generated by adjusting the lenvatinib OS curve using the HR generated by the ITC. This was based on the updated OS data from July 2015 cut-off date (Brose, et al., 2016) adjusted for the crossover of placebo patients using a Rank-Preserving Structural Failure Time model (RPSFT).The same also applies to PFS modelling for sorafenib in Table 38.
   h. **Page 138, Discrepancy between dose intensity factor stated in the report (71.666%) and value implemented in the AG economic model (72.50%).**
      Eisai agree with the later value (17.4mg/24mg = 72.50%).

Please also find attached, a completed proforma providing additional comments on the reliability of the AG's model.

References:

1. Tremblay, G. Matching-adjusted indirect treatment comparison in patients with radioiodine-refractory differentiated thyroid cancer. Comparative Effectiveness Research 2016*;* 6: 13-21
2. Schlumberger, M., et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. New England Journal of Medicine 2015; 372(7): 621-630
3. Lenvima Summary of Product Characteristics
4. Brose, M. et al. Sorafenib in locally advanced or metastatic radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. The Lancet 2014; 384(9940): 319-328

5. Brose, MS, et al. Effect of Age on the Efficacy and Safety of Lenvatinib in Radioiodine-Refractory Differentiated Thyroid Cancer in the Phase III SELECT trial. J Clin Oncol 2017;35(23): 2692-2699
6. Fordham, BA, et al. Health state utility valuation in radioactie iodine refractory differentiated thyroid cancer. Patient Preference and Adherence 2015*;* 9: 1561-157
7. Gianoukakis, A, et al. Treatment patterns, health state, and health care resource utilization of patients with radioactive iodine refractory differentiated thyroid cancer. Cancer Management and Research 2016*;* 8: 67-76

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

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

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by Kleijnen Reviews. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Agreement Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. If asked, you must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

August 2017

Issue 1 Application of adverse event costs in economic model

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Regarding cells: • Main28!Y7:Y529 • Main30!Y7:Y494 of the economic model. The costs of adverse events for sorafenib and lenvatinib (in Main28 and Main30, respectively) are applied to all alive patients, rather than to patients who remain on active treatment. The AG does not report the intended assumption; however we would consider the current implementation a technical error, as it assumes that treatment-emergent adverse events persist indefinitely beyond the discontinuation of treatment.	Costs of adverse events should be applied only to patients who remain on active treatment, i.e. column Y should reference TTD (column N) rather than OS (column L).	Costs of adverse events associated with active treatment will be reduced, and therefore the resulting ICERs will be reduced (approximately 5% improvement for lenvatinib).

Issue 2 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: Main28 and Main30	Only deaths from current cycle to be used to calculate	Negligible

Cells: AA8:AB529 and AA8:AB494 **Issue:** Terminal care costs based on the average number of deaths across three cycles, rather than just the current cycle	terminal care costs.	Correction changes sorafenib ICER from £85,644 to £85,523 Correction changes lenvatinib ICER from £65,872 to £65,845

Issue 3 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: TTEdata **Cells:** N16:N537 P16:P537 W16:W537 Y16:Y537 AG16:AG537 **Issue:** The month from the previous cycle is used to determine whether the Kaplan-Meier should be used	Month from the current cycle should be used	None; affects sensitivity analysis only

Issue 4 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: TTEdata **Cells:** AJ16:AJ537 **Issue:** In one place the cycle number is referenced instead of the number of months	Number of months should be used	None; affects sensitivity analysis only

Issue 5 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: Main28 **Cells:** I7:I529 **Issue:** The upper and lower limits of the extrapolated curve are the wrong way around	Cell references to be swapped	None; affects sensitivity analysis only

Issue 6 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: TTEdata **Cells:** AB16:AB537	Calculation to be based on column U	None; column U and column AE are identical

Issue: Calculations are based on AE16:AE537, but should be based on U16:U537		

Issue 7 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: TTEdata **Cells:** B15, L15, U15, AE15 **Issue:** Calculations are based on 30 days rather than 28 days	Calculation based on 28 days implemented	None; results for these cells are identical when using either 28 days or 30 days

Issue 8 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: Parameters **Cells:** I41:J41 **Issue:** The adverse event cost for sorafenib and lenvatinib is calculated based on use in the BSC arm	Use in the on treatment arms to be used	None; use in BSC and on treatment arms currently set to be the same

Issue 9 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: Main28 **Cells:** V7:V529 **Issue:** The drug administration cost is not applied at the same times as the drug is applied	Drug administration to be set to apply whenever the drug is given	None; the administration cost is currently set to zero

Issue 10 Calculation error

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Sheet: Main30 **Cells:** V7:V494 **Issue:** The drug administration cost is not applied at the same times as the drug is applied	Drug administration to be set to apply whenever the drug is given	None; the administration cost is currently set to zero

Response to comments

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (ID1059)

Assessment Group response to comments on its report and model

This report was commissioned by the NIHR HTA Programme as project number 16/51/20

20 September 2017

Contains data commercial in confidence

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 Comments from Eisai

1.1 Eisai comments on the AG report

Eisai provided seven main comments on the Assessment Report in addition to eight factual inaccuracies. These are summarised in Table 1 alongside the response from the AG to each issue and factual inaccuracy.

Table 1 Summary of issues on the AG report raised by Eisai

Issue	Description of issue (summary)	AG response
1	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."	The AG disagrees with Eisai for reasons discussed in the AG report. Of note, while Matching-adjusted indirect comparison (MAIC) is a technique that has been developed to allow for the comparison of two studies, while controlling for baseline characteristics, it is not clear if this would address the problem of the risk profiles in the placebo arms of the SELECT and DECISION trials being different.
2	"The generalisability of the SELECT trial 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."	The AG agrees that clinicians and nursing staff are well aware of the side-effects from TKIs and capable of managing these efficiently. However, clinical advice received by the AG is that if there is no evidence of clinically significant progressive disease (e.g. rapidly rising thyroglobulin), then often patients are not treated in order to avoid the risk of side effects (and possible negative impact on health-related quality of life) in the first place. Specialists consider multiple factors when making a treatment decision. The AG acknowledges that patients in the SELECT trial had progressive disease. The uncertainty arises in establishing to what extent the disease would also be considered rapidly or clinically significant.
3	"There are further important caveats regarding the generalisability of the findings from the SELECT trials to NHS clinical practice": a. "…while most patients participating in the trials had a diagnosis of PTC, as would be	Eisai highlight that as stated in the AG report, subgroup and exploratory analyses of the SELECT trial data showed that for unadjusted overall survival (OS), there was a statistically significant OS gain for patients with FTC treated with lenvatinib versus

Issue	Description of issue (summary)	AG response
	expected in clinical practice there more proportionally more patients with other types of DTC than would be expected in NHS clinical practice and patients with these other types of DTC are reported to have a worse prognosis." b. "…it appears that generally patients were older than may be seen in clinical practice."	placebo and that histology (favouring FTC versus PTC) was statistically significantly associated with increased OS. As also highlighted in the AG report, Eisai note that results of a subgroup analysis have also shown that there was no statistically significant difference in OS between older (≥65 years) and younger (<65 years) lenvatinib-treated patients (HR=0.78, 95% CI: 0.49-1.26, p=0.30). The AG notes that while these analyses do appear to provide evidence of the relative efficacy for lenvatinib versus placebo for these subgroups, the analyses include small numbers of patients and can only be considered exploratory. Furthermore, it is unclear if the median OS reported for patients in these subgroups can be expected to be the same as for all patients in the trial (median OS is not reported in the abstracts but is reported in the CSR, however the data are immature, taken from the first data-cut and so the median is commonly not estimable). Hence the AG considers these are important caveats that should be considered when considering the generalisability of the findings to the clinical practice.
4	"The AG has not included a separate health state for patients who responded to treatment"	The Response health state introduced in the Eisai model is based on the results of the vignette study reported by Fordham et al 2015 [Fordham, BA, et al. Health state utility valuation in radioactie iodine refractory differentiated thyroid cancer. Patient Preference and Adherence 2015*;* 9: 1561-157]. The estimated utility value for this state (0.86) is barely statistically different from the Stable health state value (0.80), and greater than the age-adjusted mean UK EQ-5D value using general population (0.844), suggesting that if there is a genuine difference in utility attributable to response to treatment it is probably overstated. Additionally, the Fordham et al 2015 analysis does not recognise that treatment-related adverse events will continue in patients still on treatment

Issue	Description of issue (summary)	AG response
		which may counter some or all of such benefit. On clinical advice, the AG concluded that the Fordham et al 2015 analysis did not yield a sufficiently robust utility value for a response state, and that a single stable disease state with AE disutilities is more credible.
5	Implementation of HRQoL in the AG's model	There is little data from any source on utility data in patients with thyroid cancer. The pragmatic decision was therefore taken to use data from the DECISION trial for both trials as the AG considered this was the best available source for patients with RR-DTC, based on real-world evidence (as opposed to the small vignette study from 100 members of the general public with no experience of the disease). The DECISION trial data includes the effect of AEs but without providing the basis for separating the incremental effects of individual AEs from the state-specific utilities. The Fordham et al 2015 study only measured the incremental effect of AEs relative to the stable disease state, but this cannot be presumed to be simply applicable to other health states (progressive disease or responders to treatment). Neither of these options is without problems, but on balance the AG judged that utility values derived directly from trial patients is more credible than the alternative.
6	Resource use data used in the AG model	Resource use data used by the AG is derived from detailed conversation with its clinical advisor. Eisai cite a paper by Gianoukakis et al 2016 [Gianoukakis, A, et al. Treatment patterns, health state, and health care resource utilization of patients with radioactive iodine refractory differentiated thyroid cancer. Cancer Management and Research 2016; 8: 67-76] as an alternative source. This international case-review study included only 72 UK patients of whom only 34 received systemic treatment. In addition, the study only reports on treatment of AEs for patients with progressing disease or responding to

Issue	Description of issue (summary)	AG response
		treatment, but not to patients in a stable state. The AG conclude that sourcing resource use from UK clinical practice using scenarios relevant to the trial populations is appropriate.
7	Methodology of calculating adverse event costs in the AG model	See response to Model Issue 1 (Section 1.2.1)
8a	Factual inaccuracy, Page 12, "Lenvatinib and sorafenib also increased the incidence of adverse events (AEs)": Eisai would like to clarify that lenvatinib is associated with increased AEs versus placebo.	Comment noted. The text used by the AG is not factually inaccurate but the AG accepts the text could have been more clearly worded. The AG has now modified its abstract to include sections on limitations and future work and so the statement in relation to adverse events has now been deleted (to keep the word count <500 words), **see Erratum to the AG report, pages 11 to 12.**
8b	Factual inaccuracy, Page 32, Table 1, Lenvima cost per year: Eisai would like to highlight that the estimated cost per year of Lenvima is £40,236, as per the company submission	The AG cited the maximum cost assuming no dose reductions, as reported in the SMC document, in order to be consistent with the cost cited for sorafenib. The AG has now clarified this in a footnote to this table**, see Erratum to the AG report, Table 1 (page 32).**
8c	Factual inaccuracy, Page 33, "Mechanism of action: Targets VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, PDGFR beta, RET and KIT" Eisai would like to highlight that lenvatinib targets both PDGFR beta and PDGFR alpha.	Thank you for drawing this error to our attention. The AG has amended the text in the table**, see Erratum to the AG report, Table 1 (page 32).**
8d	Page 41, "Recruitment period: 5 August 2012 to 4 October 2012" Eisai would like to highlight that, as per the company submission, the recruitment period for the SELECT study was from 5 August 2011 to 4 October 2012	Thank you for drawing this typographical error to our attention. The AG has amended the text**, see Erratum to the AG report, Table 4 (page 40)**.
8e	Page 45, Table 8, Average dose. Eisai have identified an error in the average dose reported in the company submission and as a result in the AG report. The average dose 17.4mg is from the first datacut (November 2013). The updated correct average dose for the August 2015 datacut is 16.3mg.	Thank you for drawing this error to our attention. The AG has amended the text in the table for the third data-cut in the table**, see Erratum to the AG report, Table 8 (page 45)**. The AG notes, however, that the average dose for the first data-cut is reported to be 17.2mg in Table 1 of the submission from Eisai which is the same as that reported in the published paper for the SELECT trial [Schlumberger M, Tahara M, Wirth LJ,

Issue	Description of issue (summary)	AG response
		Robinson B, Brose MS, Elisei R*, et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015; 372:621-30] but reported to be 17.4mg (or 17.43mg) everywhere else in the submission from Eisai.
8f	Page 89, "Hypertension was the most common reason for dose modifications or discontinuations in the SELECT trial." Diarrheoa was the most common reason for dose interruption or reduction. 1.1% of patients discontinued treatment due to hypertension.	Thank you for drawing this error to our attention. The AG has amended the text**, see Erratum to the AG report, page 59 and 89**.
8g	Page 118, Table 37- It is stated that for OS modelling for sorafenib, "Published DECISION trial OS data from first data-cut (August 2012)" was used. This is incorrect as, similarly to lenvatinib in the Bayer model, the OS curve for sorafenib was generated by adjusting the lenvatinib OS curve using the HR generated by the ITC. This was based on the updated OS data from July 2015 cut-off date (Brose, et al., 2016) adjusted for the crossover of placebo patients using a Rank-Preserving Structural Failure Time model (RPSFT). The same also applies to PFS modelling for sorafenib in Table 38.	Thank you for drawing this error to our attention. The AG has amended the text in the table**, see Erratum to the AG report, Tables 37 and 38 (Page 118)**.
8h	Page 138, Discrepancy between dose intensity factor stated in the report (71.666%) and value implemented in the AG economic model (72.50%). Eisai agree with the later value (17.4mg/24mg = 72.50%)	Thank you for drawing this error to our attention. The AG has amended the text**, see Erratum to the AG report, page 136**. However, please note AG response to 8e.

1.2 Eisai comments on the AG model

In addition to providing comments on the AG report, Eisai provided comments on the AG model. The issues it identified alongside the AG response are presented in this section.

1.2.1 Model Issue 1: Costing of Adverse Event costs

Eisai correctly point out that the AG model applies the mean cost of AEs to the overall survival estimates for both active treatments, thus over-estimating AE costs for patients no longer receiving active treatment. However, replacing OS by Time on Treatment in the calculations

then under-estimates adverse event costs for those patients who have withdrawn from active treatment but are thereafter presumed to suffer no further adverse event problem costs.

Applying this amendment correctly to the AG model (assuming that post-treatment patients incur AE costs equivalent to BSC patients) has the effect of reducing the estimated ICER for Sorafenib vs BSC by about £2,000 per QALY gained, and by about £3,000 per QALY gain for lenvatinib.

1.2.2 Model Issue 2: Terminal care costs

Eisai have misunderstood the method used by the AG to apply terminal care costs. Research shows that both costs and disutility of End of Life care are spread over the 90-day period preceding the time of death. To reflect this observation one-third of the total terminal cost estimate is applied to each patient for the 3 cycles preceding death, to give a more accurate representation of the timing of costs. The AG method is more accurate than applying all End of Life costs at the time of death.

1.2.3 Model Issue 3: Selecting PFS confidence limit data from Kaplan-Meier or extrapolation estimates

The AG acknowledges minor errors relating to PFS uncertainty estimates used in the PSA. However, the effect of these problems is very small (between 0.25% to 0.35%), and the impact on PSA results is barely detectable.

1.2.4 Model Issue 4: Calculating random number values for OS in the Sorafenib arm for PSA calculations.

The AG acknowledges this referencing error. It relates only to probabilistic sensitivity analysis, and results in alterations of results of no more than 1%.

1.2.5 Model Issue 5: Formula error on deterministic sensitivity on PFS in the BSC arm on the DECISION trial

The AG acknowledges this referencing error. It relates only to deterministic sensitivity analysis of one variable, and gives the same range of estimates if lower and upper values are generated.

1.2.6 Model Issue 6: Formula error on OS in the BSC arm of the DECISION trial

The AG considers that it is irrelevant which copy of identical sets of numbers is referenced, since the answer is always the same and has no effect on any model results.

1.2.7 Model Issue 7: Four cells calculating zero.

The AG considers that this comment is inappropriate since zero is always zero whatever you multiply it by.

1.2.8 Model Issue 8: Adverse event resource use

This is a minor formula copying error, with no effect whatever on model results, since no data is available to allow resource use to be distinguished between different treatment arm.

1.2.9 Model Issues 9 and 10: Drug administration costs

The AG considers that these issues are incorrect, and inappropriate. Self-administered oral medications are typically dispensed at the beginning of each cycle sufficiently for treatment to be self-administered for the whole of the cycle. Any administration costs incurred in prescribing and dispensing the treatment each cycle will be incurred on day 1 of each cycle, as in the AG model. Not only are these issues ill-founded, but irrelevant since none of the models in this appraisal include any administration costs.

2 Comments from Bayer

2.1 Bayer comments on the AG report

Bayer highlighted that the Assessment Group report outlines the majority of challenges associated with the appraisal of sorafenib and lenvatinib for patients with differentiated thyroid cancer after radioactive iodine (RR-DTC). Bayer's comments included some of the key conclusions drawn in the AG report that Bayer believe are of particular importance for decision makers. A brief summary of the issues raised by Bayer are summaries in Table 2 alongside the response from the AG.

Table 2 Summary of issues on the AG report raised by Bayer

Issue	Description of issue (summary)	AG response
1	Current evidence does not allow a comparative assessment of sorafenib and lenvatinib. However, in providing research priorities, the AG conclude by suggesting that "further statistical research is needed to develop reliable methods of undertaking indirect comparisons in cases where the proportional hazard assumptions are violated" (page 158). Though, as acknowledged throughout the report, due to the many underlying differences in patient populations, study design, BSC arms, prior and post study treatment, in addition to the differences in percentages of patients that crossover, in this case cross-trial differences cannot be fully adjusted for, and could not be addressed by methods that do not require the proportional hazards assumption.	The AG agrees with Bayer. The AG concurs that in this instance, even if the proportional hazards assumption had been valid, an indirect comparison would have been inappropriate for all of the other reasons highlighted by the AG. This sentence has been deleted from the research recommendations (**see Erratum to the AG report, pages 19 and 158)**
2	The relevant population for this appraisal should not be restricted to patients who are symptomatic and/or have rapidly progressing disease.	The AG reiterates that, according to clinical advice received, in the English NHS, patients who are symptomatic and/or have rapidly progressing disease (or clinically significant disease) are those who tend to **currently** receive systemic treatment, including sorafenib. The AG is not suggesting that **only** these patients should receive treatment. As noted by Bayer in their response, specialists consider multiple factors when making a treatment decision. Furthermore, as also noted by Bayer, the AG conclude

Issue	Description of issue (summary)	AG response
		there is “no objective criteria for assessing patients who are symptomatic and/or rapidly progressing” with disease status dependent “on individual patient characteristics”.
3	Issues identified with extrapolation of variables in the AG model.	See response to Model Issue 4 (Section 2.2.4).
4	EQ-5D utilities collected in the DECISION trial are inappropriate for application to the SELECT trial due to differences in the trial populations and safety profile of treatments.	No utility data are available for the SELECT trial. As highlighted by Bayer, the AG did state on page 60 of its report: “It was reported in the EPAR that while HRQoL data were not collected in the randomised part of the SELECT trial, 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." HRQoL data for patients who participated in the open-label extension phase of the SELECT trial were not included in the submission from Eisai. The pragmatic decision was therefore taken to use data from the DECISION trial for both trials as the AG considered this was the best available source for patients with RR-DTC, notwithstanding the limitations of this approach as highlighted by Bayer.
5	Sorafenib and lenvatinib should both be considered end of life treatments.	Neither trial meet the ‘End of Life’ criterion since in both trials, the mean survival of patients in the placebo/BSC arm is substantially greater than 24 months. Data reported in the background section of the AG report (pages 28 and 29) also suggests that the most pessimistic estimate of median life expectancy for patients with RR-DTC is 2.5 years (29 months) [Canadian Agency for Drugs and Technologies in Health. pan-Canadian Oncology Drug Review Final Clinical Guidance Report Sorafenib (Nexavar) for Differentiated Thyroid Cancer. Canada: CADTH; 2015]
6	Important differences in safety profiles are acknowledged by the Assessment Group.	The AG agree that there are differences in the safety profiles of lenvatinib and sorafenib.

Issue	Description of issue (summary)	AG response
7	Sequencing of sorafenib and lenvatinib treatments.	As acknowledged by Bayer, there is no evidence on the efficacy of sorafenib, following treatment with lenvatinib. Bayer have stated that 'One of the main sources of evidence described by the AG report for the sequencing is based on table 44'. Table 44 and the surrounding text is not intended to explore sequencing. Furthermore, Bayer claim that 'The tables and text used in this discussion contain multiple errors and should be corrected.' The AG provide a detailed response to the 'multiple errors' in Section 2.1.1.
8	Updated Cost-effectiveness results.	The AG has revised its model to reflect modelling issues with a non-trivial effect on cost-effectiveness results, and presented updated results, **see Erratum to the AG report, Table 44 (page 134)**. Results using updated pricing schemes are presented in a revised Confidential Appendix to the AG report.

In addition, Bayer proposed alterations to the AG report. These are summarised in Table 3 alongside the AG response. Two of the issues warrant a more detailed response from the AG and these are presented in Sections 2.1.1 and 2.1.2.

Bayer also produced a table of 'response to questions raised in the AG report'. The comments are summarised in Table 4 alongside the AG response to each comment.

Table 3 Bayer proposed alterations to report

Page	AG comment in report	Bayer comment/ description of proposed amendment	AG response
30	The AG report states: *"authors of the NCCN guidelines 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"*	The NCCN guidelines state that lenvatinib is preferred "based on a response rate of 65% for lenvatinib when compared with 12% sorafenib, although these agents have not been directly compared" [National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma March 31, 2017. [August 2017]. http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.]. This preference is based on a naive comparison between the DECISION and SELECT trials which the AG consider to be inappropriate due to differences in the trial populations. Please consider the use of "preferred" as this is potentially misleading given that the basis for the NCCN panel decision is not explained and this preference is not aligned with the AG's assessment, which could not conclude "whether the effectiveness of treatment with lenvatinib and sorafenib are similar, or different" (Page 18).	Text amended to explain the rationale for the author's use of the term 'preferred' **see Erratum to the AG report, page 30**.
31	The AG report states: *"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"*	Sorafenib has been available via the Cancer Drugs Fund (CDF) since prior to the launch of the indication in April 2014, and is currently funded for all patients with RR-DTC, where the treating specialist has established treatment with sorafenib may be beneficial. Between July 2013 and June 2016, there were [redacted] notifications for DTC patients to commence treatment with sorafenib. It is on this basis the company stated that for patients where systemic treatment is appropriate sorafenib has replaced BSC as the standard of care.	Thank you for providing this information. Text amended to reflect changes suggested by Bayer **see Erratum to the AG report, page 31**.
57	The AG report states:	Table 18 presents a comparison of all serious adverse events reported by ≥2% of patients in any arm of the SELECT and	Thank you for providing these data.

<table>
<tr><th>Page</th><th>AG comment in report</th><th>Bayer comment/ description of proposed amendment</th><th>AG response</th></tr>
<tr><td></td><td>“The following AEs are reported as <2% due to a lack of information provided in source documents“</td><td>DECISION trials. Many of the sorafenib AEs are presented as <2% due to these events not being included in the source documents.

Please find an updated table reflecting treatment related AEs from the DECISION trial. These are in the CSR supplied with the submission.

<table>
<tr><th rowspan="2">Outcome, n (%)</th><th colspan="2">DECISION trial</th></tr>
<tr><th>Sorafenib N=207</th><th>Placebo N=209</th></tr>
<tr><td>SAEs</td><td>77 (37.2)</td><td>55 (26.3)</td></tr>
<tr><td>Pneumonia</td><td>1 (0.5)</td><td>0</td></tr>
<tr><td>Hypertension</td><td>0</td><td>0</td></tr>
<tr><td>Dehydration</td><td>0</td><td>2 (1.3)</td></tr>
<tr><td>General physical health deterioration</td><td>2 (1)</td><td>0</td></tr>
<tr><td>Dysphagia</td><td>2 (1)</td><td>1 (0.7)</td></tr>
<tr><td>Dyspnoea</td><td>6 (2.9)</td><td>7 (3.3)</td></tr>
<tr><td>Haemoptysis</td><td>0</td><td>2 (1.3)</td></tr>
<tr><td>Secondary Malignancy</td><td>9 (4.3)</td><td>4 (1.9)</td></tr>
<tr><td>Pleural effusion</td><td>6 (2.9)</td><td>4 (1.9)</td></tr>
</table></td><td>The AG did not originally extract the data from the CSR as the data for some AEs appears differ by table and it was unclear to the AG which table should be used. For example, data for dyspnea provided here by the company in response to the AG report appear to match Table 14.3.5 / 14 but these data are not the same as reported in the submission from Bayer or other sections of the CSR (Synopsis, page 13 and Table 14.3.5 / 3). The AG has therefore not changed the data for dyspnoea (7 vs 6 as opposed to 6 vs 7).
For dysphagia, data provided here by the company differs to that in Table 14.3.5 / 14 (but is consistent with Table 14.3.6 / 1, however this latter table includes the open-label phase). Nonetheless, the AG has incorporated the data for dysphagia, pneumonia, hypertension, dehydration,</td></tr>
</table>

Page	AG comment in report	Bayer comment/ description of proposed amendment	AG response
			general physical health deterioration and haemoptysis from the provided table**, see Erratum to the AG report, Table 18 (page 57)**. The AG would appreciate clarification on which Table(s) of the CSR the data should be extracted from
118	The AG report states: *"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, to represent the experience of patients receiving BSC (EQ-5D values were obtained from the DECISION trial)."*	Please consider revising this statement: 1. Utility values used by Bayer in the submission to the SMC are the same as those used in this submission, as described in the following SMC guidance, *"EQ-5D data were collected in the DECISION study and were used to estimate utility values for the model. The weighted average of all EQ-5D scores per cycle while patients were on treatment was assumed to represent the pre-progression utility value for each treatment arm. This resulted in utility values of 0.72 and 0.8 for the sorafenib and BSC arms respectively."* [Scottish Medicines Consortium (SMC). Detailed advice on the assessment of sorafenib (Nexavar) for the treatment of patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, rafractory to radioactive iodine. 5th June 2015]	Text amended to reflect the fact that with the exception of the progressive state, utility values used by Eisai were not the same as in the DECISION trial**, see Erratum to the AG report, page 118 (Section 5.3.5)**.

Page	AG comment in report	Bayer comment/ description of proposed amendment	AG response
		2. Utilities used in the Eisai model for lenvatinib, sorafenib, and BSC in the stable or response disease states are not aligned to valuations derived from the DECISION trial or previously submitted by Bayer to the SMC. Only the progressive health state utility is taken from the DECISION trial in the Eisai model. 3. Use of utility values from the DECISION trial for lenvatinib patients is highly uncertain due to the differences highlighted by the AG in the trial populations and safety profiles of treatments. This was not mentioned when reporting on appropriateness of selected utilities for each treatment.	
119	The AG report states: *"no additional utility decrements associated with AEs were included in the (Bayer) model"*	Please consider revising this statement. EQ-5D responses collected in the DECISION trial were averaged across all patients in a given health state and reflect utility decrements associated with adverse events. To further account for these with additional utility decrements would result in double counting.	The text in the AG report is correct. The AG was not implying there was a problem with the approach employed. No changes to the report are required.
134	Table 44 does not correspond with results from the AG model.	Please update table 44 with correct values and amend any text or conclusions in the report citing this data.	***See Section 2.1.1 for detailed response.***
134	The AG report states: *"It is particularly noteworthy that 73% of the PFS benefit achieved in the lenvatinib*	This conclusion is based upon incorrect data in table 44 (noted above). Updated values change the direction of the final conclusions made here.	***See Section 2.1.1 for detailed response.***

Page	AG comment in report	Bayer comment/ description of proposed amendment	AG response
	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."	Although benefits of treatment are often, and in the case of sorafenib here, can be seen in both pre and in the post progression period, which also needs to be taken into account. Should this conclusion hold, it could be reversed to indicate the superiority of sorafenib. For more information see Section 7 of this response.	
135	The AG report states: "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"	EQ-5D data was collected in DECISION at each follow-up appointment. For the economic model all valuations collected were averaged across all patients in the given health state. The AG conclude that this approach assumes that AE disutilities persist in perpetuity whilst the patient is in that health state. This is not correct, as EQ-5D values reflect the average patient's utility including experiences of, and recovery from adverse events.	Thank you for highlighting this. The AG agrees with the company. Text deleted**, see Erratum to the AG report, page 135**.
142	Commercial in confidence markings have been applied to the BSC costs instead of the sorafenib costs	Please update the commercial in confidence markings.	The AG apologizes for the error. Correct marking has now been applied**, see**

Page	AG comment in report	Bayer comment/ description of proposed amendment	AG response
			Erratum to the AG report.
144	Implementation of the “least of TTD and PFS” treatment assumption for sorafenib	The implementation of this scenario in the model is incorrect. Bayer has provided data for this scenario, based on the patient level data from the DECISION trial, where every patient stops treatment at the latest at disease progression. The AG model instead of this data, looks at the average discontinuation of the whole cohort and compares it to the average PFS of the cohort to make sure the average time to treatment discontinuation is not greater than the average PFS, i.e. that the curves do not cross. However since some patients stop treatment early before progression, while others stop after progression, in average, the time to treatment discontinuation is similar to PFS as seen in (Table 1 of main response). This leads to the AG model overestimating the proportion of patients on treatment (Figure 3 of main response) and thus the drug costs, when assuming patients stop at progression.	***See response to Model Issue 1 (Section 2.2.1).***

Page	AG comment in report	Bayer comment/ description of proposed amendment	AG response
147	The AG report states: *"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."*	The probabilistic sensitivity analysis (PSA) described in the AG report and included in the AG model appear to be limited. To better represent the uncertainty, the PSA should include all parameters with parameter uncertainty. However the PSA provided, excludes the efficacy parameters, TTD and the dose intensity from the analyses, which are all influential parameters. In addition, while the use of normal distribution for most parameters can be appropriate sufficient care needs to be taken that the normal distribution, where needed, is limited ta realistic range.	***See Section 2.1.2 for detailed response.***
150	The AG report states: "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)."	Please update this data and conclusions in line with errors identified in Table 44. Please ensure that any other references to this are updated.	***See Section 2.1.1 for detailed response.***

2.1.1 Apparent discrepancies between the estimates of time-to-event variables in Table 44 of the AG report, and results from the AG model

Bayer draw attention to apparent discrepancies between the estimates of time-to-event variables in Table 44 of the AG report, and results from the AG model. These are of three types:

- Several minor differences for estimates of PFS, OS and PPS for the lenvatinib vs placebo comparison using SELECT trial data
- Estimates of the mean use of the active treatments in the two trial measured in terms of cycles of treatment
- More substantial discrepancies relating to PFS, OS and PPS estimates for the sorafenib vs placebo comparison based on DECISION trial

The minor discrepancies in PFS, OS and PPS estimates in Table 44 are generated by the structure of the AG decision model by treatment cycles (28 or 30 days), rather than on a continuous basis using individual patient days. This is a common method used to make models more manageable, but results in approximating the data for disease progression and death derived from clinical trials, which is measured in 1 day intervals.

The results shown in Table 44 of the AG report are derived from Kaplan-Meier patient data expressed in terms of days and so are necessarily more accurate that those derived from the model. The common practice of using mid-cycle corrections to moderate this difference is only partially successful. In addition, the estimation of PFS or OS beyond the available data using an exponential trend is based on a continuous function which continues the same discrepancy to the time horizon of the model (40 years in the AG model). The AG has checked all these disputed minor differences in Table 44, and can confirm that there are no errors in the values shown.

The estimates for the mean number of cycles of active treatment received in the two trials have been reviewed by the AG. In both cases, the estimates are based on clinical trial Kaplan-Meier results provided by the respective companies, and careful examination of the analysis confirms that the Table 44 estimates are correct.

The more substantial discrepancies in Table 44 all relate to estimates made to data from the DECISION trial. Originally Bayer did not provide requested Kaplan-Meier results for PFS, OS and PPS as requested by the AG. During the course of model development, the AG identified sets of Kaplan-Meier results within the Bayer model and attempted to use these to inform the

time-to-event variables in the AG model. However, it was not clear whether these data were correct, and in particular whether they included the RPSFT adjustment for crossover. The AG sent a request via NICE seeking clarification. When the AG received an appropriate set of alternative data, it was very late in the AG's development and report writing period and unfortunately some mis-transcription of revised results went unnoticed in submitted AG report, and as a consequence the commentary on Table 44 was inaccurate.

The revised text and table are shown below (revised text in red, **see also Erratum to the AG report, page 134**).

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. The main difference occurs in the PFS results where lenvatinib provides substantially greater benefit than sorafenib (34 additional months before progression compared to only 6 months). However, the estimated OS results are very similar (55 vs 57 months), and consequently estimated PPS is reduced with lenvatinib treatment but increased for sorafenib treatment). Thus, it appears that lenvatinib shows effect more strongly in initially delaying progression, but does not offer additional benefit over sorafenib in terms of long-term survival. 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)	13.8	56.8	42.9	14.4 (*28 day*)
Placebo (DECISION)	7.6	43.8*	36.2	-
Gain due to sorafenib	*+6.3*	*+13.0*	*+6.7*	-

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

2.1.2 Probabilistic Sensitivity Analysis

Bayer comment on the PSA undertaken by the AG, and in particular that it did not include the efficacy outcomes (overall survival, and progression-free survival), time to treatment discontinuation and dose intensity.

The AG acknowledges these omissions which were are due to the absence of necessary data to populate these important components of uncertainty in a way that has credibility and can be equally applied to assessment of both products, as follows:

Assessing uncertainty of variables based on Kaplan-Meier data (OS, PPS and TTD) requires either a full set of results including all patient events with the confidence intervals around each calculated event value, or the individual patient data to allow the analysis to be rerun by the AG. Bayer provided only the event estimates without any uncertainty measures, so it would not have been possible to obtain reliable uncertainty parameters for the sorafenib vs placebo comparison

Bayer did include an estimated standard error for the dose intensity parameter for sorafenib, but did not use a reliable source for the standard error of the lenvatinib parameter, assuming instead a notional 10% of the mean value without justification

The AG regrets that its PSA results have been restricted in this way, and therefore could not capture the full extent of uncertainty for this appraisal.

The text on page 147 of the AG report is amended as follows (revised text in red, **see also Erratum to the AG report**):

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.

Unfortunately, information relating to the key outcome variables (PFS, OS and TTD) was not provided to the AG by one of the companies in the form requested, and information on

uncertainty in the estimated treatment dose intensity was not included by the other company in their submission or their model. Without these key data items, it was not possible to incorporate these important components of the normal PSA on this occasion. Therefore, the results presented below should be treated with caution.

Table 4 Bayer comments on the AG questions in the report

Page	AG comment in report	Bayer response	AG response
31	The AG report states: *"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"*	Estimates provided by the company are reflective of the agreed final scope of this Appraisal. The AG acknowledged there is "no universally accepted objective criteria for assessing patients who are symptomatic and/or rapidly progressing" and on this basis it is difficult to further segment the population. CDF notifications for sorafenib (approximately [redacted] per year) are less than population based estimates, and reflect clinical judgement currently exercised by specialists.	Text amended to reflect changes suggested by Bayer**, see Erratum to the AG report, page 31**.
46	The AG report states: *"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)."*	Bayer did not collect data on the specific agents used during the trial follow-up. In the DECISION trial sorafenib patients could continue treatment past progression. In the SELECT trial did not allow patients to continue treatment with lenvatinib outside of the double-blind period. Whilst it can be argued that lenvatinib patients did not receive the clinical benefit from continuing lenvatinib treatment past progression, some lenvatinib patients in the SELECT trial did continue treatment with other TKIs (sorafenib and pazopanib), these were not costed into the economic evaluation. TKIs taken after lenvatinib would have been likely to have a similar effect as continuing sorafenib past progression. The current base case of the AG model assumes, that while sorafenib patients will continue after progression with TKI treatment, lenvatinib patients will not receive any TKI treatment post-progression. This is inconsistent. The differences in the	Regarding the evidence for clinical effectiveness, text on page 46 of the AG report amended to reflect changes suggested by Bayer**, see Erratum to the AG report, page 46**. Regarding the economic evaluation, the AG are only able to use a common value set across both comparisons where equivalent compatible trial data are available from both trials for specific model variables to populate the model. However, the decision to model the two active treatments separately, due to the incompatibility of trial

Page	AG comment in report	Bayer response	AG response
		trial design of allowing patients continuing with the same TKI (DECISION trial) or allowing patients to switch to other TKI (SELECT) is potentially due to the timing of the trials. When the DECISION trial was conducted, no other TKI was available for this patient population, while when the SELECT trial was conducted, patients could receive, and have received sorafenib after progression. If, based on the assumption used for lenvatinib, patients will not receive TKI treatment post-progression in clinical practice, the time to treatment discontinuation curve used in the base case for the Bayer submission should be used for sorafenib. This assumes that sorafenib patients will also stop TKI treatment at progression. This is reflective of UK clinical practice	populations, renders any attempt to reconcile every aspect of the modelling unrealistic. It remains for the companies to present their case for special consideration of factors which could not be adequately captured by modelling, and for the Appraisal Committee to consider how relevant these are to their decision-making.
125	The AG report states: *"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."*	While Bayer agrees in the choice of exponential distribution for the DECISION trial, basing the choice of distribution on the SEER data assumes, that the population in the database (patients diagnosed with Stage 3 or 4 (locally advanced or metastatic) thyroid cancer in the USA and recorded on the SEER database) matches the population in the DECISION trial. However there are clear differences, e.g. the SEER data is not restricted to iodine refractory patients. Alternatively, it assumes that the pattern of survival is not dependent on the differences between populations within stage 3/4 thyroid cancer. However the different pattern seen in the DECISION and SELECT trials suggests otherwise. The company recommends tests for statistical, visual and clinical plausibility should conducted as outlined in the NICE DSU technical support document.	The analysis of the SEER data is presented simply to establish the general position that long-term exponential extrapolation is a legitimate approach to estimating overall survival. No values from SEER analysis have been used in developing the AG model. Of course it would be ideal to use a more specific subset of SEER thyroid patients, but would require a much more detailed and time-consuming procedure

Page	AG comment in report	Bayer response	AG response
			to apply accurate coding to patient selection, and inevitably would lead to a considerably smaller sample size. There is no conflict between using real-world registry data to guide survival analysis and using the 'standard' methods for model fitting.

2.2 Bayer comments on the AG model

In addition to providing comments on the AG report, Bayer provided comments on the AG model. The issues it identified alongside the AG response are presented in this section.

2.2.1 Model Issue 1: Method for calculating option 3 for treatment discontinuation (TTD or PFS)

Options 1 and 2 in the AG model for estimating the duration of active treatment are those which are based on the trial protocol i.e. Option 1 recognises that treatment should normally continue until disease progression, and Option 2 recognises additionally the specified circumstances under which treatment should be prematurely discontinued. The AG did not consider Option 3 to be a valid method of estimation from the perspective of the NHS, and therefore only added the third model option as a broad indication of the relative impact of using such an approach. Cost-effectiveness results for the AG base case use Option 2, which more closely recognises both planned and unplanned termination of treatment.

The AG did not have access to the individual patient data necessary to validate the type of analysis undertaken by the company for their preferred option, but understands that it was developed to minimise the total estimated cost of sorafenib treatment. However, in practice oral medications are dispensed at the beginning of each cycle, so some wastage is unavoidable as any unused doses at discontinuation of treatment must be discarded.

2.2.2 Model Issue 2: Calculation of upper and lower confidence bound for sorafenib/lenvatinib PFS utility uses the untreated utility not the PFS utility

Bayer is correct. This is a formula copying error. However, the estimated deterministic ICER is unaffected and the impact on the probabilistic ICER is minor.

2.2.3 Model Issue 3: Dose intensity for sorafenib used has been rounded. The value should be 81.375% and not 81.4%

This was a minor transcription error due to the corresponding figure in the Bayer model having been formatted to only 1 decimal place. Adjustment of this parameter value in the AG model reduces the incremental cost per patient by £12.68, and the estimated ICER for sorafenib vs BSC by £24.00 per QALY gained. In the cross-trial comparison the ICER is reduced by £11.02 per QALY gained. Correcting this error results in only minor changes in cost-effectiveness results.

2.2.4 Model Issue 4: Method of extrapolating long-term TTE outcomes underestimates PFS, OS for sorafenib and TTD for lenvatinib.

PFS extrapolation

Figures 1a and 1b show the fitting of exponential trends to DECISION PFS trial data provided by Bayer on 23rd August 2017.

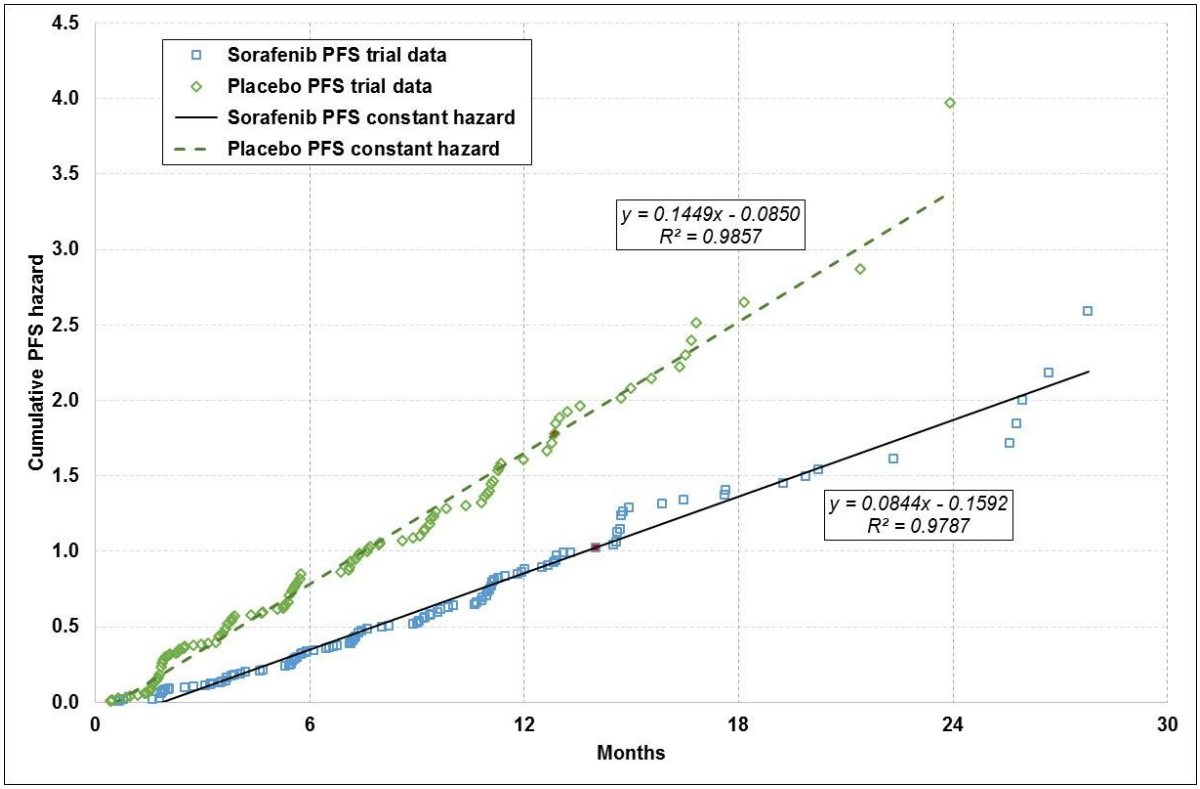


Figure B1a: Linear PFS hazard trends fitted to Bayer DECISION trial data

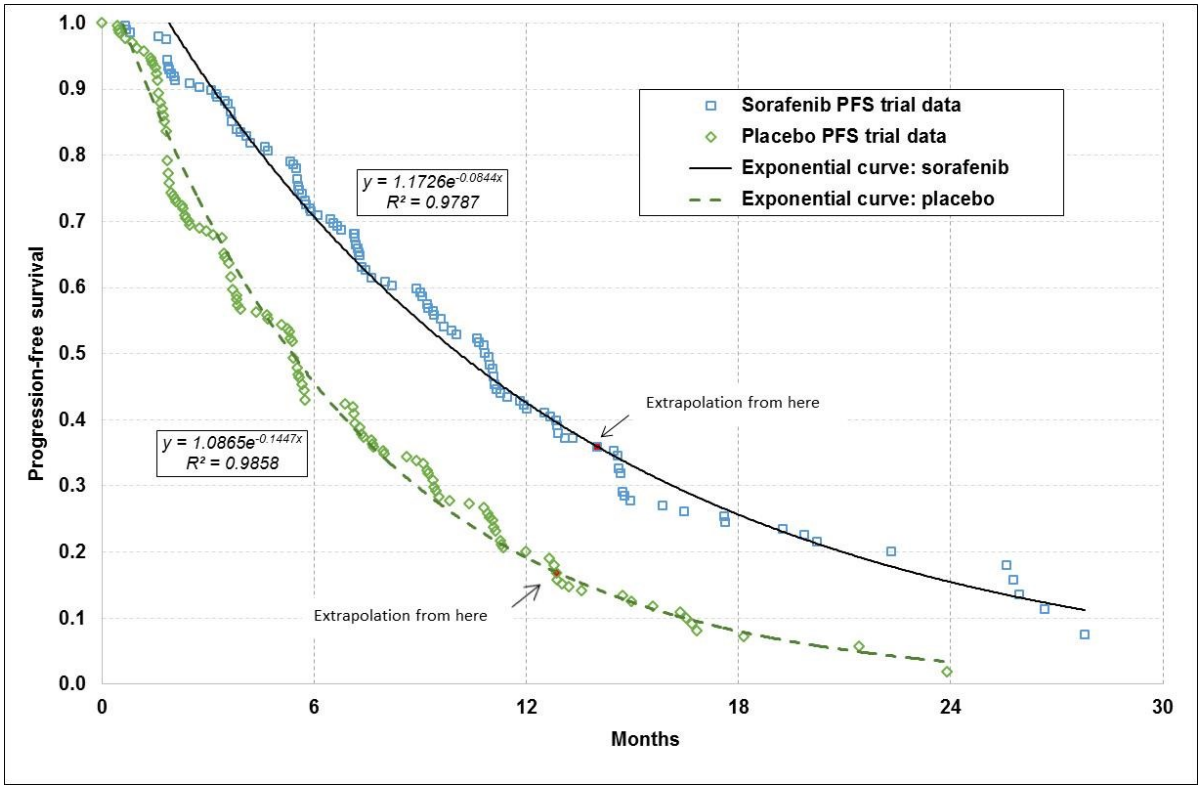


Figure B1b: Exponential PFS trends fitted to Bayer DECISION trial data

Also marked are the data points at which the Area Under Curve (AUC) from the Kaplan-Meier data gave way to extrapolation using the fitted extrapolation models (426 days for Sorafenib and 391 days for Placebo). These points were chosen as the points with the minimum difference between the K-M PFS estimate and the fitted PFS curve (a difference of -0.00054 for Sorafenib and -0.00055 for Placebo).

The lifetime PFS estimates are as follows:

Sorafenib: AUC 291.6 days + Extrapolation 129.7 days = 13.84 months

Placebo: AUC 194.6 days + Extrapolation 35.5 days = 7.56 months

Net lifetime PFS gain = +6.28 months Sorafenib vs Placebo

OS extrapolation:

Figures 2a and 2b show the fitting of exponential trends to DECISION PFS trial data provided by Bayer on 23rd August 2017.

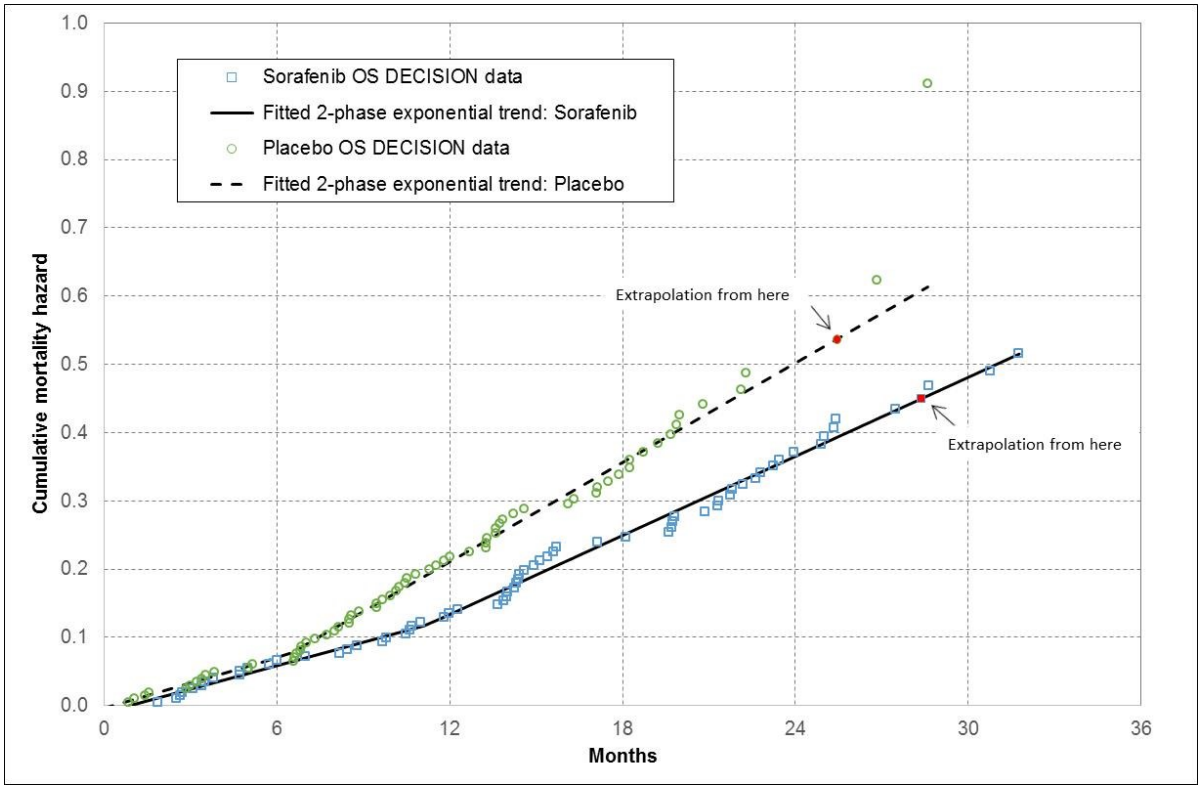


Figure B2a: 2-phase linear OS hazard trends fitted to Bayer DECISION trial data

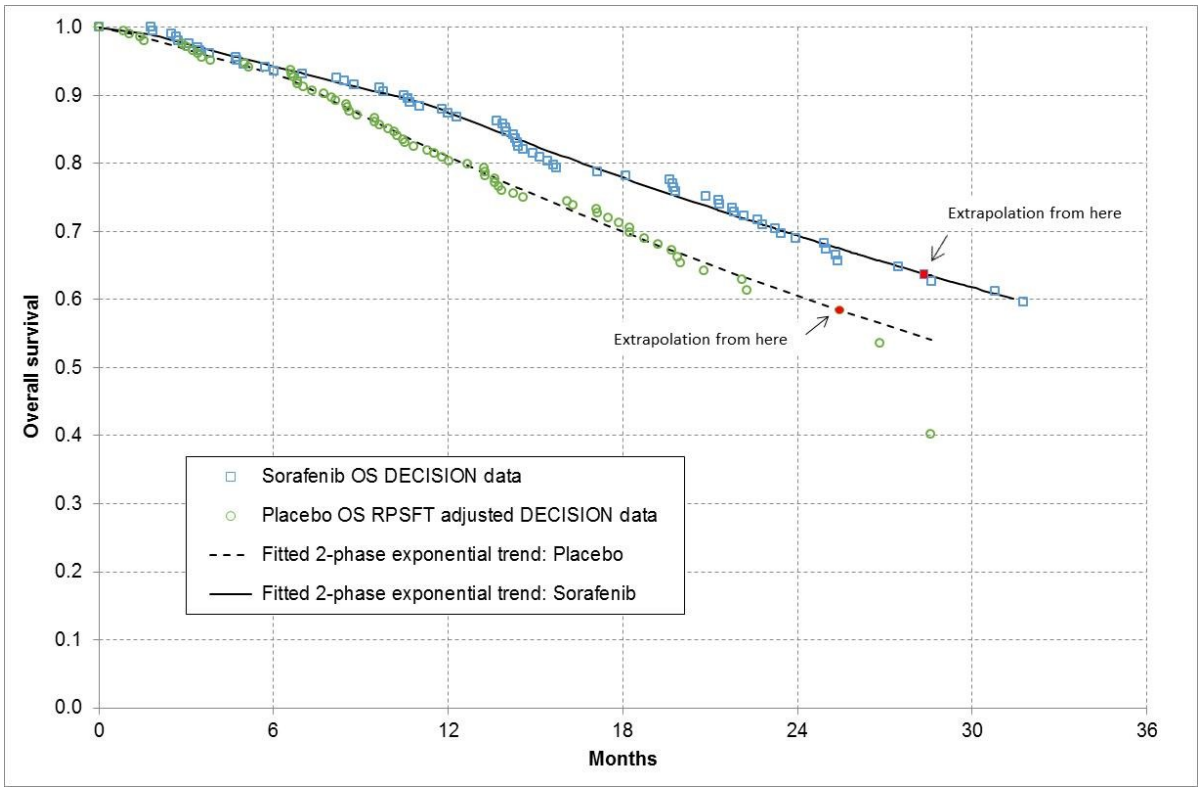


Figure B2b: 2-phase exponential OS trends fitted to Bayer DECISION trial data

The data points are marked at which the Area Under Curve (AUC) from the Kaplan-Meier data give way to extrapolation using the fitted extrapolation models (863 days for Sorafenib and 774 days for Placebo). These points were chosen as the points with the minimum difference between the K-M PFS estimate and the fitted OS curve.

The lifetime OS estimates are as follows:

Sorafenib: AUC 722.7 days + Extrapolation 1005.1 days = 56.77 months

Placebo: AUC 621.1 days + Extrapolation 711.7 days = 43.79 months

Net lifetime OS gain = +12.98 months Sorafenib vs Placebo

Time on treatment (lenvatinib)

The time on treatment data used in the AG model relies solely on data reported from the SELECT trial, including the final data point shown in Figure 13 of the AG report. The AG fitted a limited end-stage trend to the final points of the data, which is parallel to the long-term trend in the SELECT placebo arm. This would suggest that the very few remaining patients in the lenvatinib arm experienced loss of efficacy equivalent to that experienced by placebo patients. The AG considers this to be a reasonable conservative assumption.

2.2.5 Model Issue 5: Incidence of AEs for BSC from the DECISION trial are incorrect

The AG model uses a value of 4 cases of hypertension from 207 patients in the BSC arm of the DECISION trial during the double-blind trial period. Bayer suggest that this should have been 5 cases from 209 patients. However, Table 10 of the Bayer submission document indicates that the correct rate of Grade 3/4 hypertension in the placebo arm of the DECISION trial is 4 cases from 209 patients.

Applying this slightly reduced incidence rate (1.914% instead of 1.932%) increases the incremental cost per patient of Sorafenib vs BSC by £2.62 and the estimated ICER by £4.96 per QALY gained. For the cross-trial comparison the ICER for Lenvatinib is reduced by £4.44 per QALY gained.

Thus, both the AG and Bayer have used slightly erroneous incidence rates, but correcting this in line with the figures shown in the Bayer submission results in minimal alterations in the ICER.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

(Version 1.2)

Submission by Bayer PLC

March 2017

Contents

List of Abbreviations

AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATA	American Thyroid Association
AWMSG	All Wales Medicines Strategy Group
b.d.	twice daily
BIC	Bayesian information criterion
BNF	British National Formulary
BP	Blood Pressure
BSC	Best Supportive Care
BTA	British Thyroid Association
CDF	Cancer Drugs Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curves
CHRC	Central Histology Review Committee
CI	Confidence interval
CMU	Commercial Medicines Unit
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease Control Rate
DOR	Duration of Response
DTC	Differentiated Thyroid Cancer
DSU	Decision Support Unit
EBRT	External Beam Radiation therapy
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol five dimensions questionnaire
ERK	Extracellular Signal-related kinase
ESMO	European Society for Medical Oncology
EWB	Emotional Well-being
FACT-G	Functional Assessment of Cancer Therapy - General
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fludeoxyglucose F18 positron emission tomography
FLT3	fms-related tyrosine kinase
FWB	Functional well-being
GBq	Giga-becquerel
HCC	Hepatocellular carcinoma
HFSR	Hand-foot skin reaction
HR	Hazard ratio
HRQoL	Health-related quality of life
IPE	Iterative parameter estimation

IQR	Inter-quartile range
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention to treat
IVRS	Interactive voice response system
KM	Kaplan Meier
KOL	Key Opinion Leader
LY(G)	Life-Years (gained)
MAIC	Matched adjusted indirect comparison
MAPK	Mitogen-activated protein kinase
mCi	Millicurie
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAPK / ERK kinase
Mg	Milligram(s)
MID	Minimal Clinically Important Difference
MKI	Multiple kinase inhibitor
MRI	Magnetic Resonance Imaging
MTA	Multiple technology appraisal
mU/L	Milliunits per litre
N	Number of patients
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
ORR	Objective tumour response rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free Survival
PR	Partial response
PRO(AS)	Patient reported outcomes (Analysis Set)
PS	Performance Status
PPS	Per protocol analysis set
PWB	Physical Well-being
QALY	Quality Adjusted Life Year
RAI	Radioactive iodine
RAI-R	Radioactive iodine refractory
RAI-R DTC	Radioactive iodine refractory differentiated thyroid cancer
RCC	Renal cell carcinoma
RCT	Randomised Clinical Trial
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Rearranged during Transfection
RPSFT	Rank Preserving Structural Failure Time
RR	Response Rate
RRA	Radioiodine Remnant Ablation

SAE	Serious Adverse Event
SAF	Safety analysis set
S.D.	Standard deviation
SD	Stable disease
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	System Organ Class
SWB	Social / family well-being
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TTP	Time to progression
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

Executive summary

Differentiated thyroid cancer (DTC) accounts for 94% of thyroid cancer cases (1), with around 225 new patients diagnosed each year (section 5) in England and Wales. In a small proportion of patients with differentiated thyroid cancer (5-15%), the disease becomes refractory to radioactive iodine (RAI) treatment (RAI-R) (2, 3). RAI-R DTC has a poor prognosis, is more difficult to treat, and patients often experience multiple complications (4). Treatment options for patients with locally advanced or metastatic DTC unresponsive to radioactive iodine are limited. Chemotherapy such as doxorubicin has uncertain and limited efficacy, with significant associated toxicities (5, 6). Clinical guidelines recommend use of approved multiple / tyrosine kinase inhibitors or participation in clinical trials, alongside best supportive care as the current standard of care for patients with advanced DTC refractory to RAI (7-10).

Sorafenib (Nexavar®), is an orally administered multiple kinase inhibitor (MKI) licenced as a treatment for patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/ Hürthle cell) thyroid carcinoma, refractory to radioactive iodine. Sorafenib targets several pathways implicated in the pathogenesis of differentiated thyroid cancer (DTC) including those regulating tumour cell proliferation, tumour progression and angiogenesis (11, 12).

Summary of the clinical effectiveness analysis

Evidence to support the use of sorafenib for the treatment of locally advanced / metastatic RAI-R DTC is provided by results from the phase 3 double-blind, randomised placebo-controlled trial, DECISION (13-16) (section 2).

DECISION showed a clinically meaningful, statistically significant prolongation of progression-free survival (PFS) in patients with RAI-R DTC treated with sorafenib compared to placebo (median PFS 10.8 vs. 5.8 months) (hazard ratio [HR] =0.59; 95% confidence interval: 0.45, 0.76; p<0.0001).

Treatment with sorafenib also resulted in a statistically significant improvement in time to progression (TTP), compared to placebo (11.1 months vs. 5.8 months, respectively; HR=0.557; p<0.0001), in addition to disease control (DCR) and

response rates (RR). Additionally many sorafenib-treated patients (77%) experienced target lesion tumour shrinkage compared to placebo (28%). The toxicity profile of sorafenib was manageable in RAI-R DTC with adverse events consistent with the known safety profile of sorafenib in other tumour types such as hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC).

Comparative assessment

In the absence of head-to-head evidence versus lenvatinib, a systematic review was conducted to identify randomised controlled trial (RCT) evidence for sorafenib and lenvatinib. Based on the findings of the review an indirect treatment comparison was conducted based on the DECISION and SELECT phase III trials (section 3).

Both RCTs were confounded by treatment crossover, and as such should be interpreted with a degree of caution. The indirect comparison found no statistical difference in overall survival benefit between sorafenib and lenvatinib, [HR] = [redacted](95% CI [redacted], [redacted]) for the treatment crossover corrected population. With this estimate further confounded by post study anti-cancer treatment received by 37% of lenvatinib patients in the SELECT trial, and 20.3% of sorafenib patients in the DECISION trial. Whilst lenvatinib may be found to increase progression-free survival versus sorafenib, there is no evidence to suggest this translates into an absolute improvement in overall survival versus sorafenib.

Safety outcomes assessed via the ITC found sorafenib to result in statistically fewer grade 3-4, and serious adverse events versus lenvatinib [HR] =[redacted] (95% CI [redacted], P<0.0001) and [HR] = [redacted] (95% CI [redacted] P<0.0001) respectively. Sorafenib was also found to result in fewer discontinuations due to adverse events, suggesting it to be a tolerable treatment [HR] = [redacted] (95% CI [redacted], [redacted]).

These outcomes support sorafenib as 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.

Summary of the cost-effectiveness analysis

Sorafenib versus best-supportive care

The economic evaluation considered a comparison of sorafenib versus best-supportive care, based on results of the DECISION trial. Both sorafenib and BSC have been used in UK clinical practice, and clinical experience was used to inform development of the cost-effectiveness analysis.

Sorafenib was associated with an ICER of [redacted]/QALY versus best supportive care, with the ICER robust to variation through both deterministic and probabilistic sensitivity analyses. The ICER remained below the threshold for an end-of-life treatment (£50,000/QALY) for all analyses and close to £30,000/QALY for the majority of analyses.

Sorafenib versus lenvatinib

The economic evaluation versus lenvatinib was based on results of an indirect treatment comparison. This comparison is highly uncertain as the ITC is informed by two RCTs with identified differences in study design. Results of the analysis reflect the overlapping confidence intervals for overall survival between the two treatments.

Both sorafenib and lenvatinib were found to be cost-effective versus BSC, and associated with substantial health benefits. The comparative analyses are restricted by the absence of health-related quality-of-life data for lenvatinib and uncertainty regarding the comparative treatment duration. These uncertainties were assessed via sensitivity analysis.

Lenvatinib was associated with an ICER of [redacted]/QALY versus sorafenib, though the probabilistic sensitivity analysis found wide overlapping confidence intervals in health outcomes obtained between treatments.

On the basis of the analysis conducted both treatments would lead to large health benefits for patients with RAI-R DTC, however the economic case for sorafenib versus BSC based on the DECISION trial is considered significantly more robust than that based on the indirect treatment comparison.

1. Background

1.1 Disease overview

Thyroid cancer is a rare cancer in England and Wales, representing only 1% of all malignancies (7), with only around 225 new cases diagnosed each year (section 5). The incidence appears to be increasing and there is a higher prevalence in women than men (ratio of 2:1). Patients diagnosed with thyroid cancer are typically of working age with a dependable family, and a median age of approximately 45 years (5).

There are three main histologic types of thyroid carcinoma: differentiated, medullary and anaplastic. Differentiated thyroid cancer accounts for most thyroid cancers (94%), in particular papillary, follicular and Hürthle cell types.

In the early stages of disease, thyroid cancer is usually asymptomatic, often discovered incidentally (e.g. thyroid nodule or lump) during a routine examination (5). As thyroid cancer progresses, patients may experience 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 (7).

Treatment for patients with differentiated thyroid cancer typically involves thyroidectomy followed by lifelong thyroxine for thyroid stimulating hormone suppression (7). In addition, depending on disease stage, patient age, and histopathologic factors, ablation of the thyroid remnant with radioactive iodine 131 (RAI) is performed. In a small proportion of patients with DTC (5-15%), the disease becomes refractory to radioactive iodine (RAI) treatment (RAI-R) (2, 3). RAI-R DTC has a poor prognosis, is more difficult to treat, with patients often experiencing multiple complications (4). The main goals of treatment in RAI-R DTC are to gain local disease control in the neck and manage systemic disease (17). Median survival for patients with RAI-R DTC and distant metastases ranges between 1.6–3.5 years (18-20) and at this stage of disease tyrosine kinase inhibitors represent the final line of therapy.

Treatment options for patients with locally advanced or metastatic DTC unresponsive to radioactive iodine are limited. Chemotherapy such as doxorubicin, cisplatin and bleomycin have previously been used for the treatment of RAI-R DTC, but have limited

efficacy, with durable responses uncommon and significant associated toxicities (5, 6) – this is supported by a lack of recommendations for chemotherapy in current guidelines. The lack of available options represents an unmet medical need for the small number of patients with RAI-R DTC, who are underrepresented in terms of treatment funding.

1.2 Current guidance on the treatment of RAI-R DTC

There are currently no relevant NICE guidance, pathways or commissioning guides related to RAI-R DTC. Due to the small number of patients suffering from RAI-R DTC, sorafenib was not previously selected for appraisal in this indication by NICE.

The Scottish Medicines Consortium (SMC) accepted sorafenib in July 2015 (1055/15) and lenvatinib in October 2016 (1179/16) for use in the treatment patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine. The appraisal of sorafenib was conducted under the SMCs ultra-orphan and end-of-life criteria (21).

Other guidelines

Several organisations around the world have published comprehensive guidelines on the treatment of thyroid carcinomas. Generally, treatment guidelines recommend the use of (TKIs) in patients with RAI-R DTC (see

Table 1). All guidelines acknowledge the shortcomings of cytotoxic chemotherapy, doxorubicin.

The British Thyroid Association's 'guidelines for the management of thyroid cancer' outlines treatment options for DTC which include surgery, chemotherapy and radiotherapy (7). Where further surgery or radioiodine is ineffective or impractical, external beam radiotherapy (EBRT) and chemotherapy are discussed, however, the guideline notes that use is being superseded in clinical practice by targeted therapies, such as sorafenib and lenvatinib.

Table 1: Summary of Treatment Guidelines for Differentiated Thyroid Cancer

	BTA (2014) (7)	NCCN (2015) (9) and ATA (2015) (8)	ESMO (2012) (10)
Initial Treatment	• Total thyroidectomy, or • Near total thyroidectomy	• Total thyroidectomy, or • Unilateral lobectomy *(individualised to patient)*	• Total thyroidectomy, or • Near total thyroidectomy
Post-operative Treatment	• Radioiodine remnant ablation (RRA)	• RAI ablation • If iodine refractory: radiotherapy + corticosteroids	RAI ablation
Follow-up	Levothyroxine to suppress TSH to <0.1 mU/L	Levothyroxine to suppress TSH to <0.1 mU/L	Levothyroxine to suppress TSH to <0.1 mU/L
Recurrent or Metastatic Disease	• External beam radiotherapy	• Systemic chemotherapy • Enrolment in clinical trials • If no trials available, TKIs recommended	• Enrolment in TKI clinical trials
RAI-R DTC	• External beam radiotherapy or chemotherapy • For radiologically progressive, symptomatic disease, refractory to conventional treatments: Targeted therapies such as sorafenib or lenvatinib (in a cancer unit only), via a trial or endorsed by the multi-disciplinary meeting	• For progressive or symptomatic metastatic disease, not otherwise amenable to local control using other approaches, Kinase inhibitor therapy should be considered (either FDA approved or via a trial).	• Chemotherapy no longer indicated for treatment of distant metastases due to lack of effectiveness • Enrolment in trials with TKIs

*Not frequently used. ATA=American Thyroid Association; BTA=British Thyroid Association; ESMO=European Society for Medical Oncology; FDA=Food and Drug Administration; NCCN=National Comprehensive Cancer Network; RAI=radioactive iodine; RAI-R=radioactive iodine-refractory; RRA=Radioiodine remnant ablation; TKI=tyrosine kinase inhibitor; TSH=thyroid-stimulating hormone.

1.3 Sorafenib

1.3.1 Overview of sorafenib

Sorafenib (Nexavar®), is an orally administered multiple kinase inhibitor (MKI), available as a 200mg film-coated tablet.

It was the first available MKI treatment for patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/ Hürthle cell) thyroid carcinoma, refractory to radioactive iodine (European Medicines Agency [EMA] approval: 23rd May 2014). Sorafenib is approved in many countries worldwide for the treatment of hepatocellular carcinoma, and advanced renal cell carcinoma in patients

who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

Sorafenib targets several pathways that are implicated in the pathogenesis of differentiated thyroid cancer (DTC) including the RAF/MEK/ERK pathway (also referred to as the MAP kinase pathway) that regulates tumour cell proliferation, and the receptor tyrosine kinases (VEGFR2 and PDGFR-β) involved in tumour progression and angiogenesis (11, 12). Specifically, sorafenib targets include C-RAF, B-RAF, VEGF receptor-2, -3, PDGF receptor-β, RET, c-kit, and FLT-3 (22).

1.3.2 Dose and administration

The recommended dose of sorafenib in adults is 400 mg sorafenib (two tablets of 200 mg) twice daily (equivalent to a total daily dose of 800 mg) (22). In UK clinical practice sorafenib is administered until disease progression or until unacceptable toxicity[1]. Sorafenib has a simple dosing regimen and no dose adjustment is needed for age, sex, bodyweight, mild, moderate or severe renal impairment or mild to moderate hepatic impairment. Suspected adverse drug reactions may be managed by temporary interruption or dose reduction (22).

Additional service provision, tests or investigations are not needed for sorafenib use in routine clinical practice.

The recommended dose of lenvatinib is 24mg once daily; with a daily requirement of 3 tablets, (2 x 10mg tablet and 1 x 4mg tablet). The daily dose is to be modified as needed according to the dose/toxicity management plan (23).

1.3.3 Comparative price of sorafenib

The cost of sorafenib is £3576.56 for a pack of 112 x 200mg tablets (24). A commercial arrangement made available for this submission via the Commercial Medicines Unit (CMU) framework agreement, results in a discount of [redacted] and a per pack cost of [redacted]. This equates to a per day cost, using trial based dosage, of [redacted] with the commercial arrangement.

[1] Confirmed with a UK clinical expert (March 2017)

Lenvatinib is available as a pack of 30 x 4mg tablets or 30 x 10mg tablets, both of which have a list price of £1,437. This equates to a daily cost of £102.89 per treatment day (15, 25). Treatment costs are presented in Table 2.

Table 2: Trial based daily treatment cost/ pack cost of sorafenib and lenvatinib

Treatment/ trial dose	Per treatment day (trial dose)	Per pack
sorafenib* (651.2mg)	[redacted]	[redacted]
lenvatinib (17.2mg)	£102.89	£1,437

* Inclusive of CMU commercial arrangement

1.3.4 Innovation

Sorafenib was the first licensed MKI treatment for radioactive iodine-refractory advanced and progressive differentiated thyroid cancer. Currently available to patients under the Cancer Drugs Fund (CDF), sorafenib became the standard of care, replacing best-supportive / palliative care. This resulted in a step-change to the management of the condition, a new line of therapy, and improved outcomes to patients who had become refractory to radio-iodine treatment.

Beyond direct health benefits successful treatment could allow patients to return to normal daily activities such as caring for their children or returning to work and thus contribute to family life. There is also an important psychological benefit to patients and carers of receiving an active treatment rather than palliative care (21).

1.3.5 Evidence presented in this submission

The evidence presented in this submission includes:

Section 2: Clinical efficacy and safety of sorafenib - One randomised-controlled trial (RCT) was identified from a systematic literature review (DECISION)

Section 3: Systematic review and indirect treatment comparison - No direct head-to-head trials of sorafenib versus lenvatinib were identified. An indirect comparison has been conducted to provide comparative efficacy and safety evidence for sorafenib versus lenvatinib.

Section 4: Cost-effectiveness evaluation - A cost-utility analysis has been conducted for the comparison of sorafenib versus lenvatinib and BSC.

Section 5: A NHS budget impact assessment conducted for sorafenib

2. Clinical effectiveness – sorafenib in RAI-R DTC

2.1 Introduction

Sorafenib is an oral multi-kinase inhibitor. Kinase inhibitors offer a promising development in the treatment of differentiated thyroid cancer (DTC) due to their ability to selectively target cancer cells. Sorafenib has a novel mechanism of action targeting several pathways that are implicated in the pathogenesis of DTC (26).

2.2 Summary of clinical evidence

Evidence to support the use of sorafenib for the treatment of locally advanced / metastatic RAI-R DTC is provided by results from the phase III double-blind, randomised placebo-controlled trial, DECISION involving 417 patients, of whom 207 received sorafenib (15).

DECISION showed a clinically meaningful, statistically significant prolongation of progression-free survival (PFS) in patients with RAI-R DTC treated with sorafenib compared to placebo (median PFS 10.8 vs. 5.8 months), representing a 41% risk reduction of disease progression or death compared to treatment with placebo (hazard ratio [HR] =0.59; 95% CI: 0.45, 0.76; p<0.0001). PFS improvement was observed in all pre-specified clinical and genetic biomarker subgroups analysed.

Treatment with sorafenib also resulted in a statistically significant improvement in time to progression (TTP), compared to placebo (11.1 months vs. 5.8 months; HR=0.557; p<0.0001), in addition to disease control (DCR) and response rates (RR). Additionally, 42% of patients in the sorafenib arm had stable disease for ≥ 6 months compared to 33% with placebo and many sorafenib-treated patients (77%) experienced target lesion tumour shrinkage compared to placebo (28%). The toxicity profile of sorafenib was manageable in RAI-R DTC and is well understood with its use in other tumour types such as hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC).

DECISION allowed patients from the placebo arm to cross-over into the sorafenib arm at the point of disease progression. Due to a high level of crossover (>70% of placebo patients received sorafenib upon progression), overall survival results were confounded. At the time of primary analysis data cut-off, median overall survival had not been reached for sorafenib or placebo-treated patients.

Exploratory statistical analyses were performed to adjust for crossover on the initial and subsequently available data cuts. Using the RPSFT (Rank Preserving Structural Failure Time) and IPE (iterative parameter estimation) methods, a trend in OS prolongation favouring sorafenib was observed consistently over successive time points.

2.3 Sorafenib RCTs identified from the systematic literature review

To inform the clinical evidence base and indirect treatment comparison (ITC) a systematic literature review (SLR) was conducted to identify randomised controlled trials (RCTs) that met the decision problem. Full details of the SLR, and studies identified to support the ITC are described in section 3.1 and a full list of excluded studies and reasons for exclusion is available in appendix 7.4.

One RCT (DECISION study) was identified for sorafenib relevant to the decision problem, which considered the use of sorafenib for the treatment of patients with progressive, locally advanced or metastatic RAI-R DTC. No relevant ongoing studies or updated analyses are anticipated to provide additional evidence within the timescale of this appraisal.

2.4 DECISION; Study 14295 - A double-blind randomised phase III study evaluating the efficacy and safety of sorafenib compared to placebo in locally

advanced/metastatic patients with radioactive Iodine refractory differentiated thyroid cancer (15, 27, 28)

2.4.1 Overview of study design and methodology

DECISION was a randomised, double-blind, placebo-controlled, multicentre, phase 3 trial to evaluate the efficacy and safety of sorafenib in the treatment of patients with RAI-R DTC.

The primary objective of the study was to compare sorafenib and placebo treatment in terms of progression-free survival (PFS) in patients with RAI-R DTC. Secondary objectives included evaluation of overall survival (OS), time to progression (TTP), disease control rate (DCR), response rate, duration of response, and safety.

Patients were randomised on a 1:1 basis to receive either sorafenib (400mg bd) or placebo. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Upon progression, treatment was unblinded, and patients could enter an open-label period, where those randomised to sorafenib could continue treatment and placebo patients could 'crossover' and receive sorafenib. Figure 1 provides a schematic of study design and Table 3 summarises the study methodology.

Figure 1: DECISION study design. Adapted from reference (15)

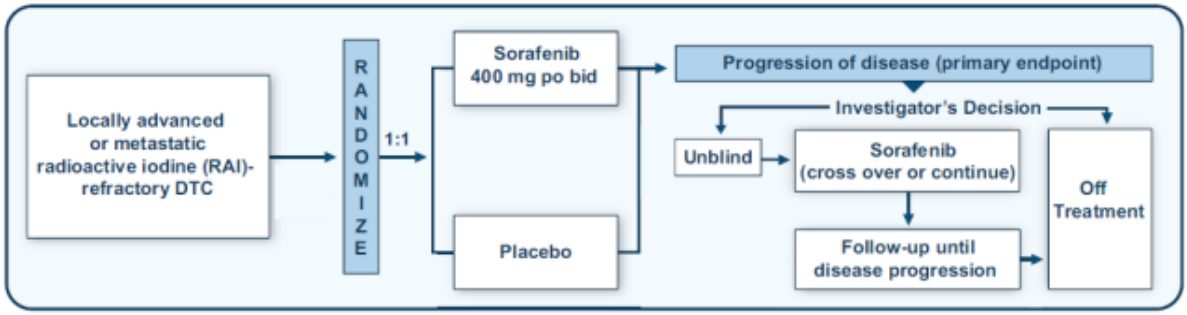


Table 3: Summary of methodology: DECISION study

DECISION (NCT00984282)	

Location	• 81 study centres in 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)

Design	Randomised, double-blind, placebo-controlled, multicentre, phase 3 trial
Patient population	RAI-refractory locally advanced or metastatic DTC (papillary, follicular, Hürthle cell, or poorly differentiated carcinoma)
Trial Duration	Study enrolment started in October 2009 and was completed in July 2011.
Randomisation	• Patients randomised 1:1 to receive sorafenib or matching placebo via interactive voice response system (IVRS) using a pre-prepared randomisation list. • Stratification by age (<60 years vs. ≥60 years) and geographical region (North America, Europe, and Asia). • Patients assigned unique identification code to determine treatment, corresponding to unique drug pack number, pre-printed on trial medication.
Blinding	• Patients, investigators, and study sponsor masked to treatment assignment through unique drug pack numbers pre-printed onto trial medication. • Sorafenib and placebo identical in appearance. • Review of histopathological slides - by blinded Central Histology Review Committee (CHRC) • Study imaging to determine overall tumour responses at each time point, determining the time point of disease progression and the best overall response per case – by blinded independent radiologists.
Key inclusion criteria	• Age 18 years or older with written informed consent; • Locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (papillary, follicular [including Hürthle cell], and poorly differentiated) that had progressed within the past 14 months according to Response Evaluation Criteria in Solid Tumors (RECIST); • At least one measurable lesion by CT or MRI according to RECIST; • Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; • Adequate bone marrow, liver, and renal function; • Serum thyroid-stimulating hormone concentration < 0.5 mIU/L. Radioactive iodine-refractory differentiated thyroid cancer defined as the presence of at least one target lesion without iodine uptake; or patients whose tumours had iodine uptake and either progressed after one radioactive iodine treatment within the past 16 months, or progressed after two radioactive iodine treatments within 16 months of each other (with the last such treatment administered more than 16 months ago), or received cumulative radioactive iodine activity of ≥22·3 GBq (≥600 mCi).
Key exclusion criteria	• Patients who had received previous targeted therapy, thalidomide, or chemotherapy for thyroid cancer were excluded (prior low-dose chemotherapy for radiosensitisation allowed); • Previous or 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 (Ta, Tis, or T1) bladder tumours); • Grade ≥3 haemorrhage or bleeding event according to NCI-CTCAE within 3 months prior to randomisation;

DECISION (NCT00984282)	
	• 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 enrolment in the study); • Clinically significant cardiac disease and/or uncontrolled hypertension (>150/90 mmHg) despite optimal treatment; • Known or suspected allergy to sorafenib or hypersensitivity to sorafenib or any agent given during the course of the study.
Intervention (n) and comparator (n)	**Intervention**: Sorafenib 800mg per day [400mg (2x200mg), orally, twice daily (b.d.)]; n = 207 **Comparator:** Placebo (two tablets) b.d; n = 210 Each dose of sorafenib or placebo taken approximately 12 hours apart, without food, at least 1 hour before or 2 hours after a meal. Study drug could be reduced to 600mg daily in divided doses, then to 200mg twice daily, then to 200mg once daily. Dose interruption and reductions were specified for haematological, non-haematological, and skin adverse events, and for hypertension (see Appendix 7.2). After improvement of non-haematological adverse reactions, dose of study drug could be re-escalated back to maximum of 800mg daily.
Permitted and disallowed concomitant medication	**Permitted (with monitoring):** Narrow therapeutic index medication e.g. warfarin; medications known to be metabolised by the liver (due to sorafenib inhibiting a variety of liver metabolic enzymes in vitro). **Disallowed:** Concomitant RAI, chemotherapy, or other investigational therapy; or any substances known to induce CYP3A4 (e.g. St. John's Wort, dexamethasone >16mg daily, phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital) within 7 days of randomisation.
Primary outcome	• Progression-free survival (PFS)
Secondary outcomes of relevance	• Overall survival (OS) • Time to progression (TTP) • Disease Control Rate (DCR) • Objective Response Rate (ORR) • Duration of Response (DOR) • Safety - Adverse events (AEs) (Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 / Common Terminology Criteria for Adverse Events (CTCAE) version 3.0).
Exploratory outcomes of relevance	• Health Related Quality of Life (HRQoL) and Health Utility Values, assessed using the Functional Assessment of Cancer Therapy General Version 4.0 (FACT-G) and EuroQol-5 Dimensions (EQ-5D) questionnaires, respectively.
Populations analysed	**Primary population for efficacy analysis including PFS, OS, TTP endpoints:** full analysis set (FAS) (which is the intention-to-treat [ITT] population) Sorafenib n=207; Placebo n=210. **Population for safety analysis:** SAF**,** all patients who received at least one dose of study medication. Sorafenib n=207; Placebo n=209. **Analysis of DCR, ORR and DOR endpoints:** Per Protocol Set (PPS) i.e. Randomised patients who were evaluable for tumour response with imaging data, had exposure to study medication, and no major protocol deviations. Sorafenib n=196; Placebo n=201.
Statistical Analyses	• **Null hypothesis**: both treatment arms have the same PFS distribution; Alternative hypothesis: distribution of PFS in the two arms will differ per Lehmann's alternative, equivalent to the assumption of proportional hazards between the treatment arms. • **Primary analysis**: PFS, in the ITT population, after approximately 267 PFS events (Actual data cut-off: August 31st 2012 after 250 PFS

DECISION (NCT00984282)	
	events). Treatment groups compared using stratified one-sided log rank test with overall alpha of 0.01 stratified by age (<60 years vs. ≥60 years) and geographical region (North America, Europe and Asia). Kaplan-Meier curves, median time to PFS, hazard ratios and 95% confidence intervals (from a Cox proportional hazards model). • **Sensitivity analyses of primary endpoint**: 1. Times to first, second, and subsequent tumour evaluations 2. Unstratified log-rank test and Cox model 3. Local investigators assessment including radiological progression and any clinical progression 4. Local investigators assessment - radiological assessments only 5. Central radiological assessment including radiological progression and any clinical progression 6. Central radiological assessment - radiological assessments only 7. Analysis of concordance and discordance in radiological progression between investigators and central assessments during the double-blind study phase. • **Sample size and power calculation**: Assuming one-sided alpha of 0.01, a power of 90%, 55.5% increase in median time to PFS, and a randomisation ratio of 1:1 between experimental and control arm, 267 events were required. 420 patients had to be enrolled to observe 267 events after approximately 29 months. • **Analyses of secondary endpoints**: OS, TTP, ORR, and DCR tested using one-sided significance level of 0.025 (α = 0.025). TTP and OS analysed by Kaplan-Meier method and compared using the log-rank test. Response rate and DCR analysed using Cochran-Mantel-Haenszel test (one-sided significance level of 0.025). Tests adjusted for the same stratification factors as PFS. • **Missing data, patient withdrawals**: If progression occurred after missed or non-evaluable assessments, PFS was censored at the date of last evaluable scan before the missing assessments. PFS for patients without disease progression or death at the time of analysis or unblinding was censored at last date of tumour evaluation before unblinding. For patients who discontinued or withdrew early from study without documented progression or death, PFS was censored on date of last evaluable tumour assessment. Patients with missing survival status information censored at last date known to be alive. • **Overall survival**: Interim analysis of OS performed at time of PFS analysis (data cut-off Aug 31, 2012). Planned follow-up analysis of OS scheduled approximately 9 and 36 months after date of primary completion. Rank Preserving Structural Failure Time (RPSFT) method and an iterative parameter estimation (IPE) method were used for pre-planned secondary analyses of OS that corrected for the effects of cross-over from placebo to sorafenib in the placebo arm.
Pre-planned subgroups	• Geographical region (North America, Europe, Asia), • Age (<60 years, ≥60 years), • Gender, • Histology subtype of thyroid cancer (papillary, follicular – Hürthle cell, follicular – other subtypes, poorly differentiated), • Lung only metastases versus lung and/or other metastases, • Bone metastases and/or other metastases vs no bone metastases, • FDG-PET uptake (positive, negative), • Prior RAI cumulative dosing <600 mCi (22.2 GBq) vs. ≥ 600 mCi (22.2 GBq), • Tumour burden as measured by number of target or non-target lesions (below versus above-median),

DECISION (NCT00984282)	
	• Tumour burden as measured by sum of target diameters (below versus above-median),

2.4.2 Summary of patient population

Baseline characteristics in the DECISION study were similar between treatment groups, with no major imbalances. Approximately half of the patients in each treatment group were female (sorafenib 49.8%; placebo 54.8%) and nearly 60% of patients in both treatment groups were White, from Europe, had an ECOG performance status (PS) of 0, and were ≥60 years old. Approximately 57% patients had papillary carcinoma, approximately 25% had follicular thyroid carcinoma and 10% patients had poorly differentiated thyroid cancer (11.6% sorafenib vs. 7.6% placebo patients). Patients were also assessed for Hürthle cell adenocarcinoma, an aggressive variant of DTC; this was measured by investigator only with a higher prevalence in the sorafenib arm (11.6% sorafenib vs. 6.7% placebo) (28). Median time from initial diagnosis to enrolment was approximately 67 months. Patient disposition as at primary data cut-off (August 2012) is shown in

Figure 2.

Table 4: Baseline demographic and disease characteristics (FAS) (15, 27)

Characteristic		Sorafenib N=207 n (%)	Placebo N=210 n (%)
Sex	Male	104 (50.2%)	95 (45.2%)
	Female	103 (49.8%)	115 (54.8%)
Age (years)	Median (range)	63.0 (24-82)	63.0 (30-87)
	<60	80 (38.6%)	81 (38.6%)
	≥60	127 (61.4%)	129 (61.4%)
Race	White	123 (59.4%)	128 (61.0%)
	Black	6 (2.9%)	5 (2.4%)
	Asian	47 (22.7%)	52 (24.8%)
	Hispanic	2 (1.0%)	2 (1.0%)
	Uncodeable	0	1 (0.5%)
	Missing*	29 (14.0%)	22 (10.5%)
Geographic Region	Europe	124 (59.9%)	125 (59.5%)
	North America	36 (17.4%)	36 (17.1%)
	Asia	47 (22.7%)	49 (23.3%)
ECOG PS	0	130 (62.8%)	129 (61.4%)
	1	69 (33.3%)	74 (35.2%)
	2	7 (3.4%)	6 (2.9%)
Histology per central assessment [a]	Papillary carcinoma	118 (57.0%)	119 (56.7%)
	Follicular, oncocytic (Hürthle cell)	37 (17.9%)	37 (17.6%)
	Follicular non-Hürthle cell	13 (6.3%)	19 (9.0%)
	Poorly differentiated thyroid cancer	24 (11.6%)	16 (7.6%)
	Well differentiated thyroid carcinoma	2 (1.0%)	1 (0.5%)
	Oncocytic carcinoma	2 (1.0%)	0 (0.0%)
	Non-diagnostic	6 (2.9%)	6 (2.9%)
	Carcinoma, NOS	0 (0.0%)	3 (1.4%)
	missing	7 (3.4%)	8 (3.8%)
	Medullary carcinoma	0 (0.0%)	1 (0.5%)
	Non-thyroid carcinoma	0 (0.0%)	1 (0.5%)
Metastases	Locally advanced	7 (3.4%)	8 (3.8%)
	Distant	200 (96.6%)	202 (96.2%)
Most Common Metastatic Lesion Sites	Lung	178 (86.0%)	181(86.2%)
	Lymph nodes	113 (54.6%)	101(48.1%)
	Bone	57 (27.5%)	56 (26.7%)
	Pleura	40 (19.3%)	24 (11.4%)
	Head and neck	33 (15.9%)	34 (16.2%)
	Liver	28 (13.5%)	30 (14.3%)
Time from diagnosis (months)	Median (range)	66.2 (3.9-362.4)	66.9 (6.6 (6.6-401.8)
Any previous systemic anticancer therapy		7 (3.4%)	6 (2.9%)
Cumulative dose of RAI (mCi)	Median	400.0	376

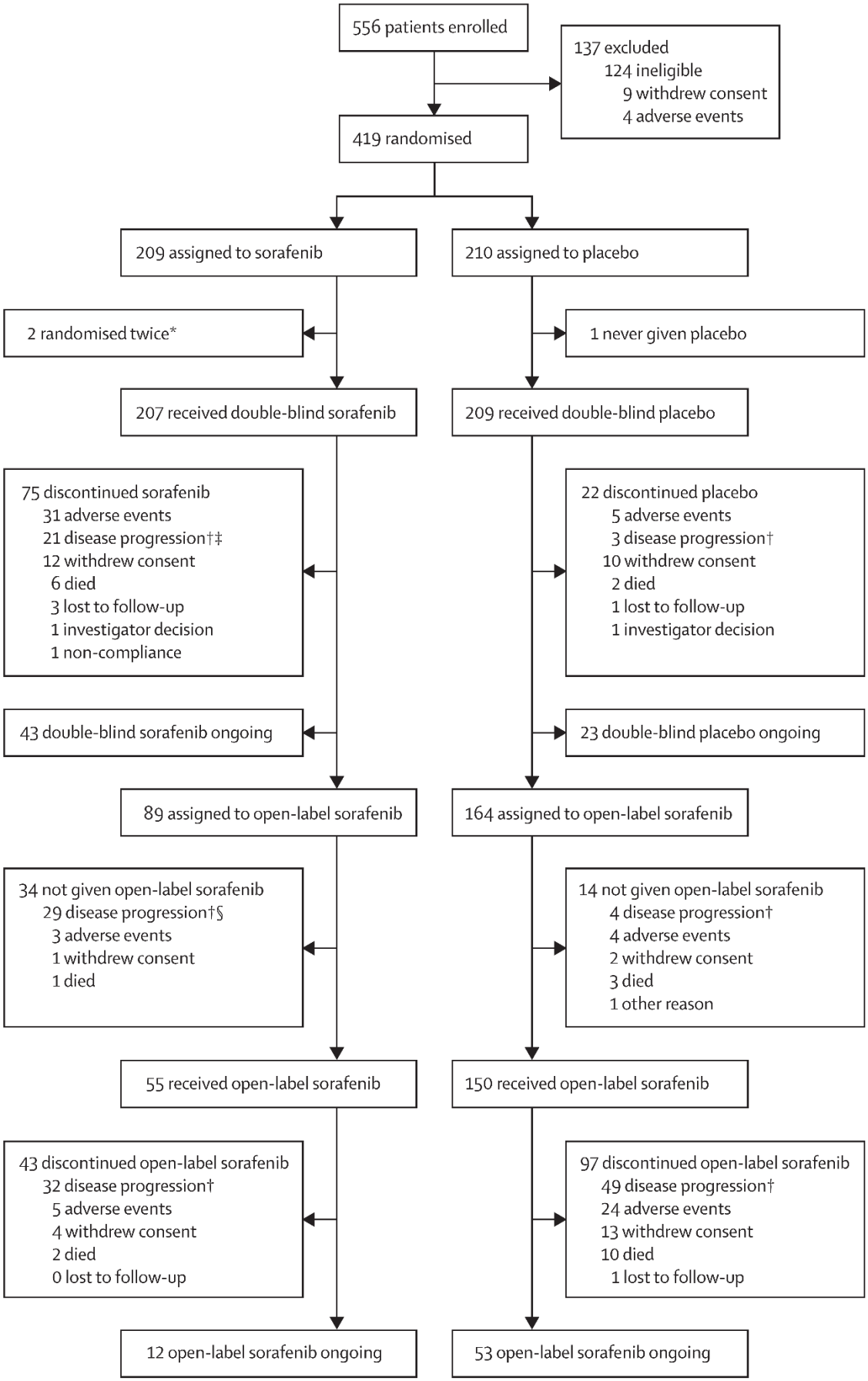
Characteristic		Sorafenib N=207 n (%)	Placebo N=210 n (%)
Prior thyroidectomy		207 (100%)	208 (99.0%)
Prior Loco-regional or EBRT[b]		83 (40.1%)	91 (43.3%)
Baseline FDG uptake	Positive	161 (77.8%)	159 (75.7%)
	Negative	14 (6.8%)	15 (7.1%)
	Missing	32 (15.5%)	36 (17.1%)

ECOG PS=Eastern Cooperative Oncology Group performance status; FDG=2-(18F)-fluoro-2-deoxy-d-glucose; NOS=not otherwise specified; S.D.=standard deviation;

* The missing patients in the race category are from France, where race was not collected due to local regulations.

[a] All patients had differentiated thyroid cancer according to investigator assessment. 2 patients in the sorafenib group and one in the placebo group were assigned two different histologies on the basis of multiple samples.[b] Defined as any kind of prior radiotherapy or radiotherapy ablation.

Figure 2: Patient Disposition in DECISION (15)


556 patients enrolled
137 excluded
124 ineligible
9 withdrew consent
4 adverse events
419 randomised
209 assigned to sorafenib
210 assigned to placebo
2 randomised twice*
1 never given placebo
207 received double-blind sorafenib
209 received double-blind placebo
75 discontinued sorafenib
31 adverse events
21 disease progression†‡
12 withdrew consent
6 died
3 lost to follow-up
1 investigator decision
1 non-compliance
22 discontinued placebo
5 adverse events
3 disease progression†
10 withdrew consent
2 died
1 lost to follow-up
1 investigator decision
43 double-blind sorafenib ongoing
23 double-blind placebo ongoing
89 assigned to open-label sorafenib
164 assigned to open-label sorafenib
34 not given open-label sorafenib
29 disease progression†§
3 adverse events
1 withdrew consent
1 died
14 not given open-label sorafenib
4 disease progression†
4 adverse events
2 withdrew consent
3 died
1 other reason
55 received open-label sorafenib
150 received open-label sorafenib
43 discontinued open-label sorafenib
32 disease progression†
5 adverse events
4 withdrew consent
2 died
0 lost to follow-up
97 discontinued open-label sorafenib
49 disease progression†
24 adverse events
13 withdrew consent
10 died
1 lost to follow-up
12 open-label sorafenib ongoing
53 open-label sorafenib ongoing

2.4.3 Efficacy results of the DECISION study

DECISION study results at the time of primary efficacy analysis (August 2012) are summarised in Table 5. Two follow-up analyses of overall survival were conducted at 9 months (May 2013) and 36 months (July 2015) are reported later in this section.

Table 5: Summary of key results from DECISION

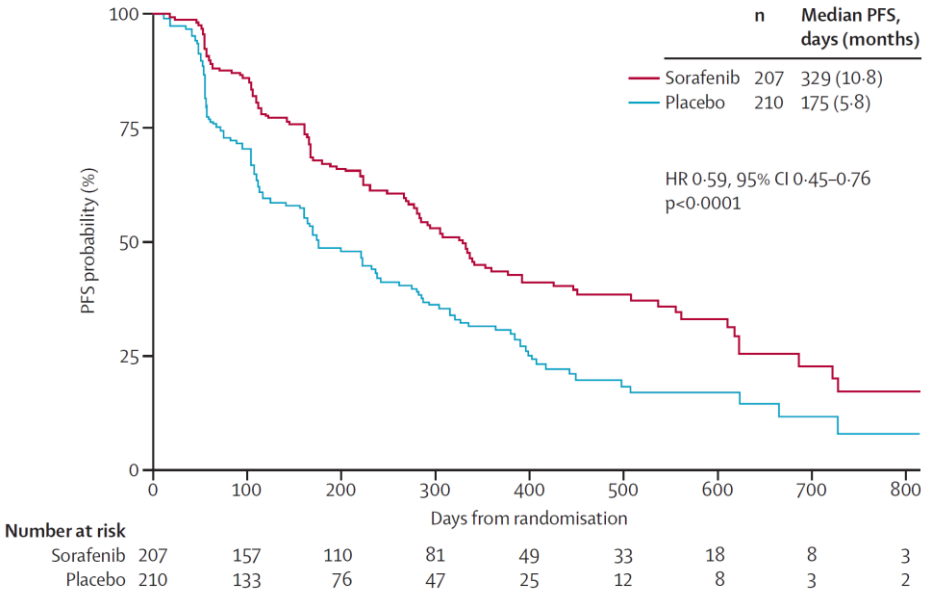
	Sorafenib N=207	**Placebo N=210**
Primary endpoint – Progression-free survival (PFS)		
Number of patients (%) with event	113 (54.6%)	137 (65.2%)
Number of patients (%) censored	94 (45.4%)	73 (34.8%)
Median PFS (days) [95% CI]	329 [278; 393]	175 [160; 238]
Median PFS (months) [a]	10.8	5.8
PFS range (days; without censored values)	20-728	14-728
Hazard ratio (sorafenib / placebo)	0.59	
95% CI for hazard ratio	[0.45; 0.76]	
p-value (one-sided from stratified log-rank test)	<0.0001	
Secondary endpoints		
Overall survival (FAS – data cut-off Aug 2012)		
Number of patients (%) with event	45 (21.7%)	54 (25.7%)
Number of patients (%) censored	162 (78.3%)	156 (74.3%)
Median OS (days) [95% CI]	Value could not be estimated b	Value could not be estimated b
OS Range (days, without censored values): uncorrected	(57-771)	(26-766)
OS range (months[a], without censored values): uncorrected	1.9-25.3	0.9-25.2
Hazard ratio (sorafenib / placebo): uncorrected	0.80	
95% CI for hazard ratio	[0.54; 1.19]	
p-value (one-sided from stratified log-rank test): uncorrected	0.14	
Time to progression – central assessment (FAS)		
Total with event (progressed, %)	105 (50.7%)	135 (64.3%)
Total censored	102 (49.3%)	75 (35.7%)
Median TTP (days) [95% CI]	337 [283; 451]	175 [160; 238]
Median TTP (months) a [95% CI]	11.1	5.8
Range (days; without censored values)	(20-728)	(14-728)
Hazard ratio (sorafenib / placebo)	0.56	
95% CI for hazard ratio	[0.43; 0.72]	
p-value (one-sided from stratified log-rank test)	<0.0001	
Response rates – central assessment (PPS) (n, % [95% CI])		
Response (Complete Response + Partial Response)	24 (12.2% [8.0; 17,7])	1 (0.5% [0.0; 2.7])
p-value (one-sided)	<0.0001	
CR	0	0
PR	24 (12.2% [8.0; 17,7])	1 (0.5% [0.0; 2.7])
SD c	145 (74.0% [67.3; 80.0])	149 (74.1% [67.5; 80.0])
PD	20 (10.2% [6..4; 15.3])	46 (22.9% [17.3; 29.3])
Progression by clinical judgement		1 (0.5% [0.0; 2.7])
NA	7 (3.6% [1.5; 7.2])	4 (2% [0.5; 5.0])
Disease Control Rate		
DCR (CR+PR+SD) d	169 (86.2% [80.6; 90.7])	150 (74.6% [68.0; 80.5])
p-value (one-sided)	0.0015	

CI=confidence interval; CR=complete response; DCR=disease control rate; FAS=full analysis set; NA=not analysed; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PPS=per protocol analysis set; PR=partial response; SD=stable disease; TTP=time to progression. a) Months = days/30.4, b) Value could not be estimated due to immature data, c) SD was assessed at 4 weeks for this analysis
d Patients with CR, PR, or SD for at least one month

2.4.3.1 Primary efficacy endpoint (Progression-free survival (PFS))

Progression-free survival (PFS) was assessed every 8 weeks by central independent blinded review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.0. DECISION showed a statistically significant prolongation of median PFS in patients treated with sorafenib compared to placebo (10.8 months vs. 5.8 months placebo), in locally advanced and metastatic differentiated thyroid cancer refractory to radioiodine (RAI-R DTC) (see Figure 3). Treatment with sorafenib was associated with a 41% risk reduction of disease progression or death compared to treatment with placebo (hazard ratio [HR] 0.59, 95% CI 0.45–0·76; p<0.0001). The treatment effect of sorafenib was robust - consistent across all pre-specified subgroups analysed (Appendix 7.3) and the various sensitivity analyses performed.

Figure 3: Kaplan-Meier Curve of progression-free survival in the DECISION study (Central assessment; ITT) (15)



PFS= progression-free survival, HR=hazard ratio; CI=confidence interval

Sensitivity analyses: Progression free survival

Investigator-assessed progression-free survival closely matched that in the central review, with median progression-free survival of 10.8 months in the sorafenib group vs 5.4 months in the placebo group (HR 0.49, 95% CI 0.39–0.61; p<0.0001) (Table 6). Results of other sensitivity analyses of PFS were supportive of and consistent with the primary analysis, which showed statistically and clinically significant improvement in the sorafenib group compared with the placebo group.

Table 6: Sensitivity analyses of PFS (27)

	Number of patients (%) with event	Number of patients (%) censored	Median PFS [95% CI], days	Median PFS, months [a]	Range (without censored values), days	HR (sorafenib / placebo) [95% CI]	p-value
PFS (primary analysis)							
Sorafenib (N=207)	**113 (54.6%)**	**94 (45.4%)**	**329 [278; 393]**	**10.8**	**20-728**	**0.587 [0.454; 0.758]**	**<0.0001**
Placebo (N=210)	**137 (65.2%)**	**73 (34.8%)**	**175 [160; 238]**	**5.8**	**14-728**		
PFS – investigators' assessments							
Sorafenib (N=207)	140 (67.6%)	67 (32.4%)	330 [280; 360]	10.8	20-846	0.49 [0.39; 0.61]	<0.0001
Placebo (N=210)	184 (87.6%)	26 (12.4%)	165 [119; 175]	5.4	13-728		
PFS – investigators' assessments; radiological progression only							
Sorafenib (N=207)	126 (60.9%)	81 (39.1%)	338 [305; 393]	11.1	20-846	0.478 [0.375; 0.608]	<0.0001
Placebo (N=210)	164 (78.1%)	46 (21.9%)	174 [162; 224]	5.7	13-728		
PFS – central assessment; radiological and all clinical progression							
Sorafenib (N=207)	115 (55.6%)	92 (44.4%)	326 [278; 378]	10.7	20-728	0.567 [0.441; 0.729]	<0.0001
Placebo (N=210)	145 (69.0%)	65 (31.0%)	169 [125; 224]	5.6	14-728		
PFS – central assessment; radiological progression only							
Sorafenib (N=207)	108 (52.2%)	99 (47.8%)	333 [283; 426]	10.9	20-728	0.584 [0.449; 0.759]	<0.0001
Placebo (N=210)	131 (62.4%)	79 (37.6%)	200 [162; 262]	6.6	20-728		

CI=confidence interval; HR=hazard ratio; PFS=progression-free survival

[a] Months = days/30.4, Median and 95% Cis computed using Kaplan-Meier estimates

2.4.3.2 Secondary endpoints

Time to progression (TTP): Sorafenib treatment resulted in a statistically significant improvement in time to progression (TTP), compared to placebo (11.1 months vs. 5.8 months, respectively; [HR 0.56, 95% CI 0.43–0.72; p<0.0001]), with results based on the central and investigators' assessments showing consistency.

Response and Disease Control Rate: A significant difference in disease control (DCR) and response rates (RR) was also observed in sorafenib treated patients. Partial responses were observed in 12.2% of patients receiving sorafenib compared with 0.5% in the placebo arm ($p<0.0001$). Additionally, 42% of patients in the sorafenib arm had stable disease for ≥6 months compared to 33% with placebo. The median duration of response for patients with a partial response to sorafenib was 10.2 months (95% CI 7.4–16.6). Tumour shrinkage in target lesion size was observed in approximately 77% of sorafenib-treated patients and 28% patients in the placebo arm. Of note, tumour shrinkage in symptomatic patients was often sufficient to alleviate symptoms, despite often not being sufficient to class as a confirmed response (as per RECIST) (29).

Overall Survival - August 31st 2012 (15)

At the date of the primary analysis 71.4% of patients randomised to placebo had crossed over to treatment with open-label sorafenib. Median overall survival (OS) (before adjustment for treatment crossover) had not been reached at the time of analysis. There was no statistical difference in the OS between the unadjusted treatment groups at the time of primary analysis

Overall survival - 31st May 2013 (27)

Nine months after the original data cut-off, 74.8% of patients randomised to placebo had crossed over to treatment with open-label sorafenib. 66 patients (31.9%) in the sorafenib group and 72 patients (34.3%) in the placebo group had died. Median OS for sorafenib (before adjustment for treatment crossover) had still not been reached by the second analysis and median OS for patients treated with placebo was 36.5 months (95% CI: 32.2–not estimable) (HR 0.88, 95% CI 0.63–1.24; p=0.24).

Overall survival – 14th July 2015 (13)

After 36 months from the original data cut-off, 75% of patients randomised to placebo had crossed over to treatment with open-label sorafenib. 103 patients (49.8%) in the sorafenib group and 109 patients (51.9 %) in the placebo group had died. Median OS (before adjustment for treatment crossover) was 39.4 months with

sorafenib (95% CI: 32.7, 51.4) and was 42.8 months with placebo (95% CI: 34.7, 52.6) (HR, 0.92 [95% CI: 0.71, 1.21]; P=0.28, one-sided, ITT population).

Overall survival: statistical corrections for crossover (13)

Given the crossover design of DECISION, overall survival results are confounded by the large proportion of patients in the placebo arm who crossed over to open-label sorafenib treatment, upon disease progression during the double-blind phase of the study. Results of all crossover analyses using both the rank preserving structural failure time model (RPSFT) and iterative parameter estimation (IPE) are summarised in Table 7.

Table 7: Overall survival: RPSFT and IPE adjustments for treatment crossover

Data cut-off	HR (Cox Model 95% CI); p-value (Bootstrapping 95% CI)	
Data	**IPE**	**RPSFT**
August 2012	0.70 (0.47, 1.04); p=0.0388 (0.40, 1.38)	0.61 (0.40, 0.94); p=0.0125 (0.18, 2.16)
May 2013	0.79 (0.57, 1.11); NR (0.46, 1.61)	0.69 (0.49, 0.99); NR (0.33, 1.65)
July 2015	0.80 (0.61, 1.05); NR (0.48, 1.71)	0.77 (0.58, 1.02); NR (0.42, 1.79)

CI=confidence interval; HR=hazard ratio: IPE=iterative parameter estimation; ITT=intent to treat; RPSFT=rank preserving structural failure time; NR=not reported.
*Unadjusted for treatment switch.

2.4.3.3 Relevant exploratory endpoints (as specified in NICE Scope)

Patient reported outcomes

Health utility values were measured using the EQ-5D, and to analyse health-related quality-of-life, the EQ-5D, EQ-5D VAS and the FACT-G were used. Completion of EQ-5D and FACT-G questionnaires was high (>96%).

2.4.3.3.1 Health Related Quality of Life (HRQoL)

The FACT-G is a 27-item, self-administered, multi-dimensional, validated questionnaire designed to assess the following dimensions: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB) and functional well-being (FWB) in cancer patients. FACT-G total score ranges from 0 to 108; the higher the score, the better the patient quality of life.

A small difference in total score in favour of placebo, driven by “physical well-being”, was observed. At baseline total scores were comparable to a normative adult cancer population: placebo 82 – 14 (mean – SD) and sorafenib 81 – 15 (108=maximal score possible). The sorafenib group had a lower score at first assessment (cycle 2, day 1; 76 – 15), possibly related to side effects of treatment, which remained relatively constant thereafter, while the placebo group remained near baseline.

A mixed linear model estimated that the FACT-G score was 3.45 points lower in the sorafenib group (p = 0.0006) (30), just reaching the minimally important threshold for the differences (MID for FACT-G total score: 3-7 points) and suggesting a mild difference in HRQoL in favour of the placebo arm.

Table 8: Analysis of treatment effect on FACT-G subscale and total scores, double-blind period, time-adjusted AUC (PROAS) (27)

Subscale	Sorafenib			Placebo		
	n	Mean	SD	n	Mean	SD
Physical well-being	194	20.548	4.502	195	23.033	4.479
Social/family well-being	194	21.477	4.836	195	21.751	4.446
Emotional well-being	195	17.678	4.445	195	17.832	3.707
Functional well-being	196	17.196	5.759	195	18.372	5.563
FACT-G total score	193	76.885	15.271	194	80.967	13.934

AUC=area under the curve; FACT-G=Functional Assessment of Cancer Therapy-General; PROAS=patient reported outcomes analysis set; SD=standard deviation.

Most dimensions in the physical well-being domain of FACT-G seemed sensitive to AEs, most notable “bothered by side effects” where “quite a bit” and “very much” increased from 2% prior to cycle 1, to about 30% prior to cycle 2 and about 25% prior to cycle 3. Despite dose reductions and interruptions, about 15% of the patients reported after cycle 6 that they were quite a bit or very much bothered by side effects. This suggests that a mild difference in overall quality of life between the sorafenib and placebo arm is likely due to side effects of sorafenib. On the other hand, about 55% were ‘not at all’ or ‘a little bit bothered’ at cycle 6 and on.

No baseline factors predictive of HRQoL on therapy were identified after additional subgroup analyses.

Table 9: Number of patients and their response to the question "I am bothered by side effects" in FACT-G physical well-being domain (double-blind period, sorafenib arm, Cycles 1-13; PROAS) (27)

Visit		I am bothered by side effects					
	Number of patients	Missing n (%)	Not at all n (%)	A little bit n (%)	Somewhat n (%)	Quite a bit n (%)	Very much n (%)
Cycle 1 Day 1	**196**	17 (8.7)	136 (69.4)	28 (14.3)	12 (6.1)	2 (1.0)	1 (0.5)
Cycle 2 Day 1	**186**	1 (0.5)	28 (15.1)	54 (29.0)	48 (25.8)	35 (18.8)	20 (10.8)
Cycle 3 Day 1	**178**	1 (0.6)	24 (13.5)	55 (30.9)	54 (30.3)	28 (15.7)	16 (9.0)
Cycle 4 Day 1	**165**	1 (0.6)	21 (12.7)	62 (37.6)	39 (23.6)	32 (19.4)	10 (6.1)
Cycle 5 Day 1	**158**	1 (0.6)	22 (13.9)	56 (35.4)	46 (29.1)	19 (12.0)	14 (8.9)
Cycle 6 Day 1	**149**	0	16 (10.7)	67 (45.0)	41 (27.5)	18 (12.1)	7 (4.7)
Cycle 7 Day 1	**143**	2 (1.4)	15 (10.5)	54 (37.8)	48 (33.6)	19 (13.3)	5 (3.5)
Cycle 8 Day 1	**133**	3 (2.3)	18 (13.5)	59 (44.4)	31 (23.3)	18 (13.5)	4 (3.0)
Cycle 9 Day 1	**125**	2 (1.6)	19 (15.2)	53 (42.4)	33 (26.4)	12 (9.6)	6 (4.8)
Cycle 11 Day 1	**113**	2 (1.8)	14 (12.4)	49 (43.4)	33 (29.2)	10 (8.8)	5 (4.4)
Cycle 13 Day 1	**87**	0	12 (13.8)	40 (46.0)	28 (32.2)	7 (8.0)	0

2.4.3.3.2 EQ-5D

There was a statistically significant group mean difference that was detected in a mixed linear model for the EQ-5D Index and EQ-5D VAS, favouring the placebo arm. This was not unexpected taking adverse reactions into account. Dimensions in the EQ-5D sensitive to adverse reactions included mobility, usual activities and pain/discomfort. The between group differences were statistically significant (-0.07012 and -6.7521, respectively) but did not reach the clinically minimal important difference (MID) – a change of at least 0.10 to 0.12 points on the EQ-5D Index is considered clinically meaningful (using ECOG performance status as the anchor), and a change of at least 7 points on the EQ-5D VAS is considered as clinically meaningful (31).

The lack of MID in the EQ-5D results supports treatment with sorafenib as being tolerable. More information regarding patient health-related quality-of-life, including results of the systematic searches can be found in section 2.4.4.

Figure 4: EQ-5D Index questionnaire scores – means and 95% confidence intervals (PROAS) (27)

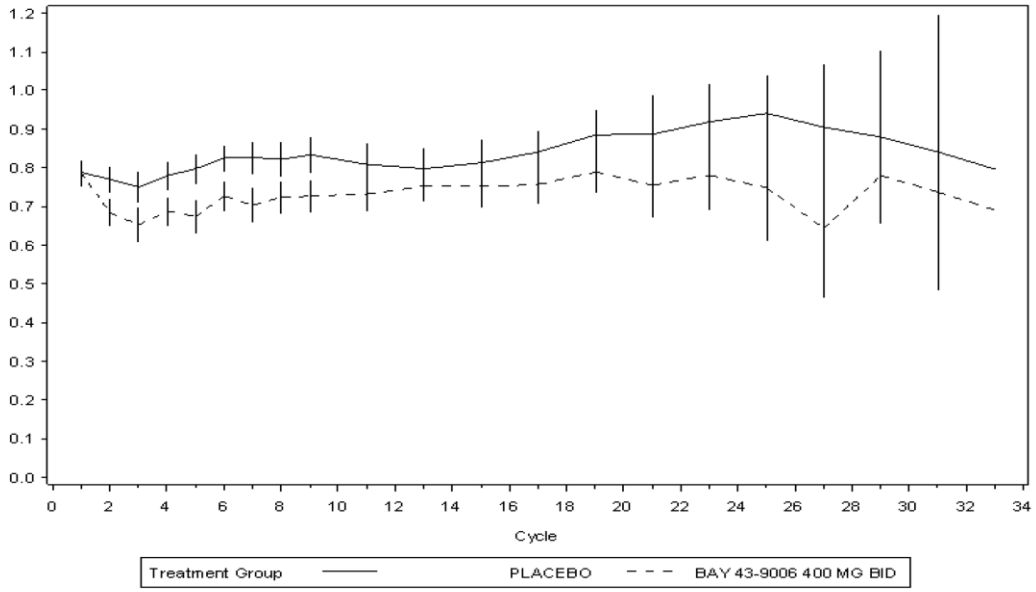
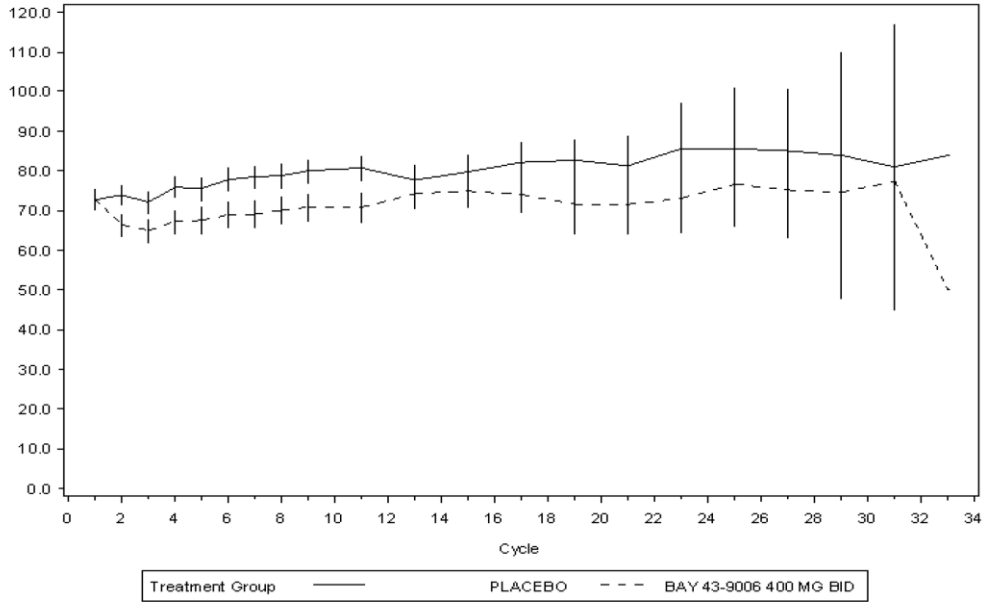


Figure 5: EQ-5D VAS questionnaire – means and 95% confidence intervals (PROAS) (27)



2.4.4 Safety profile of sorafenib in RAI-R DTC

Sorafenib has been licenced and marketed since July 2006, with adverse reactions in the DECISION study consistent with the known safety profile of sorafenib observed in other indications.

The toxicity profile of sorafenib is effectively managed with dose modifications and supportive care. Despite the requirement for dose modifications, relative dose intensity was largely preserved among sorafenib-treated patients in the DECISION trial.

Sorafenib is currently available for patients with DTC via the Cancer Drugs Fund, meaning clinicians currently have experience in managing safety events.

Results of a comparative safety assessment provide evidence for the relative tolerability of sorafenib in terms of grade 3-4, serious adverse events and trial based discontinuations (section 3.3.7)

The safety of sorafenib is demonstrated to be manageable in the context of the patient population in UK clinical practice defined in the decision problem. UK clinicians have experience in using sorafenib and are familiar with the management of sorafenib-related AEs.

2.4.4.1 DECISION safety analysis - Introduction

Patients were evaluated every 28 days (i.e. 1 cycle) for the first 8 months and every 56 days (2 cycles) thereafter for safety outcomes in the DECISION study. Data on all adverse events (AEs) and laboratory abnormalities were coded according to MedDRA (Medical Dictionary for Regulatory Activities) version 15.1 and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 3.0). Blood pressure was also monitored weekly for the first six weeks of treatment.

The primary safety analysis in the DECISION trial included treatment-emergent adverse events (TEAEs) that occurred during the double-blind period. The safety analysis set (SAF) comprised 416 patients who had received at least one dose of study medication (sorafenib, n=207; placebo, n=209). During the double-blind

treatment period, among patients included in the safety analyses, the median overall duration of exposure to study treatment was 10.6 months (IQR 5.3-15.7) in the sorafenib group versus 6.5 months (3.3-12.9) in the placebo group. Sorafenib patients received a mean of 81.4% of the maximum dose and placebo patients received a mean of 99.2% of the maximum dose.

A secondary safety analysis included TEAEs for all patients who received any dose of sorafenib during the double-blind and/or open-label period (primary data cut-off August 2012). In the open label phase of the study, 150 patients randomised to placebo received open label sorafenib, therefore the number of patients exposed to sorafenib at the time of primary data cut-off in DECISION is 357.

2.4.4.2 Summary of treatment-related adverse events

Adverse events that started or worsened during treatment (including during 30 days after the last dose) were considered 'treatment emergent' (TEAE). Most patients experienced at least one TEAE (mainly grade 1 or 2) during the double-blind period of the study (sorafenib, n=204 [98.6%]; placebo, n=183 [87.6%]). In most patients (77.8% sorafenib patients and 30.1% placebo patients) TEAEs were managed by dose modification (i.e. dose interruption or reduction).

The most commonly reported TEAEs (≥10%; any grade) during the double-blind period are summarised in Table 10. In the sorafenib arm, these included hand-foot skin reaction (HFSR), diarrhoea, alopecia, rash, fatigue and weight loss. Inherent in mechanism of action of sorafenib is a higher risk of hypertension, which occurred in 38.2% of patients receiving sorafenib compared with 11% for placebo. Most of the TEAEs in the sorafenib arm were considered drug-related, 96.6% patients experienced a TEAE compared with 53.6% in the placebo arm. Grade 3/4 TEAEs were reported in 64.3% of sorafenib patients compared with 30.1% of placebo patients.

Table 10: TEAEs occurring in ≥10% sorafenib patients during the DECISION study (by MedDRA SOC and PT; SAF) (27)

	Double-blind treatment				Double-blind + open-label sorafenib[a]	Open-label sorafenib after crossover (prior placebo)[b]
	Sorafenib		Placebo			
	N=207 n (%)		N=209 n (%)		N=207 n (%)	N=150 n (%)
	All grade	Grade 3/4	All grade	Grade 3/4		
Any AE	**204 (98.6)**	**133 (64.3)**	**183 (87.6)**	**63 (30.1)**	**204 (98.6)**	**149 (99.3)**
Skin & Subcutaneous tissue disorders						
Palmar plantar erythrodysaesthesia syndrome (HFSR)	143 (69.1)	40 (19.3)	16 (7.7)	0	145 (70.0)	85 (56.7)
Alopecia	138 (66.1)	0	16 (7.7)	0	139 (67.1)	85 (56.7)
Rash	73 (35.3)	10 (4.8)	15 (7.2)	0	74 (35.7)	44 (29.3)
Pruritus	42 (20.3)	1 (0.5)	22 (10.5)	0	42 (20.3)	18 (12.0)
Dry skin condition	27 (13.0)	1 (0.5)	10 (4.8)	0	28 (13.5)	14 (9.3)
Erythema	21 (10.1)	0	1 (0.5)	0	21 (10.1)	13 (8.7)
Gastrointestinal Disorders						
Diarrhoea	140 (67.6)	12 (5.8)	31 (14.8)	2 (1.0)	143 (69.1)	84 (56.0)
Nausea	43 (20.8)	0	24 (11.5)	0	45 (21.7)	41 (27.3)
Constipation	32 (15.5)	0	16 (7.7)	1 (0.5)	35 (16.9)	25 (16.7)
Stomatitis	23 (11.1)	1 (0.5)	5 (2.4)	0	23 (11.1)	14 (9.3)
Vomiting	23 (11.1)	1 (0.5)	12 (5.7)	0	23 (11.1)	11 (7.3)
Abdominal pain	22 (10.6)	2 (1.0)	6 (2.9)	1 (0.5)	24 (11.6)	17 (11.3)
Investigations						
Weight decreased	101 (48.8)	12 (5.8)	29 (13.9)	2 (1.0)	104 (50.2)	62 (41.3)
Blood TSH increased d	69 (33.3)	0	28 (13.4)	0	72 (34.8)	35 (23.3)
Alanine aminotransferase (ALT) increased	26 (12.6)	6 (2.9)	9 (4.3)	0	26 (12.6)	12 (8.0)
Aspartate aminotransferase (AST) increased	23 (11.1)	2 (1.0)	5 (2.4)	0	23 (11.1)	9 (6.0)
General Disorders & Administrative site conditions						
Fatigue	85 (41.1)	10 (4.8)	42 (20.1)	2 (1.0)	87 (42.0)	37 (24.7)
Asthenia	25 (12.1)	0	14 (6.7)	0	27 (13.0)	19 (12.7)
Pyrexia	22 (10.6	2 (1.0)	10 (4.8)	0	24 (11.6)	19 (12.7)
Mucosal inflammation	21 (10.1)	3 (1.5)	1 (0.5)	0	22 (10.6)	13 (8.7)
Metabolism & Nutrition Disorders						
Decreased Appetite	63 (30.4)	4 (1.9)	10 (4.8)	0	66 (31.9)	38 (25.3)
Hypocalcaemia	34 (16.4)	18 (8.7)	10 (4.8)	3 (1.5)	36 (17.4)	21 (14.0)
Musculoskeletal & Connective Tissue Disorders						
Pain in extremity	30 (14.5)	2 (1.0)	14 (6.7)	0	33 (15.9)	22 (14.7)
Arthralgia	21 (10.1)	0	16 (7.7)	3 (1.4)	22 (10.6)	14 (9.3)
Back pain	21 (10.1)	2 (1.0)	22 (10.5)	5 (2.4)	25 (12.1)	15 (10.0)
Muscle spasms	21 (10.1)	0	6 (2.9)	0	22 (10.6)	6 (4.0)
Respiratory, Thoracic & Mediastinal Disorders						
Cough	31 (15.0)	0	29 (13.9)	0	32 (15.5)	17 (11.3)
Dysphonia	26 (12.6)	1 (0.5)	7 (3.3)	0	27 (13.0)	10 (6.7)
Dyspnoea	25 (12.1)	9 (4.3)	22 (10.5)	7 (3.4)	28 (13.5)	18 (12.0)
Nervous System Disorders						
Headache	35 (16.9)	0	13 (6.2)	0	36 (17.4)	16 (10.7)
Vascular Disorders						
Hypertension	79 (38.2)	19 (9.2)	23 (11.0)	4 (1.9)	81 (39.1)	43 (28.7)

HFSR=hand foot skin reaction; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

a AEs reported during both the double-blind and open-label periods (cumulative)

b AEs reported during the open-label period only during treatment with sorafenib in patients receiving placebo during double-blind phase

c One patient randomised to placebo was erroneously dispensed sorafenib for cycle 1. AEs are captured in the placebo arm

d Elevations in blood TSH ≥ 0.5 mIU/L are reported under this term

2.4.4.2.1 Adverse events of Special Interest (AESIs) and comparison with use in other indications

The safety of sorafenib is well characterised in other indications (renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC)) and oncologists are familiar with the management of sorafenib-related AEs. The adverse reactions reported in the DECISION study were in general well-known for sorafenib, although hand foot skin reactions (HFSR), alopecia, diarrhoea, hypertension, hypocalcaemia and keratocanthoma / squamous cell carcinoma of the skin occurred at a higher frequency than previously reported in RCC (27). The frequency of keratocanthoma/squamous cell cancer has been revised to 'common' in the SmPC. Patients with thyroid carcinoma are at increased risk of developing secondary malignancies (32). In the DECISION study, if squamous cell carcinoma of the skin (a known side effect of sorafenib) is excluded, there is no excess of secondary malignancies while on sorafenib treatment compared to those patients with no exposure to sorafenib.

Hypocalcaemia grade 3 and 4 occurred in 6.8% and 3.4% of sorafenib-treated patients in DECISION. The underlying causes of hypocalcaemia and secondary hyperparathyroidism have not been conclusively defined, but the reason for the observed increased risk in patients with thyroid cancer is highly likely to be related to thyroidectomy (4).

'Increased thyroid stimulating hormone (TSH)' grade 1-2 was observed in about 1 in 3 patients treated with sorafenib, versus about 1 in 8 placebo patients. Therefore, when using sorafenib in differentiated thyroid carcinoma patients, close monitoring of TSH level is recommended (see section 4.4 of the sorafenib SmPC).

2.4.4.2.2 Serious adverse events (SAEs)

Serious adverse events were observed in 77 (37.2%) patients randomised to sorafenib and 55 (26.3%) patients randomised to placebo, during the double-blind treatment period. SAEs that occurred in 2% or more of patients receiving sorafenib were secondary malignancy (4.3% [9/207]), dyspnoea (3.4% [7/207]), and pleural effusion (2.9% [6/207]); the corresponding rates with placebo were 1.9% (4/209), 2.9% (6/209), and 1.9% (4/209), respectively. In the sorafenib group, secondary

malignancies occurred in nine patients, including seven with squamous cell carcinomas of the skin (one patient also had melanoma) and one each with acute myeloid leukaemia and bladder cancer. In the placebo group, there were single cases of bladder cancer, colon carcinoma, pulmonary carcinoid tumours, and gastric cancer.

2.4.4.2.3 Laboratory parameters

Mean changes in haematology parameters were modest with most patients experiencing no or low grade events.

Thyroid-stimulating hormone (TSH) levels were intentionally therapeutically managed at below normal levels (<0.5 m IU/L). Values rising above this threshold were counted as an AE (occurring in 33.3% of sorafenib-treated patients vs. 13.4% placebo-treated patients). This could be anticipated as sorafenib is believed to enhance T4 and T3 metabolism by possibly increasing type-3 deiodination (33) and by a sorafenib-related decrease in the clearance of thyrotropin (34).

During the double-blind period, the most commonly observed biochemical abnormalities (>30% patients) in the sorafenib group were: elevation of ALT (58.9%), elevation of AST (53.6%), hyperglycaemia (52.7%), and hypocalcaemia (35.7%). Grade 3 or 4 toxicities were uncommon. Clinically, these abnormalities had limited impact, as evidenced by the low rate of treatment discontinuation due to AEs based on laboratory abnormalities.

2.4.4.2.4 Adverse events leading to withdrawal

AEs that led to permanent discontinuation of treatment were higher in the sorafenib treated group (18.8%, n=39) than in the placebo group (3.8%, n=8) - the most frequently cited reason for discontinuation being hand–foot skin reaction (HFSR) in the sorafenib group (5.3%, n=11) and weight loss (1.0%, n=2) in the placebo group.

Dose interruptions and reductions because of adverse events occurred in 66.2% (137/207) and 64.3% (133/207) of patients, respectively, receiving sorafenib, and in 25.8% (54/209) and 9.1% (19/209) of patients, respectively, receiving placebo.

HFSR was the most common reason for sorafenib dose interruptions (55/207 [26.6%]) and dose reductions (70/207 [33.8%]).

2.4.4.2.5 Deaths

There were 12 treatment-emergent deaths in the sorafenib group and six in the placebo group during the double-blind phase, with one death in each group deemed to be drug-related [sorafenib: myocardial infarction; placebo: subdural haematoma]. In the sorafenib group, seven deaths were attributable to underlying disease, two to unknown causes, and one each to lung infection, chronic obstructive lung disease, and myocardial infarction. In the placebo group, four deaths were attributable to underlying disease and one each to pulmonary embolism and subdural haematoma.

2.4.4.2.6 Subgroup analyses: safety

A subgroup analyses on safety parameters, performed for the double-blind treatment period of DECISION, showed no clinically relevant differences in the AE profile of sorafenib by region, body mass index, sex, and age.

2.4.4.2.7 Open-label phase

Overall, the AEs reported in the open-label period were similar in pattern of occurrence and severity to those observed in patients treated with sorafenib in the double-blind period (Table 10). Mean dose received by patients randomised to sorafenib during the open label period was similar to the double-blind period (651mg vs. 648mg).

2.5 Discussion and conclusions – Interpretation of clinical evidence of sorafenib in RAI-R DTC

Patients with differentiated thyroid carcinoma refractory to RAI have limited treatment options. Without intervention, disease progression leads to significant morbidity related to disease burden, including death and complications arising from recurrent neck lesions or distant metastases in the lungs, bones or other sites (4). Kinase inhibitors, such as sorafenib, have the potential to stabilise the disease, preventing some of the morbidity associated with disease progression. Clinical evidence for the

use of sorafenib in RAI-R DTC is provided by the results of the DECISION study (see section 2.4).

Outcome measures in the DECISION study were based around assessment of treatment effects on slowing disease progression, improvements in survival, amelioration of symptoms, and health-related quality of life, all of which are directly relevant to patients with RAI-R DTC in clinical practice. All efficacy and safety assessments in DECISION were standard variables and methods for clinical studies in oncology and widely recognised as valid, reliable, accurate and relevant to clinical practice.

The DECISION trial demonstrated the efficacy of sorafenib in locally advanced or metastatic RAI-R DTC by meeting its primary endpoint, showing a statistically significant, clinically meaningful prolongation of PFS based on central assessment in patients treated with sorafenib compared to placebo (median PFS 329 days [10.8 months] versus 175 days [5.8 months], HR 0.59 (95% CI: 0.45, 0.76, one-sided $p<0.0001$). Treatment with sorafenib was associated with a 41% risk reduction of disease progression or death compared to treatment with placebo (hazard ratio [HR] 0.59, 95% CI 0·45–0·76; $p<0·0001$). All subgroup and sensitivity analyses for PFS were consistent and supportive of the overall primary analysis results of PFS.

At the time of study initiation in 2009, promising results from phase II studies with sorafenib in RAI-R DTC meant that sorafenib was included in the US National Comprehensive Cancer Network (NCCN) 2009 guidelines (version 1). This led to sorafenib use in routine clinical practice in a number of countries as a treatment for RAI-R DTC. In the opinion of leading experts in thyroid carcinoma at the time, the conduct of a placebo-controlled phase 3 study without the option for patients randomised to placebo to cross-over to open label sorafenib was unethical. Therefore, a provision for cross-over was included in the design of the study.

Crossover makes it difficult to detect and attribute improvements in overall survival (OS) associated with experimental treatment; hence, progression free survival (PFS) was chosen as the primary endpoint of the study and OS used as the key secondary endpoint. OS was analysed initially at the data cut-off date for the PFS endpoint (August 2012). At this time, median OS had not been reached for either arm. Further

analyses of OS, at 9 months and 36 months after the original data cut-off, showed a consistent separation of the KM curves in favour of sorafenib.

Other secondary endpoints included time to progression (TTP), disease control rate (DCR), and response rate (RR), which further assessed the ability of sorafenib to halt or slow disease progression. Sorafenib treatment produced a statistically significant improvement in time to progression (TTP), compared to placebo (11.1 months vs. 5.8 months, respectively; HR 0.56, 95% CI 0·43–0·72; p<0·0001), and disease control (DCR) and response rates (RR). Partial responses were observed in 12.2% of patients receiving sorafenib compared with 0.5% in the placebo arm (P<0.0001). Additionally, 42% of patients in the sorafenib arm had stable disease for ≥ 6 months compared to 33% with placebo. Notably most sorafenib-treated patients (77%) experiencing target lesion tumour shrinkage (vs. 28% of patients in the placebo arm).

Exploratory analyses of health utility values and HRQoL slightly favoured the placebo arm over sorafenib. When comparing active therapy to placebo in advanced cancer patients, a lower quality of life for the active therapy is an expected outcome, however when assessed with EQ-5D differences between sorafenib and placebo did not meet the minimally important clinical difference.

The safety profile and patient tolerability of sorafenib was also evaluated at every study visit throughout DECISION. Overall, AEs in DECISION 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.

The results of the DECISION trial are directly relevant to the progressive RAI-R DTC patients within routine clinical practice in England. Patients who were eligible to participate in DECISION included adults >18 years old with locally advanced or metastatic, RAI-R DTC (papillary, follicular, Hürthle cell and poorly differentiated) whose disease had progressed within the last 14 months. Patients had received no prior chemotherapy for thyroid cancer (with the exception of low dose chemotherapy for radiosensitisation), tyrosine kinase inhibitors, thalidomide or any of its derivatives. Additionally, DECISION participants had an ECOG PS ≤2; adequate TSH suppression (<0.5 mU/L); and adequate bone marrow, liver, and renal function. It is

reasonable to generalise the clinical benefit seen in the DECISION trial to patients in clinical practice in the UK. The extensive subgroup analyses within efficacy and safety support this view, indicating the robustness of the results of the DECISION study and applicability to a broad spectrum of patients.

The main issue for those involved in the treatment of progressive RAI-R DTC in the UK is the lack of effective treatment options available for patients. The option of sorafenib provides clinically meaningful and statistically significant prolongation of PFS, target lesion shrinkage with a manageable safety profile, giving a favourable benefit/risk profile. The use of sorafenib enables the potential to stabilise disease or induce a partial response, preventing or delaying some of the morbidity associated with disease progression whilst maintaining quality-of-life.

2.6 End of life consideration

In England and Wales there is no active treatment routinely available for patients suffering from RAI-R DTC. Best supportive/palliative care is the only treatment option for patients resulting in a high unmet need for this population.

RAI-R DTC is an ultra-orphan condition with an incidence of 225 patients per year (section 5), with sorafenib meeting the EMA's criteria for an ultra-orphan medicine for treating patients with RAI-R DTC when licensed. Upon appraisal by the SMC, sorafenib was approved under both ultra-orphan and end-of-life criteria.

Whilst changes to NICE's end-of-life criteria mean that orphan status is now not given explicit consideration, there is a strong justification that patients suffering from RAI-R DTC should be given end of life consideration.

1. **The treatment is indicated for patients with a short life expectancy, normally less than 24 months**

For the small number of patients who become refractory to radioactive iodine (5-15%) patient prognosis shifts from a manageable disease to one with a terminal diagnosis (2, 3) .

In the guidance it is noted that end-of-life is '*normally'* considered for patients with a life expectancy of less than 24 months. Median overall survival from DECISION and SELECT, the two pivotal phase III trials for treatments in this MTA show the following median overall survival in the placebo arm (after RPSFT correction for treatment crossover):

- SELECT: 19.1 months (95% CI: 14.3 months, not estimable) (20)
- DECISION: 34.26 months (95% CI: 29.7 months, 43.56 months) (13)

There are other reasons to believe that RAI-R should be considered an end-of-life condition.

- RAI-R DTC has a terminal diagnosis
- No active treatment options or additional lines of therapy are available
- RAI-R DTC meets the EMA criteria for an ultra-orphan population
- Extension of life sufficiently exceeds the 3-month criteria

2. There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment

Results from the economic model show sorafenib to increase life expectancy by 1.3 years versus BSC over a lifetime horizon (section 4). The BSC arm of the DECISION study was confounded by crossover, after adjustment for crossover, (RPSFT and IPE), sorafenib was found to extend median OS by 8.54 months (35).

Table 11: End-of-life criteria

Criterion	Evidence to support end-of-life
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	• Patients RAI-R DTC in the placebo arm of the SELECT trial have a median survival of 19.1 months (20)
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Estimates from the economic model show sorafenib to extend life by 1.3 years versus BSC over the lifetime horizon of the model. • Median overall survival in the DECISION study is extended by 8.54 months with sorafenib versus BSC.

3. Systematic Review and Indirect Comparison

Comparative assessment: indirect comparison

In the absence of head-to-head evidence versus lenvatinib, a systematic review was conducted to identify RCT evidence for sorafenib and lenvatinib. Based on the findings of the review an indirect treatment comparison was conducted based on the DECISION and SELECT phase III trials (the only identified RCTs).

Both DECISION and SELECT were confounded by treatment crossover, and as such results should be interpreted with a degree of caution. The indirect comparison found no statistical difference in overall survival between sorafenib and lenvatinib, [HR] = [redacted] (95% CI [redacted], [redacted]) for the treatment crossover corrected population, however this estimate is further confounded by post study anti-cancer treatment received by 37% of lenvatinib patients in the SELECT trial, and 20.3% of sorafenib patients in the DECISION trial. Lenvatinib was found to increase progression-free survival versus sorafenib in the ITC; however there is no evidence to suggest that this benefit translates into a statistical benefit in overall survival.

Safety

Safety outcomes assessed via the ITC found sorafenib to result in statistically fewer grade 3-4, and serious adverse events versus lenvatinib [HR] = [redacted] (95% CI [redacted], P<0.0001) and [HR] = [redacted] (95% CI [redacted], P<0.0001) respectively. Sorafenib was also found to result in fewer discontinuations due to adverse events, suggesting it to be a tolerable treatment [HR] = [redacted] (95% CI [redacted]).

These outcomes support sorafenib as 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.

Scenario analysis: Matched adjusted indirect comparison

A matched adjusted indirect comparison (MAIC) conducted by Tremblay et al was identified via the SLR. Whilst results of the feasibility assessment found an ITC to be

a robust approach, the use of population-adjustment was considered in a scenario analysis.

Using patient level data from the DECISION trial, sorafenib patients not meeting the SELECT inclusion criteria were removed from the Tremblay et al MAIC results, resulting in a closer alignment of populations. If population-adjustment is considered necessary, results from this analysis should be used, however analyses presented in this section suggest that this is not the case.

Results following this adjustment found improved PFS for lenvatinib, but no statistical difference in overall survival for [HR] = [redacted] (95% CI [redacted]).

3.1 Summary of systematic review and comparative evidence

3.1.1 Search strategy and sources

A systematic review was conducted to identify RCT evidence for the clinical effectiveness of sorafenib or lenvatinib in differentiated thyroid carcinoma, refractory to radioactive iodine. The search for clinical effectiveness data was undertaken using the following databases:

- Medline (from database inception to 02/11/2016)
- Embase (from database inception to 02/11/2016)
- Medline in process (from database inception to 02/11/2016)
- Cochrane Central Register of Controlled Trials (CENTRAL - from database inception to 03/11/2016)

In addition, proceedings from five major conferences were searched for relevant abstracts/posters, to include results of recent and updated trials:

- American Society of Clinical Oncology (ASCO) (2010, 2011, 2012, 2013, 2014, 2015, 2016 meeting abstracts)
- American Thyroid Association (ATA) (2009, 2011, 2012, 2013, 2014, 2015, 2016 meeting abstracts)
- European Thyroid Association (ETA) (2009, 2012, 2014, 2016 meeting abstracts)
- International Thyroid Congress (ITC) (2010, 2015 meeting abstracts)

- European Society for Medical Oncology (ESMO) (2010, 2012, 2014, 2015, 2016 meeting abstracts)

3.1.2 Study selection

The systematic review was conducted in 2 phases. The first review, conducted on the 20th September 2013, entailed a broad systematic review to inform on current management of RAI-R DTC. The second comprised of a systematic review of literature for RCT data published since the 2013 review (i.e. added to or updated in databases between 2013 and 2016). The update conducted on the 3rd November 2016, focused on identifying sorafenib or lenvatinib RCTs, when used as a single agent only, in RAI-R DTC, in line with the decision problem (including any studies directly comparing sorafenib and lenvatinib). Indirect comparisons of sorafenib and lenvatinib RCT data were also included to inform the approach to obtaining comparative efficacy and safety estimates.

Inclusion and exclusion criteria of the search are summarised in Table 12. The population of interest included adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine. Interventions included sorafenib and lenvatinib. As few clinical trials have been performed for these comparators in this context, dose was not included in the search criteria.

Data collection and abstract screening was conducted by two independent reviewers with differences to be reconciled by a third independent reviewer. Publications that appeared to be potentially relevant were ordered for a full review of the text and assessed for inclusion by two reviewers using the same approach as initial abstract screening. Data extraction of the included studies was also undertaken by two reviewer process with differences reconciled by an independent reviewer.

Table 12: Summary of inclusion/ exclusion criteria (PICOS framework)

Clinical evidence	Inclusion	Exclusion
Patient population	Adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine.	Patients with medullary or anaplastic thyroid cancer.
Interventions	Sorafenib or lenvatinib	Sorafenib or lenvatinib in combination with other agents.

Clinical evidence	Inclusion	Exclusion
Comparators	Placebo Best Supportive Care (BSC) [or other active agent]	-
Outcome measures	Efficacy outomes e.g. progression-free survival (PFS), overall survival (OS), Time to progression (TTP), disease control rate (DCR), response rate (ORR), duration of response (DOR). Safety outcomes e.g. adverse events Health-related Quality of life (HRQoL)	-
Study design	Randomised controlled Trials (RCTs) Indirect comparisons between sorafenib and lenvatinib RCT data	Single-arm studies. Observational study design including prospective, retrospective cohort studies, case series. Case reports, comments, letters, editorials, In vitro, animal, genetic or histochemical studies.
Restrictions	Language: English	Non-English studies

3.2 Indirect treatment comparison: Objectives and scope

3.2.1 Indirect comparison: objectives

In identifying approaches to informing a comparative assessment between sorafenib and lenvatinib, the following objectives were determined:

- Feasibility assessment of conducting an indirect treatment comparison to inform comparative effectiveness estimates for sorafenib and lenvatinib
- Assessment of the need for population-adjustment methods to control for any differences between identified RCTs.
- To conduct an indirect treatment comparison, or population-adjusted indirect comparison (based on evaluation of the feasibility assessment)

3.3 Indirect treatment comparison: Results

3.3.1 Search results

3.3.1.1 Search results: RCTs

Two phase III RCTs were identified as meeting the predefined inclusion criteria for the indirect comparison: phase III trial of sorafenib (DECISION) and the phase III trial of lenvatinib with placebo (SELECT). Both trials were conducted in patients with RAI-R DTC. Multiple publications were extracted for each trial, as updated results became available; these are presented in Table 13. Full details of the search strategy, and papers included/excluded at full paper review are presented in Appendix 7.4.

Table 13: RCTs identified via the systematic review

Drug	Comparator	Initial publication	Intermediary data cut	Latest data cut published
Sorafenib	Placebo	Brose et al(2014). (15)	Brose MS, et al. 2014; (14)	Brose M. (2016), (13)
Lenvatinib	Placebo	Schlumberger M. et al (2015) (25)	Guo M, 2016 (20)	No further publication

3.3.1.2 Search results: Indirect comparisons

The systematic review identified two studies indirectly comparing sorafenib and lenvatinib, based on the two identified RCTs, an indirect comparison conducted by Kawalec et al (36) and a population adjusted matched adjusted indirect comparison (MAIC) conducted by Tremblay et al (37). These were both reviewed to inform the methods of the assessment, with the MAIC discussed further in section 3.3.9.

3.3.2 Indirect treatment comparison: Feasibility protocol

Once the relevant studies were identified and all baseline and study characteristics extracted, a feasibility assessment was performed. The purpose of the feasibility assessment was to assess the appropriateness of identified studies for conducting an indirect, or matched-adjusted indirect comparison. The feasibility assessment adhered to the following steps:

- Identification of baseline characteristics in the sorafenib data that were treatment effect modifiers for the efficacy endpoints of PFS and/or OS

- Review of differences in baseline characteristics that could be considered treatment effect modifiers, and study design versus the identified comparator trials

3.3.3 Indirect comparison: Feasibility results

The identification of potential treatment effect modifiers on the primary efficacy outcomes (OS and PFS) were explored via a nested cox regression. Based on results, ECOG status and site of metastasis were shown to be statistically significant effect modifiers for OS. Surgery, metastatic disease, and median cumulative radioiodine activity were shown to be statistically significant for progression-free survival. The full results of this feasibility assessment and comparison of patient populations are presented in Appendix 7.6.

A comparison of the inclusion/ exclusion criteria and study design was also conducted to assess differences between the trial populations. Whilst inclusion criteria were deemed similar between studies, some important differences were noted:

- **Post-study anti-cancer treatment:** Overall survival results of the ITC are likely to be confounded by the percentage of patients receiving post-treatment anti-cancer therapies. In the SELECT trial 37% of patients in the lenvatinib arm and 40% of patients in the placebo arm received subsequent anticancer treatment (38). This compares to 20.3% and 8.6% respectively in the DECISION trial (28). The SELECT trial occurred more recently than the DECISION trial, and as a result patients enrolled in SELECT are likely to have received subsequent targeted therapies as opposed to chemotherapies likely to be received after sorafenib in DECISION. In the ITC the effect of this bias is likely to inflate the overall survival results for lenvatinib relative to sorafenib. As only aggregate data was available on post-treatment anti-cancer therapy this difference could not be addressed via population adjustment.

- **Inclusion of patients in SELECT with prior TKI therapy:** Patients enrolled in the SELECT trial were allowed prior treatment with a TKI/VEGF therapy (25% lenvatinib, 20% placebo patients), resulting in a percentage patients having previously received first-line treatment with sorafenib. Prior TKI/VEGF

treatment was not allowed in the DECISION trial. Whilst this highlights a difference in trial populations, a subgroup analysis from SELECT shows that prior TKI/VEGF therapy did not affect median PFS in the placebo arm, with both TKI naïve and second-line patients having PFS of 3.6 months. No evidence was found to justify population adjustment on this basis.

- **Comparability of RECIST 1.0 and 1.1 used for assessment of progression free-survival:** Patients in the DECISION trial were assessed for disease progression under RECIST criteria 1.0, whilst patients in the SELECT trial were assessed using the updated RECIST criteria 1.1. Additional criteria were introduced in RECIST 1.1 for the assessment of progressive disease. In addition to a 20% increase in sum diameter of all target lesions required in RECIST 1.0, RECIST 1.1 requires an additional 5 mm absolute increase in target lesion to guard against the 'overcalling' of progressive disease (39).

- The comparability of RECIST criteria has been assessed via a pooled analysis conducted by Kim et al (40), however due to the very small number of DTC patients included in the study, it is very uncertain as to the effect of using the updated criteria on the assessment of progressive disease in RAI-R DTC. With the updated RECIST criteria potentially increasing the time to progression, this uncertainty if addressed would likely favour sorafenib. This difference in study design could not be addressed via population adjustment.

Based on the results of the feasibility assessment (appendix 7.6) it was concluded that an ITC could be conducted to inform comparative efficacy estimates for sorafenib versus lenvatinib. Treatment effect modifiers for OS and PFS were identified in the DECISION trial; however these variables were reasonably well balanced between DECISION and SELECT trials. It could not be confirmed that the between trial differences in these variables were clinically meaningful to the extent that an ITC would not be informative. Population adjustment methods can introduce as well as address uncertainty. This is discussed further in section 3.3.9.

3.3.4 Outcomes selected for the analysis

The following efficacy and safety outcomes were selected for the indirect comparison:

Efficacy endpoints

- Overall survival (OS)
- Progression free survival (PFS)

Safety outcomes

- All grade 3-4 adverse events (AEs): AEs relevant for the economic evaluation (for application of costs and disutilities)
- All serious adverse events: AEs likely to result in hospitalisation, to be life threatening or result in death
- Treatment discontinuation due to adverse events

These outcomes were selected for the following reasons:

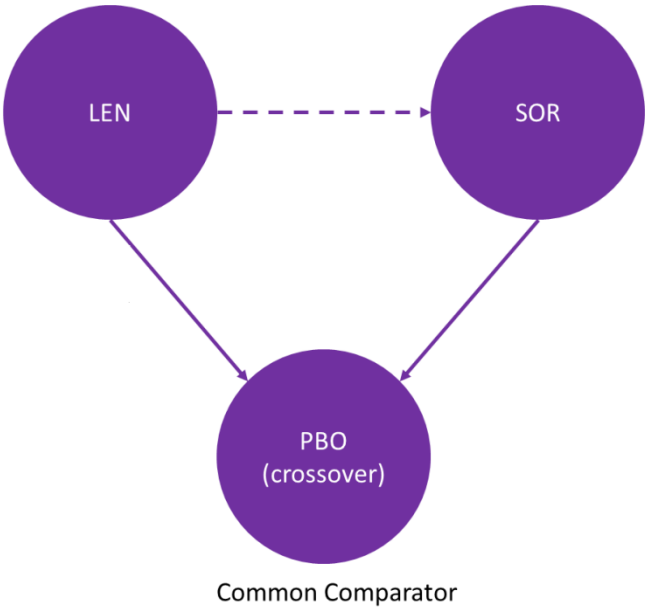
a) Priority and relevance of the outcome, with regards to NICE scope and in particular these represent key outcomes included in the economic model

b) Availability of data as a clearly defined outcome, progression-free survival (PFS) and overall survival (OS) were reported in both the DECISION and SELECT trials.

3.3.5 Indirect comparison methods

A common reference indirect treatment was used for the ITC in this analysis, as there was only one trial available for each comparator and key differences existed between the clinical trial populations. In this indirect comparison, sorafenib was compared to lenvatinib through a placebo anchor. The ITC network based on these selected studies are presented in Figure 6.

Figure 6: ITC network



A classical frequentist ITC was conducted with 95% confidence intervals. The Bucher method was applied to obtain the ITC hazard ratios for the two primary measures of efficacy, PFS and OS, and risk ratios for safety endpoints (41).

3.3.6 Data selected for the analysis

For the DECISION trial (sorafenib), three data cuts were published: (1) the initial in August 2012, (2) the intermediary in May 2013, and (3) the last in July 2015. For the SELECT trial (lenvatinib), only two data cuts were published: (1) the initial in November 2013, and (2) the last (included as 'intermediary' here) in June 2014. The follow-up periods are similar for the intermediary data cuts, which is important (especially for OS), as to avoid major crossover bias.

Median follow-up periods:

- Primary analysis: Sorafenib 17.4 months and 17.1 months for Lenvatinib
- Intermediary analysis: Sorafenib 24.1 months and 23.6 months for Lenvatinib
- Third cut: Sorafenib 36 months, Lenvatinib not available

Overall survival

Overall survival data in the ITC was based on 'crossover corrected' values. Since patients in placebo group of both trials were allowed to crossover to active treatment

upon disease progression, adjustment for crossover bias is required for both studies. The Rank Preserving Structural Failure Time Model (RPSFTM) was selected to adjust for crossover as this is the only crossover-adjusted data published for lenvatinib.

The intermediate data cut was selected for the OS analysis, due to the alignment in follow-up period (24.1 months and 23.6 months) between studies, and the lack of subsequent data available from the SELECT trial. Assessing efficacy at a comparable time point removes any time related bias in interpreting the crossover adjustment and is a recognised approach when follow-up is related to treatment effect (which is likely when cross-over adjustment is employed).

Progression free-survival

For progression-free survival, the first ('initial') data cut was used since no later information were available for the DECISION trial for this endpoint. Adjustment for crossover bias was not required for progression free survival as in both trials patients could only crossover upon progression.

Safety outcomes

Safety endpoints were based on the primary data cut for both sorafenib and lenvatinib using the ITT population. Subsequent data cuts did not record safety outcomes.

3.3.7 ITC analysis results

3.3.7.1 Efficacy results

Overall Survival

No statistically significant difference in overall survival were observed between lenvatinib and sorafenib, HR [redacted] (95% CI [redacted], [redacted]) for the ITT population, and [redacted] (95% CI [redacted], [redacted]) for the crossover-corrected population. Table 14 and Figure 7 present the ITC efficacy results for overall survival.

Results show wide overlapping confidence intervals between sorafenib and lenvatinib, showing no statistically significant difference between treatment options.

Whilst these results have been adjusted for crossover, they cannot be adjusted to reflect the greater percentage of patients receiving anti-cancer treatment, and the nature of these treatments in the SELECT trial.

Table 14: ITC results: Overall survival

	Sorafenib/Placebo			Lenvatinib/placebo			Sorafenib/Lenvatinib		
	HR	CI-	CI+	HR	CI-	CI+	HR	CI-	CI+
ITT	0.800	0.54	1.19	0.730	0.500	1.070	[redacted]	[redacted]	[redacted]
OS (RPSFT adjusted)	0.690	0.49	0.99	0.530	0.340	0.820	[redacted]	[redacted]	[redacted]

Figure 7: Overall survival: Forest plot

[redacted]

Progression-free survival

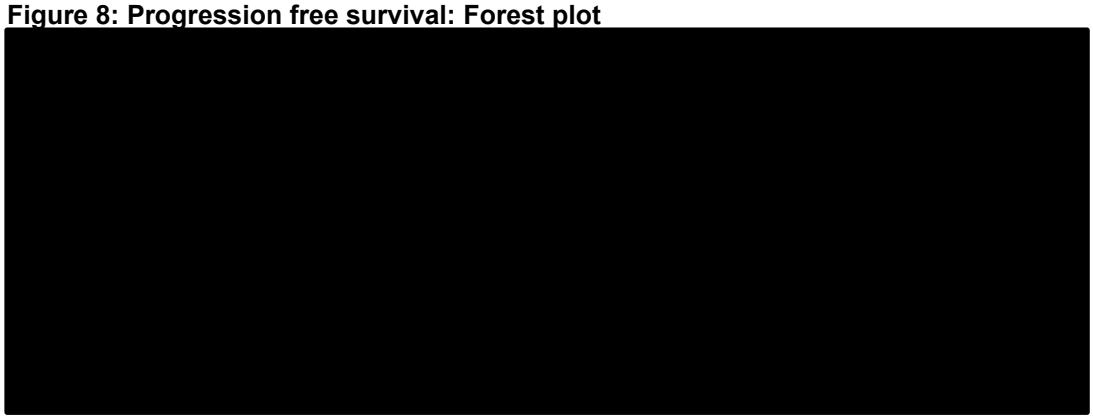
Table 15 and

Figure 8 present the ITC results for progression-free survival. The hazard ratio for sorafenib versus lenvatinib was [redacted] (95% CI [redacted]). It is not known the extent to which this analysis is affected by the differences in criteria used to assess progressive disease.

Table 15: ITC results: Progression free survival

	Sorafenib/Placebo			Lenvatinib/placebo			Sorafenib/Lenvatinib		
	HR	CI-	CI+	HR	CI-	CI+	RR	CI-	CI+
ITT	0.590	0.45	0.76	0.210	0.140	0.310	[redacted]	[redacted]	[redacted]

Figure 8: Progression free survival: Forest plot



3.3.7.2 Safety results

Results from the ITC comparing sorafenib to lenvatinib show a statistically significantly lower risk of grade 3-4 adverse events, and serious adverse events [redacted](95% CI [redacted], [redacted] p<0.001), and [redacted] (95% CI [redacted], [redacted] P<0.001) respectively.

These results show sorafenib to have a statistically superior safety profile in respect to adverse events. In the SELECT trial 76% of the patients had grade 3 or higher treatment-related toxic events, and there were an increased number of deaths during lenvatinib treatment, with 6 of the 20 deaths in the lenvatinib arm appearing to be treatment related (25). Table 16 presents the naïve and ITC safety results for all grade 3-4 AEs, whilst serious AEs are reported in Table 17 as hazard ratios and 95% confidence intervals.

Additionally sorafenib was shown to be associated with a lower risk of treatment discontinuation due to adverse events [HR] = [redacted] (95% CI [redacted], [redacted]), the results of this analysis are presented in Table 18

The safety results from the ITC 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.

Figure 9: Forest plot: comparative safety outcomes (sorafenib versus lenvatinib)

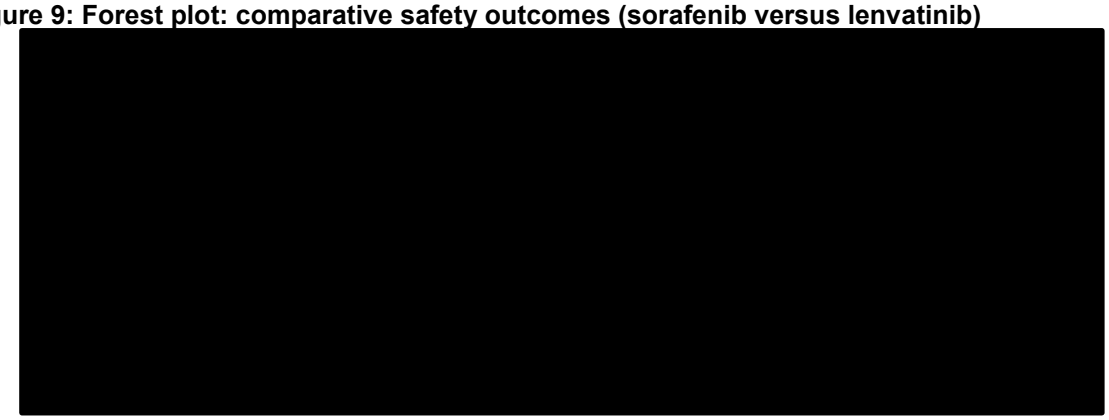


Table 16: ITC results: Grade 3/4 adverse events

	Treatment	Control arm	HR	CI-	CI+
Direct comparison	sorafenib	placebo	[redacted]	[redacted]	[redacted]
	lenvatinib	placebo	[redacted]	[redacted]	[redacted]
ITC	sorafenib	lenvatinib	[redacted]	[redacted]	[redacted]

Table 17: ITC results: Serious adverse events

	Treatment	Control arm	HR	CI-	CI+
Direct comparison	sorafenib	placebo	[redacted]	[redacted]	[redacted]
	lenvatinib	placebo	[redacted]	[redacted]	[redacted]
ITC	sorafenib	lenvatinib	[redacted]	[redacted]	[redacted]

Table 18: Discontinuations due to adverse events

	Treatment	Control arm	HR	CI-	CI+
Direct comparison	sorafenib	placebo	[redacted]	[redacted]	[redacted]
	lenvatinib	placebo	[redacted]	[redacted]	[redacted]
ITC	sorafenib	lenvatinib	[redacted]	[redacted]	[redacted]

3.3.8 ITC limitations

Limitations regarding potential differences in baseline characteristics and study design are reported under ITC feasibility (section 3.3.3).

3.3.9 Scenario analysis: Matched adjusted indirect comparison

Background

The SLR identified a matched adjusted indirect comparison (MAIC) conducted by Tremblay et al (37) (section 3.1).

A MAIC differs from an ITC by using individual patient level data (IPD) and propensity scoring methods to adjust for between-trial differences in baseline characteristics. Whilst the approach can be helpful in addressing high levels of heterogeneity between trials, the approach can also introduce further uncertainty through the assumptions made (42).

NICE DSU guidance (42) stipulates that prior to adjustment of trial populations, evidence must be provided to show:

i) there are grounds for believing that one or more of the covariates is an effect modifier, and;

ii) there is a sufficient imbalance in those effect modifiers to result in a material bias, in relation to the observed relative treatment effect modifiers.

Whilst differences in baseline characteristics and study design were identified in section 3.3.3 there was no evidence that differences between populations were clinically meaningful, or that differences between studies could be addressed via population adjustment.

Tremblay et al MAIC: Results

Matched adjusted indirect comparisons use patient level data to adjust a trial population to that of the comparator. In Tremblay et al (37) the population of the SELECT trial was adjusted through the balancing of baseline characteristics, to align with the population of the DECISION trial.

A strong convergence in results is observed when comparing the ITC results (reported in section 3.3.7) and results of the Tremblay et al MAIC. This is consistent with the ITC in finding no significant difference between treatments in overall survival, with progression-free survival favouring lenvatinib.

Based on the results presented in Table 19 it is not apparent that the small change in point estimates obtained via the MAIC is worth the cost of introducing additional uncertainty. Limitations of MAICs include the selection of patients according to their baseline characteristics; this can break randomisation when variables used in the

analysis are not pre-specified as randomisation variables, and a reduction in the sample size driving comparative estimates.

Table 19: Tremblay 2016 (37): Matched-adjusted indirect comparison results

	Sorafenib/Placebo			Lenvatinib/placebo			Sorafenib/Lenvatinib*		
	HR	CI-	CI+	HR	CI-	CI+	HR	CI-	CI+
Overall survival	0.69	0.49	0.99	0.51	0.3	0.82	[redacted]	[redacted]	[redacted]
Progression-free survival	0.59	0.45	0.79	0.19	0.13	0.29	[redacted]	[redacted]	[redacted]

*Direction of analysis inverted from publication, NR: Not reported

Tremblay et al: Assessment of MAIC approach

The SELECT trial (lenvatinib) population included both TKI experienced and TKI naïve patients, whereas the DECISION trial population (sorafenib) included only TKI naïve patients. Due to the lack of population overlap of TKI experienced patients; it is impossible for a MAIC from the sorafenib perspective to generate estimates for the full lenvatinib trial population through population adjustment.

Therefore the matching perspective employed in Tremblay et al (37) is considered to be superior to potential matching using DECISION patient level data. This is confirmed through inference made from the NICE DSU on a previously conducted MAIC, which noted that when populations cannot completely overlap after MAIC complete matching cannot take place (42).

Tremblay et al: Adjustment to MAIC

The MAIC conducted by Tremblay et al (37) adjusted the lenvatinib patient level data to match the patients enrolled in the sorafenib clinical trial. However the analysis was unable to match to the sorafenib published data for certain inclusion criteria specific to the SELECT trial, creating a misalignment in the matching of trial populations.

Patients with head and neck metastasis, those who did not undergo prior thyroid surgery, and those who did not have metastatic disease were either excluded from the lenvatinib population or information on these characteristics were not presented in the SELECT trial publications.

An additional analysis was conducted to use patient level data from the DECISION trial to more closely align to the population considered in the MAIC conducted by Tremblay et al (37) .

Excluding patients from DECISION who had head and neck metastasis, in addition to the small number of patients who did not undergo prior thyroid surgery and those that did not have metastatic disease more closely aligns trial populations ensuring a more reflective comparative assessment.

The results of this adjustment presented in Table 20 again highlight that whilst a benefit is observed in terms of progression free survival for lenvatinib, it is not apparent that this translates into an overall survival benefit, with no statistically significant difference in overall survival between the two trial populations and wide overlapping 95% confidence intervals.

Should population adjustment be deemed appropriate in this evaluation, it should be this updated analysis that is considered the most robust in terms of alignment between trials. Results using this analysis are presented as a sensitivity analysis in the economic evaluation (section 4.10).

Table 20: Tremblay et al. (2016) MAIC after exclusion (Head met, Non-Metastatic, Surgery)

	Sorafenib/Placebo			Lenvatinib/placebo			Sorafenib/Lenvatinib		
	HR	CI-	CI+	HR	CI-	CI+	HR	CI-	CI+
Overall survival									
Progression -free survival									

4. Cost effectiveness

4.1 Published cost-effectiveness studies

4.1.1 Identification of studies

A systematic review of the literature was performed to identify any cost-effectiveness studies involving sorafenib or lenvatinib in the treatment of RAI-R DTC. As per the clinical systematic review this was conducted in two phases: a broad systematic review in 2013 to inform on current management of DTC, and an update to the review conducted in November 2016 focusing on cost effectiveness studies with sorafenib or lenvatinib versus placebo or best supportive care or sorafenib versus lenvatinib in RAI-R DTC. The search is outlined briefly below with full details provided in Appendix 7.5.

4.1.2 Search strategy

The cost-effectiveness search was undertaken using the following sources: Medline, EMBASE, Cochrane libraries, EconLIT, and proceedings from ASCO, ATA, ETA, ITC, ESMO and ISPOR annual conferences. Studies were included if they met at least one of the PICOS criteria (see Appendix 7.5). Data collection, abstract screening, and data extraction were conducted in the same way as described for clinical evidence identification e.g. two independent reviewers, reconciliation by third independent person (section 3.1.2). Excluded publications were disregarded. A flow diagram of the numbers of records included and excluded at each stage is provided in Appendix 7.5.

The search in 2013 did not identify any publications of cost-effectiveness studies in RAI-R DTC. The November 2016 search yielded 67 unique citations in total from EMBASE / Medline / Cochrane / EconLit databases. From the review of conference abstracts, 15 citations were identified. After removing duplicates, 76 citations were screened at title level and 20 at abstract level. (summarised in Appendix 7.5). Four abstracts provided descriptions of cost-effectiveness analyses involving sorafenib and / or lenvatinib in RAI-R DTC (Huang 2016a (43) and 2016b (44); Erdal 2015 (45); Tremblay 2016 (46)).

Upon review none of the studies identified employed a UK perspective, and therefore were excluded from further consideration, deemed not relevant to decision making in England or Wales.

4.2 De novo analysis

4.2.1 Patient population

The economic evaluation considers patients with differentiated thyroid cancer (DTC) who are refractory to RAI, based on the inclusion and exclusion criteria of the DECISION trial (15).

For the indirect comparison with lenvatinib data from the SELECT trial (25) is used. The inclusion criteria for this trial are broadly similar to that of the DECISION trial, however there are important differences in the study design which may bias efficacy estimates, and may not be controlled for by population-adjustment methods. These are discussed in the ITC feasibility assessment (section 3.3.3).

4.2.2 Model structure

The economic model was developed using a cohort state transition model with survival partition approach. This technique is commonly used in modelling oncology, and is appropriate in capturing progressive, chronic conditions which are described with clinical outcomes requiring an ongoing, time-dependent risk, such as progression and death (47, 48). Unlike a Markov model, which also uses health states, cohort partition models do not require the estimation and use of transition probabilities. Instead, the number of patients in each health state is calculated directly from each comparator's progression-free survival (PFS) and overall survival (OS) curves. Additional assumptions are only made to estimate the extrapolated portion of the curves until all patients have died. This ensures that the fitted PFS and OS match the treatments' trial data, and does not require the model to assume that there is a definite relationship between PFS and OS as would be required in a Markov model to calculate transition probabilities between "progressed" and "dead" health states. For these reasons, the cohort partition modelling technique has been used, where PFS and OS are primary clinical endpoints.

In each cycle of the model, patients are assigned to one of three mutually exclusive health states according to the proportion of patients who are ’progression-free‘, ’post-progressed‘, or ’dead‘ (Figure 10). Patients start in the ‘progression-free’ health state and on sorafenib or best supportive care (BSC) or in the indirect comparison also lenvatinib. Within each cycle of the model, patients can either:

- Stay in that health state and on treatment or discontinue treatment and remain in the health state;
- Progress (‘progressed’) or
- Die (‘dead’)

Patients are not allowed to move backwards in the model. Patients can move between health states every cycle.

Figure 10: Model structure

Each health state and treatment status is associated with a corresponding resource use and utility. Expected costs and outcomes are calculated across cohorts according to the chosen treatment regimen. All patients on treatment are exposed to the risk of adverse events (AEs). The consequences of AEs are calculated as costs decrements for patients on treatment, while the utilities from the DECISION trial already include disutilities due to AEs.

The proportion of patients in each health state are determined by the survival functions for PFS and OS derived from the DECISION trial for sorafenib and BSC, and by applying hazard ratios from the indirect treatment comparison (ITC) to the sorafenib curves to derive values for lenvatinib. The proportion of patients in the ’progressed-free‘ health state is equal to the survival function value for PFS, while the proportion of patients in the “dead” health state is equal to 1 less the survival

function value for OS. Lastly, the proportion of patients in the ’progressed’ health state is equal to the survival function of OS – PFS (

Figure 11,

Figure 12).

According to the DECISION trial protocol, patients were allowed to continue on treatment until progression or unacceptable toxicity (15). The model allows patients on sorafenib or lenvatinib to discontinue treatment based on the survival function for time to treatment discontinuation (TTD) observed in the DECISION trial; this survival function captures multiple reasons for treatment discontinuation, such as progression, AEs, or physician discretion. However, the model also allows testing of alternative assumptions.

The health status of the patient can best be described by progression status and death, thus, the health states in the economic model were defined as no-progressive disease, progressed and death. In addition to progression status and death, receiving active treatment or not may also influence the quality of life (QoL) and, thus, utility values of the patient and resource use. Therefore, the no-progressive disease health state was further divided based on whether patients receive treatment or have discontinued, such that different costs could be assigned according to the treatment status.

The model uses a 28-day cycle length. This cycle length was selected to match the safety assessment (every 28 days) and efficacy assessment (every 56 days) from DECISION trial, and dosing schedule of sorafenib, allowing for accurate modelling of the costs and utilities. Treatment with lenvatinib is also given in 28 day cycles. Patients treated with sorafenib accrue the 28-day sorafenib pack cost on the first day of each cycle, thus accounting for any potential treatment wastage. Utilities are also applied in line with the DECISION trial, which collected EQ-5D at every monthly cycle (28). Additionally, this method allows drug cost and utility application as per the clinical assessment schedule. For example, a patient progressing in the second cycle of the model will have the routine care costs of a post-progression patient from

there forward, and will no longer accrue AE costs; the model considers the possibility that the patient would continue to have the same “on-treatment” resource use patterns until progression was confirmed.

Costs and utilities are applied to half-cycle corrected patients. The progression-free life-years, life-years, and QALYs are accrued for half-cycle corrected patients. At the end of the modelled time horizon, all costs and health benefits are summed for each treatment arm.

The economic model is designed to conduct the CEA in accordance with the requirements of the NICE guidance (49) and the ISPOR-SMDM guidelines (50). The economic model was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA).

Figure 11: Cohort survival partition modelling technique

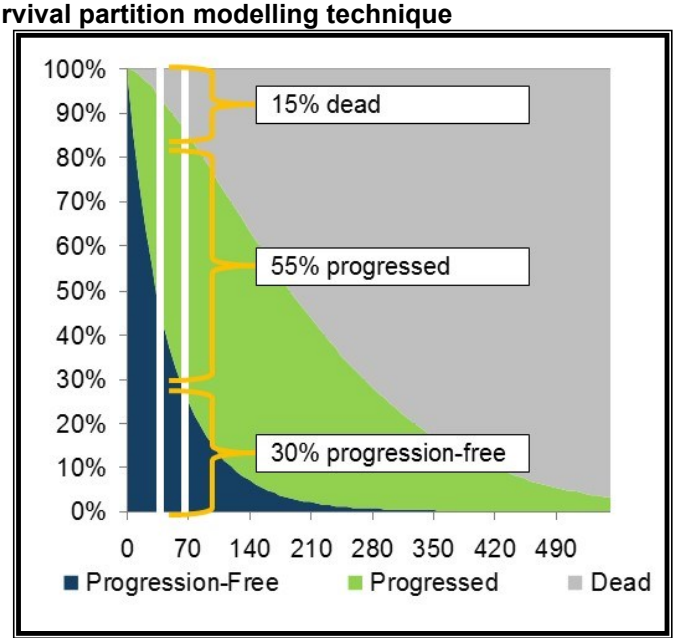


Figure 12: Schematic representation of the cohort survival partition model

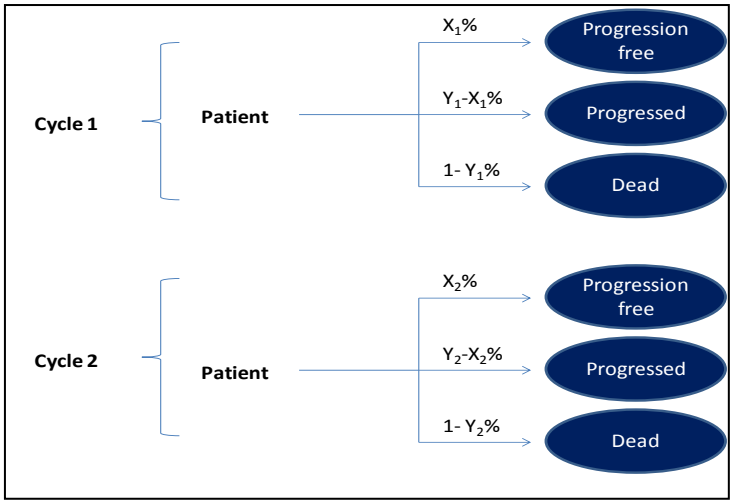


Table 21: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (30 years)	The reference case stipulates that the time should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. At this point less than 0.1% and 0.5% of patients on BSC and sorafenib arm respectively are alive with any of the distributions.
Were health effects measured in QALYs; if not, what was used?	Yes	According to NICE reference case
Discount of 3.5% for utilities and costs	Yes	According to NICE reference case
Perspective (NHS/PSS)	Yes	According to NICE reference case
PSS, personal social services; QALYs, quality-adjusted life years		

4.2.3 Intervention technology and comparators

Sorafenib is an oral kinase inhibitor of VEGFR-1, -2, and -3, RET (including RET/PTC), RAF (including BRAFV600E), and platelet-derived growth factor receptor beta. The efficacy and safety of sorafenib has been assessed in a multicentre, randomised, double-blind, placebo-controlled, phase 3 study (DECISION; NCT00984282), where compared to placebo it has significantly improved PFS (hazard ratio, 0.59; 95% confidence interval, 0.45–0.76; P<0.0001; median 10.8 vs. 5.8 months, respectively). OS was immature and crossover from placebo to sorafenib was allowed (see section 2).

BSC is the base case comparator in this analysis with lenvatinib included as a comparator through an indirect treatment comparison (see section 3).

BSC is defined as concurrent use of radiotherapy (10.6% of sorafenib and 21.4% on placebo). The majority of the patients (~14%) had radiotherapy in bone lesions (28). As per the DECISION trial protocol, disease progression in bone lesions is defined as the bone lesions that require external radiation (EBRT). As EBRT is considered a concurrent therapy to sorafenib, it is not considered to be a comparator in the cost-effectiveness analysis. Instead, it is included as part of BSC in both arms of the model.

Lenvatinib is an oral, multi-targeted tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3, FGFRs 1 through 4, PDGFR α, RET, and KIT signalling network (51). The efficacy and safety of lenvatinib has been assessed in a multicentre, randomized, double-blind, placebo-controlled, phase 3 study (SELECT) (25).

The molecular targets of sorafenib and lenvatinib do not completely overlap. Sorafenib inhibits Raf serine/threonine kinases and the tyrosine kinase receptors FLT3 (both present in tumour cells) and PDGFRβ (present in tumour vasculature), whereas lenvatinib does not.

At the time the DECISION study was conducted, there were no other TKIs licensed for use in thyroid cancer, therefore TKI experienced patients could not be enrolled. In SELECT a TKI experienced population was shown to derive clinical benefit. In terms of maximising treatment benefit, based on the differences in mechanism of action, treatment sequencing may be considered.

A recent clinical publication (February 2017) recognises differences in the two treatments could lead to benefits for different patient types. For example the author notes that if a patient experiences an infiltration or a compression of a vital organ such as the trachea it could be better to use a drug with a slower activity such as sorafenib to reduce the risk of fistula (52).

4.2.4 Treatment continuation rules

According to both the DECISION and the SELECT trial protocols, patients were allowed to continue on treatment until progression or unacceptable toxicity. For development of the economic model, this was confirmed with a UK clinical expert to be current practice in the UK.

4.3 Clinical parameters and variables

4.3.1 Incorporation of clinical data into the model

Clinical data (i.e., PFS, OS curves, treatment continuation curves and AE risks) were directly obtained from the DECISION trial, to inform the model's efficacy and safety parameters for each of the sorafenib and BSC comparators. Clinical data on the hazard ratios (HRs) for PFS and OS to inform inputs for the model's efficacy and safety parameters for the indirect comparison with lenvatinib were obtained through an indirect treatment comparison (section 3.2) . A summary of clinical variables applied in the economic model is reported in Table 22.

Table 22. Summary of clinical parameters applied in the economic model

Variable	Treatment	Data source
Overall survival	Sorafenib BSC	DECISION trial for direct comparison May 2013 data-cut
	Lenvatinib	Indirect treatment comparison based on the DECISION (May 2013 data-cut) and SELECT (June 2014 data-cut) trials
Progression-free survival	Sorafenib BSC	DECISION trial for direct comparison
	Lenvatinib	Indirect treatment comparison based on the DECISION and SELECT trials
Time on treatment	Sorafenib	DECISION trial
	Lenvatinib	Sorafenib curve calibrated for median time on treatment for lenvatinib in SELECT trial publication
AEs	Sorafenib	DECISION trial publication
	Lenvatinib	SELECT trial publication

The efficacy inputs of PFS and OS matched the primary and secondary outcomes of the DECISION trial. However, because the model evaluates the impact of treatment on costs and health benefits over a lifetime horizon, and PFS and OS curves were not complete, they needed to be extrapolated beyond the end of the DECISION trial follow-up. The recommendations by the Decision Support Unit (DSU) for NICE, published June 2011 and updated March 2013, as well as recommendations from published literature, suggest that PFS, OS and other time-to-event outcomes need to be extrapolated using parametric models, unless survival data from the clinical trial

are complete. Parametric models assume that survival times for patients follow a given theoretical distribution (53, 54).

Methods

Overall survival and progression-free survival

Parametric survival analyses were conducted for the following efficacy data from the DECISION trial:

- OS corrected for crossover
- PFS based on the primary definition of PFS: (time to first observed disease progression (radiological as determined by central radiological review or clinical progression due to bone lesions that required external radiation, whichever was earlier) or death (due to any cause)
- PFS based on the secondary definition of PFS: (time to first observed disease progression (radiological as determined by investigator or clinical progression due to bone lesions that required external radiation, whichever was earlier) or death (due to any cause))

Extrapolations were performed by fitting parametric models to the observed time-to-event data from the DECISION trial (database cut-off May 2013), using the PROC LIFEREG procedure in SAS (SAS Institute Inc., Cary, NC). Commonly used parametric survival models (Weibull, log-normal, log-logistic, exponential, gamma and Gompertz distributions) were fitted to the observed data. In all analyses, weeks were used as the time unit corresponding to the model cycle length.

The steps followed to conduct parametric survival analyses are described below:

First, an exploratory analysis was conducted where the fit of the distributions was tested using parametric plots, observed and predicted plots, long-term projections and fit statistics (i.e., Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)) for each treatment arm (sorafenib and BSC and a combined model for both groups with treatment as a predictor). The proportional hazard assumption was tested using log-cumulative hazards plots and by including an interaction term of log (time) and treatment into a Cox Proportional Model. Based on these analyses,

the best fitting distribution for the observed data was chosen. Diagnostic plots and fit statistics were used to identify plausible fits; graphs of fit against the observed data provided an assessment of internal accuracy, and long-term projections served to assess the clinical plausibility of the fits (55).

Where the exploratory analysis showed that the optimal fit for each treatment arm was based on the same distribution and that the shapes of these fits were similar, modelling the two trial arms together including a treatment indicator as a predictor in the model was considered. Otherwise the treatment arms were chosen to be modelled separately. The choice and justification on the choice of modelling treatment arms separately or together is provided in section 4.3.5.

4.3.2 Time to treatment discontinuation

In clinical practice patients stop treatment with both lenvatinib and sorafenib at progression[2], thus the model assumes that the time to treatment discontinuation (TTD) curve reflects the discontinuations observed in the double blinded period for both sorafenib and lenvatinib. The TTD curve captures multiple reasons for treatment discontinuation, such as progression, AEs, or physician discretion.

However in the sensitivity analyses, TTD included patients with open label sorafenib use. This does not reflect the clinical practice, nor the SELECT trial for lenvatinib (25). In addition, the reporting of the data for the open label period of the DECISION trial is limited as sorafenib use was not followed up throughout the open label period. In case of an absence of treatment data patients were often assumed to be on treatment, which would overestimate the duration. However to explore the effect of the treatment duration, an increased TTD was estimated including the open label use assuming patients discontinued by the end of the open label period.

TTD survival data were not available for the SELECT trial; however median treatment duration (13.8 months) was reported in the trial publication (25). This duration is shorter than the median PFS (18.3 months) demonstrating that, similarly to DECISION trial, patients discontinue treatment before progression. However the treatment duration reported included patients both on first line and second line treatment. This would potentially underestimate the treatment duration on first line

[2] Confirmed with UK clinical expert

lenvatinib, since patients on average are likely to be on treatment for a shorter amount of time in second line. To assess TTD for lenvatinib, the sorafenib curves were calibrated to go through the observed median duration, assuming the same shape for lenvatinib as for sorafenib resulting in a HR of 0.729 (see Appendix 7.9).

A time to treatment discontinuation (TTD) curve defined as time to treatment discontinuation or progression in the DECISION trial (database cut-off May 2013) was complete, extrapolation and thus parametric survival analysis was not required. The model uses the Kaplan-Meier product-limit survival estimates for the 28-day cycles.

4.3.3 Adverse events

Number of patients with grade 3 and 4 AEs were taken from the clinical trials (DECISION and SELECT) and rates of each AE were estimated (Table 23). Rates were transformed into probabilities.

Only those grade 3 or 4 AEs were included that occurred in more than 5% of the patients in the sorafenib arm of the DECISION trial or in the lenvatinib arm of the SELECT trial publications and were assumed to have cost consequences. Rarer AEs were assumed not to have important cost consequences on a population level. Additionally, since AEs were not reported separately for grades 3 and 4 for lenvatinib, all grade 3 and 4 lenvatinib AEs were assumed be grade 3 AEs. This will potentially underestimate the cost of adverse events for lenvatinib.

Table 23: Rate of adverse events

Adverse Event	Grade 3 Adverse Event Rate (per 28 days)			Grade 4 Adverse Event Rate (per 28 days)		
	BSC	Sorafenib	Lenvatinib	BSC	Sorafenib	Lenvatinib
Hypertension	0.43%	0.76%	3.55%			Reported together with grade 3 AEs
Fatigue	0.14%	0.44%	0.64%		0.04%	
Weight loss	0.19%	0.58%	0.67%			
Hand-foot skin reaction	--	1.64%	0.23%			
Diarrhoea	0.09%	0.51%	0.55%		0.04%	
Hypocalcaemia	0.05%	0.47%	0.18%	0.14%	0.25%	

Source of data: DECISION trial Clinical Study Report, SELECT trial publication
Includes both grade 3 a 4 AEs

4.3.4 Correction for crossover

The OS endpoint is defined as the time from date of randomisation to date of death due to any cause. The DECISION trial allowed crossover of patients from the placebo arm to the treatment arm after progression (56). Since the DECISION trial conducts intent-to-treat (ITT) analysis, the OS curve for the placebo arm includes patients who have crossed over to the sorafenib arm (56) . Correction for this crossover in the placebo arm was evaluated in a secondary analysis using the both the Iterative Parameter Estimate (IPE) and Rank Preserving Structural Failure Time (RPSFT) methods. The RPSFT method was chosen due to the method being designed specifically for use in the context of analysing RCT data (57). The estimated corrected hazard ratios (HR) for OS of sorafenib to placebo were 0.69 (95% CI: 0.326; 1.650) and the prolongation factor was 1.358 (95% CI: 0.644; 2.316).

To obtain the crossover adjusted placebo S(t) for proportional hazard models the inverse of hazard ratio (1/HR) derived from the crossover adjustment methods is applied to the sorafenib survival function (S(t)). For accelerated failure time models the log of the prolongation factor is applied to the sorafenib survival function (S(t)). Parametric survival analyses were conducted on the crossover adjusted curves.

4.3.5 Results

Overall Survival (OS)

The proportional hazards assumption held for both the 2013 and 2015 data cuts (see appendix 7.7).

For the May 2013 data cut of the crossover corrected OS (using RPSFT), all distributions had very similar AIC/BIC. In the sorafenib arm the log-cumulative hazard plots and probability plots showed a better fit with log-normal, log-logistic and gamma distribution, while the comparison of the predicted and observed curves suggested Weibull, log-logistic and generalised gamma distributions.

In the assessment of clinical plausibility, published epidemiological studies have reported 10-year survival in patients with DTC to be between 10%, and 12% (58, 59). In addition, according to clinical experts for BSC the 5-year survival rate is between 20-30%, the 10-year rate is around 10-15%, and the 15 year 5-10%.

According to these predictions Weibull, gamma and Gompertz underestimated long-term survival. Depending on the time point, log-logistic, log-normal, exponential and in the earlier years gamma distributions provided good approximation. Looking at the curves, clinical experts suggested log-logistic, exponential and generalized gamma distributions were the most clinically plausible. In the placebo arm, similar results were seen (Table 24).

For the 2015 data cut, all distributions had similar AIC/BIC. In the log-cumulative hazard plots and probability plots the Weibull, lognormal, and log-logistic distributions appear to fit poorly for the initial time points, while the exponential distribution fits well initially, however deviated from the trendline towards the very end of the trial period. In the probability plots all distributions deviate in the initial time period, but fit well towards the end. Lognormal, gamma and Gompertz provided good face validity in the short term, however underestimated survival in the long term. In the long-term exponential and log-logistic distributions were clinical plausible.

The fit of all distributions was close in terms of short term fit, however distributions provided very different long-term predictions. Clinical plausibility suggested the choice of loglogistic or exponential distribution. Predicted medians were similar; however for placebo the prediction by the exponential distribution was closest to the observed median. For the indirect comparison, to incorporate the HRs, proportional hazard models are required. As the proportional hazard assumptions held, from the proportional hazard models, exponential distribution was selected as in the base case due to the similar statistical fit and better clinical plausibility. Separately fitted curves were selected as they resulted in slightly better fits compared to ones with a treatment predictor. For more details, please see appendix 7.7.

For the indirect comparison, to incorporate the HRs, proportional hazard models are required. As the proportional hazard assumptions held, from the proportional hazard models, exponential distribution was selected as in the base case due to the similar statistical fit and better clinical plausibility. For more details, please see Appendix 7.7.)

Indirect comparison

To estimate OS for lenvatinib the HR from the ITC analyses was used in the base case (HR: [redacted] 95% CI:[redacted], [redacted]), and the adjusted analysis based on Tremblay et al (37) was applied in the sensitivity analyses to the selected sorafenib OS curve (HR: [redacted] (95% CI [redacted]) (see section 3.3.7 and 3.3.9).

Progression free survival (PFS)

For PFS, log-logistic, log-normal and generalised gamma distributions had the lowest AIC/BIC. The log-cumulative hazard plots and probability plots showed a better fit with log-normal, log-logistic, generalised gamma and exponential distribution, while the comparison of the predicted and observed curves suggested Weibull and Gompertz distributions. Clinical expert validation suggested log-logistic, exponential and generalized gamma distributions (Table 24). Similarly to OS, for the indirect comparison, to incorporate the HRs, proportional hazard models are required. As the proportional hazard assumptions held, from the proportional hazard models, exponential distribution was selected as in the base case due to the similar statistical fit and better clinical plausibility. As separately fitted curves resulted in the same fit as those with a treatment predictor, fits with a treatment predictor were selected (see appendix 7.8).

To estimate PFS for lenvatinib the HR from the ITC analyses was used in the base case (HR: [redacted], 95% CI: [redacted], [redacted], and the adjusted analysis for Tremblay et al (37) was applied in the sensitivity analyses (HR: [redacted] (95% CI [redacted], [redacted] (see section 3.3.7 and 3.3.9).

Table 24: Akaike information criterion (AIC) and Bayesian information criterion (BIC) criteria

	AIC	BIC
Progression-free survival		
Treatment as predictor/central assessment		
Weibull	984.24	996.34
Lognormal	949.88	961.98
Loglogistic	963.20	975.30
Exponential	989.50	997.56
OS (RPSFT crossover adjusted 2013)		
Sorafenib		

Weibull	357.83	364.50
Lognormal	355.61	362.28
Loglogistic	356.49	363.16
Exponential	361.70	365.03
Gamma	357.60	367.60
Gompertz	361.37	368.03
Placebo		
Weibull	360.86	367.55
Lognormal	362.88	369.57
Loglogistic	360.92	367.62
Exponential	366.97	370.31
Gamma	362.75	372.79
Gompertz	363.06	369.75
OS (RPSFT crossover adjusted 2015)		
Sorafenib		
Weibull	454.53	461.19
Lognormal	453.31	459.97
Loglogistic	452.93	459.60
Exponential	459.29	462.62
Gamma	454.31	464.31
Gompertz	458.31	464.97
Placebo		
Weibull	465.60	472.29
Lognormal	467.91	474.60
Loglogistic	465.10	471.79
Exponential	470.03	473.38
Gamma	466.68	476.73
Gompertz	468.57	475.27

4.3.6 Transition probabilities

The transition between health states does not necessarily need to be characterised by transition probabilities from one health state to another, as semi-Markov models allow the use of a partition approach. By calculating the area under the survival curves at each cycle, the distribution of the patient cohort between the different health states defined by these curves are estimated. The partition model approach has been used extensively in oncology because it is particularly suited to conditions in which ongoing risks exist, although the size of these risks may vary over time. OS and PFS curves for sorafenib and BSC were derived from patient-level clinical trial data. The PFS curve defines the ‘progression-free’ state, while the ‘post-progression’ state is defined by all patients surviving (OS) less those who remain progression free

(PFS); thus, the calculation to determine the patients in the 'post-progression' state is OS-PFS. The 'dead' state is defined as 1-OS. A half cycle correction is used to adjust the number of patients in each health state.

4.3.6.1 Transition probabilities over time

DTC is a progressive disease; therefore both PFS and OS vary over time. This time dependency was taken into account with the parametric fittings for PFS and OS respectively in the model base case. AEs in the model are assumed to be time-independent.

4.3.7 Use of clinical expert opinion

Clinical experts provided clinical plausibility for the long-term extrapolation of the OS and PFS inputs, estimates for adverse event management and resource use, as detailed in section 4.5.3. For further details of the clinical expert interviews please see Appendix 7.10.

4.4 Measurement and valuation of health effects

4.4.1 Health-related quality-of-life data from clinical trials

The DECISION trial reported quality of life using two instruments EQ-5D-3L with the Visual Analog Scale (EQ-VAS), and Functional Assessment of Cancer Therapy – General (FACT-G). Results of these are presented in section 2.4.3. According to the NICE reference case (49), the EQ-5D indices were incorporated into the model.

4.4.2 Health-related quality-of-life studies

A systematic review of the literature was performed to identify any relevant health-related quality-of-life (HRQOL) studies in RAI-R DTC. As per the clinical and cost-effectiveness systematic reviews, the HRQOL review was conducted in 2 phases: a broad systematic review in 2013 to inform on current management of RAI-R DTC (or DTC if no evidence on RAI-R DTC), and then updated in November 2016 with a focus solely on RAI-R DTC.

4.4.2.1 Search strategy & results

Searches for HRQOL data were undertaken on the 4th-5th November 2016 (and October 2013) using the following sources: Medline, EMBASE, Cochrane libraries, EconLIT, and proceedings from ASCO, ATA, ETA, ITC, ESMO and ISPOR annual conferences. Studies were included if they met at least one of the PICOS criteria (see Appendix 7.5). Data collection, abstract screening, and data extraction proceeded in the same way as described for clinical evidence identification e.g. two independent reviewers, reconciliation by third independent person.

The literature review, restricted to studies that included HRQOL data in RAI-R DTC, identified 694 unique publications to screen. After title (608 excluded) and abstract screening (17 excluded), 7 publications remained for 'full text' review. Of these, 4 provided HRQOL data in RAI-R DTC (Schlumberger 2013 (30); Tremblay 2015 (60) Kerr 2014 (61) and Fordham 2015 (62)). The four identified publications describe 3 studies. Full details of the literature search strategy including search terms employed and PRISMA diagram are provided in Appendix 7.5.

The literature review identified one reference reporting early results for the impact of sorafenib on HRQOL in DECISION (Schlumberger 2013 (30)). Details of HRQOL analyses in the DECISION study are reported in section 2.4.3.3, and sections 4.4.4 and 4.4.6.

The Fordham 2015 study (62) elicits utilities for RAI-R DTC patients and evaluates the impact of treatment response and toxicities on quality of life. The health states used were: 1) stable/no response, 2) response (partial and complete), 3) progressive disease, 4) stable/no response with grade III diarrhoea, 5) stable/no response with grade III fatigue, 6) stable/no response with grade III hand-foot syndrome (HFS), and 7) stable/no response with grades I and II alopecia. Following piloting, health states underwent valuation by 100 members of the UK public during time trade-off interviews. Mean utilities and descriptive distribution statistics were calculated, and a logistic regression analysis was conducted. All of the treatment response and AE health states were shown to be statistically significant in predicting transformed utility. No response/stable disease had an adjusted utility value of 0.87, with a corresponding gain of +0.04 following a treatment response and a decline of –0.35 for disease progression. Adverse events were associated with utility decrements between –0.47

(grade III diarrhoea) and –0.05 (grade I/II alopecia). This work was earlier published as a poster (Kerr 2014 (61)).

The Tremblay et al 2015 study (60) applies health state utilities and adverse event disutilities derived in the Fordham 2015 vignette study to clinical and adverse event data from the phase 3 DECISION and SELECT (25) clinical studies to develop treatment specific (lenvatinib or sorafenib) utilities.

4.4.3 Discussion of identified utilities

EQ-5D collected in the DECISION trial represents the most appropriate and robust source of HRQoL for sorafenib. As EQ-5D was directly derived from patients enrolled in the DECISION trial the estimates are inherently linked to the efficacy evidence presented in this evaluation.

No estimates of HRQoL or PROs were collected for lenvatinib in the SELECT trial, with the manufacturer instead conducting a vignette study (62). In determining which utilities were most applicable for the economic evaluation, the following limitations were identified with the Fordham et al vignette study (62):

1) Health states are valued based on descriptions provided by 6 clinical experts from the USA and UK, and not reported directly from the patients, as requested in the NICE reference case (49).

2) Results of the vignette study lack face validity. Mean utilities reported in both the base state (patients with stable disease/ no response) and the response to therapy state are both markedly higher estimates than the UK population norm utilities for the age group enrolled into the study (ages 45-54). Health state utility values are presented in Table 25.

Table 25: Results from Fordham et al (62) versus UK population norms (63)

Health state	Utility	Source
UK population norm (ages 45-54)	0.85	(63)
Stable disease/ no response (unadjusted/adjusted)	0.86/ 0.87	(62)
Response to therapy (adjusted/unadjusted)	0.90	(62)

3) In trial EQ-5D elicited for sorafenib in the DECISION trial incorporates disutilities from adverse events. The vignette study elicits disutilities for selected adverse events, however key adverse events are not considered. For example hypertension is omitted from valuation on the basis that in most cases it is asymptomatic. Hypertension was reported in 72.8% of lenvatinib-treated patients, with reactions being grade 3 or higher in 44.4% of lenvatinib treated patients (38).

4) Descriptions of adverse events valued in the vignette are not sufficient to elicit accurate utility decrements. Diarrhoea is associated with a utility decrement of -0.48 (unadjusted) and -0.47 (adjusted). The authors note that this decrement is higher than seen in other vignettes in oncology metastatic breast cancer -0.1, renal cell carcinoma, -0.26 and -0.04 in non-small cell lung cancer (64-66). Upon review of these publications the difference in disutilities may be due to the other studies emphasising the short term and periodic nature of such events.

The identified poster by Tremblay et al (60) derives treatment specific utilities and adverse event disutilities for lenvatinib and sorafenib using the results of the vignette study conducted by Fordham et al (62). For estimates of sorafenib and BSC utilities, EQ-5D estimates collected at each cycle in the DECISION trial, averaged over health states are considered to be more robust, reflective of adverse events, and inherently linked efficacy and safety profile presented in this evaluation (also from the DECISION trial). For estimation of lenvatinib treatment utilities, the limitations identified with the Fordham et al vignette are relevant.

4.4.4 Details of the included studies in which HRQL was measured

Summaries of the studies identified from the HRQOL searches are provided in Table 26.

Table 26: Characteristics of the HRQOL and utility studies identified in the systematic literature review

	Schlumberger 2013 (30)	Fordham 2015 (62)	Tremblay 2015 (60)
Population	• RAI-R DTC	• RAI-R DTC	• RAI-R DTC
Participants Sample size (n) Interventions and comparators	• Phase III RCT study DECISION study • (n=417). • Sorafenib vs. placebo	• Health state descriptions informed via a previous qualitative study conducted in patients with RR-DTC (n=14) • • Input and iterative review via interviews with US/UK clinical experts (n=6) were used to develop and finalise health state descriptions. • • Valuation of final health states via face to face interview. from general UK population (n=100)	• Utilities derived from Fordham 2015 were combined with event data from DECISION and SELECT
Health states	• NR.	• stable/no response, • response (partial and complete), progressive disease, • stable/no response with grade III diarrhoea, • stable/no response with grade III fatigue, • stable/no response with grade III hand-foot syndrome (HFS), • stable/no response with grades I and II alopecia.	• stable/no response, • response (partial and complete), progressive disease, • stable/no response with grade III diarrhoea, • stable/no response with grade III fatigue, • stable/no response with grade III hand-foot syndrome (HFS), • stable/no response with grades I and II alopecia.
Method of elicitation	• FACT-G, EQ-5D index questionnaire and Visual Analogue Scale (VAS). questionnaires.	• Vignette study. Participants completed EQ-5D-3L and SF-6D questionnaires	• Derived from vignette study (Fordham 2015) and SELECT/DECISION clinical trials, no new primary data presented
Method of valuation	• FACT-G questionnaire. • General health status was measured using the • Questionnaires self-administered at baseline and day 1 of every 28-day cycle.	• 0–100 visual analogue scale (VAS) and TTO.	• No new primary data presented

Mapping	• No mapping was conducted	• No mapping was conducted	• No mapping was conducted
Results	• Study presents early HRQoL findings from the DECISION study. Full results of EQ-5D and FACT-G are presented in section 2.4.3.	Observed utility (before adjustments) • stable/no response: 0.80 • response: 0.86 • progressive disease: 0.50 • fatigue: 0.72 • hand-foot syndrome (HFS): 0.52 • alopecia 0.75	Sorafenib: • Stable disease state: 0.76 • Response state: 0.82 • Progressive state: 0.5 Lenvatinib: • Stable disease state:0.68 • Response state: 0.74 • Progressive state: 0.5
Limitations	• Insufficient data to appraise.	Study sample: • Small sample (n= 100) • Evidence from EQ-5D-3L data suggests sample may have been healthier than the UK general population of enrolled age • Omission of key adverse events i.e. hypertension • Issues identified in the description of adverse events and comparability to other published estimates (see section 4.4.3)	• Age of patients enrolled in the vignette study were younger than patients enrolled in DECISION and SELECT • Limitations of vignette discussed in section 4.4.3

4.4.5 Adverse reactions

Additional utility decrements associated with AEs are not included in the model. Utility values were derived from EQ-5D data obtained in the DECISION trial among patients who were receiving treatment. Therefore, the effect of treatment-related AEs is already reflected in their responses, with EQ-5D averaged over each health state.

4.4.6 Health-related quality-of-life data used in cost-effectiveness analysis

Utilities were assumed to depend only on the health states and treatment status and to be constant over time as long as patients are in a given health state.

A weighted average of all EQ-5D index scores (while on treatment in DECISION trial) collected at each 28 day cycle was calculated and is assumed to represent the mean progression-free utility in the model for sorafenib and BSC. The mean utility for patients post-progression is based on the weighted average of the EQ-5D index at the end of treatment assessment with sorafenib and placebo. Since this might overestimate the average utility of patients all along the post-progression health state, sensitivity analyses were conducted using this value. The model assumes that post-progression, patients have the same quality of life irrespective of initial treatment received.

Due to the short life expectancy in this patient population and the disease progression, further deterioration of utilities due to aging is not required to be taken into account. In the progressive health state, patients are likely to experience an important drop in HRQL during the end of life care in the final few weeks of life. However, since most patients go through end of life care, this drop in HRQoL would be the same for almost all patients between treatment arms. Thus, patients would incur the same average utility decrement and undiscounted QALY reductions in both treatment arms. As a consequence, the model does not account for these HRQoL changes incurred during end of life care.

For lenvatinib no utility data was available from the SELECT trial. A vignette study has been published which estimated the utilities in stable/no response, response to therapy and progressive disease health states and selected AEs (62). The health state utilities varied between 0.91-0.52. The AE disutilities varied between 0.08-

0.47). Severe limitations of this study are discussed in section 4.4.3, based on these findings these estimates were not incorporated in the analyses.

Due to the absence of reliable treatment specific utilities for lenvatinib, the pre-progression utilities for sorafenib were also applied for lenvatinib. However due to the favourable adverse event profile of sorafenib (section 3.3.7), this is likely to result in an overestimate for lenvatinib. To assess the effect of potential differences in pre-progression utilities between lenvatinib and sorafenib, in a scenario analyses the effect of 10% reduction for lenvatinib was included (section 4.10).

Table 27 Utilities: Based on EQ-5D collected in the DECISION trial

Treatment Arm	Mean	SE
Sorafenib: Progression-free	0.72	0.08
Lenvatinib: Progression-free	0.72	0.08
BSC: Progression-free	0.80	0.07
Post-progression	0.64	0.06

4.5 Cost and healthcare resource use identification, measurement and valuation

4.5.1 Resource identification, measurement and valuation studies

A systematic review was conducted in 2 phases closely following the approach detailed in section 4.1. The first systematic review was conducted in September 2013 and did not find any relevant studies considering resource use for patients treated for RAI-R DTC.

An updated systematic review was conducted in November 2016. 7 studies were identified (1 full publication, 6 abstract) at full text, however upon review none of these were deemed to be useful in assisting decision making in England, or development of the economic model for this appraisal. Results of the SLR are presented in appendix 7.5.

4.5.2 Identification of unit costs

Unit costs of resources were obtained from National Schedule of Reference Costs 2015-16 (67) and the Personal Social Services Research Unit (PSSRU) report (68) and unit costs of drugs were obtained from British National Formulary 2016 (24).

4.5.3 Clinical Experts consultation on resource use

Oncologists who practice in the UK, were interviewed to obtain expert opinions related to current patient management after progression of DTC despite the failure of RAI. The objective of the survey was to better understand standard care for DTC patients failing RAI, including pharmaceutical treatments that patients may receive as part of BSC or in association with an active treatment regimen, health care resource utilization due to routine care of DTC, and AE management. Details of the methods used in clinical expert consultation can be found in Appendix 7.10.

4.5.4 Intervention and comparators' costs and resource use

A 112-tablet pack of sorafenib costs £3,576.56 at list price and [redacted] with the commercial arrangement, representing a discount of [redacted]. To account for dose modifications or other factors that may cause deviation from planned dosing, and to ensure that the cost of sorafenib is consistent with clinical outcomes from the DECISION trial, the model adjusts the cost per dose by the dose intensity. In the DECISION trial, patients received a mean of 81.4% (std. error 1.4%) of the planned 800 mg daily dose. Drug costs are accrued at the beginning of each treatment cycle (not half-cycle corrected).

BSC arm is assumed to have no drug costs. The cost of pharmaceuticals given to patients for palliation of symptoms is covered by routine care of DTC.

For lenvatinib two formulations are available, 4mg and 10mg in 30-tablet packages. Both packages are priced at £1,437 according to British National Formulary 2016 (24). The dosage for lenvatinib is 24mg a day over a 28 day cycle leading to a per cycle cost of £4,023.60. The model assumes that the dose intensity for lenvatinib is 71.7% based on the recommended dose (24mg) and the reported dose in SELECT of 17.2mg per day (25).

4.5.5 Health-state unit costs and resource use

Consultation with oncologists provided estimates of the resources utilised in various settings of care (inpatient, outpatient, and pharmaceutical), the proportion of patients utilising the resource, and the frequency of utilisation per 28 days, for routine care of RAI refractory DTC while receiving either oral active treatment or BSC and post-

progression. Details for unit costs of routine management of RAI refractory DTC are presented in Appendix 7.10.

Using oncologist responses and unit costs, the cost per 28 days for routine care of RAI refractory DTC patients is estimated and presented in Table 28.

Due to a lack of treatment specific information on resource use the model assumes that resource use for lenvatinib is the same as for sorafenib. Costs are highest pre-progression for sorafenib/lenvatinib mainly due to the increased imaging in this health state.

Table 28: Routine care costs for RAI refractory DTC (per 28 days)

	Treatment Arm	Inpatient*		Outpatient		Pharmaceutical	
		Mean	SE	Mean	SE	Mean	SE
Pre-progression	BSC	[redacted]	20%	[redacted]	20%	[redacted]	20%
	Sorafenib	[redacted]	20%	[redacted]	20%	[redacted]	20%
	Lenvatinib	[redacted]	20%	[redacted]	20%	[redacted]	20%
Post-progression	All	[redacted]	20%	[redacted]	20%	[redacted]	20%

NOTE: No routine impatient care is assumed based on clinician opinion. Due to lack of data, resource use for lenvatinib is assumed to be the same as for sorafenib.

4.5.6 Adverse reaction unit costs and resource use

Due to the lack of published AE management costs, similarly to routine disease management, expert opinion was elicited to inform treatment patterns. Using the probability of patients experiencing each AE in DECISION and SELECT trial (see section 2.4.4), the oncologist estimates of resources used to manage the event, and unit costs of the resources, management costs per 28-day cycle are estimated.

Details of management costs are presented below for grade 3 and grade 4 adverse events. Oncologists provided the proportion of patients treated in various settings of care (inpatient, outpatient, and pharmaceutical), and the resources utilised per event. Unit costs of resources were obtained from National Schedule of Reference Costs 2015-16 (67) and British National Formulary 2016.

AEs were not reported separately for grades 3 and 4 for lenvatinib, all grade 3 and 4 lenvatinib AEs were conservatively assumed to have the cost of grade 3 AEs.

Table 29: Adverse event management costs (per 28 days)

Treatment Arm	Inpatient		Outpatient		Pharmaceutical	
	Mean	SE	Mean	SE	Mean	SE
Sorafenib	£0.20	£0.04	£1.38	£0.28	£0.02	£0.00
Lenvatinib	£0.83	£0.17	£6.19	£1.24	£0.10	£0.02
BSC	£0.91	£0.18	£8.74	£1.75	£0.09	£0.02

Table 30: Cost of Grade 3 Adverse Event Management per Patient per 28 Days (resource use is based on physician surveys)

Adverse Event	Cost per Grade 3 adverse event (per 28 days)			Cost per Grade 4 adverse event (per 28 days)		
	Inpatient	Outpatient	Pharmaceutical	Inpatient	Outpatient	Pharmaceutical
Hypertension	-	£158.00	-	-	£63.00	£2.06
Fatigue	-	£61.00	-	-	£74.00	-
Weight loss	£63.00	£270.00	£12.00	No events reported		
Hand-foot skin reaction	-	£153.00	£2.00	No events reported		
Diarrhoea	£120.00	£103.00	-	£39.00	£63.00	-
Hypocalcaemia	-	£9.00	-	-	£9.00	-

4.6 Summary of base-case de novo analysis inputs and assumptions

4.6.1 Summary of base-case de novo analysis inputs

The base case of the analyses and the scenario based on the above sections are summarised in Table 31. Base case inputs with their variations are available in appendix 7.14.

Table 31: Summary of base case and scenario analyses

	Base case	Sensitivity analysis
Time horizon	Lifetime (30 years)	10,20
Discount rate	3.5% Costs, 3.5% health	1.5% costs, 1.5% health
PFS Source	Central Assessment	Local assessment
PFS distribution for direct comparison	Exponential	Lognormal
PFS distribution for indirect comparison	Exponential	Weibull
OS data cut	2013	2015
OS source direct comparison	RPSFT cross-over adjusted	-
OS source indirect comparison	RPSFT cross-over adjusted	-
OS distribution for direct comparison	Exponential	Lognormal, log logistic
OS distribution for indirect comparison	Exponential	Weibull
TTD source for sorafenib	DECISION trial	-
TTD source for lenvatinib	SELECT trial	-
TTD Option	Treat until progression or time to discontinuation from trial	Treat until discontinuation
Post-progression utilities	DECISION trial EQ-5D index	-
Pre-progression utilities	DECISION trial EQ-5D index Same for lenvatinib as for sorafenib	10% reduction in the lenvatinib utilities
Indirect comparison HRs	Based on ITC analyses	Based on adjusted MAIC data

4.6.1.1 Assumptions

For this economic evaluation the following assumptions have been made:

- The efficacy data from the DECISION trial is applicable to England and Wales and to the local treatment practices;
- The PFS and the OS observed in the treatment and the placebo group over the trial duration can be extrapolated to the desired time horizons, using exponential distribution;
- Patients cease treatment with sorafenib and lenvatinib treatment on progression;
- Once patients stop their initial treatment (e.g. sorafenib), no further treatment is given, and only routine care cost and health state utility are incurred;
- Resource use for routine care and adverse event management, estimated based on UK oncologist survey results, are assumed to be representative of the current treatment patterns;
- Resource use for those on lenvatinib treatment is the same as those on sorafenib treatment
- Only treatment-related grade 3 and/or 4 AEs have consequences for additional costs and utilities;
- The rate of AEs is assumed to be constant over the duration of treatment;
- The efficacy, safety and dose intensity data from the DECISION trial is similar to what would be observed in real-world practice;
- Use of a 28-day cycle length assumes clinical decisions, such as progression, changes in quality of life, overall survival, and cost applications are made at 28-day intervals.

4.7 Sensitivity analysis

Various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including parameter uncertainty and structural uncertainty. Parameter uncertainty was assessed in the univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA). Structural uncertainty was explored in a series of scenario analyses, including assumptions around structural form of OS and

PFS, the sources used to inform parameters and assumptions regarding the underlying calculations detailed below.

Structural uncertainty, arising from simplifications and scientific judgments required to construct and interpret the model, was formally tested through scenario analysis. For purposes of this section, we have defined ‘structural uncertainty’ as the type of uncertainty that does not easily fit into the categories of parameter or methodological uncertainty (69, 70). Structural uncertainty was explored by assessing the effect on the results of using alternative functional forms, assumptions or sources for key input parameters. These are detailed in Table 31.

4.7.1 Univariate sensitivity analyses

Univariate deterministic sensitivity analysis was performed where each parameter was varied according to its 95% CI or standard error, while holding all other parameters constant. Where the published study or source for parameter values did not report standard errors or CIs, a standard error of 20% of the mean was assumed. All uncertain parameters were included in the sensitivity analyses. Time-horizon and discount rates were not varied as these where not subject to parameter uncertainty, however, the impact of alternative discount rates and time horizons were examined in scenario analysis, as described above.

The parameters varied in the one-way sensitivity analysis included OS, PFS, TTD, risk of AE, utilities, drug costs, cost of administration, routine management costs, and costs of AEs. Unit costs and resource use for non-drug resources were not independently varied. They were, however, varied in aggregate form. For a detailed list of parameters varied and range of variation tested in the one-way univariate sensitivity analysis see Appendix 7.11.

4.7.2 Probabilistic sensitivity analysis

In order to account for variability in outcomes due to parameter uncertainty, PSA was performed. The probabilistic analyses were run for 1,000 replications where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for costs and QALYs. PFS, OS, TTD, HRs, costs and utilities were varied simultaneously and independently of each other. Time horizon and discount rates were excluded from the PSA, since they are not subject

to parameter uncertainty. Drug costs and the number of administrations per cycle according to dosing schedule were also excluded for the same reason.

To vary TTD, the KM estimate in the first cycle of each of the curves was sampled using a lognormal distribution. KM estimates in subsequent cycles were varied based on the sampled value in the first cycle using z-scores and the method described by Schauer and Eckman 2014 (71) by applying the following formula:

Mean + standard error of each KM estimate in each cycle x (sampled value in first cycle – mean value in first cycle)/ standard error

Parametric distributions were varied using the means and variance-covariance matrices of the parameters in Cholesky decomposition (47). This helped to account for the correlation between parameters.

The natural logarithm of the HRs can be assumed to be normally distributed as the central limit theorem is often employed to estimate the CIs of these parameters in clinical trials. A log-normal distribution for the HRs and RRs was therefore used assuming a prior that converges to a sensible finite value using a mean equal to exp[log(HR)-0.5*se^2].(72)

A gamma distribution was applied to the costs as these distributions have a constrained interval at 0 (47). A gamma distribution avoids generation of “negative costs” and can reflect the natural skew in costs and durations. Dose intensity was assumed to follow beta distribution.

The risk of AEs was modelled using a beta distribution. For utilities a beta distribution was used due to the bounds of the distribution (i.e., 0 to 1), using the standard error as the source of variation to calculate alpha and beta parameters of the distribution (47). Utilities were assumed to be correlated between treatments and the pre- and post-progression periods of the same treatment (using the same random number draw). This ensures that quality of life decreases with disease progression. It also captures the idea that an RAI refractory DTC patient with a higher baseline utility would probably also have a higher pre-progression utility, when compared with the average RAI refractory DTC patient. For more details please see Appendix 7.11.

4.8 Base-case results

The sections below describe the results of the economic evaluation from the direct comparison (sorafenib vs. BSC) based on the DECISION trial (15) (see section 2) and from the indirect comparison (Section 3; based on the ITC of sorafenib, lenvatinib and BSC) using data from both the DECISION and the SELECT trials (25).

Results were estimated using the CMU price for sorafenib, and the list price for lenvatinib.

4.8.1 Base case results for the direct comparison

The results for the direct comparison have been presented based on the results of the DECISION trial (25). The main focus of all analyses is the discounted results; however, undiscounted results are also presented for completeness in Appendix 7.14.

Base-case incremental cost effectiveness analysis results

Over a lifetime time horizon, sorafenib was associated with 0.81 additional QALYs compared to BSC and an additional cost of [redacted]. This resulted in an ICER of [redacted]/QALY for sorafenib compared to BSC.

In terms of life-years (LYs) gained, sorafenib was associated with 1.30 additional LYs, which resulted in an ICER of [redacted]/LY gained for sorafenib compared to BSC (Table 32). For undiscounted results, please see Appendix 7.14.

Table 32: Incremental cost-effectiveness ratios – Direct comparison based on the DECISION (15) trial (Sorafenib and BSC)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (LYs)	ICER ( ) incremental (QALYs)
BSC	[redacted]	3.49	2.35					
Sorafenib	[redacted]	4.79	3.16	[redacted]	1.30	0.81	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
Note: Slight differences in the calculations are due to rounding.

4.8.1.2 Disaggregated health results

Discounted health benefit results from the economic evaluation comparing sorafenib versus BSC in terms of mean LYs and QALYs are shown in Table 33. For undiscounted results, please see Appendix 7.14.

Over a lifetime time horizon, the mean LYs estimated by the model were 4.79 years for patients treated with sorafenib, of which 1.28 LYs were spent in the progression-free health state and 3.51 LYs were spent in the progressed health state. For patients treated with BSC, mean LYs estimated by the model were 3.49 years in total, of which 0.79 and 2.71 LYs were in progression-free and progressed health states, respectively. Incremental LYs were 1.30 for sorafenib compared to BSC, with the majority (62%) of the gain observed post-progression (0.50 incremental LYs gained pre- and 0.81 post-progression).

Similarly, over a lifetime time horizon, the mean total QALYs estimated by the model for sorafenib were 3.16 and for BSC were 2.35 with an incremental QALY gain of 0.81. 36% of incremental QALYs were gained in the progression-free health state and 64% in the progressed health state.

Table 33: Health benefits – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

Health state	LY Sorafenib	LY BSC	QALY Sorafenib	QALY BSC	Increment (QALY)	Absolute increment (QALY)	% absolute increment (QALY)
Progression-free	1.28	0.79	0.92	0.63	0.29	0.29	36%
Progressed	3.51	2.71	2.24	1.72	0.51	0.51	64%
Total	4.79	3.49	3.16	2.35	0.81	0.81	100%
QALY, quality-adjusted life year; LY, life-year							

4.8.1.3 Disaggregated cost results

Total discounted cost incurred over the lifetime time horizon among patients receiving sorafenib and BSC was £[redacted] and £[redacted] respectively, leading to an incremental cost of £[redacted] compared to BSC. For undiscounted results, please see Appendix 7.14.

The increase in cost was largely driven by drug costs associated with sorafenib treatment and the outpatient routine care costs. The drug costs accounted for [redacted] of incremental costs, while the outpatient routine care costs for [redacted]. This later increase was due to:

- The higher per cycle outpatient routine care costs for sorafenib in progression-free cycle. While less visits were required for patients on sorafenib compared to BSC, the number of monitoring tests, especially scans were higher for patients on sorafenib.

- Due to the longer progression-free and overall survival, routine care costs were accrued for a longer time horizon.

Table 34 and Figure 13 below details results by health state and cost category.

Table 34: Summary costs by health state, treatment phase and category of costs– Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

	Cost intervention Sorafenib (£)	Cost comparator BSC (£)	Increment (£)	% increment
Progression-free				
Inpatient				
Routine care	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	9.51	2.18	7.32	0.0%
Outpatient				
Routine care	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	70.54	14.85	55.69	0.2%
Treatment administration	[redacted]	[redacted]	[redacted]	[redacted]
Pharmaceutical				
Routine care	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	1.17	0.24	0.93	0.0%
Anti-cancer medication	[redacted]	[redacted]	[redacted]	[redacted]
Progressed				
Inpatient - Routine care	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient - Routine care	[redacted]	[redacted]	[redacted]	[redacted]
Pharmaceutical - Routine care	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	**100.0%**

Figure 13: Summary of costs by category of costs – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

4.8.1.4. Sensitivity analyses for the direct comparison

To assess the uncertainty surrounding the results various sensitivity analyses were conducted including:

- Probabilistic analyses to test parameter uncertainty with results presented as:
  - probabilistic means and 95% confidence intervals
  - percentage or number of iterations in the four quadrants of the cost-effectiveness plane
  - on scatterplots
  - as cost-effectiveness acceptability curves (CEACs)
- Deterministic one-way sensitivity analyses to identify the parameters that the results are most sensitive to with results depicted on tornado diagram
- Scenario analyses to test structural and methodological uncertainty

Probabilistic sensitivity analysis

The probabilistic mean costs and QALYs were very close to the deterministic means, with an incremental QALY of 0.86 (vs. 0.81 in the deterministic analysis) and an incremental cost of [redacted] (vs. [redacted] in deterministic analysis), leading to an ICER of £[redacted]/QALY (vs. £[redacted]/QALY in deterministic analysis) for sorafenib versus BSC.

Figure 14 presents the cost-effectiveness plane of incremental QALYs (x- axis) against the incremental cost (y-axis) of sorafenib compared to BSC. Each point on the chart represents the ICER resulting from a single probabilistic iteration of the model. The plot indicates that in 77.7% of the 1000 model iterations, sorafenib yielded more QALYs than BSC but at higher cost (

Table 36). The line in the figure shows willingness-to-pay (WTP) of £30,000.

Table 35: Probabilistic results – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

Technologies	Total costs (£) Mean	Total QALYs Mean	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
BSC	[redacted]	2.43			
Sorafenib	[redacted]	3.29	[redacted]	0.86	[redacted]
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; CI, confidence interval; INB: incremental net benefit					

Table 36: Distribution of iterations – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

More costly, less effective		More costly, more effective	
Sorafenib vs. BSC	21.5%	Sorafenib vs. BSC	77.7%
Less costly, less effective		**Less costly, more effective**	
Sorafenib vs. BSC	0.8%	Sorafenib vs. BSC	0.0%

Figure 14: Scatterplot – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

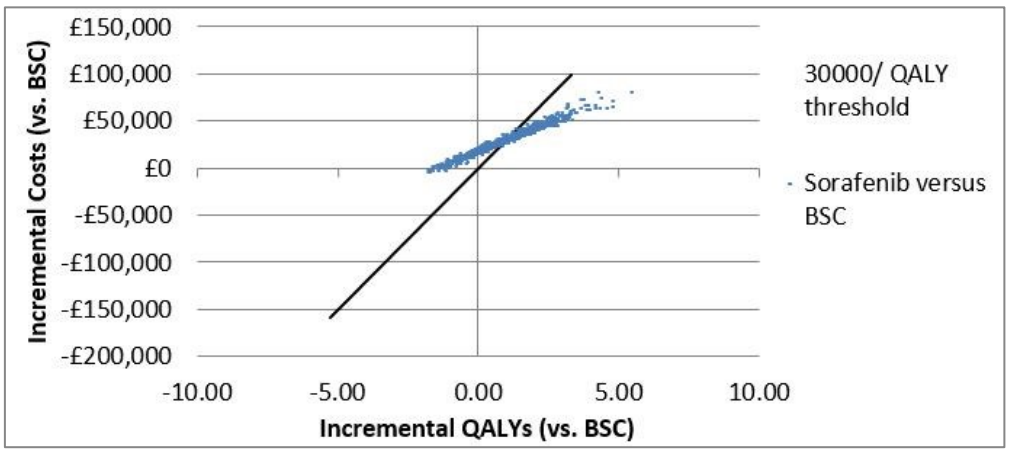


Figure 15: Cost-effectiveness acceptability curves (CEACs) – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

In the cost-effectiveness acceptability curve (CEAC) the horizontal, x-axis represents a health care payer's WTP for an additional unit of health outcome (QALY in this case), while the vertical, y-axis represents the probability of cost-effectiveness. At a WTP value of £50,000 per QALY gained the probability of sorafenib being cost effective compared with BSC is 60%, and at £30,000 per QALY gained 39% (**Error! Reference source not found.**).

Deterministic sensitivity analysis

Univariate sensitivity analyses were conducted by varying a single parameter with parameter uncertainty at a time to test its impact on the model results. As the results span more than one quadrant of the cost-effectiveness plane, incremental net benefit (INB) with the threshold of £50,000 was used instead of ICERs. The parameters with the most impact on the INBs are displayed in Figure 16. The bars show the variation from base-case value using the high and low value for each parameter. (Results for all parameters are detailed in Appendix 7.12.) The largest deviation from base case in INBs was caused by variations of the overall survival curves for BSC and sorafenib and the progression-free utilities for sorafenib and BSC.

Figure 16: Tornado diagram for the INB with a threshold of £50,000 – Direct comparison based on the DECISION trial (15) (sorafenib vs. BSC)

4.8.1.5 Scenario analysis

Scenario analyses were conducted to test the robustness of the model in light of the structural and methodological uncertainties. These included:

- Assumptions around the time horizon: 10 and 20 years
- Reduced discount rate: 1.5% for both costs and health benefits
- Assumptions around the definition of PFS: use of local, investigator assessment
- Assumptions around the distribution used for PFS: lognormal for direct comparison
- Use of the later, 2015 data cut for OS
- Assumptions around the distribution used for OS: loglogistic for direct comparison
- Definition of treatment discontinuation: allowing patients to continue sorafenib past progression (direct comparison only as there is no data available on patients continuing past progression for lenvatinib)

The scenario analyses highlighted that the ICER was sensitive to assumptions regarding (Table 37):

- **Time horizon:** Although the time horizon of 10 years is not appropriate given the duration of survival of patients with DTC, it was tested as an extreme assumption to assess the effect of time horizon on QALYs vs. costs.

Reducing the time horizon of the analysis from 30 years to 10 years reduces the incremental QALYs for sorafenib versus BSC (0.81 to 0.55 respectively) whilst having minimal impact on incremental costs versus BSC £[redacted] to £[redacted] respectively) resulting in an ICER of £[redacted]/QALY versus BSC, an increase of 29%. Reducing the time horizon means the full long-term impact of treatment with sorafenib on QALYs due to increased PFS and OS is not captured. Reducing the time horizon to the more realistic 20 years, the effect on ICER was minimal (3%).

- **Overall survival (OS):** Use of the log-logistic distribution for OS reduces the incremental QALYs for sorafenib versus BSC (0.81 for exponential to 0.62 with log-logistic) resulting in an ICER of £[redacted]/QALY for sorafenib versus BSC, a 19% increase. The log-logistic distribution predicts longer overall survival for both sorafenib and BSC with higher increase for BSC, which results in a smaller incremental difference. The incremental costs are only marginally effected £[redacted] versus BSC to £[redacted] versus BSC for exponential and log-logistic as incremental non-drug costs are largely dependent on PFS.

- **Overall survival data-cut:** using OS parameters derived from the 2015 data cut with increase proportion of patients crossing over reduces incremental QALYs versus BSC compared to the 2013 data-cut parameters (0.81 to 0.54 respectively), resulting in a 31% increase in the ICER (£[redacted]/QALY vs. £[redacted]/QALY). The 2013 data cut was selected due to the alignment in follow-up period (24.1 months and 23.6 months) between the sorafenib and lenvatinib studies. Assessing efficacy at a comparable time points, removes any time related bias in interpreting the crossover adjustment and is a recognised approach when follow-up is related to treatment effect (which is likely when cross-over adjustment is employed).

- **Post-progression treatment:** Allowing patients to continue on sorafenib treatment past progression increases the drug costs and as a result the incremental costs from £[redacted] to £[redacted] leading to an increase in

ICER by 13% (£[redacted]/QALY vs. £[redacted]/QALY). This analysis however is exploratory, as the length of treatment in the open label period was not followed up, and assumptions were required.

In addition, one further assumption had a smaller, 10% effect on the ICER:

- Reducing the discount rates decreases the ICER, as the majority of the incremental costs are accrued earlier; thereby the discount rates have smaller effect on them, while the QALYs are accrued throughout the time period and are more susceptible to changes in discount rates.

The remainder of the scenarios had negligible impact (<5% change from baseline). The model was not sensitive as result to the use of local investigator assessment (decrease in the ICER by 4%) for PFS, the use of lognormal distribution (increase in ICER by 1%) to model PFS and to reducing the time horizon to 20 years (increase in ICER by 3%)

Table 37: Scenario analyses – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC)

Scenarios	Incremental QALYs	Incremental Costs	ICER (£/QALY)	Change from baseline (base case ICER) (%)
Base case	0.81	[redacted]	[redacted]	-
Time horizon (base case: 30 years)				
Time horizon: 10 years	0.55	[redacted]	[redacted]	29%
Time horizon: 20 years	0.77	[redacted]	[redacted]	3%
Discount rate (base case: 3.5% for costs and health benefits)				
Discount rate: 1.5% for costs and health benefits	0.95	[redacted]	[redacted]	-9%
PFS (base case: central assessment, exponential distribution)				
PFS assessment: local, investigator assessment	0.82	[redacted]	[redacted]	-4%
PFS distribution: log-normal	0.80	[redacted]	[redacted]	1%
OS (base case: 2013 data cut and exponential distribution)				
OS data cut: 2015	0.54	[redacted]	[redacted]	31%
OS distribution: log-logistic distribution	0.62	[redacted]	[redacted]	19%
TTD (base case: until discontinuation or progression)				
TTD: sorafenib patients can continue past progression	0.81	[redacted]	[redacted]	13%

Summary of sensitivity analyses results

The sensitivity analyses showed that the results were most sensitive to both parameters and assumptions around overall survival. In addition utilities and routine care costs in the progression-free health state are also influential. Utilities are important, as they differ pre-progression between sorafenib and BSC, with higher utilities for BSC due to the higher rate of AEs with sorafenib. Overall the flat scatterplot suggests highly correlated incremental QALYs and costs.

4.9 Results for the indirect comparison

Results were estimated using the CMU price for sorafenib, and the list price for lenvatinib.

4.9.1 Base-case incremental cost effectiveness analysis results

Sorafenib was associated with 0.81 additional QALYs compared to BSC at an additional cost of £[redacted]. Lenvatinib was associated with 1.69 additional QALYs compared to BSC and an additional cost of [redacted] resulting in an ICER of £[redacted]/QALY and £[redacted]/QALY for sorafenib and lenvatinib respectively, compared to BSC (Table 38). In the incremental analyses, there was no dominance (Figure 17). For undiscounted results, please see Appendix 7.14.

Table 38. Incremental cost-effectiveness ratios (discounted at 3.5%) - Indirect comparison based on the DECISION (15) and SELECT trials (25) (Sorafenib, lenvatinib and BSC)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental vs. BSC (QALYs)	ICER (£) incremental (QALYs)
BSC	[redacted]	3.49	2.35					
Sorafenib	[redacted]	4.79	3.16	[redacted]	1.30	0.81	[redacted]	[redacted]
Lenvatinib	[redacted]	5.92	4.04	[redacted]	1.12	0.88	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Note: Slight differences in the calculations are due to rounding.

Figure 17. Cost-effectiveness Results - Indirect comparison based on the DECISION (15) and SELECT trials (25) (Sorafenib, lenvatinib and BSC)

[redacted]

4.9.2 Disaggregated health results

Discounted health benefit results for sorafenib, lenvatinib and BSC from the indirect comparison in terms of QALYs and mean LYs are shown in Table 39. For undiscounted results, please see Appendix 7.14.

Over a lifetime time horizon, the total QALYs for patients treated with sorafenib, lenvatinib and BSC were 3.16, 4.04 and 2.35 respectively. Thus the incremental QALY gain compared to BSC was 1.69 for lenvatinib and 0.81 for sorafenib.

Table 39. Health benefits (discounted at 3.5%) – Indirect comparison based on the DECISION (15) and SELECT trials (25) (Sorafenib, lenvatinib and BSC)

Health state	LYs lenvatinib	QALY lenvatinib	LYs sorafenib	QALY sorafenib	LYs BSC	QALY BSC
Progression-free	3.34	2.39	1.28	0.92	0.79	0.63
Progressed	2.58	1.65	3.51	2.24	2.71	1.72
Total	5.92	4.04	4.79	3.16	3.49	2.35

4.9.3 Disaggregated cost results

Total discounted cost incurred over the lifetime time horizon among patients receiving sorafenib, lenvatinib and BSC was £[redacted], £[redacted] and £[redacted] respectively, leading to an incremental cost of £[redacted] and £[redacted] for sorafenib and lenvatinib respectively compared to BSC. For undiscounted results, please see Appendix 7.14.

Lenvatinib versus BSC: The increase in cost for lenvatinib versus BSC was largely driven by drug costs associated with lenvatinib treatment, and the pre-progression outpatient routine care costs. Drug costs accounted for [redacted] of incremental costs, while the pre-progression outpatient routine care costs for [redacted].

Lenvatinib versus sorafenib: Drug costs accounted for [redacted] of incremental costs for lenvatinib versus sorafenib, while the pre-progression outpatient routine care costs also for [redacted] were somewhat offset by the lower post-progression outpatient routine care costs [redacted] The high incremental cost of lenvatinib compared to sorafenib was due mainly to the following:

- Higher per cycle cost of lenvatinib (£4,024 vs. [redacted] for lenvatinib vs. sorafenib respectively)

- The longer treatment duration with lenvatinib (median treatment duration: approximately 9 cycles and 12 cycles for sorafenib and lenvatinib respectively)
- The longer LYs with lenvatinib resulted in accruing routine care costs for a longer period

The treatment duration for lenvatinib is taken from the SELECT trial, which includes both first line and second line patients and subgroup results were not available. Assuming second line patients are likely on treatment for a shorter duration of time, the model underestimates the treatment duration for first line lenvatinib, and consequently underestimates the drug costs.

Table 40 and Figure 18 below details results by health state and cost category:

Table 40. Summary costs (discounted at 3.5%) by health state, treatment phase and category of costs- Indirect comparison based on the DECISION (15) and SELECT(25) trials (Sorafenib, lenvatinib and BSC)

	Cost intervention Sorafenib (£)	Cost comparator BSC (£)	Cost comparator Lenvatinib (£)
Progression-free			
Inpatient			
Routine care	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Outpatient			
Routine care	[redacted]	[redacted]	[redacted]
Adverse events	70.54	14.85	126.18
Treatment administration	[redacted]	[redacted]	[redacted]
Pharmaceutical			
Routine care	[redacted]	[redacted]	[redacted]
Adverse events	1.17	0.24	1.23
Anti-cancer medication	[redacted]	[redacted]	[redacted]
Progressed			
Inpatient - Routine care	[redacted]	[redacted]	[redacted]
Outpatient - Routine care	[redacted]	[redacted]	[redacted]
Pharmaceutical - Routine care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Figure 18. Summary of costs by category of costs – Indirect comparison based on the DECISION (15) and SELECT (25) trials (Sorafenib, lenvatinib and BSC)

4.9.4 Base case results using HRs from the adjusted MAIC (section 3.3.9)

Due to potential uncertainty surrounding the HRs for the indirect comparison, results were also presented using the adjusted MAIC (PFS HR: [redacted], OS HR: [redacted]). (See Section 3.3.9 and Table 20 for further details.) Sorafenib was still associated with 0.81 additional QALYs compared to BSC at an additional cost of [redacted]. However results for lenvatinib changed. Using the MAIC HRs, lenvatinib was associated with 1.59 additional QALYs compared to BSC, slightly lower than with ITC (1.69). This was at additional cost of £[redacted] (also slightly lower than the £[redacted] with ITC) resulting in ICERs of £[redacted]/QALY and £[redacted]/QALY for sorafenib and lenvatinib respectively, compared to BSC (Table 39). In the incremental analyses, there was no dominance.

The change in ICER is small, since the MAIC compared to ITC only has important effect on the PFS and not on the OS. PFS influences only the utilities and the routine care costs, where the increase of pre-progression costs has been partly offset by the decrease in post-progression costs. The PFS should also influence the time on treatment, since patient took lenvatinib until progression or treatment limiting toxicities. Thus with the increased PFS, time on treatment (TTD) would probably also increase, together with total costs and the ICER. However matched TTD has not been reported, and as a result, this analysis couldn't take it into account, underestimating the ICER.

Table 41. Incremental cost-effectiveness ratios (discounted at 3.5%) - Indirect comparison based on the MAIC (Sorafenib, lenvatinib and BSC)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental vs. BSC (QALYs)	ICER (£) incremental (QALYs)
BSC	[redacted]	3.49	2.35					
Sorafenib	[redacted]	4.79	3.16	[redacted]	1.30	0.81	[redacted]	[redacted]
Lenvatinib	[redacted]	5.73	3.94	[redacted]	0.93	0.78	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Note: Slight differences in the calculations are due to rounding.

Figure 19. Cost-effectiveness Results - Indirect comparison based on MAIC (Sorafenib, lenvatinib and BSC)

[redacted]

4.10 Sensitivity analyses for the indirect comparison including lenvatinib

To assess the uncertainty surrounding the results various sensitivity analyses were conducted including:

- Probabilistic analyses to test parameter uncertainty with results presented as:
  - probabilistic means and 95% confidence intervals
  - percentage or iterations in the four quadrants of the cost-effectiveness plane
  - on scatterplots
  - as cost-effectiveness acceptability curves (CEACs)

- Deterministic sensitivity analyses to identify the parameters that the results are most sensitive to with results depicted on tornado diagram
- Scenario analyses to test structural and methodological uncertainty

4.10.1 Probabilistic sensitivity analysis

The probabilistic mean costs and QALYs were very close to the deterministic means, with total QALYs of 2.36, 3.22 and 4.06 (vs. 2.35, 3.16 and 4.04 in the deterministic analysis) and total cost of £[redacted], £[redacted] and £[redacted] (vs. £[redacted], £[redacted] and £[redacted] in the deterministic analysis) for BSC, sorafenib and lenvatinib respectively. This led to ICERs of £[redacted]/QALY and £[redacted]/QALY for sorafenib and lenvatinib vs. BSC respectively (Table 42).

Lenvatinib was associated with an ICER of £[redacted]/QALY vs. sorafenib. The 95% confidence intervals for costs and QALYs widely overlap for both treatments, reflecting a lack of a statistically significant difference in terms of both outcomes (see Section 3.3.7).

Figure 20 presents the cost-effectiveness plane of incremental QALYs (x- axis) against the incremental cost (y-axis) of sorafenib and lenvatinib compared to BSC. Each point on the chart represents the ICER resulting from a single probabilistic iteration of the model. The plot indicates that in 75.8% of the 1000 model iterations vs. BSC, lenvatinib yielded more QALYs but at higher cost (

Table 43). The line in the figure shows a willingness-to-pay (WTP) threshold of £30,000.

Table 42. Probabilistic results – Indirect comparison based on the DECISION (15) and SELECT(25) trials (Sorafenib, lenvatinib and BSC)

Technologies	Total costs (£) Mean (95% CI)	Total QALYs Mean (95% CI)	Incremental costs (£)	Incremental QALYs	ICER (£) incremental vs. BSC (QALYs)	ICER (£) incremental (QALYs)
BSC	[redacted]	2.36 (0.18-5.25)				
Sorafenib	[redacted]	3.22 (1.65-5.08)	[redacted]	0.86	[redacted]	[redacted]
Lenvatinib	[redacted]	4.06 (1.89-6.65)	[redacted]	0.83	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; CI, confidence interval; INB: incremental net benefit

Table 43. Distribution of iterations – Indirect comparison based on the DECISION (15) and SELECT trials (25) (Sorafenib, lenvatinib and BSC)

More costly, less effective		More costly, more effective	
sorafenib vs. BSC	23.4%	sorafenib vs. BSC	75.8%
sorafenib vs. lenvatinib	0.0%	sorafenib vs. lenvatinib	0.3%
Less costly, less effective		**Less costly, more effective**	
sorafenib vs. BSC	0.8%	sorafenib vs. BSC	0.0%
sorafenib vs. lenvatinib	89.6%	sorafenib vs. lenvatinib	10.1%

Figure 20. Scatterplot – Direct comparison based on the DECISION trial (15) (Sorafenib and BSC) and indirect comparison based on DECISION and SELECT trial (25) (lenvatinib and BSC)

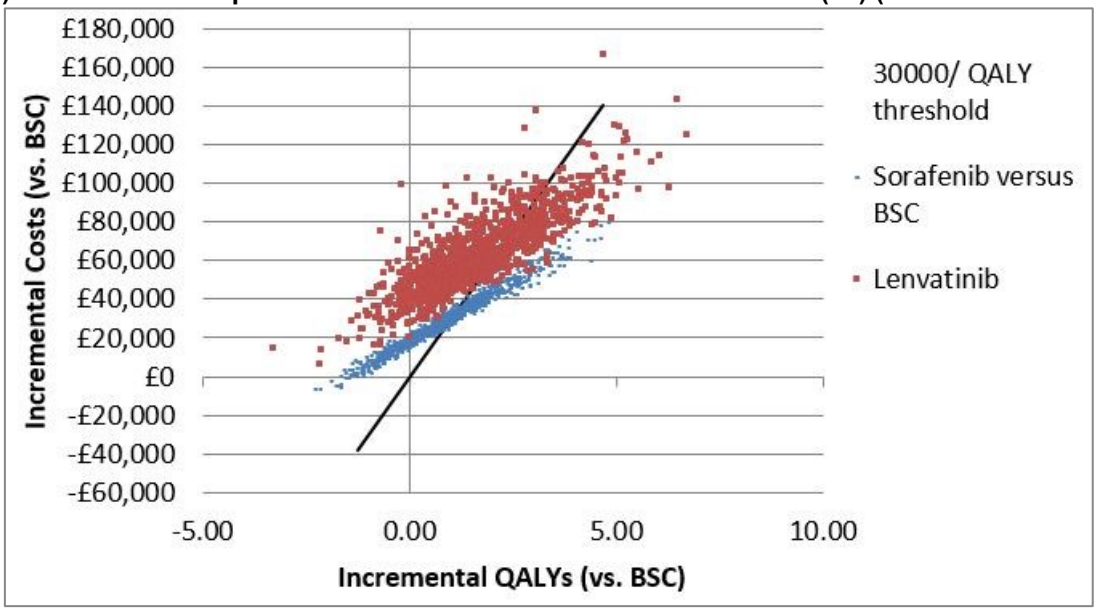


Figure 21. Cost-effectiveness acceptability curves (CEACs) – Indirect comparison based on the DECISION (15) and SELECT trials (25) (Sorafenib, lenvatinib and BSC)

In the CEAC the horizontal, x-axis represents a health care payer's WTP for an additional unit of health outcome (QALY in this case), while the vertical, y-axis represents the probability of cost-effectiveness. At a WTP value of £30,000/QALY gained the probability of sorafenib being cost-effective was 27%, BSC 56% and lenvatinib 17% (Figure 21). As the WTP increases the probability of lenvatinib being cost-effective also increases and crosses BSC at £42,000/QALY.

4.10.2 Deterministic sensitivity analysis

Univariate sensitivity analyses were conducted by varying a single parameter with parameter uncertainty at a time to test its impact on the model results. The parameters with the most impact on the ICERs are displayed in Figure 22 and Figure 23 showing the comparisons of lenvatinib vs. BSC and sorafenib vs. lenvatinib. The bars show the variation from base-case value using the high and low value for each parameter. (Results for all parameters are detailed in Appendix 7.12.) The largest deviation from base case in ICERs was caused by variations of the OS HR for lenvatinib in both cases. In addition results were sensitive to the progression-free health state utilities, the outpatient routine care costs and the OS curves.

Figure 22. Tornado diagram for the INB with a threshold of £50,000 – Indirect comparison based on the DECISION trial (15) and SELECT trial (25) (lenvatinib vs. BSC)

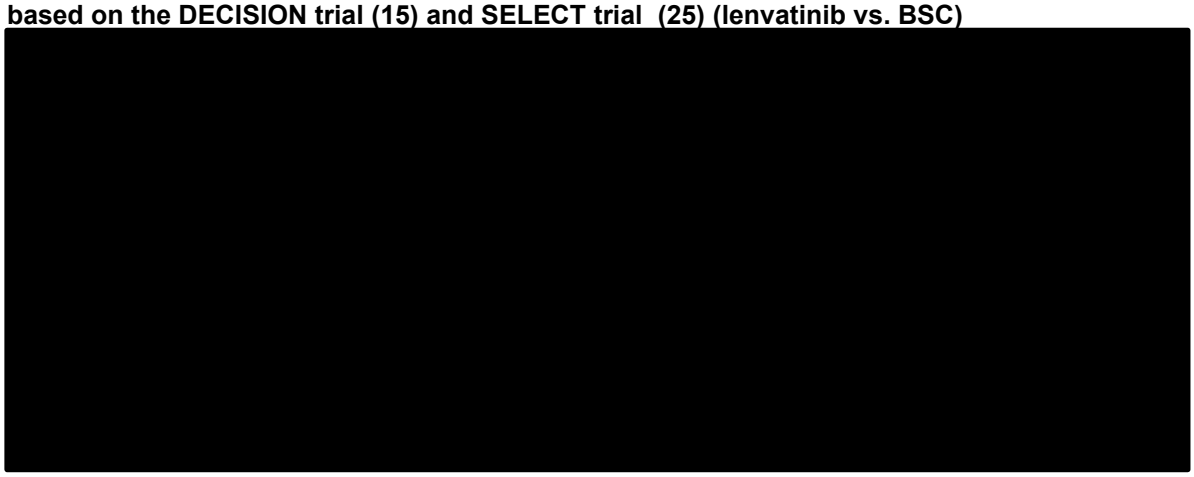
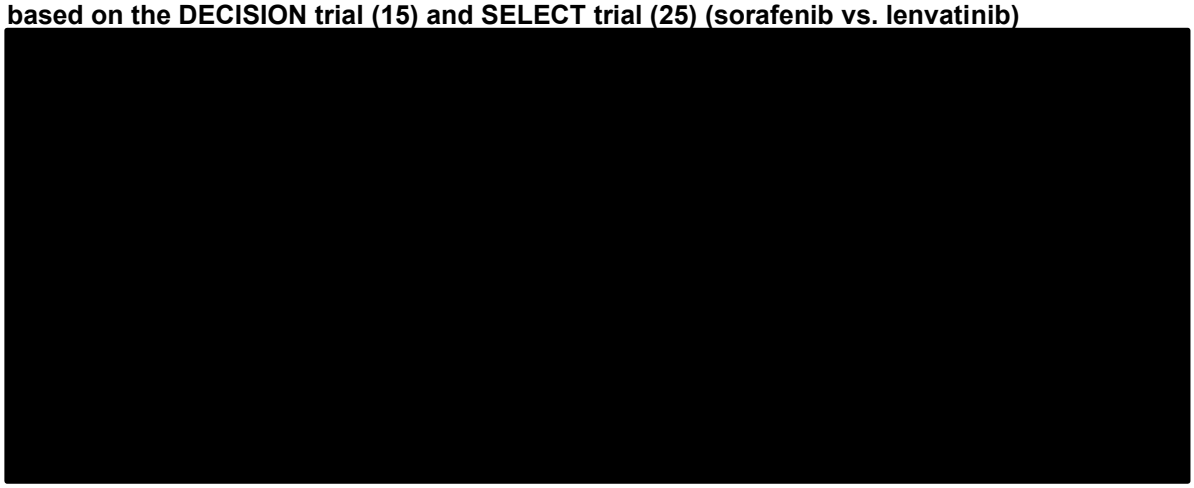


Figure 23. Tornado diagram for the INB with a threshold of £50,000 – Indirect comparison based on the DECISION trial (15) and SELECT trial (25) (sorafenib vs. lenvatinib)



Scenario analysis

Scenario analyses were conducted to test the robustness of the model in light of the structural and methodological uncertainties. These included:

- Assumptions around the time horizon: 10 and 20 years
- Reduced discount rate: 1.5% for both costs and health benefits
- Assumptions around the distribution used for PFS: Weibull distribution (as only proportional hazard models can be used for the indirect comparison)
- Assumptions around the distribution used for OS: Weibull distribution (as only proportional hazard models can be used for the indirect comparison)

- Utility for lenvatinib: allowing a lower utility value for lenvatinib in the progression-free health state to reflect differences in AE profile seen in section 3.3.3.
- Use of adjusted HR from the MAIC
- As the HR for TTD underestimates the treatment duration with lenvatinib (as it includes both first and second line patients), the effect of this was explored using a HR of 0.5

Similar to the scenario analysis for direct comparison, the scenario analyses for indirect comparison highlighted that the ICERs were sensitive to assumptions regarding the OS and the time horizon independently of the comparison:

- **Time horizon:** Although the time horizon of 10 years is not appropriate given the duration of survival of patients with DTC, it was tested as an extreme assumption to assess the effect of time horizon on QALYs vs. costs. Reducing the time horizon from 30 years to 10 years results in a 34% increase for ICER for lenvatinib versus BSC to £[redacted]/QALY (from £[redacted]/QALY respectively) and 40% increase in the ICER for lenvatinib versus sorafenib to £[redacted]/QALY from £[redacted]/QALY respectively). Therefore reducing the time horizon has a greater impact on lenvatinib than sorafenib.
- **Overall survival:** using a Weibull distribution for overall survival results in a 33% increase in ICER for lenvatinib versus BSC to £[redacted]/QALY (vs. £[redacted]/QALY for exponential) and a 28% increase in ICER for lenvatinib versus sorafenib to £[redacted]/QALY (vs. £[redacted]/QALY for exponential OS).
- **Lenvatinib pre-progression utility:** The extreme scenario showed that the results are very sensitive to this uncertain parameter, resulting in 16% increase in the ICER for lenvatinib vs. BSC (£[redacted]/QALY from £[redacted]/QALY) and a 36% increase for lenvatinib vs. sorafenib [redacted]/QALY from £37,789/QALY).
- **Increased treatment duration (TTD) for lenvatinib:** increased the ICER for lenvatinib vs. sorafenib by 35% (£50,874/QALY from £37,789/QALY) and vs. BSC by 19% (£[redacted]/QALY from £[redacted]/QALY).

- **HRs from the MAIC:** the use of MAIC HRs had increased the ICER for lenvatinib vs. BSC by 3% (£[redacted]/QALY from £[redacted]/QALY) and by 7% for lenvatinib vs. sorafenib (£[redacted]/QALY from £[redacted]/QALY). This is due to lenvatinib increasing the duration of the pre-progression period, thereby having only minor effect on the utilities, while increasing the routine care costs, which are the highest in the pre-progression period. However this underestimates the effect of the increased PFS on costs, as the TTD curves were not modified due to lack of data. The increased PFS would most likely also increase the time on treatment.

Additionally the lower discount rates decreased the ICERs by 9-11%. As the majority of the incremental costs are accrued earlier, thereby the discount rates have smaller effect on costs, while the QALYs are accrued throughout the time period and are more susceptible to changes in discount rates. The remainder of the scenarios had negligible impact (~5% change from baseline).

Table 44. Scenario analyses – Indirect comparison based on the DECISION trial and SELECT trial (Sorafenib, lenvatinib and BSC)

Scenarios	ICER (£/QALY) Sorafenib vs. BSC	Change from baseline (base case ICER) (%)	ICER (£/QALY) Lenvatinib vs. sorafenib	Change from baseline (base case ICER) (%)	ICER (£/QALY) Lenvatinib vs. BSC	Change from baseline (base case ICER) (%)
Base case	[redacted]	0%	[redacted]	0%	£[redacted]	0%
Time horizon (base case: 30 years)						
Time horizon: 10 years	[redacted]	29%	[redacted]	40%	[redacted]	34%
Time horizon: 20 years	[redacted]	3%	[redacted]	6%	[redacted]	4%
Discount rate (base case: 3.5% for costs and health benefits)						
Discount rate: 1.5% for costs and health benefits	[redacted]	-9%	[redacted]	-11%	£[redacted]	-10%
PFS (base case: exponential distribution)						
PFS distribution: Weibull distribution	£[redacted]	0%	[redacted]	5%	£[redacted]	3%
OS (base case: exponential distribution)						
OS distribution: Weibull distribution	[redacted]	38%	[redacted]	28%	£[redacted]	33%
Utility for lenvatinib in progression-free health state (base case: 0.72)						
Utility: 0.648	[redacted]	0%	[redacted]	36%	£[redacted]	16%
HR for the indirect comparison (base case [redacted] for PFS and [redacted] for OS)						
HRs: [redacted] for PFS and [redacted] for OS	[redacted]	0%	[redacted]	7%	£[redacted]	3%
Treatment duration (base case HR sorafenib vs. lenvatinib: [redacted])						
HR sorafenib vs. lenvatinib: 0.5	[redacted]	0%	[redacted]	35%	£[redacted]	19%

Summary of sensitivity analyses results

The scatterplot for lenvatinib seemed more spread, indicating higher uncertainty and less correlated incremental QALY and costs for lenvatinib than for sorafenib, probably due to the use of an extra parameter, the HR from the ITC. The HRs themselves have high uncertainty, with no statistically significant value for the most influential parameter, the OS. The cloud for lenvatinib was consistently above that for sorafenib, indicating the lenvatinib had both higher incremental costs and higher incremental QALYs. The ITC HR was also the most influential parameter in the analyses involving lenvatinib. However the HRs from the MAIC resulted in small changes in the ICER compared to using the ITC. This is due to the similar non-statistical difference in OS and that although there is a statistically significant

difference in PFS, it has minor influence on health outcomes and overall costs. Due to lack of data, this analysis is exploratory, as the full effect of the differences in the patient populations could not be explored.

There was no treatment duration reported for the appropriate subgroup for lenvatinib, which is likely to be higher, further increasing costs and the ICER. An exploratory scenario analyses showed that the HR for TTD has a large effect on the ICER.

Results were also sensitive to other aspects of the OS parameters, and the pre-progression utility values. In this later there is also substantial uncertainty, as the SELECT trial did not report utility values, and the published vignette utilities lacked face validity. In this analysis, the conservative assumption of equal utilities for sorafenib and lenvatinib was assumed. However if due to additional AEs, the utility values for lenvatinib were be lower, it could increase the ICER for lenvatinib substantially.

Assessment of factors relevant to the NHS and other parties

5.1 Budget impact analysis

5.1.1 Purpose

A budget impact analysis was developed to assess the annual impact of the introduction of sorafenib for the treatment of radioactive-iodine refractory locally advanced/metastatic, differentiated thyroid cancer in the UK. As a scenario the analysis also considers the impact of introducing lenvatinib either alone or alongside sorafenib.

5.1.2 Eligible population

The calculation of eligible population in England and Wales is composed of the estimation of prevalence and incidence of thyroid cancer and the proportion of thyroid cancer patients with the licenced indication (locally recurrent or metastatic, progressive, differentiated thyroid cancer (DTC) that is refractory to radioactive iodine treatment). The eligible population considered in the model is shown in Table 45.

1.1 Prevalence rate of thyroid cancer per 100,000 in the UK in 2012; 1.9 for males and 5.9 for females (73)

1.2 Incidence rate of thyroid cancer per 100,000 in the UK 2014: 3 males and 7.4 females (74)

1.3 Number of deaths from thyroid cancer in England: Males 73, Females 167 (75). Number of deaths in Wales from codes C73-C75 including endocrine cancer: Males 4, Females 10 (76). Number of wales deaths reweighted using English ICD codes: Males 3, Females 7. Total deaths for England and Wales used in calculations: Males 76, Females 174. Therefore the weighted average mortality rate for thyroid cancer patients is 4.9%

1.4 Population size England and Wales population estimates for males and females: Mid 2014: males 28,294,511 and 29,114,143 females (77)

1.5 Proportion of thyroid cancer patients that have the histology of differentiated thyroid cancer: 90% (59)

1.6 Of patients with differentiated thyroid cancer 5% are metastatic iodine refractory. (78)

The model assumes that 100% of the cohort with licensed indication are eligible to receive new medicine. The number of patients treated is estimated to increase from 28 patients in year 1 to 113 patients in year 5.

Table 45 Summary of estimated patients treated (subsequent 5 years)

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated number of patients with the condition	5,259	5,259	5,259	5,259	5,259
Mortality rate of patient cohort with the condition	4.87%	4.87%	4.87%	4.87%	4.87%
Net number of patients with the condition	5,003	5,003	5,003	5,003	5,003
Proportion of patient cohort with the condition treatable under the licence (eligible patients)	4.50%	4.50%	4.50%	4.50%	4.50%
Potential number of eligible patients treated each year in licence	225	225	225	225	225
Proportion of eligible patients treated with new medicine	100.00%	100.00%	100.00%	100.00%	100.00%
Potential number of eligible patients treated each year	225	225	225	225	225
Discontinuation rate	12.50%	25.00%	37.50%	50.00%	50.00%
Number of patients treated in each year	**28**	**56**	**84**	**113**	**113**

5.1.3 Assumptions

- Current analysis of budget impact does not include any subpopulation. Therefore, the analysis assumes that 100% of the cohort with licensed indication are eligible to receive new medicine.

- The cost of sorafenib considered in the budget impact analysis is [redacted] for 28 days which is included based on commercial arrangement. The list price of lenvatinib is used.

- The impact of treatment discontinuation is considered in the length of treatment, which includes the impact of treatment discontinuations due to various reasons such as progression and adverse-events.

- Sorafenib and lenvatinib usage is not indicated with additional supportive medicines. The DECISION trial protocol did not include additional medicines with sorafenib. However, additional medicines are provided as a part of best supportive care to patients while on treatment with sorafenib or lenvatinib and off treatment/ post-progression. Based on clinical opinion, medicines included in best supportive care are administered at the same frequency while on treatment and off treatment. Hence, this analysis assumes that there are no additional supportive medicines provided alongside sorafenib

- The estimated cost of medication per annum per patient in the base case is based on an assumption that sorafenib will be the only treatment on the market for the indication (inclusion of lenvatinib alongside sorafenib is also considered)

5.1.4 Costs

In addition to technology costs, two factors were considered: additional costs due increased resource use and increased adverse event management costs on sorafenib and lenvatinib

The incremental use of resources while receiving sorafenib or lenvatinib compared to no active treatment was considered as additional cost to the payer. Clinical opinion was elicited to understand resource use when receiving active treatment with sorafenib and receiving best supportive care (no active treatment) (see section 4.5.3). The estimated additional costs due to increased resource use on sorafenib compared to best supportive care is [redacted] per patient (see section 4.5.5 with costs calculated for a month rather than for the 28 day cycle from the cost-effectiveness analyses) and assuming a treatment duration of 10.6 months (15) the incremental resource use is [redacted]. For lenvatinib resource use is assumed to be the same per month (see section 4.5.5) ,however duration of treatment is longer (13.8 months) (25) and therefore the incremental difference compared with BSC is higher at [redacted]

As per DECISION and SELECT trials, different safety profiles were observed on sorafenib, lenvatinib and best supportive care. The incremental costs on sorafenib or lenvatinib compared to best supportive care due to management of adverse events was considered as additional costs to the payer. Incidence of adverse event for sorafenib was based on DECISION trial, for lenvatinib on the SELECT trial. Grade 3 or 4 AEs occurring in >5% of patients in the sorafenib arm of the DECISION trial or the lenvatinib arm of the SELECT trial were considered (see section 4.4.5). The cost of management was based on clinical opinion (see section 4.5.6). The estimated additional costs due to increase adverse event management costs compared to best supportive care for their respective treatment duration is £63.61 for sorafenib, and for lenvatinib is £121.90.

Table 46 Total additional costs associated with treatment per patient

Sorafenib	[redacted]
Lenvatinib	[redacted]

5.1.5 Potential resource savings

There were no resource savings included.

5.1.6 Summary of estimated annual budget impact

Using the number of patients treated in each year, the budget impact is estimated to be £[redacted] in year 1 after the introduction of sorafenib only, increasing to £[redacted] in year 5 (

1.7 Table 47). The estimated budget impact of introducing both lenvatinib and sorafenib with a 50% market share is shown in

Table 48, and with lenvatinib only in Table 49.

Table 47 Estimated annual budget impact – sorafenib only

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated in each year	28	56	84	113	113
Budget impact (net medicine cost; new medicine and supportive medicine costs only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 48. Estimated annual budget impact – sorafenib and lenvatinib 50/50 split

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients treated in each year	28	56	84	113	113
Budget impact (net medicine cost; new medicine and supportive medicine costs only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 49. Estimated annual budget impact – lenvatinib only

	Year 1	Year 2	Year 3	Year 4	Year 5

Number of patients treated in each year	28	56	84	113	113
Budget impact (net medicine cost; new medicine and supportive medicine costs only)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net total budget impact	£[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Dear NICE and Assessment Group,

Please find below responses to questions received on the 14th June 2017 regarding the ongoing appraisal of sorafenib for the treatment of differentiated thyroid cancer after radioactive iodine.

Question 1: In the Bayer economic model, please could you indicate whether the data included in the model in the range 'Efficacy Inputs'!AJ22:AK422 is unadjusted Kaplan-Meier data for the placebo arm of the DECISION trial, or whether it has been adjusted for crossover.

If the data are unadjusted, please could you provide the equivalent data after RPSFT adjustment?

Answer:

The data in range 'Efficacy Inputs'!AJ22:AK422 are unadjusted. The adjusted values (RPSFT) are provided in the accompanying file titled 'ID1056 OSRPSFT KMs May2013 CiC'.

Question 2: It would also be helpful to know how many patients with death recorded were recensored during the RPSFT analysis.

Answer:

For the RPSFT data the placebo arm (ITT) has [redacted] death events, whereas placebo RPSFT has [redacted] death events, resulting in [redacted] patients transitioning from death to censored in the RPSFT analysis. Details can be found in the table below:

31 May 2013 (Overall survival)	**Arm**	**N (deaths)**
	placebo ITT	[redacted]
	placebo RPSFT	[redacted]

Dear NICE and Assessment Group,

Please find below a response to the clarification question received on the 21st June 2017 regarding the ongoing appraisal of sorafenib for the treatment of differentiated thyroid cancer after radioactive iodine.

Question 1: Comparison of new placebo OS data with K-M data in the Bayer submitted model appears to be consistent with an RPSFT adjustment. However, comparison of OS sorafenib data in the submitted model with the new sorafenib data seems to show longer follow-up in the new data set following a different (less advantageous) trajectory. Please clarify if a later data cut is used in the new sorafenib data set and whether this is consistent with the other OS data used in the submitted model.

Answer:

Thank you for contacting us regarding inconsistencies found in the overall survival data in the sorafenib economic model. Apologies for any confusion this has caused.

The data found in cells (AH24:AI422) of the 'Efficacy inputs' tab in the economic model, which the Assessment Group correctly highlighted as having a shorter follow-up time, is from the original 2012 data cut (1). Data in these cells are not used in any of the model calculations, other than one graph titled 'Visual Comparison' which can be found on the 'OS Detail' sheet in cells D35:L64. This graph is used to provide a visual comparison between overall survival parametric fits and the KM data but is not linked to the cost-effectiveness calculations.

Historically the economic model was developed with the 2012 overall survival data. Model validation for this submission was conducted on all cells used to calculate model results; unfortunately the data in question was not updated. Further to receipt of this request we have conducted a full model validation and can confirm that no overall survival data from the 2012 data cut is used in the calculation of any model results.

Submitted with this response is a version of the economic model with a correction to the data in cells (AH24:AI422) of the 'Efficacy inputs' tab.

Please let us know if you have any further questions.

Kind Regards,

[redacted]

References:

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Multiple technology appraisal [ID1059]

Lenvatinib for treating differentiated thyroid cancer after radioactive iodine

Eisai submission

April 2017

Contents

List of tables

List of figures

Abbreviations

AE	Adverse event
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DTC	Differentiated Thyroid Cancer
ECOG	Eastern Cooperative Oncology Group
EBRT	External beam radiation therapy
EMA	European Medicines Agency
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
GBq	Gigabecquerel
GI	Gastrointestinal
HR	Hazard ratio
HRQOL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMRT	Intensity Modulated Radiation Therapy
IIR	Independent imaging review
ITT	Intent-to-treat
KM	Kaplan-Meier
LL	Log logistic
LY	Life year
MAIC	Matching-adjusted indirect comparison
MCi	Millicurie
MRI	Magnetic resonance imaging
N/A	Not applicable
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazard
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/pharmacodynamics
PM	Parametric
PP	Per protocol

PR	Partial response
PSA	Probabilistic sensitivity analysis
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RAI	Radioactive Iodine
RCT	Randomised, controlled trial
RECIST	Response evaluation criteria in solid tumours
RPSFT	Rank preserving structural failure time
SA	Sensitivity analysis
SAE	Serious adverse event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable disease
SELECT	Study of [E7080] LEnvatinib in 131I-refractory differentiated Cancer of the Thyroid
SPC	Summary of product characteristics
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
VEGFR	Vascular endothelial growth factor receptor

1 Executive summary

Overview

Radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC) is an ultra-orphan disease with a very poor prognosis. The course of the disease is unpredictable and variable. It is aggressive and difficult to treat, with a tendency to progress and metastasize.

Patients with DTC have a long natural history of disease. Many patients with RAI-refractory DTC have problematic disease-related symptoms which are experienced for a long time and can severely impact on quality of life. Response rates and progression-free survival are therefore very meaningful endpoints in this group of patients. In these symptomatic patients, whose quality of life is being impacted, it is also important to achieve a quick response.

Since chemotherapy yields very disappointing results, tyrosine kinase inhibitors (TKI) are becoming the standard of care for those patients needing systemic therapy. Sorafenib was the first TKI approved by the EMA, based on the DECISION study which showed a 5 month progression free survival benefit over placebo, and as indicated in the scope of this MTA, is currently available on the NHS through the Cancer Drugs Fund (CDF).

Lenvatinib is the second TKI to market after EMA authorisation on the basis of its outstanding results in progression free survival and tumour shrinkage, and its manageable safety profile. It yields a rapid and durable response in progressive RAI-refractory DTC and demonstrates a significant PFS benefit in patients who have not received prior TKI therapy. Therefore, it is important that clinicians in England and Wales have access to lenvatinib as a first-line treatment option for patients with progressive, symptomatic RAI-refractory DTC.

A partition survival cost effectiveness model was developed that compared lenvatinib versus sorafenib and best supportive care treatment in RAI-refractory DTC. Lenvatinib is show to be a cost-effective option against sorafenib at a willingness-to-pay threshold of £25,000 per QALY.

A number of additional scenarios and deterministic and probabilistic sensitivity analyses confirm the base case findings and add to the robustness of the economic case. In conclusion, lenvatinib represents a cost-effective treatment option in a difficult to treat RAI-refractory DTC population with limited treatment options.

Summary of the clinical effectiveness analysis

Background and unmet medical need in RAI-refractory DTC

Thyroid cancer is the most common of endocrine malignant neoplasms, although it represents 1% only of all malignancies. In England and Wales, in 2014, there were just over 3,000 reported cases of thyroid cancer. Differentiated thyroid cancer (DTC) accounts for 90% of thyroid carcinomas. DTC is usually a slowly progressing disease and patients are asymptomatic for long periods of time. Initial treatment of DTC generally involves surgery (thyroidectomy) followed by radioactive iodine (RAI) ablation of remaining thyroid tissue. At this stage of the disease there is a very good prognosis and treatment is curative for most patients.

However, about 10% of patients with DTC will eventually develop RAI-refractory DTC, which has a poor prognosis. The course of the disease is unpredictable and variable. It is aggressive and difficult to treat, with a tendency to progress and metastasize. The disease burden of RAI-refractory DTC can be significant as metastatic DTC causes problematic disease-related symptoms that patients experience for a long time. Increasing tumour burden can cause severe symptoms for patients due to airways obstruction. These can include pain, difficulty swallowing, coughing up blood, hoarseness, and trouble breathing

leading to asphyxia. Symptoms can become profoundly debilitating and cause patients to rely on carers.

Systemic therapy should be considered for tumours that are not amenable to surgery and/or local radiation therapy. It is widely acknowledged that RAI-refractory DTC is not sensitive to chemotherapy, a fact highlighted during the scoping consultation for this MTA. Since chemotherapy yields very disappointing results, this means that treatment options for these patients are very limited. Recently published guidelines recommend the use of targeted therapies (TKIs) as the first option in radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC), replacing chemotherapy. Patients with RAI-refractory DTC are monitored regularly by the clinician as part of their ongoing active surveillance. The decision to initiate a TKI is generally based on the observed progression of the disease and the impact of symptoms. This means that clinical trial endpoints such as PFS, response rates and time to response become even more important considerations when determining the treatment options.

Lenvatinib – Clinical effectiveness

Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs. It exhibits rapid binding to the target molecule and prolonged retention time due to slow dissociation rates, resulting in potent inhibition of kinase activity.

In the pivotal phase III trial, SELECT, lenvatinib significantly prolonged PFS by almost 15 months relative to placebo: median 18.3 months versus 3.6 months for placebo (HR = 0.21; 95% CI: 0.14, 0.31). The PFS rates for the lenvatinib arm compared with the placebo arm were estimated as follows: the 12-month rate, 63.0% versus 10.5%; and the 24-month PFS rate for the lenvatinib arm was 44.3% while the rate was not estimable for the placebo arm.

It is important to note that the PFS benefit associated with lenvatinib was maintained in all prespecified subgroups in the SELECT study. The majority of patients (76.3%) had not received prior TKI treatment and in these patients, the median PFS was 18.6 months. This highlights the efficacy of lenvatinib as a first-line treatment option for patients with RAI-refractory DTC.

The SELECT study demonstrated that lenvatinib yields a rapid and durable response in progressive RAI-refractory DTC. As stated previously, in these symptomatic patients, whose quality of life is being impacted, it is important to achieve a quick response. The median time to objective response in the SELECT study was only 2 months and lenvatinib is the only therapy that has reduced tumour size in the majority of patients (65% in the SELECT trial, including 4 complete responses).

In addition, lenvatinib significantly improved OS versus placebo (HR = 0.54; 95% CI: 0.36, 0.80) in an updated survival analysis from the SELECT trial using RPSFT adjustment for crossover.

As stated above, sorafenib is the only other drug licensed for use in the UK in RAI-refractory DTC. Although direct head to head comparative data between lenvatinib and sorafenib are not available, their respective phase III pivotal trials, SELECT and DECISION, are similar to allow indirect comparison.

The results of an indirect treatment comparison of the most recent data-cuts for both TKIs demonstrate that an advantage in PFS was shown for lenvatinib compared to sorafenib in

RAI-refractory DTC patients ([redacted]). No difference was observed in OS ([redacted]).

Lenvatinib – Safety information

The most frequently encountered adverse effects of lenvatinib are consistent with those of other antiangiogenic drugs targeting VEGF/VEGFR and can be managed with dose interruption or reduction and conventional medical care, generally in an outpatient setting. Life-threatening adverse events are rare.

The SELECT trial used an algorithm to manage treatment interruption due to adverse events (AEs) and subsequent reintroduction at a lower dose. As a result, the majority of patients were able to continue therapy in the SELECT trial with adverse events leading to study drug withdrawal in only 16.5% of patients receiving lenvatinib.

The most common adverse event in the SELECT trial was hypertension, which is manageable and rarely leads to adverse effects on quality of life. Only 1.1% of patients discontinued treatment due to hypertension.

Comparative safety information with sorafenib has shown that lenvatinib has a different safety profile from sorafenib.

The most frequent AEs for sorafenib in the DECISION trial, hand-foot skin reaction (76.3%) and alopecia (67.1%), which are known to greatly impact patients' daily lives, were reported much less frequently (32.2% and 12.3%, respectively) for lenvatinib patients in the SELECT trial. Incidence rates of diarrhoea, weight decrease and fatigue or asthenia were very similar in both trials. On the other hand, hypertension, decrease appetite and gastrointestinal symptoms other than diarrhoea were more frequently reported with lenvatinib than with sorafenib. Proteinuria was reported in 32.2% patients in the SELECT trial whilst there were no reports in DECISION.

Lenvatinib adverse events are manageable with dose interruption/reduction and conventional medical care. It is not expected that medical treatment of these adverse events adds significant extra costs to patients' management.

Summary of the cost-effectiveness analysis

A partition survival cost effectiveness model was developed that compared lenvatinib versus sorafenib and best supportive care treatment in RAI-refractory DTC using data from the SELECT trial as well as comparator data from the DECISION trial and resource use and unit costs based on UK reference costs. A comprehensive cost effectiveness analysis was conducted using validated methodological approaches and yields cost effective results vs sorafenib at a willingness-to-pay threshold of £25,000 per QALY.

A number of additional scenarios and deterministic and probabilistic sensitivity analyses confirm the base case findings and add to the robustness of the economic case.

In conclusion, lenvatinib represents a cost-effective treatment option in a difficult to treat RAI-refractory DTC population with limited treatment options.

2 The technology

2.1 Description of the technology

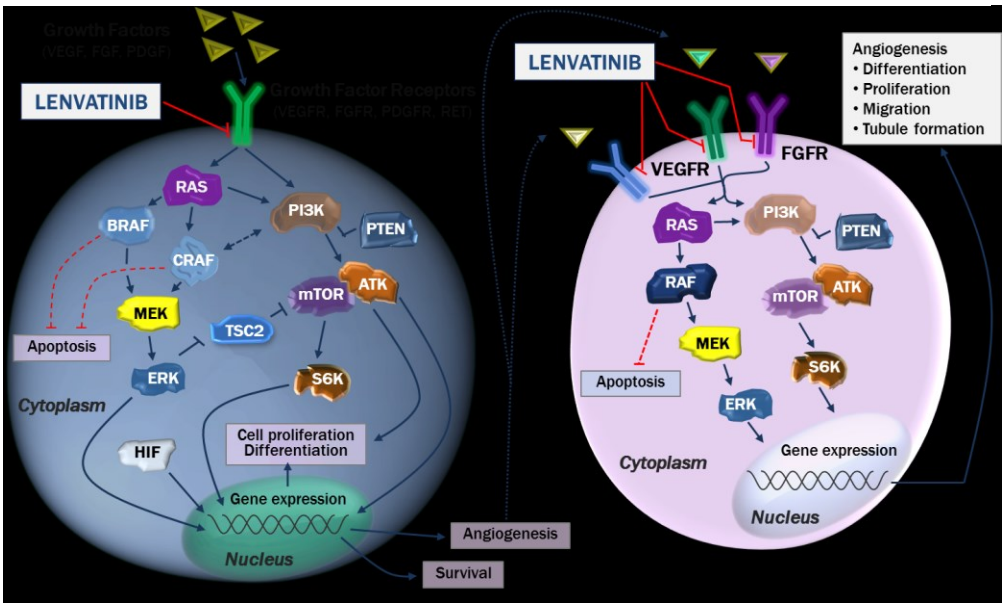
Lenvatinib (Lenvima®), is an orally administered multiple receptor tyrosine kinase inhibitor (TKI), available in two doses (4mg and 10mg) and given as a once daily hard capsule.

There are various molecular pathways involved in the growth and metastasis of thyroid cancer and multi-targeted tyrosine kinase inhibitors such as lenvatinib and sorafenib work on these pathways. There are, however, differences in the pathways that they target.

Lenvatinib has a novel binding mode that selectively inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, 2 and 3) and fibroblast growth factor (FGF) receptors (FGFR1, 2, 3 and 4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor [PDGF] receptor PDGFRα; KIT; and RET) involved in tumour proliferation.

Furthermore, it has been confirmed through X-ray co-crystal structural analysis to demonstrate a new binding mode (Type V) to VEGFR2. It exhibits rapid binding to the target molecule and prolonged retention time due to slow dissociation rates, resulting in potent inhibition of kinase activity.

Figure 1. Mechanism of action of lenvatinib on tumour cells and endothelial cells



Source: (Andrae, et al., 2008; de Groot, et al., 2006; Matsui, et al., 2008; Matsui, et al., 2008; Turner, 2010; Folkman, 2002)

The mechanism of action of lenvatinib involves effects on both endothelial cells, which are involved in tumour angiogenesis, and directly on tumour cells (Figure 1). In preclinical models, lenvatinib displayed potent antiangiogenic and antilymphogenic activity, inhibited tumour cell proliferation, induced tumour regression, and inhibited cell migration and invasion (Bruheim, et al., 2011; Glen, et al., 2011; Matsui, et al., 2008; Matsui, et al., 2008; Ogino, et al., 2011; Okamoto, et al., 2013).

Sorafenib inhibits VEGFRs 1,2, and 3, PDGFR β, Raf-1, RET, c-KIT, and BRAF. No noticeable activity is seen at the FGFR receptors.

2.2 Marketing authorisation/CE marking and health technology assessment

Lenvatinib is indicated for the treatment of adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI). (Appendix 1 – Summary of Product Characteristics)

Health technology assessment

Lenvatinib in this indication is not currently the subject of any other health technology assessment in the UK.

SMC advice (1179/16)

Lenvatinib is accepted for use within NHS Scotland in adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI).

http://www.scottishmedicines.org.uk/SMC_Advice/Advice/1179_lenvatinib_Lenvima/lenvatinib_Lenvima

2.3 Administration and costs of the technology

Please see Table 1 below.

Table 1 Costs of the technology being appraised

Pharmaceutical formulation	Lenvima® is supplied as 4mg and 10mg hard capsules, available in packs of 30.
Acquisition cost (excluding VAT) *	The list price for the 4mg and 10mg packs is £1,437.00.
Method of administration	Oral
Doses	The recommended daily dose of lenvatinib is 24 mg. The daily dose is to be modified as needed according to the dose/toxicity management plan in the SPC (Appendix 1)
Dosing frequency	Once daily
Average length of a course of treatment	The average length of a course of treatment is 14 months.In the Phase III SELECT study (Schlumberger, et al., 2015), the median duration of treatment for patients taking lenvatinib was 13.8 months.
Average cost of a course of treatment	In the Phase III SELECT study, >80% required a dose reduction after 12 weeks and the mean dose of lenvatinib was 17.2mg. (Eisai Ltd., 2015).Therefore it is anticipated that the average cost of lenvatinib per month is £2,874 which equates to £40,236 for a course of treatment.
Anticipated care setting	Lenvatinib treatment should be initiated and supervised by a health care professional experienced in the use of anticancer therapies. Therefore it is anticipated that lenvatinib treatment will be managed in a secondary care setting.

Source: Lenvima SPC (Appendix 1), unless otherwise stated

2.4 Changes in service provision and management

Lenvatinib is an orally administered drug that can be given at an outpatient clinic and/or taken at home, not requiring hospital stays.

Compared to sorafenib, lenvatinib adds the convenience of once daily administration, which potentially could improve treatment adherence. In principle, tests or investigations for selection or monitoring of patients are not expected to differ when either sorafenib or lenvatinib is prescribed. In the same way, no changes in the pattern of services provided are expected.

2.5 Innovation

Eisai consider lenvatinib to be innovative as it is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs (Matsui, et al., 2008).

Unlike sorafenib, it has been shown that fibroblast growth factor FGF23 is significantly upregulated with lenvatinib and this was associated with longer PFS, which is suggestive of the essential role of FGFR inhibition on lenvatinib efficacy in patients with RAI-refractory DTC. (Tahara M, 2017)

Lenvatinib exhibits rapid binding to the target molecule and potent inhibition of kinase activity, yielding a rapid and durable response in progressive RAI-refractory DTC.

Lenvatinib is the only therapy that has reduced tumour size in the majority of patients (65% in the SELECT trial, including 4 complete responses) and the median time to objective response was 2 months (95% CI, 1.9-3.5) (Schlumberger, et al., 2015).

3 Health condition and position of the technology in the treatment pathway

3.1 Disease Overview

Thyroid cancer is the most common of endocrine malignant neoplasms, although it represents 1% only of all malignancies. Over the last decade, thyroid cancer incidence rates have increased by more than two-thirds (71%) in the UK. In 2014, there were 3,064 patients diagnosed with thyroid cancer in England and Wales (Cancer Research UK, 2014).

Differentiated thyroid cancer (DTC) accounts for 90% of thyroid carcinomas (Pacini, et al., 2012). Differentiated thyroid cancers are made up of three main subtypes: papillary (~80% of thyroid cancers), follicular (about 10%), and Hürthle cell (about 3%) (Busaidy & Cabanillas, 2012).

DTC is usually a slowly progressing disease and patients are asymptomatic for long periods of time. Initial treatment of DTC generally involves surgery (thyroidectomy) followed by radioactive iodine (RAI) ablation of remaining thyroid tissue. Most patients with DTC have an excellent prognosis after receiving standard treatment (Burns & Zeiger, 2010).

However, about 10% of patients with DTC will eventually develop radioactive iodine (RAI)-refractory DTC, an ultra-orphan oncology indication. RAI-refractory DTC is generally defined as disease in which malignant/metastatic tissue is unable to take up radioactive iodine—either from the beginning of treatment or following previous successful uptake (Pacini, et al., 2012)

RAI-refractory DTC is a life-threatening form of thyroid cancer that has a poor prognosis. The disease is aggressive and difficult to treat, with a tendency to progress and metastasize. The 10-year survival rate among patients with radioiodine-refractory DTC is 10% from the time of metastasis detection (Durante, et al., 2006; Busaidy & Cabanillas, 2012)

3.2 Disease Burden

The disease burden of RAI-refractory DTC can be significant. Increasing tumour burden can causes severe symptoms for patients. Depending on the location of the metastatic disease, these can include pain, difficulty swallowing, coughing up blood, hoarseness, and trouble breathing leading to asphyxia (Greenblatt & Chen, 2007; Lin, et al., 2004; Kim, et al., 2005; Goyal, et al., 2012). Symptoms can become profoundly debilitating and cause patients to rely on carers.

3.3 Clinical Pathways of Care

In RAI-refractory DTC, systemic therapy should be considered for tumours that are not amenable to surgery and/or local radiation therapy. Since the role of chemotherapy in the treatment of these patients is very limited, TKIs are being increasingly used in this setting.

Sorafenib and lenvatinib are the only two TKIs currently approved in this indication by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). In England, sorafenib is currently available to patients on the NHS through the Cancer Drugs Fund for metastatic or inoperable papillary and follicular thyroid cancer, which is refractory to radioiodine. Lenvatinib was approved by the EMA in May 2015 and is yet to be made available on the NHS in England and Wales.

3.4 Clinical Guidelines

To date, NICE have not issued any guidelines on the management and treatment of thyroid cancer.

Recently updated guidelines such as the National Comprehensive Cancer Network (NCCN) guidelines on Thyroid Carcinoma, updated in August 2016 (National Comprehensive Cancer Network, NCCN, 2016) and the American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, updated in January 2016 (Haugen, et al., 2016) fully recommend the use of targeted therapies (TKIs) as the first option in radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC), replacing chemotherapy.

The European Society of Medical Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up of Thyroid Cancer were issued in 2012 (Pacini, et al., 2012) enlarging and updating previous guidance focused on DTC (Pacini, et al., 2009). In addition, as mentioned in the scope for this MTA, the British Thyroid Association's 'Guidelines for the management of thyroid cancer' outlines treatment options for differentiated thyroid cancer which include surgery, chemotherapy and radiotherapy (Perros, et al., 2014).

It is very important to note that both of the above mentioned guidelines were published in 2012 and 2014, before the targeted therapies became available.

The recommendations from all guidelines are summarised below.

NCCN Guidelines

In accordance with the NCCN guidelines, systemic therapy can be considered for tumours that are not surgically resectable; are not responsible to 131I; are not amenable to EBRT treatment, SBRT, IMRT or other local therapies; and have clinically significant structural disease progression during the last 6 to 12 months. Overall, traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimal efficacy in patients with metastatic DTC. Lenvatinib and sorafenib are recommended for the treatment of RAI-refractory DTC.

The NCCN guidelines include a number of principles for kinase inhibitor therapy, one of which is that the pace of disease progression should be factored into treatment decisions. Patients with indolent disease who are asymptomatic may not be appropriate for kinase inhibitor therapy, particularly if the side effects of treatment will adversely affect the patient's quality of life, whereas patients with more rapidly progressive disease may benefit from kinase inhibitor therapy, even if they have drug-induced side effects.

American Thyroid Association Guidelines

The American Thyroid Association (ATA) has published their updated Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer in January 2016 (Haugen, et al., 2016). With regards to the use of kinase inhibitors, their recommendation is that they should be considered in RAI-refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to local control using other approaches.

The guidelines include a recommendation regarding the use of chemotherapy and states that has a very limited role due to its disappointing results. It can be considered in RAI refractory DTC patients with metastatic, rapidly progressive, symptomatic, and/or imminently threatening disease not otherwise amenable to control through other approaches, including kinase inhibitors. Too few data exist to recommend specific cytotoxic regimens, and use within the context of a therapeutic clinical trial is preferred (Recommendation 100, weak recommendation, low-quality evidence) (Haugen, et al., 2016).

European Society of Medical Oncology Guidelines

They state that EBRT may be indicated for local and regional recurrence and metastatic DTC when there is no significant radioiodine uptake in the tumour and complete surgical excision is not possible (level of evidence IV, based on retrospective cohort studies or case-control studies; degree of recommendation B, strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended). Chemotherapy is no longer indicated for metastatic disease because of lack of effective results (level of evidence IV; grade of recommendation D, moderate evidence against efficacy or for adverse outcome, generally not recommended) and should be replaced by enrolment of the patients in experimental trials with targeted therapy (Pacini, et al., 2012).

The Guidelines also state that although preliminary results of clinical trials testing tyrosine kinase inhibitor trials against DTC are promising and indicate that targeted therapy might become the first line treatment of metastatic refractory thyroid cancer patients in the near future, they are not standard therapy today and should be administered only in the context of clinical trials (Pacini, et al., 2012).

British Thyroid Association Guidelines

The guidelines which were published in July 2014, review EBRT, chemotherapy and targeted therapy for palliative care in the small percentage of patients with recurrent/ persistent or end-stage disease and include the following recommendations (Perros, et al., 2014):

- Palliative EBRT to localised areas of symptomatic metastatic disease may be appropriate in good performance status patients with anticipated survival of more than 6 months.
- Palliative chemotherapy has largely been superseded by targeted therapies. It can however be considered in good performance status patients with rapidly progressive, symptomatic, ^{131}I refractory, locally advanced/metastatic disease when targeted therapies are unavailable or have proved unsuccessful.
- The agents used are doxorubicin and cisplatin, but durable responses are uncommon (level of evidence 4, expert opinion; grade of recommendation D, Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+)
- Targeted kinase inhibitors (axitinib, motesanib, sorafenib, pazopanib, lenvatinib, sunitinib, cabozantinib, vandetanib) have demonstrated efficacy for progression-free survival, but not overall survival, in phase 2 or 3 studies.
- Sorafenib and lenvatinib are the agents that have shown the most activity and clinical benefit to date

3.5 Current clinical practice

As highlighted above, since the role of chemotherapy in the treatment of patients with RAI-refractory DTC is very limited, TKIs are being increasingly used in this setting.

In England, sorafenib is currently the only TKI available to patients on the NHS through the Cancer Drugs Fund for metastatic or inoperable papillary and follicular thyroid cancer, which is refractory to radioiodine.

4 Clinical effectiveness of lenvatinib. SELECT Study

4.1 Identification and selection of relevant studies

In order to provide information for the evidence submission for NICE technology assessment, a search strategy was developed and a literature search carried out to identify relevant research in the clinical efficacy and safety profile of therapies for the treatment of patients with RAI-refractory DTC. The review question was framed in terms of the PICOS elements and a review protocol was written to address search strategy, study selection, data extraction and quality assessment.

Specific details of the search terms and all strategies for the literature searches are provided in the Systematic Literature Review Report (Appendix 2).

Study selection

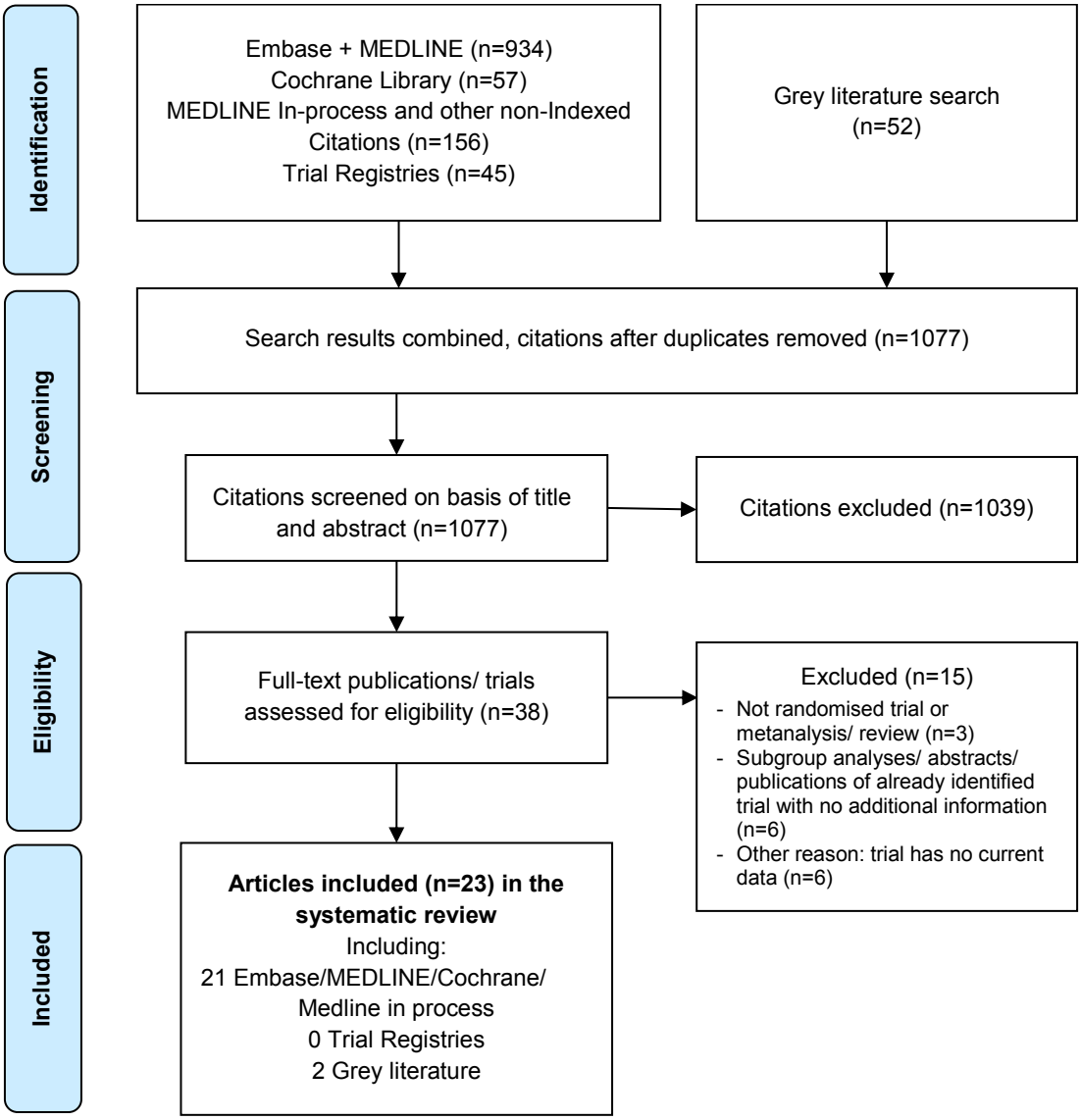
The searches were limited to records for English language articles, excluding non-human studies and publications that are reviews (except for systematic reviews, meta-analyses or pooled analyses), case reports, editorials, letters and notes/comments, where the indexing allowed. Table 2 below summarises the inclusion and exclusion criteria, language restrictions and the study selection process.

Table 2. Eligibility criteria used in the search strategy for clinical studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Radioiodine-refractory Differentiated Thyroid Cancer	Population investigated was not limited to patients with RAI-refractory DTC or mixed population with no separate results for RAI-refractory DTC population
Intervention / Comparators	Drug therapy	Diagnostic / radiology / surgical technique
Outcomes	Progression free survival Overall survival Response rate Quality of Life	
Study design	Randomised trials Systematic reviews Meta-analyses Pooled analyses	Experimental or non-human studies Reviews (except for systematic reviews, meta-analyses or pooled analyses) Case reports, editorials, letters and notes/comments Subgroup analyses/ abstracts/ publications of already identified trial with no additional information provided
Language restrictions	English	Non-English language

Source: Systematic Literature Review Report (Appendix 2)
Abbreviations: DTC, Differentiated Thyroid Cancer; RAI, radioactive iodine

Figure 2. PRISMA flow diagram for clinical study selection



The PRISMA flow diagram of the number of studies included and excluded at each stage is shown in Figure 2. The complete reference list for excluded studies is provided in the Systematic Literature Review Report (Appendix 2).

4.2 List of randomised controlled trials

The systematic literature review identified 2 full publications plus 13 conference abstracts (11 from Embase/ Medline/ Cochrane library and 2 from grey literature) and 8 meta-analyses and systematic reviews. The main trial identified for lenvatinib was SELECT (Schlumberger, et al., 2015). There were eight SELECT sub-studies identified, all of which were conference abstracts (Brose, 2015; Choi, 2015; Guo, et al., 2015; Habra, et al., 2015; Kiyota, 2015; Newbold, 2015; Tahara, 2015; Gianoukakis, 2016).

The DECISION study was the main trial identified for sorafenib (Brose, et al., 2014). There were five DECISION sub-studies identified, all were conference abstracts (Bastholt, 2014; Brose, 2014; Worden, 2014; Paschke, 2015; Fassnacht, 2016).

Full details on the two RCTs are provided in Table 3.

The next sections will focus on the phase III trial for lenvatinib, the SELECT trial. Please note that the response to the data analysis requests from the Assessment group can be found in Appendix 3.

Table 3 List of relevant randomised controlled trials

Trial Acronym	Population	Intervention	Comparator	Primary study reference
SELECT	Males or females age ≥18 years Histologically or cytologically confirmed diagnosis of DTC Measurable disease according to Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1) and confirmed by central radiographic review 131I-refractory/resistant disease Evidence of disease progression within 12 months prior to signing informed consent (+1 month screening window) Prior treatment with 0 or 1 VEGF or VEGFR-targeted therapy	Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule) continuous once daily oral dosing.	Placebo	Schlumberger, et al., 2015
DECISION	Age ≥18 years Locally advanced or metastatic differentiated thyroid cancer (papillary, follicular At least one measurable lesion by CT or MRI according to RECIST Progression within the past 14 months according to Response Evaluation Criteria in Solid Tumours (RECIST) Eastern Cooperative Oncology Group performance status 0–2 Radioiodine refractoriness	Sorafenib 400 mg (2 × 200 mg tablets) twice daily for a total daily dose of 800 mg.	Placebo	Brose, et al., 2014

Abbreviations: CT, Computed tomography; DTC, Differentiated Thyroid Cancer; MRI, Magnetic resonance imaging; RECIST, Response evaluation criteria in solid tumours; VEGFR, Vascular endothelial growth factor receptor

4.3 Summary of the methodology of SELECT

Trial design

The SELECT trial (E708-G000-303) is a two-arm, parallel-group study in which eligible patients were randomly allocated in a 2:1 ratio to receive either oral lenvatinib at a dose of 24 mg or matching placebo. Randomisation was performed centrally by an interactive voice and web response system (IVRS). Patients were stratified according to age (≤65 years or >65 years), geographical region (Europe, North America, Other) and receipt or non-receipt of prior VEGF targeted therapy (0, 1). (EisaiDOF, 2014)

Patients, investigational personnel involved with their management, independent investigators reviewing and assessing disease progression and statisticians were kept blind to study medication for the whole length of the study.

Eligibility criteria

Study participants were adult (≥18 years of age) male or female patients with measurable histologically or cytologically confirmed diagnosis of DTC showing 131I-resistant disease and evidence of disease progression within 12(+1) months prior to signing informed consent and a score ≤2 in the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS). 131I-refractory/resistant disease was defined by at least one of the following:

- One or more measurable lesions that did not demonstrate iodine uptake on any radioiodine scan;
- One or more measurable lesions that had progressed, according to RECIST 1.1, within 12 months of 131I 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 131I of >600 mCi or 22 Gigabecquerels (GBq), with the last dose administered at least 6 months prior to study entry
- Disease progression was defined according to RECIST 1.1 criteria and assessed and confirmed by central radiographic review of CT and/or MRI scans.

Subjects could have received 0 or 1 prior VEGF/VEGFR-targeted therapy (e.g. sorafenib, sunitinib, pazopanib) (Table 6). Before patients were recruited into this study, some patients already had access to other VEGF/VEGFR-targeted therapies, mainly sorafenib, through prior recruitment into other trials (Schlumberger, et al., 2015)

Subjects were not eligible for participation in the study if they had anaplastic or medullary carcinoma of the thyroid, had received 2 or more prior VEGF/VEGFR-targeted therapies, or had received any anticancer treatment within 21 days or any investigational agent within 30 days prior to the first dose of study drug.

Settings and locations for data collection

Outpatients at secondary and tertiary care facilities were recruited by qualified oncologists and endocrinologist under the sponsorship of Eisai at 117 investigational sites located in Europe (60), North America (31), Asia Pacific (13), Japan (6), and Latin America (7). Recruitment took place between August 2011 and October 2012.

Seven investigational sites were located in the UK, five of them in England:

- The Christie NHS Foundation Trust, Withington, Manchester
- Guys Hospital, London
- Sheffield Teaching Hospitals, Sheffield
- Gartnavel General Hospital, Glasgow
- Aberdeen Royal Infirmary, Aberdeen
- The Royal Marsden NHS Foundation Trust, London and Sutton, Surrey

Trial drugs and concomitant medications

Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule) and matching placebo capsules were taken orally once daily (QD), continuously.

Dose reductions occurred in succession based on the previous dose level (24, 20, 14, and 10 mg QD). Any dose reduction below 10 mg QD had to be discussed with the sponsor. Once the dose was reduced, it could not be increased at a later date. Dose reduction and interruption instructions for subjects who experience treatment-related toxicity were as described in Table 4.

Table 4 Study treatment dose reductions and interruption instructions

Treatment-related toxicity	During therapy	Adjusted dose
Grade 1a,b	Continue treatment	No change
Intolerable Grade 2c or Grade 3		
First occurrence	Interrupt until resolved to Grade 0-1 or baseline	20 mg orally once a day (one-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	14 mg orally once a day (one-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	10 mg orally once a day (one-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt until resolved to Grade 0-1 or baseline	Discuss with sponsor
Grade 4d	Discontinue study treatment	

Note: Grading according Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v4.0). All CTC grades of adverse events, decreasing and increasing, were collected.
a: A delay of study treatment for more than 28 days (due to treatment-related toxicities) required a discussion with the sponsor before treatment could be resumed.
b: Optimal medical management for nausea, vomiting, and/or diarrhoea was initiated prior to any study treatment interruption or dose reduction.
c: Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable.
d: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

Primary, secondary and tertiary outcomes

The primary efficacy outcome was Progression Free Survival (PFS), defined as the time from the date of randomisation to the date of first documentation of disease progression or death (whichever occurred first) as determined by blinded Independent Imaging Review (IIR) conducted by the imaging core laboratory using RECIST 1.1.

Secondary efficacy outcomes were the following:

- Overall Response Rate (ORR), defined as the proportion of subjects who had Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) as determined by blinded IIR using RECIST 1.1.
- Overall Survival (OS) measured from the date of randomisation until date of death from any cause.

In addition, the following exploratory efficacy outcomes were measured:

- Disease Control Response (DCR), defined as the proportion of subjects who had a BOR of CR, PR, or Stable Disease (SD). SD had to be achieved ≥7 weeks after administration of the first dose of study drug to be considered BOR.
- Clinical Benefit Rate (CBR), defined as the proportion of subjects who had a BOR of CR, PR, or durable SD (duration ≥23 weeks)
- Durable SD rate, defined as the proportion of subjects with duration of SD ≥23 weeks.

Table 5 summarises the methodology of the SELECT trial.

Table 5 Summary of SELECT trial methodology

	SELECT
Location	Multicentre trial carried out at 117 sites (Europe, 60; North America, 31; Asia Pacific, 13; Japan, 6; Latin America, 7).
Trial design	Parallel-group, randomised, double-blind, placebo-controlled
Eligibility criteria for participants	Adult subjects with histologically or cytologically confirmed diagnosis of DTC. Measurable disease as confirmed by central radiographic review 131I-refractory/resistant. Evidence of disease progression within 12 (+1) months prior to signing informed consent, according to RECIST 1.1 assessed and confirmed by central radiographic review of CT and/or MRI scans. 0 or 1 prior VEGF/VEGFR-targeted therapy. ECOG Performance Status (PS) 0-2.
Settings and locations where the data were collected	Outpatient Oncology and Endocrinology clinics at secondary and tertiary care facilities.
Trial drugs	Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule) and matching placebo capsules taken orally once daily, continuously. Treatment of complications or AEs or therapy to ameliorate symptoms could be given at the discretion of the investigator, unless it was expected to interfere with the evaluation of, or to interact with, study drug.
Permitted and disallowed concomitant medications	Subjects were not permitted to receive other anti-tumour therapies during the study other than thyroid hormone suppressive therapy.
Primary outcomes (including scoring method and timings of assessments)	PFS, as determined by blinded Independent Imaging Review (IIR) conducted by the imaging core laboratory using RECIST 1.1.
Secondary / tertiary outcomes (including scoring method and timings of assessments)	ORR, defined as the proportion of subjects who had BOR of CR or PR as determined by blinded IIR using RECIST 1.1. OS, measured from the date of randomisation until date of death from any cause.
Pre-planned sub-groups	Age: ≤65 years or >65 years. Geographic region: Europe, North America, Other. Receipt or non-receipt of prior VEGF targeted therapy.

Source: SELECT study CSR (Eisai Ltd., 2015), SELECT study primary reference (Schlumberger, et al., 2015)
Abbreviations: BOR, Best overall response; CR, Complete response; CT, Computed tomography; DTC, Differentiated Thyroid Cancer; ECOG, Eastern Cooperative Oncology Group; MRI, Magnetic resonance imaging; ORR, Objective response rate; OS, Overall survival; PR, Partial response; PFS, Progression free survival; RECIST, Response evaluation criteria in solid tumours; VEGFR, Vascular endothelial growth factor receptor

4.4 Statistical analysis and definition of study groups in SELECT

The study was designed to have 90% power to detect a 75% improvement in progression-free survival with lenvatinib versus placebo (hazard ratio for progression or death, 0.57) at a

two-sided alpha level of 0.01, assuming a median progression-free survival of 14 months in the lenvatinib group and 8 months in the placebo group. At least 214 progression events or deaths in 392 enrolled patients were required for the primary analysis of progression-free survival.

No interim analyses were performed. The rates of PFS and OS in the intention-to-treat (ITT) population for the primary analysis were estimated and plotted with the use of the Kaplan–Meier method and compared by using a stratified log-rank test. The hazard ratio and 99% (and 95%) confidence intervals were estimated using a stratified Cox proportional-hazards regression. Response rates, clinical benefit, and disease control were compared using a Cochran–Mantel–Haenszel tests at a two-sided α level of 0.05.

Subgroup analyses were performed according to age, sex, geographic region, histologic findings, thyrotropin level and receipt or non-receipt of one prior tyrosine kinase inhibitor treatment.

The analysis of OS was reported both as unadjusted and as adjusted for a potential crossover bias with the use of the rank preserving structural failure time (RPSFT) model.

4.5 Patient Population and participant flow

Overall, differences in baseline characteristics between the lenvatinib and placebo groups in baseline characteristics were minor (Table 6 below)

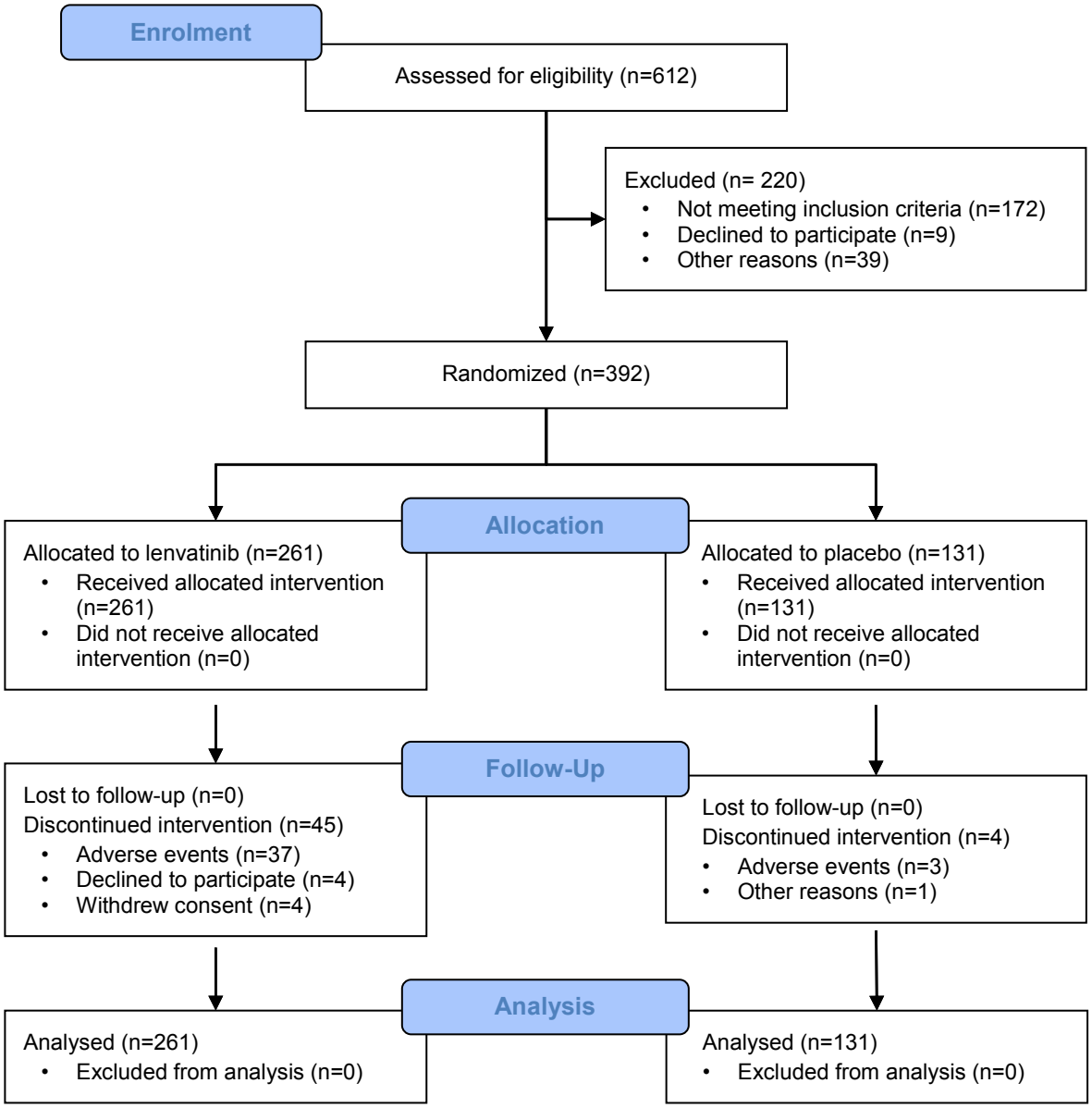
Table 6 Baseline Disease and Tumour Characteristics: Study 303 (SELECT) (ITT Population)

Trial no. (acronym) Characteristic	Lenvatinib	Placebo	Total
Study 303 (SELECT)	**(n = 261)**	**(n = 131)**	**(n = 392)**
Median time from diagnosis of DTC to randomisation, months (range)	66 (0.4, 573.6)	73.9 (6.0, 484.8)	67.5 (0.4, 573.6)
Median time from metastatic diagnosis to randomisation, months (range)	39.3 (0.4, 433.1)	41.6 (3.3, 258.3)	40.1 (0.4, 433.1)
Median time from recent disease progression to randomisation, months (range)	0.7 (0.2, 12.5)	1.1 (0.2, 13.6)	0.9 (0.2, 13.6)
Histologic subtype of DTC, n (%) Papillary Follicular	 169 (64.8) 92 (35.2)	 90 (68.7) 41 (31.3)	 259 (66.1) 133 (33.9)
ECOG performance status, n (%) 0 1 2 3	 144 (55.2) 104 (39.8) 12 (4.6) 1 (0.4)	 68 (51.9) 61 (46.6) 2 (1.5) 0	 212 (54.1) 165 (42.1) 14 (3.6) 1 (0.3)
No. prior VEGFR-targeted therapy, n (%) 0 1	 195 (74.7) 66 (25.3)	 104 (79.4) 27 (20.6)	 299 (76.3) 93 (23.7)

Source: SELECT study CSR (Eisai Ltd., 2015), SELECT study primary reference (Schlumberger, et al., 2015)
Abbreviations: DTC, Differentiated Thyroid Cancer; ECOG, Eastern Cooperative Oncology Group; ITT, Intent-to-treat; VEGFR, Vascular endothelial growth factor receptor

Figure 3 shows the participant flow in the SELECT trial.

Figure 3. CONSORT 2010 Flow diagram SELECT study



Source: SELECT study primary reference (Schlumberger, et al., 2015)

4.6 Quality assessment of SELECT

The methodological quality of SELECT was examined using the NICE methodology checklist to evaluate any potential biases affecting validity. Responses to each of the assessment criteria are tabulated in Table 7.

Table 7 Quality assessment of RCTs

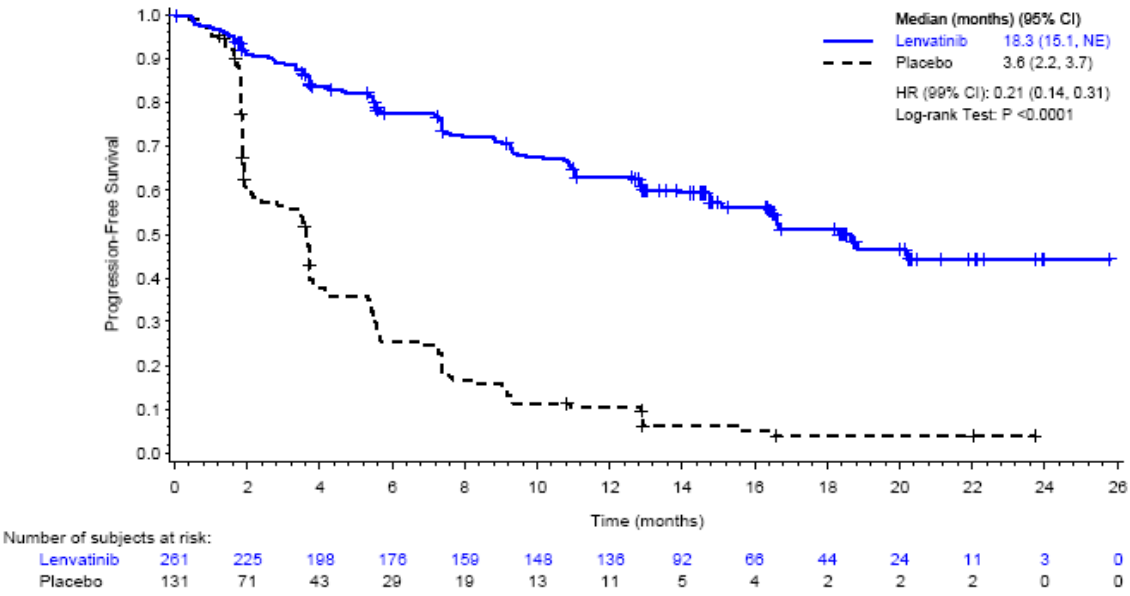
Trial acronym	SELECT
Was the randomization method adequate?	Yes
Was the allocation adequately concealed?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Where the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	Not clear
Is there any evidence to suggest that author measured more outcomes that reported?	No
Did the analysis include in intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

SELECT is considered to closely reflect routine clinical practice in England.

4.7 Clinical effectiveness results of SELECT

At the time of the primary analysis of progression-free patients, 202 had disease progression (93 [35.6%] in the lenvatinib group and 109 [83.2%] in the placebo group), and 18 patients had died before disease progression (14 in the lenvatinib group and 4 in the placebo group). The median progression free survival was 18.3 months (95% CI, 15.1 to not estimable) with lenvatinib as compared with 3.6 months (95% CI, 2.2 to 3.7) with placebo (hazard ratio for

Figure 4. Kaplan-Meier analysis of Progression-free Survival in the Intention-to-treat population (Schlumberger, et al., 2015)



progression or death, 0.21; 99% CI, 0.14 to 0.31; P<0.001). Figure 4 below shows the Kaplan-Meier curve and the results of the survival analysis for PFS.

Lenvatinib was associated with significant improvement in the response rate (64.8% in the lenvatinib group vs. 1.5% in the placebo group; odds ratio, 28.87; 95% CI, 12.46 to 66.86; P<0.001). CR occurred in 4 patients (1.5%) in the lenvatinib group as compared with no patients in the placebo group; PR occurred in 165 patients (63.2%) and 2 patients (1.5%), respectively; and DSD for 23 weeks or longer occurred in 40 patients (15.3%) and 39 patients (29.8%), respectively. Progressive disease occurred in 18 patients (6.9%) in the lenvatinib group as compared with 52 patients (39.7%) in the placebo group. In all 4 patients who had a complete response, the response was maintained through the last time point assessed (range, 84 to 124 weeks). Lenvatinib was associated with a median time to objective response of 2 months (95% CI, 1.9 to 3.5).

The difference in overall survival between the groups was not significant (hazard ratio for death, 0.73; 95% CI, 0.50 to 1.07; P = 0.10 by a stratified log-rank test); this difference became larger when a potential crossover bias was considered (RPSFT model; hazard ratio, 0.62; 95% CI, 0.40 to 1.00; P = 0.05 when calculated with the bootstrap method), indicating a trend for longer survival for the lenvatinib arm vs placebo crossover arm. As per the EMA request, the OS analysis was updated at a later cut-off on Jun 15th 2014. The RPSFT adjusted HR showed a significant difference in overall survival between the treatment groups (HR 0.53; 95%CI, 0.34 to 0.82, nominal P=0.0051).

Results from a further analysis performed on Aug 21st 2015, not published, confirmed this statistically significant difference in OS. Results for the planned and updated analysis of OS are summarised in Table 8. Full OS, PFS and ORR results from the updated analysis are available in the Eisai data on file reference (Eisai DOF, 2015).

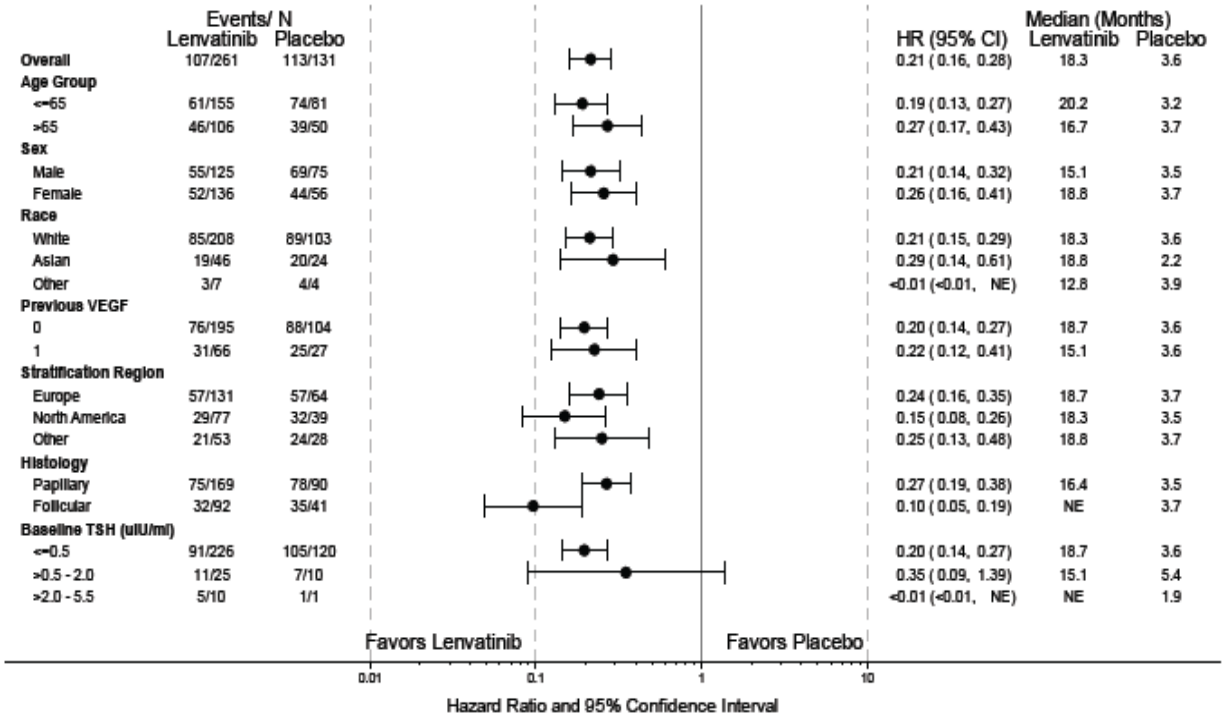
Table 8. Overall Survival from SELECT

	Lenvatinib (n = 261)	**Placebo (n = 131)**
1st Data Cut (15 November 2013) (Schlumberger, et al., 2015)		
Number of deaths (%)	71 (27.2)	47 (35.9)
Median OS in months (95% CI)	NE (22.0-NE)	NE (14.3-NE)
Unadjusted HR (95% CI), p value	0.73 (0.50-1.07), p=0.1032	
RPSFT adjusted HR (95% CI), p value	0.62 (0.40-1.00), p=0.0510	
2nd Data Cut (15 June 2014) (Guo, et al., 2015)		
Number of deaths (%)	93 (35.6)	55 (42.0)
Median OS in months (95% CI)	NE (30.9-NE)	19.1 (21.7-NE)
Unadjusted HR (95% CI), p value	0.80 (0.57-1.12), nominal p=0.1993	
RPSFT adjusted HR (95% CI), p value	0.53 (0.34-0.82), nominal p=0.0051	
3rd Data Cut (21 August 2015) (Eisai DOF, 2015)		
Number of deaths (%)	121 (46.4)	70 (53.4)
Median OS in months (95% CI)	41.6 (31.2, NE)	34.5 (21.7, NE
Unadjusted HR (95% CI), p value	0.84 (0.62-1.13), nominal p=0.2475	
RPSFT adjusted HR (95% CI), p value	0.54 (0.36-0.80), nominal p=0.0025	

Abbreviations: CI, Confidence interval; HR, Hazard ratio; NE, Not estimable; OS, Overall Survival; RPSFT, Rank-preserving structural failure time

4.8 Subgroup analysis in SELECT

Figure 5. Forest Plots of the HR for lenvatinib versus placebo for PFS in the SELECT study Subgroups (ITT Population)



Since Study 303 (SELECT) was a global study, and recognising differences in clinical practice and drug availability, patients were pre-stratified by geographical region, age group and prior VEGFR therapy. Pre-planned subgroup analyses explored the effect of these strata, as well as some other relevant characteristics.

Source:SELECT study CSR (Eisai Ltd., 2015)

Abbreviations: CI, Confidence interval; HR, Hazard ratio; NE, Not estimable; TSH, Thyroid stimulating hormone; VEGFR, Vascular endothelial growth factor receptor

Pre-planned subgroup analyses included were as follows:

- Strata: Geographic region (Europe, North America, Other); age (≤65, ≥65 years) and prior VEGFR therapy (0,1)
- Demographic characteristics: sex (male, female); race (white, Asian, other)
- Disease characteristics: baseline TSH (≤0.5, >0.5-2.0, >2.0-5.5, >5.5 mIU/L); histology (papillary, follicular)

PFS benefit associated with lenvatinib was maintained in all prespecified subgroups in the SELECT study. The median PFS with lenvatinib was 18.7 months among patients who had not received previous treatment with a TKI and 15.1 months among those who had received one prior treatment regimen with a tyrosine kinase inhibitor. The results within this particular sub group shows the greater PFS benefit that was seen in the patient group that had not received a prior TKI compared to those that did. The prior TKI sub group results should also be interpreted with caution due to the smaller number of patients (25% and 20% of the lenvatinib and placebo groups respectively had a prior TKI). Figure 5 shows the results of the subgroup analysis performed.

4.9 Adverse reactions

Table 9 summarises treatment emergent adverse events (TEAEs) reported in SELECT.

It is important to note that the median duration of treatment in study SELECT was more than 3 times longer in patients treated with lenvatinib than in those who received placebo (13.8 vs. 3.9 months, respectively). Therefore, the rate of adverse events should be considered in the light of this relatively long treatment duration and exposure for lenvatinib versus placebo.

Table 9 Summary of AEs (n [%]) reported in SELECT

	Lenvatinib (n=261)	Placebo (n=131)
Any AE	260 (99.6%)	118 (90.1%)
Any treatment-related AE	254 (97.3)	78 (59.5)
Any SAE	133 (51.0%)	31 (23.7%)
Any treatment-related SAE	79 (30.3)	8 (6.1)
Any Fatal AE	20 (7.7%)	6 (4.6%)
Any Treatment related fatal AE	6 (2.3%)	0
AEs that led to discontinuation	43 (16.5)	6 (4.6)
AEs that led to dose interruption	215 (82.4)	24 (18.3)
AEs that led to dose reduction	177 (67.8)	6 (4.6)
AEs of CTCAE ≥ Grade 3	223 (85.4)	39 (29.8)
Treatment-related AEs of CTCAE ≥ Grade 3	198 (75.9)	13 (9.9)

Source: SELECT Study CSR (Eisai Ltd., 2015)
Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, Serious adverse event

The most frequently reported (≥30% of subjects in either treatment arm) AEs, all of which occurred more frequently with lenvatinib than with placebo were (respectively): hypertension (69.3% vs. 14.5%), diarrhoea (66.3% vs. 16.8%), decreased appetite (53.3% vs. 18.3%), weight decreased (50.6% vs. 14.5%), nausea (46.4% vs. 25.2%), fatigue (42.1% vs. 24.4%), headache (38.3% vs 11.5%), stomatitis (35.6% vs. 6.9%), PPE syndrome (32.2% vs. 0.8%) and proteinuria (32.2% vs. 3.1%). Table 10 below lists all AEs of any grade in ≥10% of patients and of grade ≥3 in ≥2% of patients in the lenvatinib and placebo arms in SELECT.

Table 10 Adverse events of any grade in ≥10% of patients and grade ≥3 in ≥2% of patients

Adverse event	Lenvatinib (n=261)		Placebo (n=131)	
	Any grade (%)	Grade ≥3 (%)	Any grade (%)	Grade ≥3 (%)
Hypertension	181 (69.3)	112 (42.9)	19 (14.5)	5 (3.8)
Diarrhoea	173 (66.3)	22 (8.4)	22 (16.8)	0
Decreased appetite	139 (53.3)	15 (5.7)	24 (18.3)	1 (0.8)
Weight decreased	132 (50.6)	31 (11.9)	19 (14.5)	1 (0.8)
Nausea	121 (46.4)	6 (2.3)	33 (25.2)	1 (0.8)
Fatigue	110 (42.1)	12 (4.6)	32 (24.4)	2 (1.5)
Headache	100 (38.3)	8 (3.1)	15 (11.5)	1 (0.8)
Stomatitis	93 (35.6)	11 (4.2)	9 (6.9)	0
PPE syndrome	84 (32.2)	9 (3.4)	1 (0.8)	0
Proteinuria	84 (32.2)	26 (10.0)	4 (3.1)	0
Asthenia	65 (24.9)	15 (5.7)	17 (13.0)	3 (2.3)

Dyspnoea	39 (14.9)	4 (1.5)	24 (18.3)	4 (3.1)
Dysphagia	29 (11.1)	4 (1.5)	10 (7.6)	4 (3.1)

Source: SELECT Study CSR (Eisai Ltd., 2015)

Abbreviations: PPE, Palmar-plantar erythrodysaesthesia

Overall, serious treatment emergent adverse events (SAEs) were reported more frequently in the lenvatinib arm (51.0%) than in the placebo arm (23.7%) (Table 9). The most frequently reported (≥2% of subjects in either treatment arm) treatment-related SAEs in the lenvatinib and placebo arms, respectively, were pneumonia (3.8% vs. 2.3%), hypertension (3.4% vs. 0), dehydration (2.7% vs. 0) general physical health deterioration (2.3% vs. 0), dyspnoea (1.1% vs. 3.8%), dysphagia (1.1% vs. 2.3%) and haemoptysis (0 vs. 2.3%) (Eisai Ltd., 2015)

It is worth noting that when the rates of SAEs are adjusted for treatment duration, which is more than 4 times greater for lenvatinib than for placebo (298.8 vs. 67.1 person-years), the difference between lenvatinib and placebo becomes marginal for non-fatal SAEs (0.93 and 0.78 episodes per person-year, respectively) and absent for fatal events (0.07 and 0.10 episodes per person-year, respectively) (Lee, 2015)

The incidence of treatment-related AEs was 97.3% in the lenvatinib group vs. 59.5% in the placebo-arm. (Table 9) Grade 3 or higher treatment-related AEs were reported by 75.9% of patients in the lenvatinib group and 9.9% of patients treated with placebo. The most frequently reported (≥30% of subjects in either treatment arm) treatment-related AEs (all grades), all of which occurred more frequently with lenvatinib than with placebo were (respectively): hypertension (67.8% vs. 9.2%), diarrhoea (59.4% vs. 8.4%), decreased appetite (50.2% vs. 11.5%), weight decreased (46.4% vs. 9.2%), nausea (41.0% vs. 13.7%), fatigue (39.5% vs. 19.1%), stomatitis (35.6% vs. 3.8%), PPE syndrome (31.8% vs. 0.8%) and proteinuria (31.0% vs. 1.5%) (Schlumberger, et al., 2015).

For lenvatinib, grade ≥3 treatment-related AEs with an incidence ≥5% were hypertension (41.8%), proteinuria (10.0%), decreased weight (9.6%), nausea (9.2%), diarrhoea (8.4%) and decrease appetite (5.4%). The incidence of ≥grade 3 treatment-related AEs was much lower in the placebo arm, with the following being reported: hypertension, fatigue or asthenia (both, 2.3%), pulmonary embolism (1.5%) and abdominal pain and nausea (both, 0.8%).

Treatment-related SAEs were reported in 31.0% of subjects in the lenvatinib group and 6.1% of subjects in the placebo arm. The most frequently reported (≥2% of subjects in either treatment arm) treatment-related SAEs in the lenvatinib and placebo arms, respectively, were hypertension (3.4% vs 0%), pneumonia (2.3% vs 0%), and haemoptysis (0% vs 2.3%).

Adverse events leading to study drug withdrawal were reported in 37 (14.2%) of patients receiving lenvatinib and 3 (2.3%) patients in the placebo group. Most frequently reported AE leading to discontinuation in the lenvatinib group were asthenia and hypertension (1.1% each).

SELECT used an algorithm to manage treatment interruption due to AEs and subsequent reintroduction at a lower dose. (Appendix 1 – Summary of Product Characteristics) More patients in the lenvatinib arm than in the placebo group had either a treatment interruption (82.4% vs. 18.3) or a dose reduction (67.8% vs. 4.6%). Events requiring dose reduction or interruption in ≥15% of lenvatinib-treated subjects were diarrhoea (22.6%), hypertension (19.9%), proteinuria (18.8%) and decreased appetite (18.0%).

4.10 Interpretation of clinical effectiveness and safety evidence

As described in section 4.2, results from a systematic literature review (Appendix 2) identified one RCT each for lenvatinib (SELECT study) and for sorafenib (DECISION study). (Table 3)

Since the initial publication of these phase III pivotal trials, updated efficacy information has been identified for SELECT (Eisai DOF, 2015) and DECISION (Brose, et al., 2016). As the trials are similar enough to allow indirect comparison, these results have been used to conduct an indirect treatment comparison (ITC).
Details of the methodology and the full results of this ITC can be found in the Lenvatinib ITC report (Appendix 4). A summary of the results can be found in Table 11 and Figure 6 below.

Table 11 ITC results

	Lenvatinib/Placebo			**Sorafenib/placebo**			**Lenvatinib/Sorafenib**		
	HR	CI-	CI+	HR	CI-	CI+	**RR**	**CI-**	**CI+**
OS	[redacted]								
PFS	[redacted]								

Figure 6 ITC Forest Plot

[redacted]

Table 12 below summarises the safety results of both trials.

Table 12 Summary of safety results of studies SELECT and DECISION

	SELECT study		**DECISION study**	
	Lenvatinib n=261 (%)	**Placebo n=131 (%)**	**Sorafenib n= 207 (%)**	**Placebo n=209 (%)**
AEs	260 (99.6)	118 (90.1)	204 (98.6)	183 (87.6)
Serious AEs	133 (51.0)	31 (23.7)	77 (37.2)	55 (26.3)
Fatal AEs				
Total	20 (7.7)	6 (4.6)	12 (5.8)	6 (2.9)
Treatment related	6 (2.3)	0	1 (0.5)	1 (0.5)
AE leading to dose				
Discontinuation	43 (16.5)	6 (4.6)	39 (18.8)	8 (3.8)
Interruption	215 (82.4)	24 (18.3)	137 (66.2)	54 (25.8)
Reduction	177 (67.8)	6 (4.6)	133 (64.3)	19 (9.1)
Adverse events of any grade reported in ≥30% of patients across studies				
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	139 (53.3)	24 (18.3)	66 (31.9)	10 (4.8)
Weight decreased	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 (1.9)	15 (7.2)
Stomatitis	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)	NR	NR

	SELECT study		DECISION study	
	Lenvatinib n=261 (%)	**Placebo n=131 (%)**	**Sorafenib n= 207 (%)**	**Placebo n=209 (%)**
PPE Syndrome / Hand-foot skin reaction	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: SELECT Study CSR (Eisai Ltd., 2015), DECISION Study ((Brose, et al., 2014)
Abbreviations: AEs, Adverse Events; NR, Not reported; PPE, Palmar-plantar erythrodysaesthesia

In the DECISION trial, more patients in the sorafenib arm than in the placebo group withdrew treatment (18.8% vs. 3.8%) or had a dose interruption (66.2% vs. 25.8%) or reduction (64.3% vs. 9.1%). Hand-foot skin reaction was the most common AE leading to sorafenib withdrawal (5.3%) and dose interruption (26.6%) and reduction (33.8%).

The median duration of treatment in the DECISION trial was 10.6 months with sorafenib and 6.5 months with placebo. The mean daily dose of sorafenib used during the trial was 651mg.

Hardly unexpected considering their common mechanism of action targeting VEGF/VEGFR, most AEs reported for sorafenib in DECISION were also reported for lenvatinib in SELECT. Incidence rates of diarrhoea, weight decrease and fatigue or asthenia were very similar in both trials. The most frequent AEs for sorafenib in the DECISION trial, hand-foot skin reaction (76.3%) and alopecia (67.1%), which are known to greatly impact patient's daily lives, were reported much less frequently (32.2% and 12.3%, respectively) for lenvatinib patients in the SELECT trial. On the other hand, hypertension, decrease appetite and gastrointestinal symptoms other than diarrhoea were more frequently reported with lenvatinib than with sorafenib. Proteinuria was reported in 32.2% patients in the SELECT trial whilst there were no reports in DECISION.

In summary, 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.

4.11 Ongoing studies

Currently, there are no ongoing studies with lenvatinib in this indication which are due to complete in the next two years.

5 Cost-effectiveness

5.1 Published cost-effectiveness studies

Identification of studies

A systematic literature review was conducted to retrieve relevant information from the published literature regarding the economic implications, including the cost-effectiveness/utility and resource use, associated with therapies for the treatment of patients with RAI-refractory DTC. The review question was framed in terms of the PICOS elements and a review protocol was written to address search strategy, study selection, data extraction and quality assessment.

Specific details of the search terms and all strategies for the literature searches are provided in the Systematic Literature Review Report (Appendix 2).

Study selection

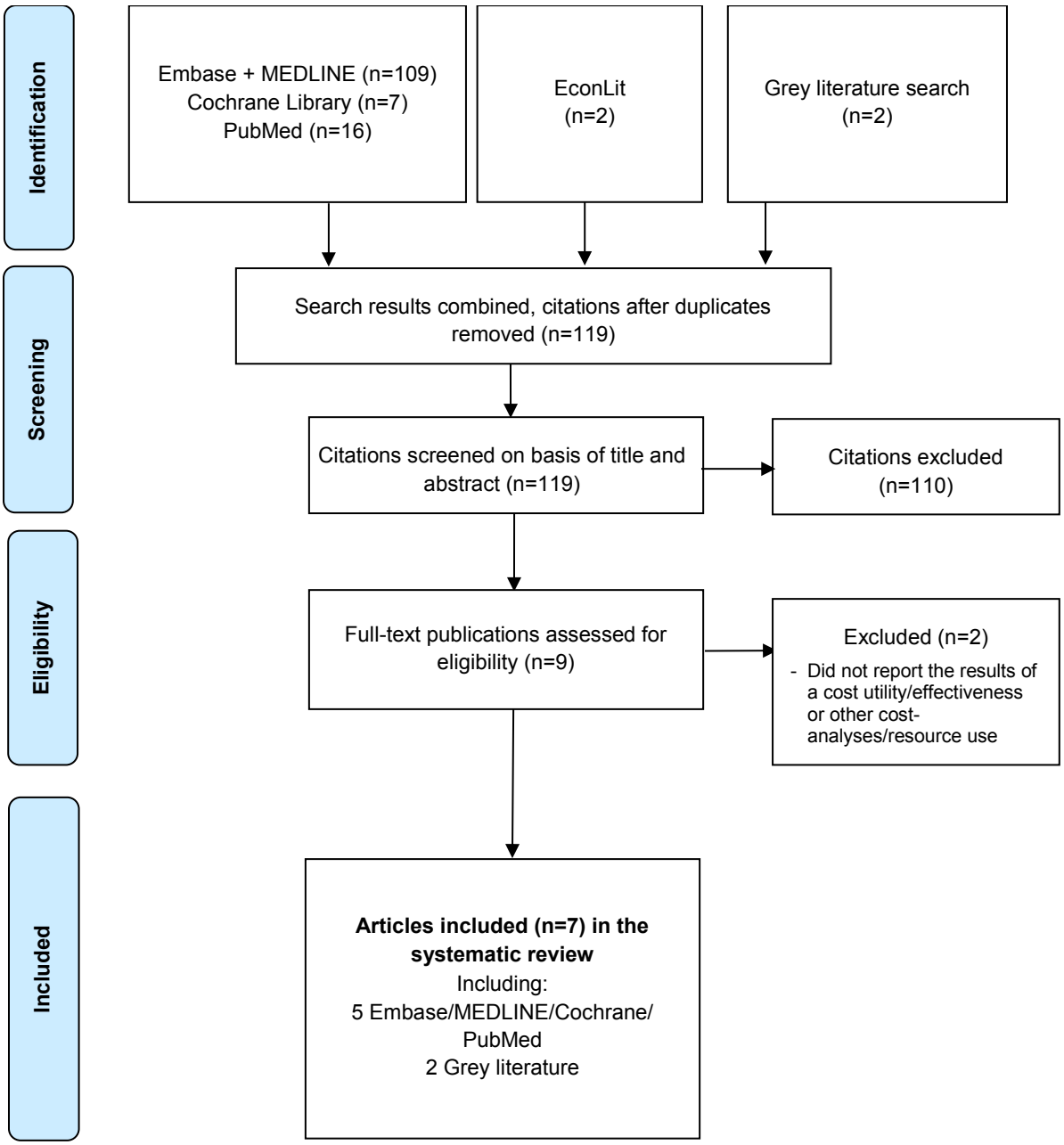
The searches were limited to records for English language articles, excluding non-human studies and publications that are reviews (except for systematic reviews, meta-analyses or pooled analyses), case reports, editorials, letters and notes/comments, where the indexing allowed. Table 13 summarises the inclusion and exclusion criteria, language restrictions and the study selection process.

Table 13. Eligibility criteria used in the search strategy for cost effectiveness studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Radioiodine-refractory Differentiated Thyroid Cancer	Population investigated was not patients with RAI-refractory DTC
Intervention / Comparators	Drug therapy	
Outcomes	Economic aspects: costs and resource utilisation; economic evaluations (cost-effectiveness, cost-utility, cost-benefit); economic models (decision analytic and Markov); burden of illness.	Did not report the results of a cost-utility/effectiveness or other cost-analysis
Study design	Randomised trials Systematic reviews Meta-analyses Pooled analyses	Experimental or non-human studies Review not published within the last three years, including reviews of economic studies published elsewhere Case reports, editorials, letters and notes/comments Subgroup analyses/ abstracts/ publications of already identified trial with no additional information provided No abstract/poster provided
Language restrictions	English	Non-English language

Abbreviations: DTC, Differentiated Thyroid Cancer; RAI, Radioactive iodine

Figure 7 PRISMA flow diagram for cost effectiveness study selection



The PRISMA flow diagram of the number of studies included and excluded at each stage is shown in Figure 7 overleaf. The complete reference list for excluded studies is provided in the Systematic Literature Review Report (Appendix 2).

Description of identified studies

The systematic reviews on the cost-effectiveness of therapies for the treatment of patients with RAI-refractory DTC identified seven studies (Abouzaid, et al., 2015; Erdal, et al., 2015; Huang, et al., 2016; Gianoukakis, et al., 2014; Sussman, et al., 2014; Tremblay, et al., 2016; Gianoukakis, et al., 2016)

From the seven identified studies, three reported on cost-effectiveness/utility analyses (Erdal, et al., 2015; Huang, et al., 2016; Tremblay, et al., 2016). However, none of the studies were conducted in the UK from the perspective of the NHS and are not relevant to decision making in England.

Therefore, to address the lack of published evidence for the cost-effectiveness of lenvatinib, a de novo analysis has been carried out (see Section 5.2).

The remaining four economic citations identified above reported on medical resource use (Gianoukakis, et al., 2014; Sussman, et al., 2014; Abouzaid, et al., 2015; Gianoukakis, et al., 2016). Therefore, the results of these studies are summarised in section 5.5.

A summary of the above mentioned published cost-effectiveness studies and a quality assessment is provided in the Systematic Literature Review Report (Appendix 2).

5.2 De novo analysis

An economic evaluation using a de novo cost utility analysis was performed to assess the cost-effectiveness of lenvatinib in clinical scope as described in earlier sections.

Patient population

The de novo analysis was conducted for the patient population as described in the final scope. In detail, the model was developed for patients with progressive RAI-refractory DTC.

In the lenvatinib SELECT study, progressive RAI-refractory DTC was defined as locally advanced or metastatic DTC confirmed by radiographic evidence of disease progression within the prior 13 months and some of the patients received prior VEGF therapy (M. Schlumberger, et al. 2015). This population may be considered more severe in contrast to patients in sorafenib DECISION study where no patient had received prior VEGF therapy and evidence of disease progression within the prior 14 months was required (Brose, et al., 2014).

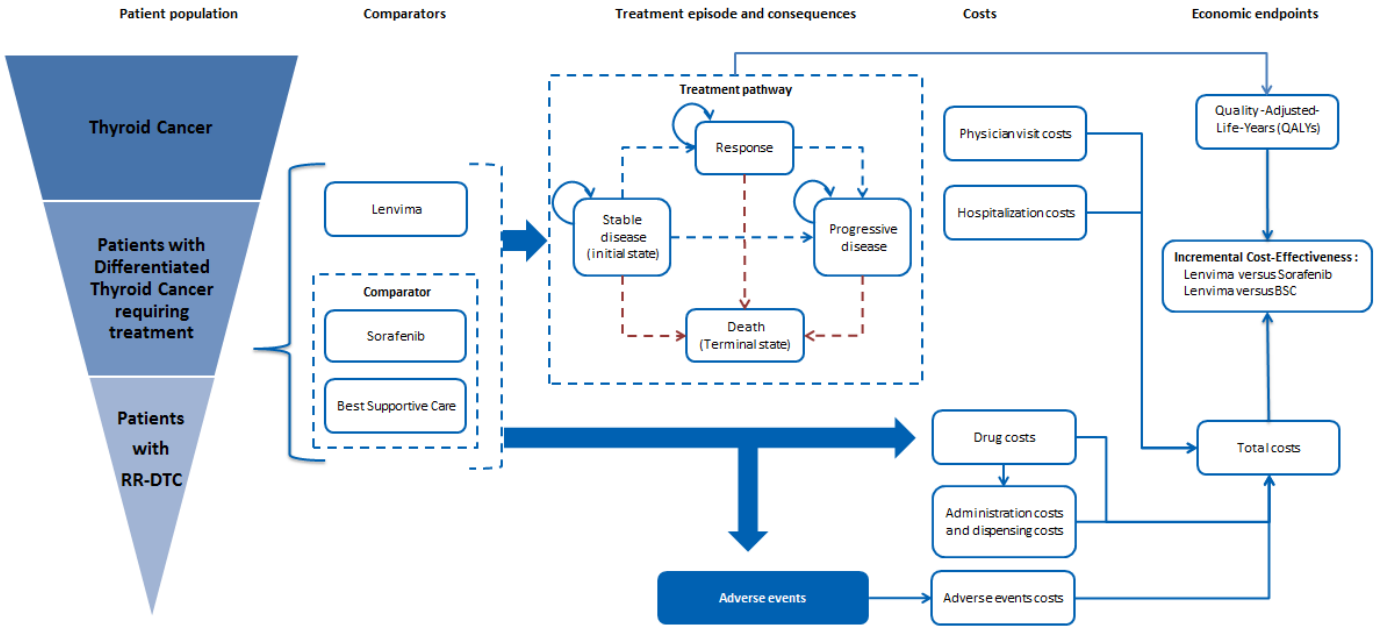
Model structure

Structure Overview

A partition survival cost-utility model was developed in Microsoft Excel to model the lifetime clinical and economic outcomes of lenvatinib vs sorafenib and/or best supportive care treatment in RAI-refractory DTC.

The structure of the model is illustrated in Figure 8 below.

Figure 8 Graphical Illustration of the treatment pathway and the model structure



Health States Structure

The proportion of patients in each health state, over the course of time, was estimated based on the Kaplan-Meier survivor function, parametric survival functions (or both) for response, PFS and OS. Post-progression survival was assumed to equal the difference between OS and PFS. Expected response, PFS and expected OS were calculated as the area under their respective survival curves. Costs and health related quality of life (HRQoL) were assumed to be conditioned on treatment and expected time in the given disease states. This approach is similar to a traditional Markov model, except that clinical trial data is directly used instead of estimating transition probabilities between states.

The model includes four health states:

- "Stable disease"(initial) health state which aims at capturing the data at baseline, at the start of the treatment
- "Response" health state aims at capturing increased health in patients with tumour response (overall response rate from the SELECT trial) during progression-free survival stage
- "Progressive" health state and
- "Death" (Terminal state)

Patients are assumed to transition between the four health states of "Stable", "Response", "Progressive" and "Death", based on time-dependent transition probabilities. Health states were defined in consistency with clinical outcomes reported in oncology clinical trials, including the SELECT study.

Patients enter the model in the "stable" state in cycle 0 when they initiate treatment with lenvatinib or sorafenib or BSC and can transition to the "response" health state from cycle 1 and also transition back from "response" to "stable" afterwards. Although a "response" state is not included in most partition survival models, doing so in this case makes a lot of clinical sense, since the value assigned by patients to both states is quite different.

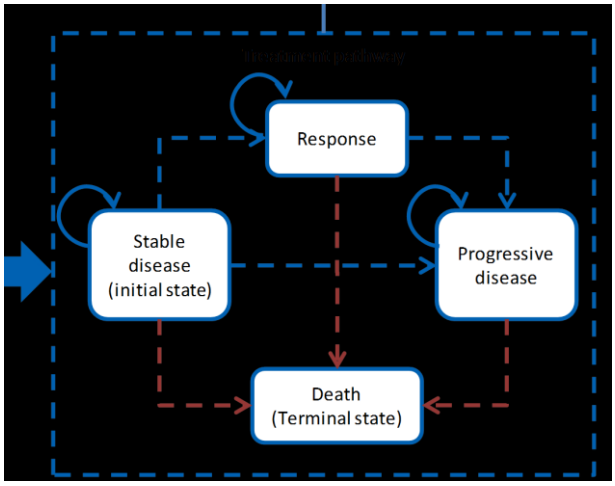
To generate the "response" partition, the patient level data from the SELECT trial were used to get the initial date of response. Then the duration of response (based on patient level data) was applied for all patients with a response based on their initial response date. This generated a new "sub-partition" for response.

The sorafenib response partition curve was modelled based on these data.

- Patients stay in these health states until disease progression, when they enter into the “Progressive” (or post-progression) health state.
- Patients in the “Progressive” state are assumed to remain in this state until death. Patients in the “Stable” health state can transition directly to the “Death” state without passing through the “Progressive State”.
- Patients continue transitioning across health states until all patients are in the “Death” state
- Every 30.43 days (one Markov cycle), patients face a risk of transition among health states based on disease status or death. Their health state at any point in time is derived from the clinical outcomes of the SELECT study – i.e. the time to event data (survival curve) for PFS and OS.
- One month cycle length was used for the purpose of convenience of calculations.
- The model health states capture the relevant clinical outcomes and resource use for patients receiving lenvatinib or sorafenib; for example OS, as this is recognised as the most definitive cancer outcome, and is one of the most important considerations to patients when making decisions regarding treatment options (Fordham, et al., 2015).

Figure 9 below presents the patient transition in different health states.

Figure 9 Patient Health States



Treatment Cycle & Markov Cycle Durations

As mentioned above, the Markov cycle of the model has one month duration, which is equal to 30.43 days.

The treatment cycle of lenvatinib and sorafenib is 28 days long. The treatment cycle for other drugs in the systemic therapy were also 28 days, based on the drug’s SPC. The treatment costs were calculated for the treatment cycles for all the drugs and converted to monthly costs.

Model Time Horizon

The base case time horizon of the model was set at lifetime (with 5 and 10 years provided as additional analyses) beginning with treatment start. Each cycle lasts for 30.43 days and the model is run for 400 cycles. Therefore, the lifetime horizon is 30.43 * 400 = 12.172 days = 33.35 years.

Costs & Utilities estimation

Costs and health-related quality of life (HRQoL) were assumed to be conditioned on treatment and expected time in the given health states. Patients were assumed to continue their primary treatment until disease progression and then switch to alternative treatments (secondary therapies) in the “Progressive” health state.

Model Perspective

The analysis was conducted from the perspective of NHS, and personal and social services in England & Wales, in line with current NICE guidelines. The analysis excluded patients' out-of-pocket expenses, carers' costs and lost productivity derived costs.

Other Structural characteristics

Discounting: Costs and benefits were discounted at the rate of 3.5% annually according to NICE guidelines. The monthly discounting rate for both costs and benefits was 0.29% and was generated using the cycle transition probability formula. i.e.

- ((1+Annual Discounting rate) ^ (1/12)-1)
- **Body Surface Area (BSA):** BSA is an important factor for calculating the dose of chemotherapy regimens (secondary therapy only). Based on the available data (mean weight and height) from the Lenvatinib clinical trial for all patients using the Mosteller technique, the BSA for patients in the UK was assumed to be 1.88 + 0.31 m2.
- **Average Dose:** Systemic treatments often require a dose reduction or dose delay in order to manage specific adverse events. The mean dose in the Lenvatinib arm was 17.4 mg based on the SELECT trial. The average dose of sorafenib based on the DECISION trial was 651 mg or 3 tablets of the actual starting dose of 800 mg (4 tablets). Dose intensity was not applied to the secondary therapy.

Table 14 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Basecase: lifetime Sensitivity scenarios: 5 & 10 years	
Were health effects measured in QALYs; if not, what was used?	Yes QALYs were used	According to NICE guidelines
Discount of 3.5% for utilities and costs	Yes, 3.5% discounting rate was used	According to NICE guidelines
Perspective (NHS/PSS)	NHS England	No social services or indirect costs were included in the model as considered non relevant.

Abbreviations: PSS, personal social services; QALYs, quality-adjusted life years

Intervention technology and comparators

As per the final scope, the three treatment arms used in the Model are lenvatinib, sorafenib and best supportive care:

- Lenvatinib - intervention arm - as the primary treatment followed by no treatment after patients entered into the "Progressive" health state.
- Sorafenib – comparator arm - as the primary treatment followed no treatment after patients entered into the "Progressive" health state.
- Best supportive care (placebo) – comparator arm - which is not associated with any additional costs

Treatment Duration

The treatment duration partition for the lenvatinib arm was derived from the patient level data from the SELECT study. The time to discontinuation data for lenvatinib were used to determine when patients discontinued treatment.

In the absence of time to discontinuation data for sorafenib, the treatment duration in the sorafenib arm is assumed to be until disease progression which is consistent which the DECISION study protocol.

As mentioned above, once patients have entered the “Progressive” health state, they are assumed to receive no treatment.

5.3 Clinical parameters and variables

Overview of Efficacy Data used in the model

Treatment outcomes of lenvatinib (response, PFS and OS) are derived from the SELECT study. (Schlumberger, et al., 2015) (Eisai DOF, 2015) Treatment outcomes of sorafenib (response, PFS and OS) are derived from publications of DECISION (Brose, et al., 2014) (Brose, 2014) (Brose, et al., 2016) study and ITC analysis (Lenvatinib IT report – Appendix 4)

Cross-Over Adjustment for Overall Survival Data

Trial Design

As described in Section 4, the SELECT study was a multicentre, randomised, double-blind, placebo-controlled trial in 392 patients with RAI-refractory DTC. The primary endpoint of the trial was PFS and one of the secondary endpoints was OS.

At the cut-off date for the primary efficacy analysis (15-Nov-2013), the median OS was not yet reached for either the lenvatinib or placebo arms. An updated OS analysis was performed at a later cut-off date (15-Jun-2014), per the request of the EMA. The median follow-up time was respectively 17.1 and 17.4 for lenvatinib and placebo arms for the first data cut and 23.6 and 24.1 for lenvatinib and placebo arms for the second data cut. A further unpublished analysis was performed on the 21st August 2015 (Eisai DOF, 2015). For this third data cut, the median follow-up time was 37.8 and 37.9 for the lenvatinib and placebo arms respectively.

According to the SELECT trial protocol, qualified placebo subjects with confirmed disease progression had the option to crossover to lenvatinib treatment in the open label extension treatment phase.

Figure 10 overleaf presents the study design using a study flow diagram. Overall, 392 participants were randomised to receive lenvatinib (n=261) or placebo (n=131). At the first cut-off date, 83.2% of placebo subjects had switched to the lenvatinib arm, while at the second cut-off date, 87.8% of placebo subjects had switched to the lenvatinib arm (see Table 15).

Figure 10 Study Design

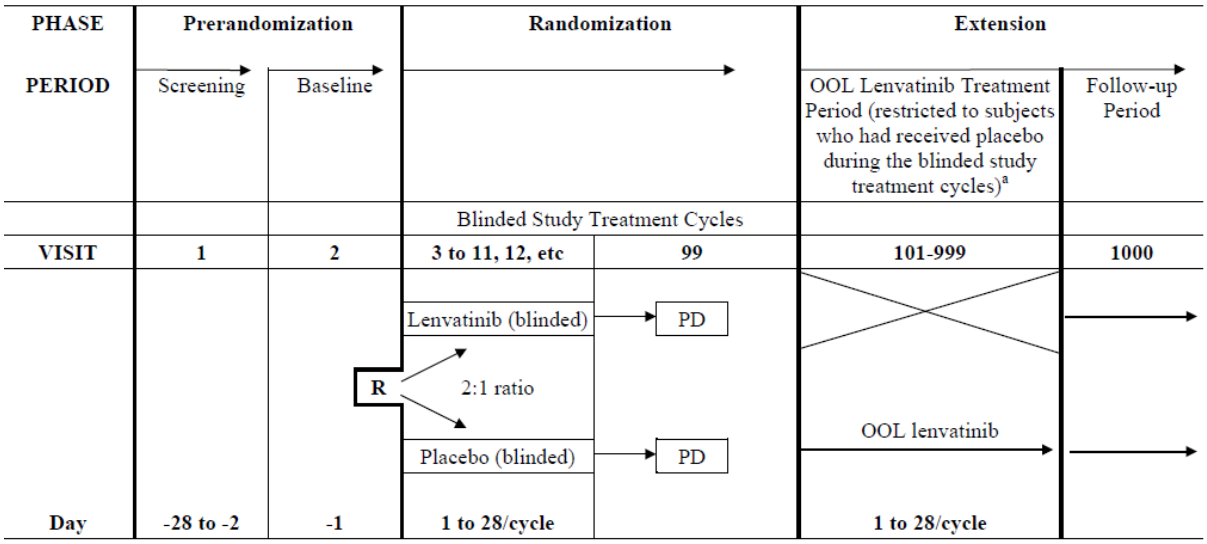


Table 15 Number of subjects who crossed

	Cut-off point	Placebo n=131 (%)
First Data Cut	15 Nov 2013	109 (83.2%)
Second Data cut	15 June 2014	115 (87.8%)
Third Data cut	21 Aug 2015	115 (87.8%)

This confounds standard intention-to-treat (ITT) analyses (which compare groups as randomised) of the treatment effect associated with lenvatinib, because the control group is contaminated by lenvatinib and therefore the randomisation of the trial is broken.

This is problematic for any stakeholder (regulators, health technology assessment agencies, payers, pharmaceutical companies, clinicians, patients) who wishes to accurately estimate the effectiveness of the new treatment compared to the standard treatment.

Assuming that placebo group patients who switched onto lenvatinib benefited from it, an ITT analysis is likely to underestimate the true benefit of lenvatinib (that is, the benefit that would have been observed in the absence of treatment switching). In order to accurately estimate the true benefit associated with lenvatinib treatment, it is necessary to adjust for the confounding effects of treatment switching.

In SELECT, crossover was allowed only after disease progression. Therefore, the ITT estimates of the treatment effect on PFS are not affected by patients who crossed over. However, estimates of the treatment effect on OS are affected, creating a need to adjust for the confounding effects of treatment switching on the OS.

<u>Cross-over Adjustment Methodology</u>

Various statistical methods are available to adjust survival estimates in the presence of treatment crossover, but each makes important assumptions and is subject to limitations.

Eisai engaged The School for Health and Related Research (ScHARR), University of Sheffield under the guidance of Dr. Nicholas Latimer to undertake a detailed analysis of the survival data from the SELECT trial in collaboration with Eisai Biostatistics and the Health Economics and Health Technology Assessment team. ScHARR initially conducted a feasibility analysis to evaluate statistical methods that could have been appropriate for adjusting for the treatment switching observed in the SELECT trial, based upon an analysis of the characteristics of the SELECT trial, the treatment switching mechanism observed in the trial, and the data available from the trial.

Detailed information can be found in Appendix 5 (Eisai RPSFT model report).

It is important to note that this report was conducted on the results of the second data cut (15-Jun-2014). As the number of placebo patients who had switched to the lenvatinib arm was unchanged between the second and third data cuts ie 115 (87.8%), it was not deemed necessary to update this report as the conclusions would also apply to the third data cut.

Appendix 5 presents a comparison of the strength and weakness of the statistical methods in the context of the lenvatinib trial. The comparison led the team to select the RPSFTM/IPE methods as most appropriate to adjust for the treatment switching observed in the SELECT trial. It should be noted that the RPSFTM and IPE methods use the same underlying model, and would therefore be expected to produce very similar results.

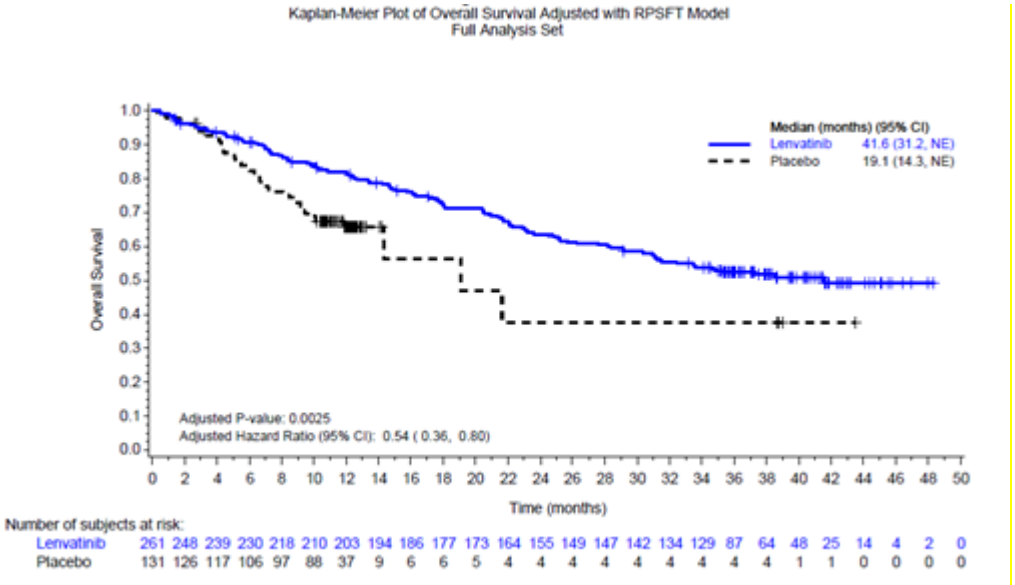
Therefore, in the initial analysis completed by the Eisai team and included as the basecase results in the model, only the RPSFTM has been applied. As mentioned above, for full details of the statistical analysis using the RPSFTM Adjustment Method, please refer to Appendix 5 (Eisai RPSFT model report).

RPSFTM Adjustment Results

As described previously in Section 4, the updated OS analysis with RPSFT adjustment showed a statistically significant difference in OS between the treatment groups (HR 0.54; 95%CI, 0.36 to 0.80, nominal p=0.0025) as determined using the resampling method (bootstrapping) (Table 8).

The adjusted Kaplan-Meier curve of the third data cut is presented respectively in Figure 11 below.

Figure 11 Kaplan-Meier Plot of Overall Survival Adjusted with RPSFT Model – Updated OS analysis (3rd data cut)



Indirect Treatment Comparison (ITC)

In the absence of direct comparative evidence, the DECISION and SELECT trial designs were considered similar to conduct an indirect treatment comparison. In a previous comparison using second datacut efficacy results for both lenvatinib and sorafenib, results from a matched adjusted indirect treatment comparison and ITC were very similar.

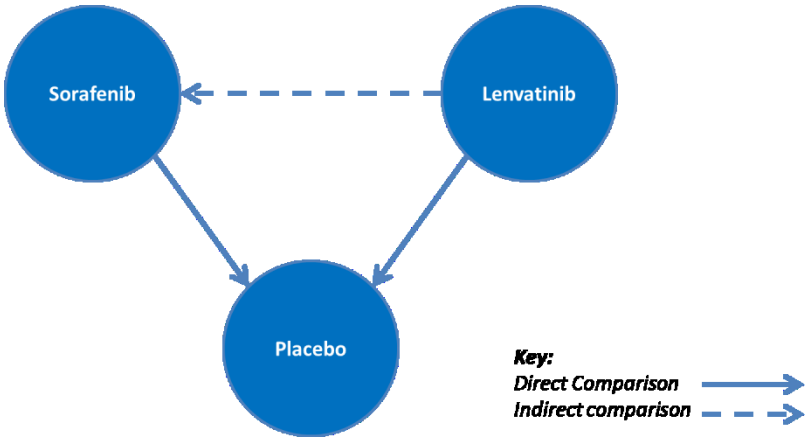
Therefore, the results of an ITC conducted on the updated "third datacuts" are used in the cost effectiveness analysis.

Full details of the methodology and results of the indirect treatment comparison are described previously in Section 4.10 and in Appendix 4.

Indirect Treatment Comparison Framework and Data

Figure 12 below presents the Indirect Treatment Comparison (ITC) framework.

Figure 12 ITC framework



The data used in the ITC analysis have the following characteristics.

Lenvatinib

- Updated OS data from August 31, 2015 cut-off date (Eisai DOF, 2015) adjusted for the cross-over of placebo patients using a Rank-Preserving Structural Failure Time model (RPSFT).
- PFS data from November 15, 2013 cut-off date (Eisai Ltd., 2015)

Sorafenib

- Updated OS data from July 2015 cut-off date (Brose, et al., 2016) adjusted for the cross-over of placebo patients using a Rank-Preserving Structural Failure Time model (RPSFT).
- PFS data from August 31 2012 cut off date (Brose, et al., 2014).

ITC Results

The results of the ITC are presented in Table 16 below and

Figure 13 overleaf. These are included as the basecase results in the model.

Table 16 Results of the ITC

	Lenvatinib/Placebo			Sorafenib/placebo			Lenvatinib/Sorafenib		
	HR	CI-	CI+	HR	CI-	CI+	**RR**	**CI-**	**CI+**
OS third datacut (RPSFTM)	[redacted]								
PFS Primary analysis (first data cut)	[redacted]								

Figure 13 Indirect treatment comparison results of OS and PFS – Lenvatinib/Sorafenib

Survival Extrapolations

Extrapolation of survival data is required when the trial data prior to cut-off does not provide enough information on overall survival and progression free survival in oncology (Tremblay, et al., 2015). The SELECT clinical trial data were evaluated to consider the need for extrapolation.

A third dataset from the SELECT study (August 31st, 2015) was used to obtain patient specific data on tumour response, PFS and OS and was used for extrapolation. Patients who were lost to follow-up and withdrawn were removed from the dataset. The RPSFT-adjusted OS data was used as the base case scenario. (Table 8)

Based on the clinical trial data, the need for extrapolation of OS was considered critical as about 50% of the patients were still alive at the cut-off data point. The extrapolation of PFS was extrapolated for consistency.

The framework used in the analysis to determine the best fitting extrapolation technique and all the details are presented in (Tremblay, et al., 2015) and an extrapolation report (Appendix 6).

Results of the extrapolation analysis for OS

- Considering all the criteria, Piecewise Exponential should be used as the best-fitting basecase.

Results of the extrapolation analysis for PFS

- Considering all the criteria, Piecewise Gamma should be used as the best-fitting basecase.

5.4 Measurement and valuation of health effects

Health-related quality-of-life data from clinical trials

Health-related quality-of-life data was not collected in the Phase II and Phase III trials for lenvatinib.

Health-related quality-of-life studies

In the absence of HRQoL data from the lenvatinib clinical studies, a systematic literature review was conducted to retrieve relevant information from the published literature regarding the HRQoL profile of therapies for the treatment of patients with RAI-refractory DTC. The review question was framed in terms of the PICOS elements and a review protocol was written to address search strategy, study selection, data extraction and quality assessment.

Specific details of the search terms and all strategies for the literature searches are provided in the Systematic Literature Review Report (Appendix 2).

Study selection

The searches were limited to records for English language articles, excluding non-human studies and publications that are reviews (except for systematic reviews, meta-analyses or pooled analyses), case reports, editorials, letters and notes/comments, where the indexing allowed.

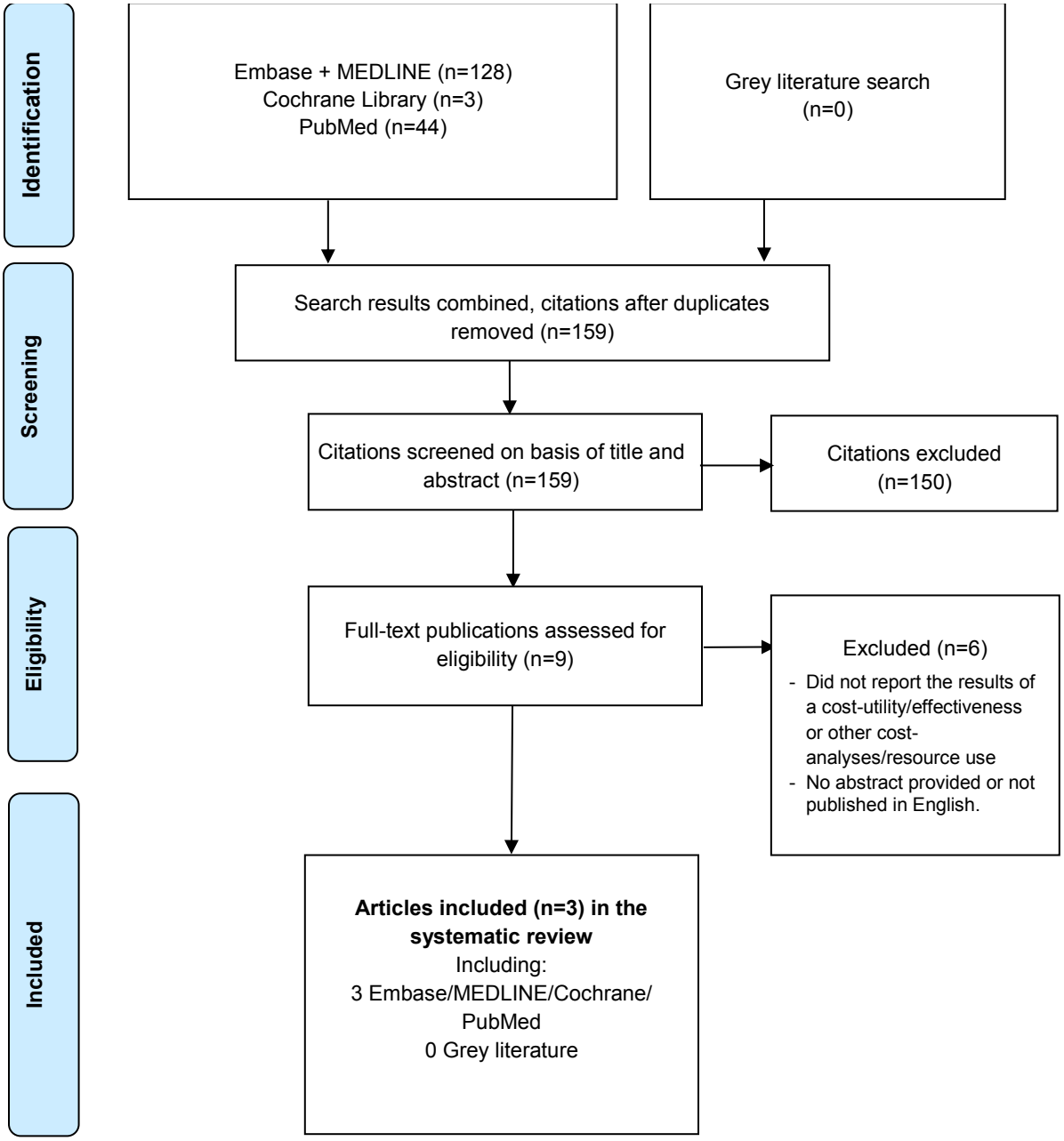
Table 17 summarises the inclusion and exclusion criteria, language restrictions and the study selection process.

Table 17 Eligibility criteria used in the search strategy for HRQoL studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Radioiodine-refractory Differentiated Thyroid Cancer	Population investigated was not patients with RAI-refractory DTC
Intervention / Comparators	Drug therapy	
Outcomes	Health related quality of life, utility values, weightings, preference, health status and specific quality of life instruments.	Does not report HRQoL outcomes
Study design	Randomised trials Systematic reviews Meta-analyses Pooled analyses	Experimental or non-human studies Review not published within the last three years, including reviews of economic studies published elsewhere Case reports, editorials, letters and notes/comments Subgroup analyses/ abstracts/ publications of already identified trial with no additional information provided No abstract/poster provided
Language restrictions	English	Non-English language

Abbreviations: DTC, Differentiated Thyroid Cancer; HRQoL, Health related quality of life; RAI, Radioactive iodine

The PRISMA flow diagram of the number of studies included and excluded at each stage is shown in Figure 15 overleaf. The complete reference list for excluded studies is provided in the Systematic Literature Review Report (Appendix 2).



Description of identified studies

The systematic review on the HRQoL profile of therapies for the treatment of patients with RAI-refractory DTC identified three studies (Fordham, et al., 2015; Kerr, et al., 2014; Schlumberger, et al., 2013). A summary of these published studies is included in the Systematic Literature Review Report (Appendix 2).

The citation by Schlumberger, et al., 2013 reports the results of patient reported outcomes from the sorafenib DECISION study. However, it is an abstract with limited information and does not report any utility values. Therefore, the data was not able to be included in the cost-effectiveness analysis.

Kerr, et al., 2014 is a conference abstract which was a preliminary communication of the peer reviewed journal article by Fordham, et al., 2015. This article reports the results of a vignette study conducted by Eisai for patients with RAI-refractory DTC.

In the absence of other relevant HRQoL data, the health state utility and disutility data from this vignette study is used as a scenario in the cost-effectiveness analysis.

Due to feedback provided at the stakeholder information meeting, for the basecase, health state utility data was taken from EQ-5D values for sorafenib.

Health-related quality-of-life data used in the basecase in the cost-effectiveness analysis

As mentioned above, the health state utility values used in the basecase were those reported in the Sorafenib SMC submission for best supportive care. These were EQ-5D values obtained from the DECISION trial. Disutilities were applied as a weighted proportion based on those obtained from the vignette study identified above in the systematic literature review and described below.

Final health state utilities used in the basecase are detailed in Table 18 below.

Table 18 Health state utility including adverse events disutility for the basecase analysis

Health State	Lenvatinib	Sorafenib	Best Supportive Care
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

Health-related quality-of-life data used as a scenario in the cost-effectiveness analysis

As described above, health state utility and disutility data was obtained from a vignette study conducted for patients with RAI-refractory DTC (Fordham, et al., 2015).

Vignette Study Design

A list of health states, some including adverse events selected by six UK and US healthcare professionals (with experience in treating RAI-refractory DTC) as the most common and relevant to the HRQoL of patients with RAI-refractory DTC, was finalised using feedback provided by the clinical experts from UK.

The states were as follows:

- stable/no response;
- response (partial and complete);
- progressive disease;
- stable/no response with grade 3 diarrhoea;
- stable/no response with grade 3 fatigue;
- stable/no response with grade 3 hand-foot syndrome (HFS); and
- stable/no response with grades I and II alopecia.

In order to standardise data collection and allow comparison of HRQoL decrement, the adverse event health states were each combined with the stable disease state. Additional adverse events to those listed in the health states were discussed however, concluded to be less relevant to the HRQoL of patients with RAI-refractory DTC. This included hypertension, which despite being reported as a relatively common event, was not included due to being asymptomatic in the majority of patients and therefore exerts little effect on HRQoL.

A total of 100 members of the UK public then underwent TTO interviews to value the above defined health states.

Analysis

Mean TTO utilities and descriptive distribution statistics were calculated for each health state from the KOSIS data. A regression analysis was conducted during which utilities were first transformed using a logistic function ($-\log\frac{1-\text{utility}}{\text{utility}}$), which resulted in an empiric distribution more closely resembling a normal distribution. In order to calculate the transformation, negative values were set to 0.02 and values of 1.0 were set to 0.98.

Vignette Study Results

Mean utility values derived from the TTO interviews indicate how participants in the study differentiated between the RAI-refractory DTC health states (Table 19).

As demonstrated by no overlap in the 95% confidence intervals, for the health states which included a grade 3 adverse event (diarrhoea, fatigue or HFS) mean utility values were significantly lower than for the no response/stable health state without the adverse event. The mean utility value for no response/stable with grades I and II alopecia was also lower than no response/stable although this difference was not statistically significant.

The incremental impact of health states on utilities was then derived compared to a base state of stable/no response with no adverse events. (Table 19)

Table 19 Mean observed utilities for RAI-refractory DTC health states and calculated incremental dis-utilities

Parameter	Observed mean utility[1]	
	Mean utility	Incremental Dis-Utility value
Base state – Stable/no response	0.80	
Response to therapy	0.86	
Progressive disease	0.50	
Diarrhoea	0.42	-0.380
Fatigue	0.72	-0.080
Hand and foot syndrome	0.52	-0.280
Alopecia	0.75	-0.050

[1] Mean observed TTO health state utilities

This derivation of the final utility used in the scenario was conducted through a stepwise approach, as follows: the incremental dis-utility for AEs for each product was first calculated by multiplying the disutility for each AE by the product specific rate for each AE (Table 20).

Table 20 AE-related Product specific dis-utilities

Adverse Event	Dis-utility	Lenvatinib AE Rate	Sorafenib AE Rate
Diarrhoea grade 3	-0.380	8.40%	5.80%
Fatigue grade 3	-0.080	4.60%	5.80%
HFS grade 3	-0.280	0.00%	20.30%
Alopecia grades I and II	-0.050	12.30%	67.10%
Disutility		-0.042	-0.117

The resultant AE disutility was then deducted from the initial utility for each health state. The AE rates were available for patients on lenvatinib and sorafenib from the phase III studies SELECT (Schlumberger, et al., 2015)and DECISION (Brose, et al., 2014).

Hence the resultant health states utilities were different for patients on lenvatinib and sorafenib (Table 21).

Table 21 Health state utility including adverse events disutility for the scenario analysis

Health State	Lenvatinib AE Rate	Sorafenib AE Rate
Stable disease state	0.80 – 0.042 = 0.76	0.80 – 0.117 = 0.68
Response state	0.86 – 0.042 = 0.82	0.86 – 0.117 = 0.74
Progressive state*	0.50	0.50

*Patients in progressive state were assumed to be on secondary chemotherapy so dis-utilities for lenvatinib or sorafenib do not apply.

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

As described previously, a systematic literature review was conducted to retrieve relevant information from the published literature regarding the economic implications, including resource use, associated with therapies for the treatment of patients with RAI-refractory DTC. Full information on the systematic literature review was summarised in section 5.1.

In further detail, the systematic literature review identified four that reported on medical resource use associated with the treatment of RAI-refractory DTC (Abouzaid, et al., 2015; Gianoukakis, et al., 2014; Gianoukakis, et al., 2016; Sussman, et al., 2014).

A summary of the above mentioned published studies is included in the Systematic Literature Review Report (Appendix 2).

(Abouzaid, et al., 2015) and (Sussman, et al., 2014) both present resource utilisation and cost information from the perspective of the US healthcare system and did not provide relevant data for England.

(Gianoukakis, et al., 2014)is a conference abstract which was a preliminary communication of the peer reviewed journal article by the same author, published in 2016 (Gianoukakis, et al., 2016)This article reports the results of an online retrospective chart review which provided healthcare resource utilisation data on 623 patients with RAI-refractory DTC, including 72 UK patients.

The article reports on the healthcare resource utilisation by disease state. This data and associated costs were applied to patients in the respective health states in the cost-effectiveness model and validated through clinical experts. Further detailed information is provided below.

Cancer services such as those for delivery of chemotherapy and radiotherapy are not currently covered by PbR tariffs.

Intervention and comparators' costs and resource use

The cost-effectiveness model includes only direct medical costs associated with primary and secondary treatments as well as the treatment of adverse events, without considering any indirect or societal costs.

Drug costs

The cost per tablet of lenvatinib (either 10 mg or 4 mg) is the list price. Daily cost of treatment is calculated according to the SPC dosing guidelines with a starting dose assumed to be 24 mg per day. The model uses a mean dose of 17.4mg, based on the data from the

clinical trial. Please note that this is calculated from the average dose distribution without accounting for dose interruption and differs from the value reported in the main publication (Schlumberger, et al., 2015) which was determined based on the average dose after accounting for dose interruption (based on a statistical analysis and not a distribution).

The cost of the sorafenib arm in the model was obtained from (Monthly Index of Medical Specialities, MIMS, 2016). The model uses an average dose of sorafenib based on the DECISION trial (Brose, et al., 2014) which was 651 mg or 3 tablets of the actual starting dose of 800 mg (4 tablets).

The prices are summarised per package/formulation in Table 22 below.

Table 22 Drug pack sizes and prices

Drug	Package/Vial size	Package Type	Price (£)
Lenvatinib	4mg x 30	Hard capsules	1,437.00
	10mg x 30	Hard capsules	1,437.00
Sorafenib	200mg x 112	Tablets	3,576.56

Source: MIMS database

Dosage and scheduling information for the estimation of the costs was extracted from the corresponding individual drug SPC's. BSA, dose intensity and wastage assumptions have also been incorporated into the drug costs estimation as mentioned under section 5.2.

The daily treatment costs were adjusted and estimated for one Markov cycle since this economic evaluation is a Markov model. One Markov cycle length in this model was one month (30.42 days):

Markov cycle treatment costs = Daily treatment costs x 30.42

Administration costs

Apart from the cost of treatment, patients in the "Stable" health state also incur the costs of administration for oral drug (lenvatinib or sorafenib).

Drug administration costs were based on NHS Reference Costs 2015 to 2016. (Government of the United Kingdom, 2016)

Chemotherapy administration costs were estimated according to the HRG codes in the table below.

Table 23 Administration costs

Type of chemotherapies	UK (NHS) cost code	Average cost (£)	Source
Oral chemotherapy	SB11z	183.50	NHS ref costs 2015-16

Table 24 below provides a brief summary of the drug and administration costs per monthly Markov cycle.

Table 24 Summary of drugs and administration costs of treatment per Markov cycle (£)

Drug	Mean daily dose, mg	Cost per mean daily dose	Cycle Length	Doses per cycle	Type of admin costs	Admin cost per dose/cycle	Cost per cycle	Cost per month
Lenvatinib	17.43	104	28	28	Oral	171	3,082	3,350

Sorafenib	651	104	28	28	Oral	171	3,094	3,363

Health-state unit costs and resource use

As previously stated, the healthcare utilisation assigned to the "Response", "Stable" and "Progressive" states in the cost-effectiveness model were obtained from physician surveys conducted in Europe (Gianoukakis, et al., 2016) and costs were estimated based on NHS Reference costs 2015 to 2016 (Government of the United Kingdom, 2016).

The healthcare utilisation inputs were validated by 4 NHS England practising clinical experts. These were selected based on their expertise in DTC and their sites of practice were Sheffield Teaching Hospitals NHS Foundation Trust, Brighton and Sussex University Hospitals, Guys and St Thomas NHS Foundation Trust and the Queen Elizabeth Hospital. The validation was conducted as part of an advisory board meeting. The clinical experts were presented with the resource utilisation estimates, related costs and the rationale around them. Following that, they were asked to confirm or rejects the inputs. In case of rejection, experts were asked to provide their rationale. The experts confirmed that the final inputs overleaf generally reflect the current clinical practice in NHS England.

In summary, the physician visit cost was the cost of a consultant medical oncology visit (WF01A; Non-Admitted Face to Face Attendance, Follow-up). The hospitalisation cost per day included the cost of a non-elective in patient short stay unit (£615.83) and, in line with feedback received by the UK clinical experts also included some cost for radiotherapy (£1,120.92). The resource utilisation per month was as per the physician survey (for EU physicians only), but the response state physician visit frequency was amended to be the same as the stable disease state, in line with feedback from the UK clinical experts.

The healthcare resource utilisation and monthly costs associated with each health state are presented in Table 25.

Table 25 Monthly healthcare utilisation and costs per Health State

	Unit cost (£)	Resource utilisation per month			Total monthly cost per health state		
		Response	Stable Disease	Progressive Disease	Response	Stable Disease	Progressive Disease
Physician visits	167.08	0.79	0.79	1.07	£128.64	£128.64	£174.37
Disease-associated hospitalisation days	615.83	0.09	0.10	0.66	£151.97	£169.33	£1,141.19
Total Cost					**£280.61**	**£297.98**	**£1,315.56**

Mortality-related costs were obtained from Nuffield Trust (2014) (Georghiou, 2014) http://www.nuffieldtrust.org.uk/sites/files/nuffield/publication/end_of_life_care.pdf) data and included acute hospital care (all hospital contacts, emergency inpatient admissions, non-emergency inpatient admissions, outpatient visits, accident & emergency visits), local authority-funded social care, district nursing care, and GP visit costs. These were summed to obtain the cost per mortality event, and were then adjusted for inflation to 2016 values, based on PSSRU inflation rates (Personal Social Services Research Unit, PSSRU, 2016). The overall mortality-associated cost for each comparator was calculated as the sum of the product of the cost per mortality and the estimated mortality (1- % OS) at each cycle (derived from the extrapolation):

$$Overall\ cost\ of\ mortality = \sum (cost\ per\ mortality) \times (1 - proportion\ of\ patients\ surviving\ at\ cycle\ n)$$

Table 26 Medical Costs at the End of Life

Mortality cost	Cost Element	2013 value in the UK (£)
Secondary (acute hospital care)	Cost of all hospital contacts	5,890
	Cost of emergency inpatient admissions	4,071
	Cost of non-emergency inpatient admissions	1,360
	Cost of outpatient visits	378
	Cost of A&E visits	80
Local authority funded social care	Cost of local authority-funded social care	444
District nursing	Cost of district nursing care	588
GP contacts	Cost of GP visits	365
Total used in the model (Inflation-adjusted for 2016)		7,450

Adverse reaction unit costs and resource use

The adverse events taken into consideration in the model are:

For Lenvatinib

- Grade 3 and 4 treatment-emergent adverse events (AEs), and
- AEs that required hospitalisation in SELECT study.

For Sorafenib

- Grade 3 and 4 treatment-emergent AE's in DECISION Study
- AE's that required hospitalisation based on proportions from SELECT study

AE prevalence for lenvatinib and sorafenib was obtained from the phase III SELECT (Schlumberger, et al., 2015) and DECISION (Brose, et al., 2014) clinical trials. The incidence of AEs is constant over time. This is an assumption made in the absence of any evidence suggesting otherwise and being consistent with the methods employed in other models that estimate AEs.

Duration of AEs (except for hand-foot syndrome) was obtained from the SELECT clinical trial and assumed to be equal between treatment arms. Hospitalisation rates due to AEs were based on the analysis of AE treatment in the SELECT trial. Since AEs hospitalisation rate was not available for sorafenib, the hospitalisation/AE prevalence ratio from the SELECT trial was applied to sorafenib.

The costs associated with hospitalisation due to adverse events were obtained from NHS Reference costs 2015/16 (Government of the United Kingdom, 2016) and/or the PSSRU Unit Costs of Health and Social Care 2016 report (Personal Social Services Research Unit, PSSRU, 2016) (Table 27). These costs were informed by the same 4 practising NHS clinicians from England described above who provided input at an advisory board.

Given the lenvatinib and sorafenib adverse events profile, drug costs of treating adverse events were considered negligible and therefore not included in the analysis. The rates of adverse events and relevant costs associated with the management of these adverse events are listed in Table 28.

It is important to note that the clinical trial collected the adverse event probability data based on the entire duration for which the patients took a certain drug. Hence, the following formula was used to calculate the monthly rates of AEs.

$$\boldsymbol{Monthly\ probability} = \ -[\boldsymbol{ln}(\mathbf{1}-\boldsymbol{p})]/\boldsymbol{t}$$

Table 27 AE hospitalisation costs (£)

Toxicities Grade 3/4	Non-Elective short stay unit cost - Source: NHS Reference costs 2015/16*	Other cost - see source	Final cost	Source
Hypertension	615.83	234.84	850.67	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of Consultant Medical oncology visit WF01A; Non-Admitted Face to Face Attendance, Follow-up (£162.84) (Source NHS Reference costs 2015/16) + 2 follow up GP visits (£36) Source: PSSRU 2016
Weight Decrease	615.83	24.00	639.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + dietician cost of £24 (Source: PSSRU 2016)
Diarrhoea	0	571.30	571.30	FZ91K Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6-10 Non-elective in patient short stay (NHS Reference costs 2015/16)
Decreased appetite	615.83	24.00	639.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + dietician cost of £24 (Source: PSSRU 2016)
Hypocalcaemia	615.83	0	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Hypokalaemia	615.83	0	615.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16)
Asthenia	615.83	43	658.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of F2F community nurse contact (Source PSSRU 2016)
Fatigue	615.83	43	658.83	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of F2F community nurse contact (Source PSSRU 2016)
Hand-foot skin reaction	0	450.35	450.35	JD07J Skin Disorders without Interventions, with CC Score 2-5 Non-elective in patient short stay (Source: NHS Reference costs 2015/16)
Proteinuria	615.83	162.84	778.67	Non-elective short stay unit cost of £615.83 (Source: NHS Reference costs 2015/16) + Cost of Consultant Medical oncology visit (£162.84) (Source NHS Reference costs 2015/16)

Table 28 Rates and costs of relevant AEs

	Total frequency of grade 3-4 AEs' hospitalisations		Cost of Hospitalisation
Toxicity	Lenvatinib	Sorafenib	Cost of Hospitalisation
Hypertension	3.50%	0.79%	851
Weight Decrease	0.40%	0.19%	640
Diarrhoea	0.40%	0.28%	571
Decreased appetite	0.40%	0.00%	640
Hypocalcaemia	0.40%	0.69%	616
Hypokalaemia	0.00%	0.00%	616
Asthenia	0.00%	0.00%	659
Fatigue	0.00%	0.00%	659
Hand-foot syndrome	0.00%	1.40%	450
Proteinuria	0.00%	0.00%	779

Miscellaneous unit costs and resource use

No miscellaneous costs were included in the model.

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

Table 29 overleaf summarises all the inputs and variables used in the economic model.

Table 29 Summary of key variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI/SE (distribution)	Reference to section in submission
Utility Values	Mean values	95% CI	
Stable/no response disease state	0.80	(0.77, 0.84); beta distribution	Section 5.4
Response state	0.86	(0.83, 0.89); beta distribution	
Progressive state	0.50	(0.45, 0.56); beta distribution	
Stable/no response + Diarrhoea grade 3	0.42	(0.36, 0.48); beta distribution	
Stable/no response + Fatigue grade 3	0.72	(0.67, 0.77); beta distribution	
Stable/no response + HFS grade 3	0.52	(0.46, 0.58); beta distribution	
Stable/no response + Alopecia grades I and II	0.75	(0.71, 0.79); beta distribution	
Drug & Administration Costs	Cost (£) / Value		
Administration		IQR	
Oral chemotherapy	£183.50	(£103, £219); log normal distribution	Section 5.5
Resource Costs	Cost (£)	IQR/Arbitrary	
Physician (Consultant medical) visit	£162.84 per visit	(£123.45, £213.45); log normal distribution	Section 5.5
Non-elective in patient short stay	£615.83 per day	(£417.9, £728.5); log normal distribution	
Disease-associated hospitalisation days (non-elective in patient short stay)	£1,736.75 per day	(£1,302.6, £2170.9); log normal distribution	
Follow up GP visit	£36 per visit	(£27, £45); log normal distribution	
Nurse contact	£43 per visit	(£32.25, £53.75); log normal distribution	
Death (Terminal State) ie Mortality costs		Arbitrary	
Cost of all hospital contacts	£5,890	(£4,417.50, £7,362.50)	Section 5.5
Cost of local authority-funded social care	£444	(£333, £555)	
Cost of district nursing care	£588	(£441, £735)	
Cost of GP visits	£365	(£273.75, £456.25)	
AE rates	%	95% CI	
Lenvatinib			
Hypertension	43	(37, 49); beta distribution	
Weight decrease	12	(8, 16); beta distribution	
Diarrhoea	8	(5%, 12%); beta distribution	
Decreased appetite	6	(3%, 9%); beta distribution	
Hypocalcaemia	5	(3%, 9%); beta distribution	

Variable	Value	Measurement of uncertainty and distribution: CI/SE (distribution)	Reference to section in submission
Hypokalaemia	3	(2%, 6%); beta distribution	
Asthenia	6	(3%, 9%); beta distribution	
Fatigue	5	(2%, 8%); beta distribution	
Proteinuria	10	(7%, 14%); beta distribution	
Sorafenib			
Hypertension	10	(6, 15); beta distribution	
Weight decrease	6	(3, 10); beta distribution	
Diarrhoea	6	(3%, 10%); beta distribution	
Hypocalcaemia	9	(6%, 14%); beta distribution	
Fatigue	6	(3%, 10%); beta distribution	
PPE Syndrome / Hand-foot skin reaction	20	(15%, 26%); beta distribution	
Hazard Ratios		95% CI	
Overall Survival	0.701	(0.43, 1.144); log normal distribution	
Progression Free Survival	0.356	(0.221, 0.573); log normal distribution	
Overall Response rate	0.581	(0.052, 6.667); log normal distribution	
Parametric survival function coefficients		95% CI	
Overall Survival ln(hr) – lenvatinib vs BSC	-0.649	(-0.988, -0.309); multivariate normal distribution	
Overall Survival_cons	-3.4	(-3.689, -3.111); multivariate normal distribution	
Progression Free Survival lenvatinib vs BSC	1.549	(1.265, 1.833); multivariate normal distribution	
Progression Free Survival_cons	1.525	(1.272, 1.778); multivariate normal distribution	
Progression Free Survival_sig	0.188	(0.069, 0.306); multivariate normal distribution	
Progression Free Survival kappa	0.172	(-0.203, 0.548); multivariate normal distribution	

Abbreviations: CI, Confidence interval; PPE, Palmar-plantar erythrodysaesthesia

Assumptions

Table 30 overleaf provides a brief overview of the main structural assumptions made by the economic model, and a summary of the justification for the decision. Please refer to the referenced section for a full overview of the assumptions in the context where they are discussed.

Table 30 Key model assumptions

Assumption	Justification	Reference to section:
OS and PFS are best characterised by a piecewise approach for extrapolation, with an exponential and gamma functional form, respectively.	An analysis was conducted to determine the best extrapolation technique and is presented in Appendix 6.	Section 5.3
Relative treatment effects are as reported by the Hazard Ratios from the ITC.	In the absence of head to head data, the trial designs were considered similar enough to conduct an ITC, which is presented in Appendix 4.	Section 5.3
The most accurate estimate of HRQoL are the sorafenib EQ-5D values obtained from DECISION trial	In the absence of HRQoL data collected in the SELECT trial, these values are considered to be the best available estimates, as highlighted in the stakeholder information meeting.	Section 5.4
Treatment duration for lenvatinib is based on time to discontinuation data from the SELECT study.	This is consistent with previous NICE submission methodology this approach was considered reasonable by 4 practising NHS clinical experts.	Section 5.2
Patients in the sorafenib arm are assumed to be treated to progression.	In the absence of time to discontinuation data for sorafenib, the treatment duration in the sorafenib arm is assumed to be until disease progression which is consistent which the DECISION study protocol.	Section 5.2
Once patients progress, they are assumed to receive no treatment.	This is in line with feedback received by NHS clinicians.	Section 5.2
In the model, the number of patients in the Response state is informed by the overall response rate from the clinical trials.	This is the best available estimate of response.	Section 5.2

5.7 Base-case results

Base-case incremental cost-effectiveness analysis results

Table 31 presents the base case and pairwise incremental results for lenvatinib versus the included comparators. Lenvatinib is shown to be a cost-effective option against sorafenib at a willingness-to-pay threshold of £25,000 per QALY.

Table 31: Base-case results; pairwise analysis, lenvatinib versus comparators

Technology/comparator	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Lenvatinib	£107,182	4.34	3.18	-	-	-	-
Sorafenib	£82,839	3.18	2.10	£24,342	1.16	1.08	£22,491
BSC	£42,115	2.80	1.84	£65,067	1.54	1.34	£48,569

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Clinical outcomes from the model

Figure 15 and Figure 16 illustrate the long-term clinical outcomes from the economic model. The Kaplan-Meier curves follow the trial data up until the last event, after which they are extrapolated using the selected parametric survival function, as described in Section 5.3.

Figure 15: Overall Survival

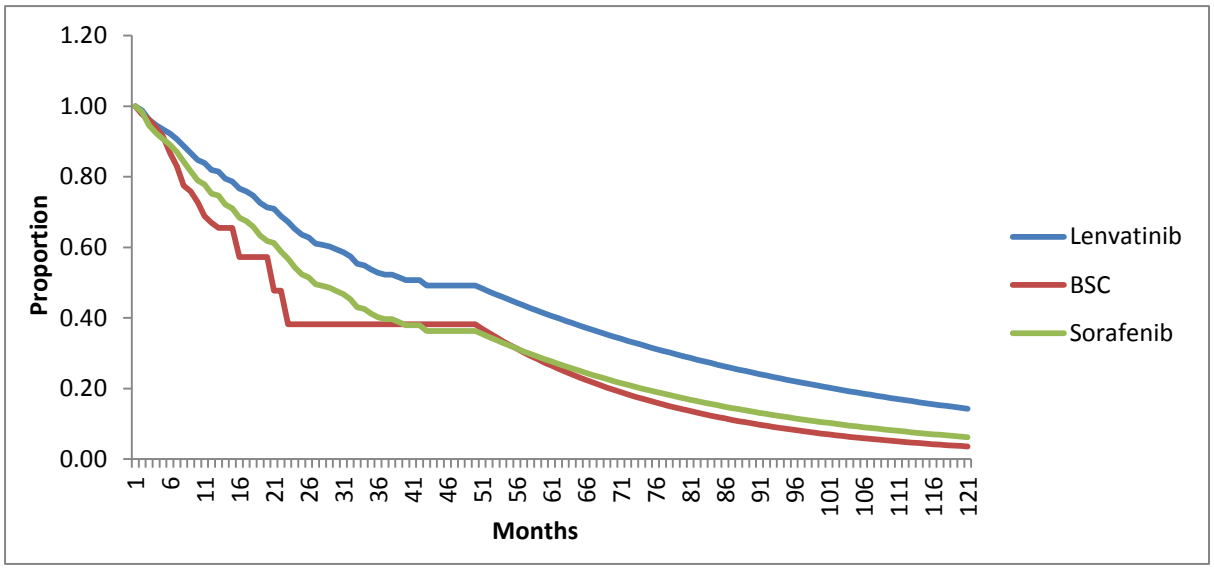
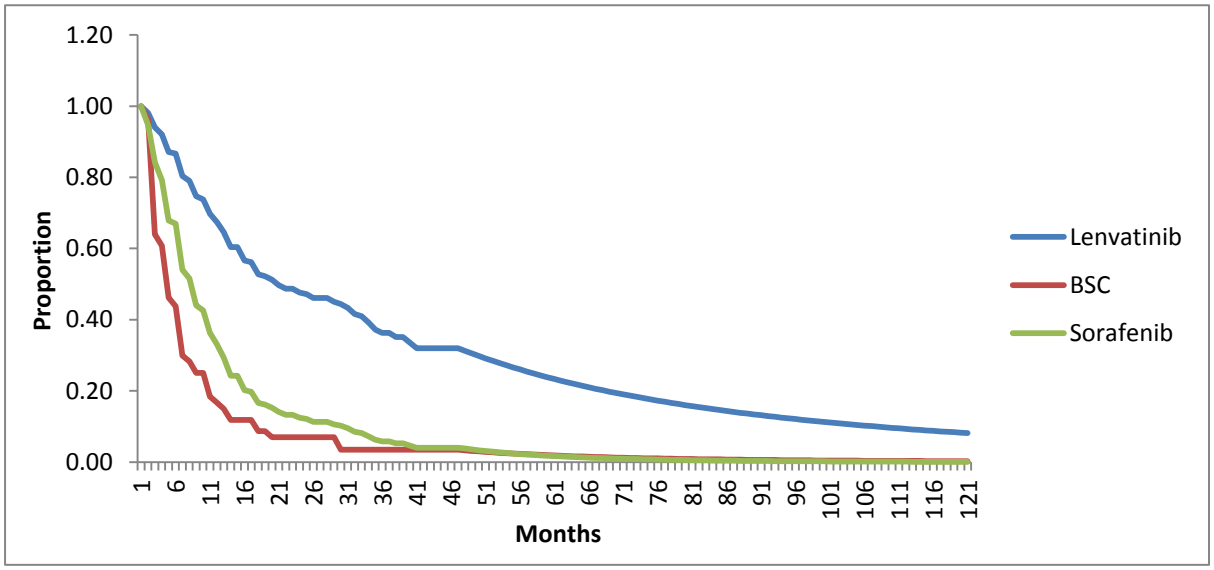


Figure 16: Progression Free Survival



Disaggregated results of the base case incremental cost-effectiveness analysis

Table 32 overleaf presents the disaggregated resource use related cost results for the base case analysis by resource use item.

Table 32 Summary of predicted resource use by category of cost; lenvatinib vs sorafenib

Resource	Lenvatinib	Sorafenib	Increment	Absolute increment	% absolute increment
Drug therapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 33 Summary of predicted resource use by category of cost; lenvatinib vs BSC

Resource	Lenvatinib	BSC	Increment	Absolute increment	% absolute increment
Drug therapy costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to explore joint parameter uncertainty in the model. Parameters were assigned distributions and varied jointly. Five thousand simulations were performed and recorded and the results were plotted on a cost-effectiveness plane (CEP), shown in Figure 17. A cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were also plotted and are shown in Figure 18 and Figure 19 respectively. The parameter ranges and probability distributions used in the PSA are presented in Table 29.

Table 34 shows the mean probabilistic ICERs as estimated by the PSA. These were close to the base case deterministic ICERs.

Table 34 Deterministic vs probabilistic ICERs; pairwise analysis

	Lenvatinib vs sorafenib	Lenvatinib vs BSC
Deterministic	£22,491	£48,569
Probabilistic	£21,578	£48,683

Figure 17 Cost-effectiveness plane

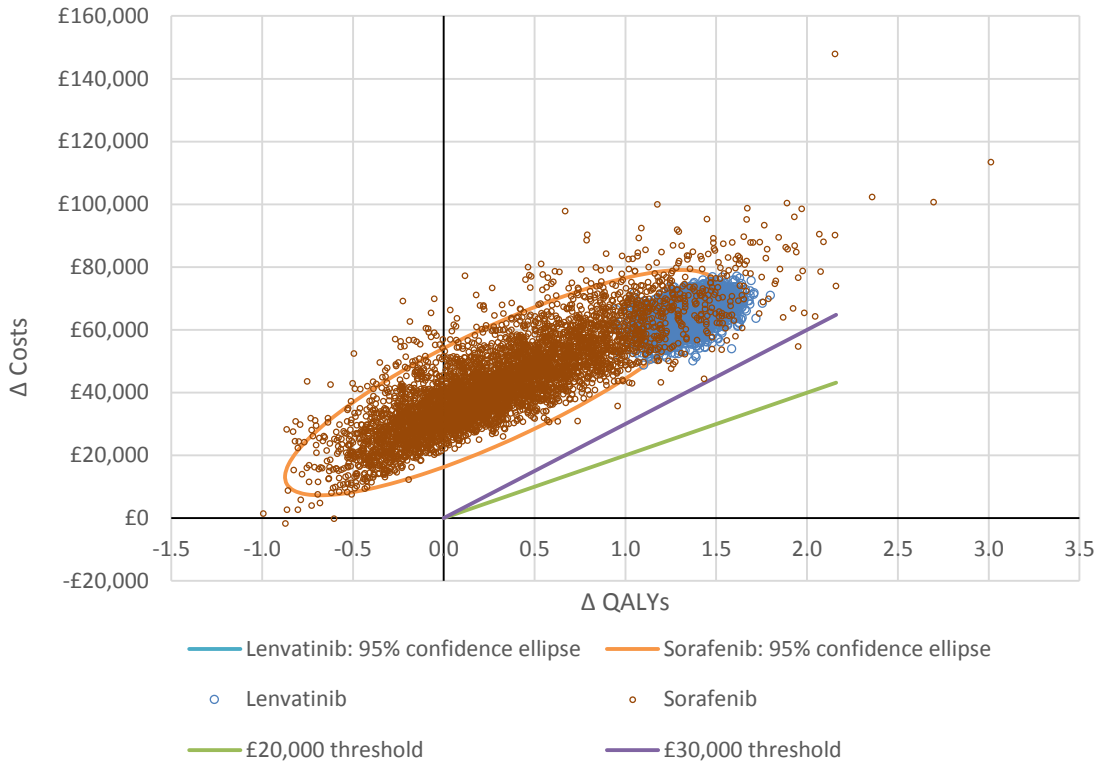


Figure 18 Cost-effectiveness acceptability curve

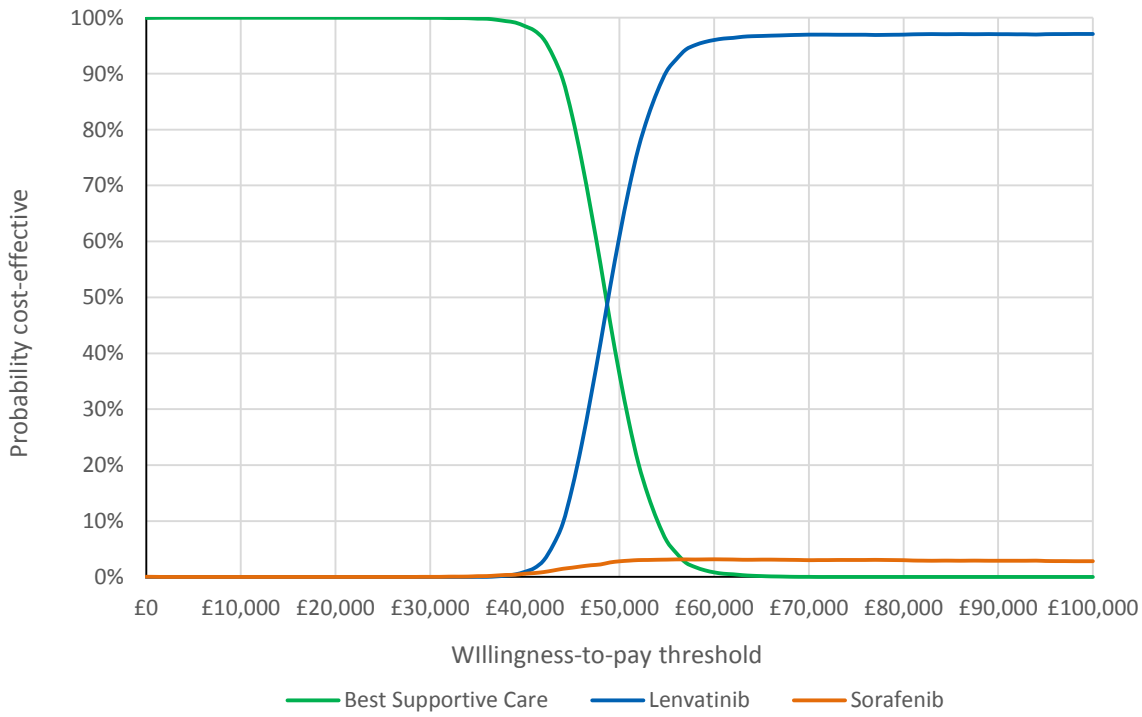
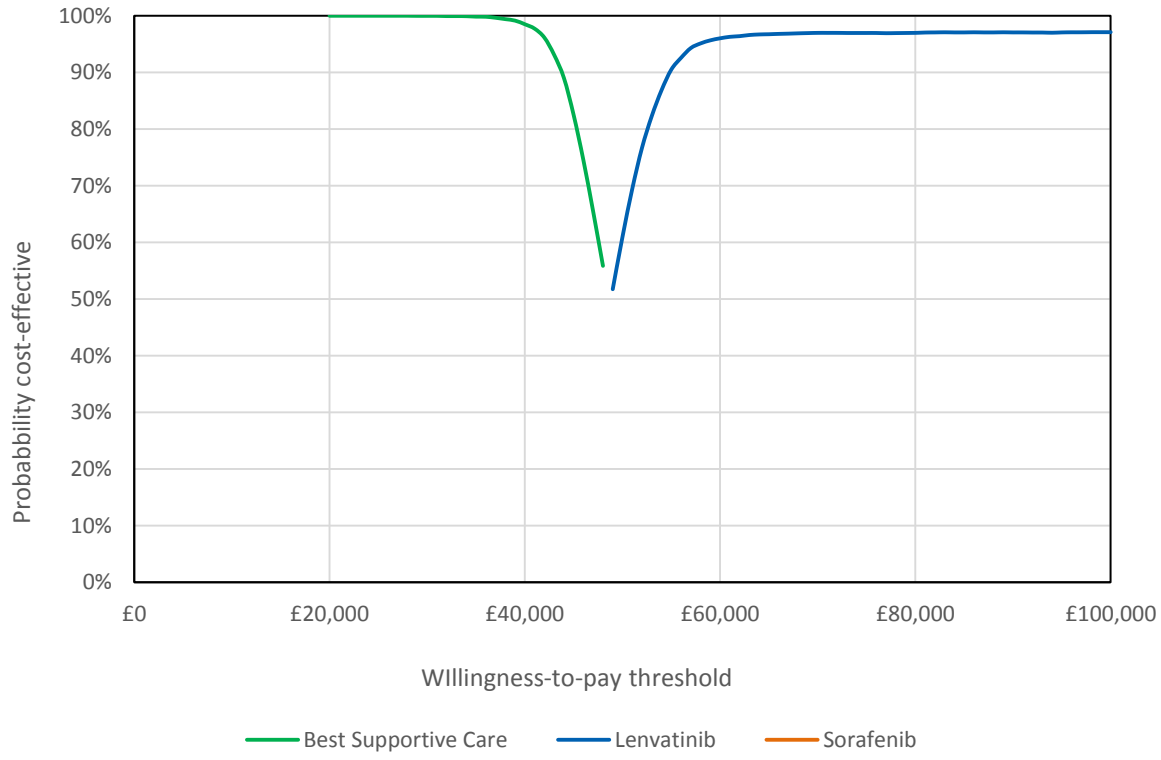


Figure 19 Cost-effectiveness acceptability frontier



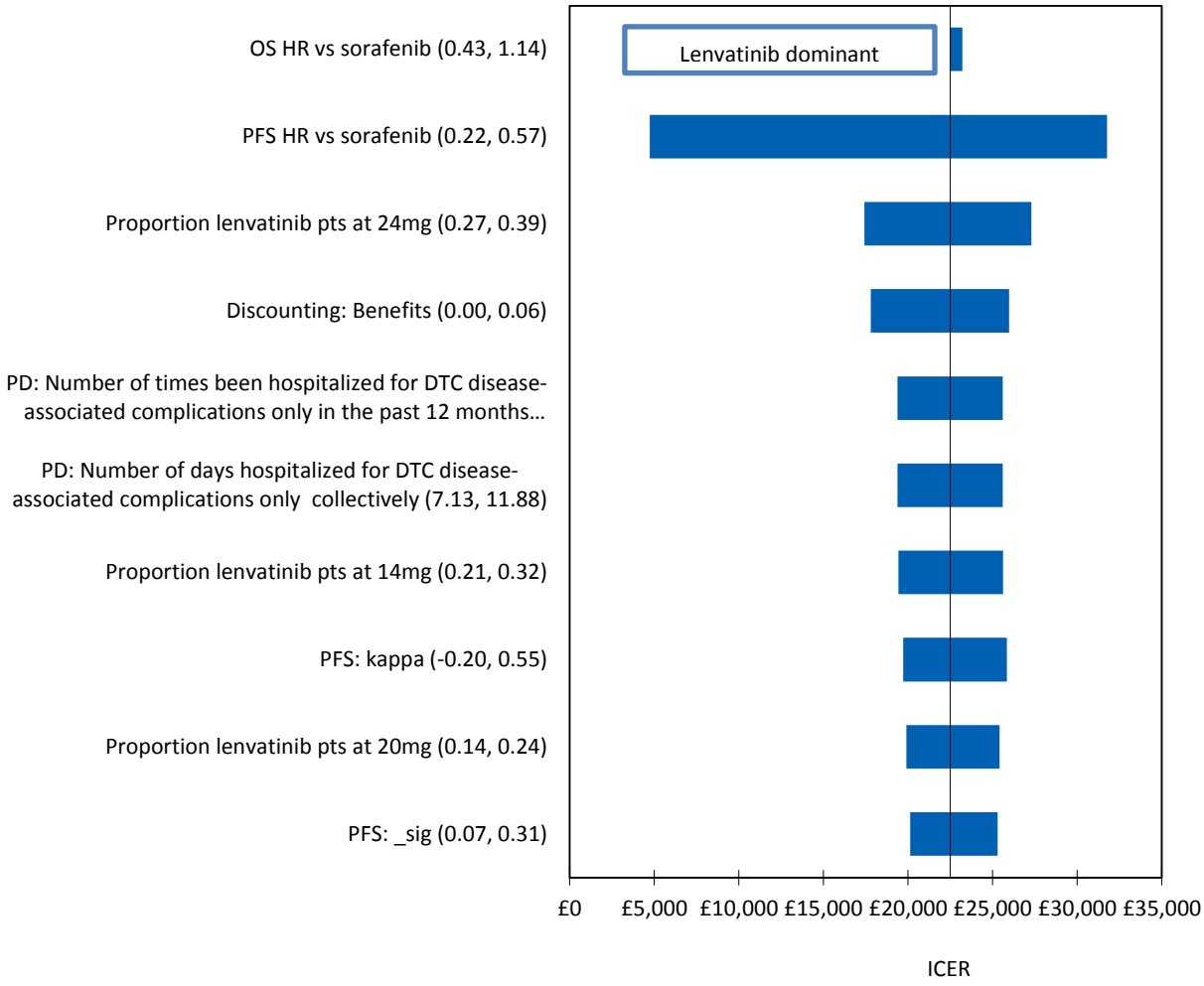
The CEP shows there is some parameter uncertainty around the mean ICERs, with considerable uncertainty for sorafenib being observed. The majority of this uncertainty is likely due to the uncertainty associated with the relative treatment effects between lenvatinib and sorafenib, and the subsequent uncertainty in the survival curve prediction of sorafenib.

Despite this, the results of the PSA suggest that lenvatinib is a cost-effective treatment option compared with sorafenib and BSC, with a 60% chance of being the most cost-effective option at a willingness-to-pay threshold of £50,000 per QALY.

Deterministic sensitivity analysis

Parameter uncertainty is tested using univariate sensitivity analysis, in which all model parameters are systematically and independently varied over a plausible range, determined by the 95% confidence interval surrounding the point estimate, interquartile range, plausible minimums and maximums, or +/-25%, where there are no estimates of precision available. The parameter ranges used in univariate sensitivity analysis are presented in Table 29. The ICER was recorded at the upper and lower bound for each parameter and the 10 most influential parameters (based on magnitude of change in the ICER between upper and lower bounds) were plotted on a tornado diagram, as shown in Figure 20.

Figure 20 Tornado diagram – lenvatinib vs sorafenib



Scenario analysis

Scenario analyses are performed, in which key assumptions are varied and ICERs reported. The scenarios considered and results obtained are detailed in Table 35.

Table 35 Summary of scenario analysis results

Parameter	Base case	Scenario	ICER vs sorafenib
Base case			**£22,491**
Discount rate (costs and benefits	3.5%	1.5%	£20,765
Medical costs	+0%	+20%	£21,403
Medical costs	-0%	-20%	£23,578
Mortality costs	+0%	+20%	£22,436
Mortality costs	-0%	-20%	£22,546
Utility values	Sorafenib SMC submission	Vignette study	£19,953
Extrapolation technique	Piecewise; OS – Exponential, PFS - Gamma	Piecewise; OS – Gamma, PFS - Gamma	£22,516
Extrapolation technique	Piecewise; OS – Exponential, PFS - Gamma	Piecewise; OS – Exponential, PFS - Exponential	£28,822
Extrapolation technique	Piecewise; OS – Exponential, PFS - Gamma	Piecewise; OS – Weibull, PFS - Weibull	£29,115
Extrapolation technique	Piecewise; OS – Exponential, PFS - Gamma	Parametric with treatment covariate; OS – Exponential, PFS – Gamma	£27,785
Extrapolation technique	Piecewise; OS – Exponential, PFS - Gamma	Parametric with treatment covariate; OS – Gamma, PFS – Gamma	£26,861
Extrapolation technique	Piecewise; OS – Exponential, PFS - Gamma	Individual models; OS – Exponential, PFS - Gamma	£20,092
Extrapolation technique	Piecewise; OS – Exponential, PFS - Gamma	Individual models; OS – Exponential, PFS - Gamma	£20,015
Cut off for OS and PFS extrapolation (weeks)	OS – 50, PFS – 47	OS – 20, PFS – 20	£29,874
Lenvatinib treatment duration	Clinical trial duration	Treat to progression	£71,978
AE disutility	Included	Excluded	£22,084
Response state utility	Higher than stable	Equal to stable	£22,847

5.9 Subgroup analysis

No subgroups were assessed.

5.10 Validation

Validation of de novo cost-effectiveness analysis

Validation of the extrapolation: For the extrapolation, the Tremblay et al decision making criteria have been used (Tremblay, et al., 2015), which led to the selection of piecewise models for and PFS. As described in Appendix 6, the Tremblay et al, 2015 decision making criteria are based on the NICE DSU 14 on survival extrapolations (Latimer, 2011). An external validation was not performed.

Validation of the costs: As described in Section 5.5, the cost inputs were predominantly based on the results of an online retrospective chart review which provided healthcare resource utilisation data on 623 patients with RAI-refractory DTC, including 72 UK patients. (Gianoukakis, et al., 2016) The results from the European physicians were used in the cost effectiveness analysis. The healthcare utilisation inputs were validated by 4 NHS England practising clinical experts who were selected based on their expertise in DTC.

External validation of the utility and disutility: As described in Section 5.4, the utility values used in the basecase were taken from EQ-5D values for sorafenib, in line with feedback provided at the stakeholder information meeting. The utility and disutility values used in the scenario analysis were validated by 4 NHS England practising clinical experts

External validation of the adverse events prevalence and costs: The AE costs were based on a HRG/DRG approach. The HRG approach is in line with the NICE guidelines. The AEs with validated by 4 NHS England practising clinical experts.

Quality control: The quality control was performed both by Eisai internal HEOR experts and an external health economist. In these processes, an economist not involved in the model adaptation reviewed the model for coding errors, inconsistencies and the plausibility of inputs.

5.11 Interpretation and conclusions of economic evidence

Overall, the economic evaluation of lenvatinib in RAI-refractory DTC patients was conducted according to all the NICE technical and clinical guidelines. In the base case, lenvatinib is shown to be a cost-effective option against sorafenib at a willingness-to-pay threshold of £25,000 per QALY.

All the scenarios analyses conducted strongly indicate that the evaluation is robust with all the ICER derivatives being within a narrow range from the basecase ICERs, with the exception of the OS and PFS Hazard ratios versus sorafenib and the treatment duration assumption.

The CEP shows there is some parameter uncertainty around the mean ICERs, with considerable uncertainty for sorafenib being observed. The majority of this uncertainty is likely due to the uncertainty associated with the relative treatment effects between lenvatinib and sorafenib, and the subsequent uncertainty in the survival curve prediction of sorafenib.

The main limitations are the uncertainty associated with the estimate of relative treatment effects and extrapolation assumptions. Despite this, the results of the economic evaluation suggest that lenvatinib is a cost-effective treatment option for the NHS compared with sorafenib and BSC.

6 Assessment of factors relevant to the NHS and other parties

The number of cases of thyroid cancer was estimated by applying an annual incidence rate (Cancer Research UK, 2014) to the population of England and Wales estimating the incidence of thyroid cancer to be 3,100. The incidence for the following years was assumed to increase in line with population annual growth rates of 0.71% (ONS, 2017) and a mortality rate of 0.001% (Cancer Research UK, 2017) was applied.

Of the 3,100 patients with thyroid cancer, it is estimated that 90% (2,790 patients) will have differentiated thyroid cancer (DTC) (Pacini, et al., 2012) and 10% (279) will have RAI-refractory DTC (Pacini, et al., 2012).

If lenvatinib becomes available, it is anticipated that [redacted] % of eligible patients will be treated with lenvatinib in year 1. This is based on internal market share assumptions. This is predicted to increase to [redacted] % in year 2, followed by [redacted]% in year 3, [redacted] % in year 4 and [redacted] % in year 5. In the budget impact model, it is assumed that sorafenib will be displaced at the same rate.

A summary of the total eligible patients for each year of the budget impact model is given in Table 36.

Table 36 Total eligible patients

Patient Flow	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
Selected population	57,415,704	57,823,355	58,233,901	58,647,362	59,063,758	59,483,111
Thyroid Cancer incidence	3,100	3,122	3,145	3,167	3,189	3,212
Patients with DTC	2,790	2,810	2,830	2,850	2,870	2,891
RAI-refractory DTC patients	279	281	283	285	287	289
Mortality rate	344	347	349	352	354	357
Annual growth rate	407,651	410,546	413,461	416,396	419,353	422,330
Eligible patients	**279**	**281**	**283**	**285**	**287**	**289**
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The drug costs (acquisition and administration costs of treatment) and adverse event costs were added together to give the total treatment cost for patients. These costs are described in more detail in Section 5.5. In the model, it was assumed that patients on sorafenib and lenvatinib were treated for a full year at the average dose based on the respective clinical trials ie 17.4mg for lenvatinib (equivalent to 3 tablets) and 651mg for sorafenib (equivalent to 4 tablets).

Table 37 shows the total costs and incremental budget impact of lenvatinib at the list price. In year 1 the budget impact is expected to be 1.42 million pounds rising to 4.45 in year 5.

Table 37 Total costs and incremental budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Lenvatinib					

Treatment cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sorafenib					
Treatment cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event cost per patient	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost per patient					
Total cost of Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost savings from sorafenib displacement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	**£1,418,251**	**£2,578,009**	**£3,473,556**	**£4,099,087**	**£4,448,718**

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8 Appendices

Appendix 1: Lenvima SPC, September 2016

Appendix 2: Systematic Literature Review Report: For the treatment of radioiodine-refractory differentiated thyroid cancer

Appendix 3: Response to data analysis requests from the Assessment group

Appendix 4: Lenvatinib Indirect Treatment Comparison report

Appendix 5: Eisai Rank-Preserving Structural Failure Time Model report

Appendix 6: Lenvatinib Extrapolation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

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

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Butterfly Thyroid Cancer Trust

Your position in the organisation: [redacted]

Brief description of the organisation:

(For example: who funds the organisation? How many members does the organisation have?)

The organisation is the only registered charity in England dedicated to providing information and support to people affected by thyroid cancer, it was set up in response to a paucity of information available when Kate Farnell, CEO, was diagnosed and treated for thyroid cancer in 2000. There has been a dedicated telephone helpline available from the inception of the charity for over 16 years, over which time we have answered thousands of calls from a vast cross section of people affected by thyroid cancer, to this end we have huge first hand experience of how thyroid cancer affects patients and their loved ones.

The organisation has available a small 'holiday' fund for families requiring respite when in hardship.

We provide up to date patient information via our patient friendly website, leaflets, folders and DVD's, all are free of charge to patients and hospital clinics. Our information is BMA approved.

Kate Farnell has worked in a voluntary role as 'Thyroid Cancer Patient advisor' within the thyroid cancer team at Freeman Hospital, Newcastle upon Tyne for over 15 years, she has an honorary contract with the Trust and as such is part of the care team. This a unique role /patient/doctor partnership and has led to many awards for the charity.

Kate has a vast wealth of experience supporting those patients with non-resectable, advanced, metastatic differentiated thyroid cancer (DTC). Kate was lead in the first multi national workshop in 2014 on the use of Tyrosine-

Kinase Inhibitors (TKIs) and what this means for patients. There was global representation from leading clinicians, patient organisations and importantly, two terminally ill patients attended to tell their thyroid cancer journey and what difference access to TKIs such as Sorafenib and Lenvima meant to them.

The organisation is funded primarily by individual fundraisers and funds provided by BACIT (Battle against Cancer Investment Trust). Some grants have been made available via pharmaceutical companies designated for annual projects, such as 'Neck Check event 2011', provision of Patient Information DVDs: " Thyroid Cancer Uncovered' and "Living with Advanced Thyroid Cancer" and The First UK Thyroid Cancer Patient/ Doctor Forum in December 2016, Royal Society of Medicine, Wimpole street, London.

The CEO has been invited to present on the patient perspective on Thyroid Cancer across Europe, the USA and Canada and at two World Thyroid Cancer Congress meetings.

BTCT attends all leading Thyroid Cancer Conferences in the UK.

The organisation comprises of one CEO, one administrative assistant, four trustees, two medical advisors, one honorary president and four patrons. There is a panel of 27 patient support contacts available nationally and there are 3000 members. The organisation works closely with a number of specialist thyroid cancer centres in the UK.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Thyroid Cancer is the most common endocrine malignancy. It is however a relatively rare cancer with approx. 3200 new cases per year in the UK with a 90-95% cure rate.

It can affect all age groups form young children to the elderly but the two main peaks of incidence are in the 20's and 60's with a preponderance of women over men. The prognosis generally decreases with advancing age at the time of diagnosis.

Most thyroid cancer cases are treated by surgery and radioiodine and only a very small percentage of these patients will go onto develop non avid, non resectable diseases.

Living with rare cancer is particularly difficult as often the vital support services readily available for the 'common cancers', such as good patient information and dedicated clinical nurse specialists in every unit are not available.

Patients will have often undergone an extensive and protracted treatment journey over a number of years, which include multiple surgeries and radio active iodine treatments.

Some will have had chemotherapy. Palliative intravenous chemotherapy in hospital which destroyed their quality of life, had severe and sometimes life threatening side effects but without any benefit .Because of this this treatment is not recommended anymore.

Sadly despite this, the disease progresses, patients know they cannot achieve a cure for their cancer.

They can often have systemic complications including:

Chest and breathing difficulties from lung metastases Breathing difficulties are often due to blockage of airways from a large tumour or Lung involvement .

Pain

Pathological bone fractures

Swallowing difficulties which leads to weight loss through poor nutrition.

Anxiety and depression

Inability to continue working has a huge impact on self esteem, and obvious strain on finances leading to stress, anxiety and further strain on personal relationships. Patients often require psychological support and treatment with anti-depressants.

There is a huge issue with respect to knowing which drugs can make a difference to patients and which ones are actually available to patients through the Health Services, this causes massive frustration when patients know that drugs are there that might help them but cannot be accessed.

Quotes from patients:

"I feel so guilty about having to rely on my husband to do so much for me. His whole life now revolves around caring for me and taking me to hospital"

"I'm a mother and I'm terrified I won't live long enough to see my children go through junior school"

"My daughter is pregnant. I need access to a drug that will help me be around to see this baby born"

'Well that was just to worst night are imaginable, my oncologist has just told us that he cannot offer anything further other than pain relief."

Patients and loved ones have no hope for the future.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The very fact that licenced drugs which can significantly improve patient's quality of life be consistently made available throughout the Health Service, rather than relying on where they are treated.

Specifically, treatment outcomes should be able to achieve a reduction in the volume of disease or at least a slowing-down of progression of the disease, and preferably show that the disease markers have been abated or significantly reduced. For the patient to have confirmation that their disease is not progressing or is abated provides a huge boost to their psychological well being, as well as potentially, improving their symptoms.

Reduction in tumour marker and tumour size results in improvements in existing symptoms such as improved breathing, reduced pain and less probability of fractures or further invasion of tumour into surrounding tissues. Any positive treatment results greatly improves the patient's sense of well being, leading to improved self esteem, reduction in anxiety, improved family relationships, ability to return to work and contribute to society, and less financial pressure. It gives hope!

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Patients who have advanced Differentiated Thyroid Cancer (DTC) have no other conventional cancer treatments other than palliative intervention.

Conventional cancer treatments have no role, chemotherapy is not effective.

Radiotherapy may be used only for pain, and symptomatic relief, ie palliative.

There is no hope of cure, getting better or even containing the disease

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Improvement in quality of life, contribute to society again, return to work. Patients and families have hope for the future. Live a 'real' life instead of severely impaired by pain and symptoms. Following many requests from patients with advanced TC, my organization has produced the first ever information DVD.

It follows a patient's 8 year battle with the disease and how she has been helped physically and emotionally by having access to a TKI. It has enabled her to see two grandchildren being born, something she had previously thought she would not live long enough to see. "My daughter is pregnant. I need access to a drug that will help me be around to see this baby born".

I have acted as a patient advocate on a number of occasions to help facilitate access to Sorafenib, and have seen first hand how this drug has transformed the lives of terminally ill people.

One young man was wheel chair dependent, had not been able to work for two years and relied entirely upon his parents to care for him.

'I feel like a child, I'm a 25 year old man and my parents have to do

everything for me, it's just horrible"
'We dont talk about the future, we are all terrified of what is going to happen, we have no hope, I feel so guilty putting them through this"
'We walk around on egg shells, afraid of speaking the truth to each other'
After three months of taking Sorafenib his quality of life was massively improved.
Scans showed a large reduction in tumour size, this was also demonstrated in tumour markers in his blood.
Over the next six months this young man was sable to return to work, travel abroad on two holidays and fulfill a lifelong ambition to learn to ride a motorbike.
Life had a sense of normality for the whole family and happy times returned.
This would not have been possible without access to Sorafenib.
Another young woman with brain metastases was having problems with her vision and seizures.
She has three young children and life revolved around hospital appointments.
After two months on Lenvima (following disease progression on Sorafenib) her seizures stopped and she is able to get out with her children and look after them properly without relying on outside assistance.
She told me 'I was able to sew the name tags into the children's' school uniforms, it made me feel like areal Mum again'
These patients are living with advanced DTC, I hope these examples will demonstrate the life changing impact this medicine can bring.□□

These new drugs are the only effective palliative systemic treatments for Iodine resistant Differentiated thyroid cancer proven by reliable clinical trials for which currently no other treatment is available.

In significant numbers of such patients these drugs halt the progression of tumour, reduce the size of the tumor leading to-enormous improvement in symptoms and thereby quality of life For months, sometimes for years, in individual patients.

Clinical trials have shown that Lenvatanib has been shown to be more effective than Sorafenib and can help patients even after Sorafenib has stopped working so to allow the use of Lenvatanib would a huge step forward for the people I deal with on a daily basis. To have these effects and then allow the hope and positive results offered by Lenvatanib would provide a massive boost to these patients as well as significantly enhancing the quality of their lives and their life-expectancy

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

There are no other treatments available

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

None

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Side effects can include sore hands and feet, hypertension and alopecia. However, all of these can be well managed by the Cancer Care Team, patients are very well supported.

This may lead to an increase in hospital visits for their management, initially.

lease list any concerns patients or carers have about current NHS treatments in England.

There are not enough treatments available for rare cancers

Please list any concerns patients or carers have about the treatment(s) being appraised.

None

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

None

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

No

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

None

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

x☐ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

I have not seen any difference

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Yes, the outcomes are very important to patients. They have shown that they can halt, and slow down disease progression improving quality of life and lengthening life expectancy

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

I am not aware of any other side effects

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes No x

If yes, please provide references to the relevant studies.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No

8. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☐x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

No other treatments available

Are there any other issues that you would like the Appraisal Committee to consider?

There are very few thyroid cancer patients who will fall into the category of requiring these medicines, perhaps 200 per year in England.

There are very few patients who will require these medicines so the cost implication would not be significant to the overall NHGS drug budget. Currently there are only 26 patients receiving Lenvima and 198 patients receiving Sorafenib (in the past three years)

In no more than 5 bullet points, please summarise the key messages of your submission.

- Tumour reduction leads to reduction in pain and symptoms
- There is no other effective treatment available for this cancer group
- Improvement in longevity and quality of life
- Patients and family have hope for the future as well as gain in self esteem and confidence, which leads to:
- Improvement in quality of life so able to contribute to society and return to work

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

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

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: The British Thyroid Foundation

Your position in the organisation: [redacted]

Brief description of the organisation:

(For example: who funds the organisation? How many members does the organisation have?)

The BTF was established in 1991 and is registered as a charity in England and Wales (No: 1006391) and Scotland (SC046037). The organisation provides information and support to people with thyroid disorders, and helps their families and carers, and the wider population to understand the condition.

The BTF is a membership organisation and currently has approximately 4,000 members. Patients receive peer support through local groups and a telephone helpline which is run by volunteers, as well as through the resources provided on the BTF website (http://www.btf-thyroid.org/) and online support forums.

The majority of the charity's funding comes from membership subscriptions, donations and community fundraising. No pharmaceutical companies are corporate members of the BTF.

Occasionally the charity has received donations and grants from pharmaceutical companies. Within the last two years the following donations have been received:

Name of company		**Purpose of funding**
EISAI	£250 (March 2016)	Donation in respect of a patient talk
AMCo Limited (now Concordia Healthcare)	£15,525 (2015-2016)	In support of BTF Newsletter
Sanofi Genzyme	£500 (2016-2017)	Donation in respect of cover design of the front cover of the revised thyroid cancer booklet

Pharmaceutical company funding represented approximately 11% of the BTF's annual income is 2015-2016 and 0.30% in the financial year 2016-2017.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition,

or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Thyroid cancer typically metastasises locally in the neck, bones, lungs, liver and brain. The group of patients eligible for this drug have metastatic disease, which is progressive and unresponsive to other standard treatments. Metastatic disease can therefore be associated with symptoms such as pain, swallowing difficulties and breathing difficulties, a reduction in activities of daily living and quality of life.

Progressive locoregional disease also causes these symptoms plus potential voice change.

The psychological impact of this disease can also be substantial with low mood and fatigue commonly reported. The natural history of thyroid cancer is such that this group of patients may survive longer than patients with other metastatic cancers, but with a poor quality of life.

It is worth stressing that if patients respond to these treatments in this setting their symptoms can significantly reduce allowing them to increase their level of activity, be more independent, improve mental wellbeing, improve their quality of life, and potentially allow reduction in opiate analgesia, reduce the need for palliative radiotherapy to painful bone metastasizes.

Importantly some people also benefit long term and it’s not just a short period of improvement that is seen. Some patients could be on treatment with maintained quality of life and independence for several years.

Patients handle this scenario differently and in an individual manner. Some cope well and look on the bright side, for example being grateful for having more years than anticipated when diagnosed. Others do not cope at all and battle related depression on top of the disease.

Some are able to compartmentalise the common side effects of lenvatinib and sorafenib. Even though these can be very restrictive, some people are able to focus on the fact that some of the side effects are OK to live with. There are also those who accept that cancer is unfortunately sometimes an incurable disease and they accept their fate.

There are others who say: '*I am not accepting it, I am fighting it with all I can, I am not giving up, I am not ready to die, there must be something out there that will to help me*.' These patients also sometimes look into alternative treatments which are offered on the internet and cling on to every bit of hope, often spending huge amounts of money on these types of supplements.

One lady wrote to tell us about her experience and in particular the loss of hope she felt when all treatments options had been exhausted. She had had five surgeries, a severe (surgery related) infection, loss of a vocal cord, long periods in hospital, and radiotherapy. One consultant told her thyroglobulin (Tg) antibodies were too high and that there was nothing more that could be done.

'*Can you imagine how my husband and I felt as we walked out of that clinic? After going through all I'd been through over a space of three years I was totally at rock bottom. What is the point of life if there is no hope?'*

Another male patient described his experience:

'My experience of the condition to date is that it has been asymptomatic which of course is a great blessing. However, psychologically it is tricky to deal with and also explain to the outside world – I seem to look well yet I have a progressive disease. [I know that] the current treatment (sorafenib) of course offers some measure of disease control but not a cure.

My quality of life remains good at present – challenges to date along the cancer journey have mainly involved dealing with treatment side effects. I have made one significant life adjustment to cope with the disease and hospital visits and, positively, to live life to the full: I took early retirement in summer last year.'

A female patient wrote about her life with the disease:

'As with any cancer it is very difficult to live with not knowing how things are going to go it's like waking up every day under a black cloud. My cancer can never be cured but can be held back and stable but for how long nobody knows. This is difficult to deal with.

I sometimes feel isolated as there does not seem to be enough information or talk about thyroid cancer as compared to the more common cancers. Things have improved a bit more now better than when I was diagnosed in 2011.'

Another woman made the following points:

'It is difficult to plan ahead and it's hard to switch off from my condition. Even though I am 75, I love life. I don't enjoy discussing my condition, or even telling anyone about it at the present time. Only our family and closest friends know.'

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The treatment outcomes that are important to patients include better symptom control and management of the pain, and this in turn would ideally offer people an improved quality of life and more time to spend with their family and friends. Some patients may also be able to return to work and other family or social commitments that had previously been interrupted by the disease.

The psychological symptoms that patients report may also be helped as new treatment options bring a return of hope that some form of therapy is available. Renewed hope, together with increased social and economic engagement, often helps patients feel valued and able to contribute which in turn improves self-esteem and confidence.

A patient told us about his hopes for the treatment outcomes:

'I am undergoing treatment with sorafenib. This treatment started very recently - so far I have only around a month's experience of the therapy, therefore it's very much early days under the drug regime.

Progression free survival with minimal side effects would be my ideal. I know that the progressing disease is not curable, so a drug which can keep the disease on hold for a period, even a number of months, would be beneficial.

I think another key treatment outcome is the continued ability to lead a normal life. I lead a busy life in retirement so I wish to continue engaging with my various hobbies and interests and live life to the full.

I'm very fortunate to remain asymptomatic at present, hopefully the treatment will also preserve this status quo.'

Another patient wrote about her current treatment:

'I am currently taking lenvatanib which I have been taking since May 2016. I was previously taking sorafenib which I took for a year and then it stopped working. In February 2016 I was told I only had months to live but here I am over a year on and still going strong.

Obviously the most important outcome would be to be cancer free but I know this will never happen to me so it's important for me to have the best treatment available.'

'The outcomes which I value most are seeing our grandchildren grow up; enjoying the opportunities which retirement has offered, being able to take the dog for walks on the beach (I can still manage about 3 miles a day), and still being able to help with our local Riding for the Disabled group.'

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Neither sorafenib nor lenvatinib are available for patients in England. Levatinib is currently only available in Scotland. Neither drug are approved for use in Wales as they have not yet been appraised. An Individual Patient Funding Request (IPFR) needs to be submitted to the patient's local health board to request the use of the drug and the response is variable.

Other systematic palliative treatments (eg palliative conventional chemotherapy) lack efficacy and are poorly tolerated. Response rates are in the region of 30% and are often of short duration.

The experience from use of sorafenib while available from the Cancer Drugs Fund was positive and preferable to conventional chemotherapy (usually doxorubicin and cisplatin).

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Sorafenib

It is vitally important to help patients by relieving the pain, anxiety, and loss of hope which is a symptom of their metastatic disease. Patients with progressive locoregional disease and/or metastatic disease frequently experience loss of independence, performance status, and struggle to maintain a good quality of life.

Even if the progression-free survival time is limited, the improved quality of life may improve self-esteem, particularly if it means that a patient can potentially return to some form of work and spend more time with their families. Research into these new targeted therapies is moving fast and it may be possible to extend the progression-free survival time and/or mitigate the side effects by using these therapies in combination or in tandem.

Professionals who have cared for patients treated with sorafenib tell us that they have seen great physical, emotional and psychological benefits. When a scan shows a reduction in size of metastases, or the symptoms decrease, there is a major boost to patients' emotional well-being. The chance of an improved quality of life and stronger self-esteem return and there is a point in living again.

One patient told us about the optimism she felt after discovering her Tg antibodies were coming down.

"For the first time in [three years] I'm not going near a hospital for six months. I know there is some hope now and I'm determined to continue to be optimistic but I need to know there is hope for new drugs to be available when I need them."

Another patient shared his thoughts about the advantages of his sorafenib treatment:

1. *'Side effects manageable: many of the known sorafenib side effects are manageable through additional medication or by varying the drug dosage.*
2. *Ease of use: sorafenib is in tablet form so easy to self-medicate and also doesn't involve time-consuming and tiring hospital/GP visits.*
3. *Ease of monitoring: monitoring for side effects can be handled straightforwardly through regular clinic check-ups and, where necessary, phone/email conversations with my Specialist Nurse.*
4. *Quality of life: for as long as the drug therapy limits progression, the treatment will enable me to sustain a busy life in retirement.*
5. *Remaining asymptomatic: the drug therapy should help me remain asymptomatic for longer.*
6. *Psychological benefit: with limited treatment options available to a radioiodine refractory patient like myself, the drug provides hope that 'something can be done'.*

A patient who is currently being treated with lenvatinib gave the following feedback:

'The advantage of the medication is that it is taken orally so no need to attend the hospital more regularly than is necessary. I do attend monthly for check ups scans etc and to collect the medication. It's easy to take, I take it first thing in the morning on an empty stomach and then do not eat for two hours. It has given me a much better quality of life than I had a year ago.'

Another levantinib patient wrote:

- *'I am still here when I did not expect to be, and we will be celebrating our golden wedding shortly. I'm still able to share time with our family and friends.*
- *I strongly prefer to take tablets, rather than have injections. I feel that I am more in control, and I strongly prefer to be able to treat myself at home.'*
- *Since I have been on lenvatinib, I have been under an oncologist in a hospital only 30 miles away, and have had regular checks. Previously I was under a consultant and needed to make a round trip of nearly 250 miles.'*

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Patients taking these drugs can expect to spend quality time at home with family and friends rather than in hospital. The side effects are usually much easier to manage than the often more harsh side effects of traditional chemotherapy.

The symptoms of the disease can be painful and distressing, both physically and psychologically. Witnessing their loved ones suffering and without hope of treatment is very upsetting for family and carers.

Knowing that there is chance of successful treatment can make an enormous difference to all those involved. There may be fewer hospital visits as patients can take the tablets as outpatients (as opposed to the symptoms being managed in hospitals) and a certain level of normal day-to-day life may be achieved.

It is so helpful for relatives to see their loved ones living with more hope, with fewer symptoms and suffering, with a better quality of life and a more positive outlook for the future.

'A better quality of life. A year ago I had trouble breathing and had to make use of a wheelchair. Now I don't need this assistance. The drug has given me a bit longer life. I was told in February 2016 that the sorafenaib was not working and I only had months to live. Within two months of taking lenvatanib there was a marked improvement. I knew in myself how well it was working, it has given myself and my family hope.'

'I hope to remain independent, and to be as useful as possible for as long as possible.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

A significant minority of patients receiving the treatments being appraised report no intolerance, whereas this is nearly never the case with conventional chemotherapy. Close patient monitoring detects side effects at an early stage

and allows toxicities to be managed before they get severe. Dose reductions and interruptions can be utilised to achieve this.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

We are not aware of any.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

These drugs do have reported side effects. Ideally however these symptoms may be manageable through good information and counselling to enable patients to make informed choices and to help them stay on treatment. However importantly the medicine offers hope where there is otherwise none.

One patient wrote about the disadvantages he had experienced:

'In my limited, month long experience of sorafenib, I've experienced the foot reaction on both feet which has subsequently led to two drug dosage reductions: currently I'm down to two tablets per day from a starting point of four per day. It's clear that the foot reaction, if left unchecked, could be very debilitating. Naturally I'm concerned that this may mean I'm intolerant to the drug and that the treatment might yet need to be discontinued. However, I'm reassured by my consultant that my body may become more tolerant of the medication over time, so there are grounds for optimism.

I am also aware of other listed side effects (eg loose bowels) which may be problematic and affect the ability to lead a normal life.'

'*The disadvantages would be the side effects but this is a small price to pay for a longer life. The current medication (lenvatinib) affects my bowel causing lots of flatulence and diarrhea but this is manageable with medication. It also gives me high blood pressure but this is controllable with amlodipine and Ramipril..It does not make my hands and feet sore like the sorafenib did.'*

Please list any concerns patients or carers have about current NHS treatments in England.

There is a frustrating lack of alternative treatments for patients with metastatic, progressive, radioiodine refractory thyroid cancer. In addition there is an inequity of access to treatments across different regions of the UK.

It is worth pointing out that patients with the more common cancers have more treatment options available and may be offered multiple lines of therapy in the palliative setting. Unfortunately because thyroid cancer is rarer, the clinical trials to support use of TKIs in second line and beyond settings are not easily achievable due to small patient numbers and limited interest from pharmaceutical companies to support these aspects of patient management.

Please list any concerns patients or carers have about the treatment(s) being appraised.

The only concern we are aware of is that the drugs will be deemed too expensive but without them there won't be any useful treatment options.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

Possibly younger patients with good baseline performance status and few or no comorbidities.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

Perhaps the opposite of the previous point could be argued in that patients of poor performance status and/or significant comorbidities or contraindications may be unsuitable for TKI treatment.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Yes

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Overall survival data are still lacking. QOL data is lacking and doesn't reflect the real world scenario which is highlighted with the comments and patients' quotes included in this submission.

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

X Yes ☐ No

If yes, please provide references to the relevant studies.

Results of the Thyroid Cancer Alliance international patient/survivor survey Banach R, Bartès B, Farnell K, Rimmele H, Shey J, Singer S, Verburg FA, Luster M. Psychosocial/informational support needs, treatment side effects and international differences in care. Hormones (Athens). 2013 Jul-Sep;12(3):428-38.

Quality-of-Life Priorities in Patients with Thyroid Cancer: A Multinational European Organisation for Research and Treatment of Cancer Phase I Study. Thyroid. 2016 Nov;26(11):1605-1613. Epub 2016 Oct 12.

Aschebrook-Kilfoy B, James B, Nagar S, Kaplan S, Seng V, Ahsan H, Angelos P, Kaplan EL, Guerrero MA, Kuo JH, Lee JA, Mitmaker EJ, Moalem J, Ruan DT, Shen WT, Grogan RH. Risk Factors for Decreased Quality of Life in Thyroid Cancer Survivors: Initial Findings from the North American Thyroid Cancer Survivorship Study. Thyroid. 2015 Dec;25(12):1313-21.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Improvement in progression-free survival is of importance and probably translates to improved survival for some patients. It is important to note that

there have been no previous treatments in radioiodine refractory disease that have stabilised and/or improved symptoms and quality of life for prolonged periods (potentially years).

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- There is currently no treatment for these patients in NHS England.
- These treatments have been demonstrated to provide patients with a period of progression-free survival.
- They offer patients the potential for improved quality of life, improved self-esteem, and improved emotional wellbeing as well as significant symptom and performance status improvements.
- It offers potential for return to work and more family time.
- Side effects are manageable through good information and counselling to enable patients to make informed choices and to help them stay on treatment.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]
Name of your organisation: NCRI/RCP/RCR/ACP

Comments coordinated by: [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Iodine refractory differentiated thyroid cancer is a relatively rare condition. Some patients will have indolent disease which is non-progressive over months and even years and does not require intervention. However, in cases where the disease is progressive, treatment is required. The only licenced disease modifying treatments are Sorafenib and Lenvatinib. Currently in England only Sorafenib is routinely available to patients in this situation via the Cancer Drugs Fund. Eisai have recently made Lenvatinib available for patients who have progressed on or failed to tolerate Sorafenib through a compassionate access programme. This will be discontinued when a decision has been made at this appraisal.
There is currently significant inequity of access across the UK. Neither drug is available to NHS patients in Wales, except by Individual Funding Request. Both drugs are currently routinely available to patients in Scotland.

Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be?

There is not significant geographical variation or difference of opinion about the best treatment for this condition amongst oncologists with an interest in thyroid cancer in the UK All would recommend treatment with Sorafenib or Lenvatinib as standard of care for a patient with progressive and symptomatic (or imminently symptomatic) disease.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

There are no other treatments proven to modify the course of the disease in this situation. Beyond the treatments being considered in this appraisal patients would be offered best supportive care which may include palliative radiotherapy, locally ablative therapies, analgesia, bisphosphonates and/or denosumab, but none of these treatments is likely to impact survival

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Clinical trials to date have failed to demonstrate any reliable biomarkers to predict increased likelihood of response to these agents. All subgroups of patients examined appear to derive similar levels of benefit.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

These drugs are currently administered within the secondary care setting and we would strongly advocate use within a specialist multidisciplinary thyroid cancer clinic for optimal care.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Specialist nursing input, with expertise in managing the side effects of Tyrosine Kinase inhibitor drugs, would be strongly recommended.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

As far as we are aware Sorafenib, the drug currently available in England, is used under its licensed indication in thyroid cancer. Lenvatinib is available in Scotland and again is used within its licensed indication.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The most recent update of the British Thyroid Association Guidelines on the management of thyroid cancer was published in 2014, before either Sorafenib or Lenvatinib had licences for use in this setting. These guidelines made the following observations-

1 The use of targeted therapies outside clinical trials should be endorsed by the MDM after careful consideration of the balance between potential benefit and harm.
2 The principal indication for targeted treatments is radiologically progressive, symptomatic disease, refractory to conventional treatment.
3 Targeted treatments should be administered in the setting of cancer units that have experience in monitoring and managing the side effects of targeted therapies.
4 Consideration should therefore be given to entry to clinical studies.

The more recent 2015 American Thyroid Association Guidelines, issued after the agents had been licenced, give a stonger recommendation-

Recommendation 96: Kinase inhibitor therapy should be considered in RAI (radioiodine)-refractory DTC (Differentiated Thyroid Cancer) patients with metastatic, rapidly progressive, symptomatic and/or imminently threatening disease not otherwise amenable to local control using other approaches.

These recommendations are based on 2 published phase 3 trials which have demonstrated significant improvements in progression free survival with the use of Sorafenib and Lenvatinib in patients with progressive, iodine refractory differentiated thyroid cancer.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

Guidelines for the management of thyroid cancer.
Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR; British Thyroid Association. Clin Endocrinol (Oxf) 2014 Jul;81 Suppl 1:1-122

2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2015

Brose MS, Nutting CM, Jarzab B et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014 Jul 26;384(9940):319-28

Schulmberger M, Tahara M, WirthLJ et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. NEJM 2015 Feb 12;372(7)621-30

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Sorafenib is already available and in routine use via the Cancer Drugs fund. Use of Lenvatinib would be very similar to use with no further practical implications. Both treatments do require additional clinical monitoring visits, especially early in the course of treatment.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

There are no known biomarkers for response to these treatments currently so no additional testing would be required.
Clinicians would be expected to follow the starting and stopping rules used in the clinical trials. Patients would be considered eligible for treatment only if they had radiological evidence of progressive disease and symptoms (or imminent symptoms). Treatment would be stopped on evidence of radiological progression, unacceptable toxicity or patient choice.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important

outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The conditions in which the trials were conducted do reflect current UK practice. Progression free survival, the primary endpoint in both trials, is significant for patients as whilst progression free patients are unlikely to develop new symptoms or require additional supportive care. The high response rate demonstrated in the SELECT trial (Lenvatinib) is also of great significance to patients as radiological response is likely to result in symptomatic improvement, particularly for example in the case of bone disease.
Overall survival is clearly of significant interest to patients. An overall survival benefit was not demonstrated in either study, in part due to a longer follow up period being required, and in part due to the study designs, with cross over to active drug being permitted for patients who developed progressive disease whilst receiving placebo.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life?

The side effects of these tyrosine kinase inhibitors are now well documented and as long as they are monitored carefully and appropriate action taken promptly they need not significantly affect quality of life. The palmar plantar syndrome caused by Sorafenib can be mitigated by the use of emollients and dose reduction when necessary. The hypertension caused by Lenvatinib can generally be easily managed with routine anti-hypertensive therapy.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

We are not aware of any additional toxicities having been identified.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

We are not aware of any additional data.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology

appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Most clinicians managing these patients will already be familiar with the use of tyrosine kinase inhibitor drugs and the management of toxicity. Additional education and training is unlikely to be required.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We do not foresee any problems in this regard.