Contains AIC

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

Multiple Technology Appraisal

Background and Clinical Effectiveness

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1st meeting: 27th September 2017

Committee D

Slides for public

NICE National Institute for Health and Care Excellence

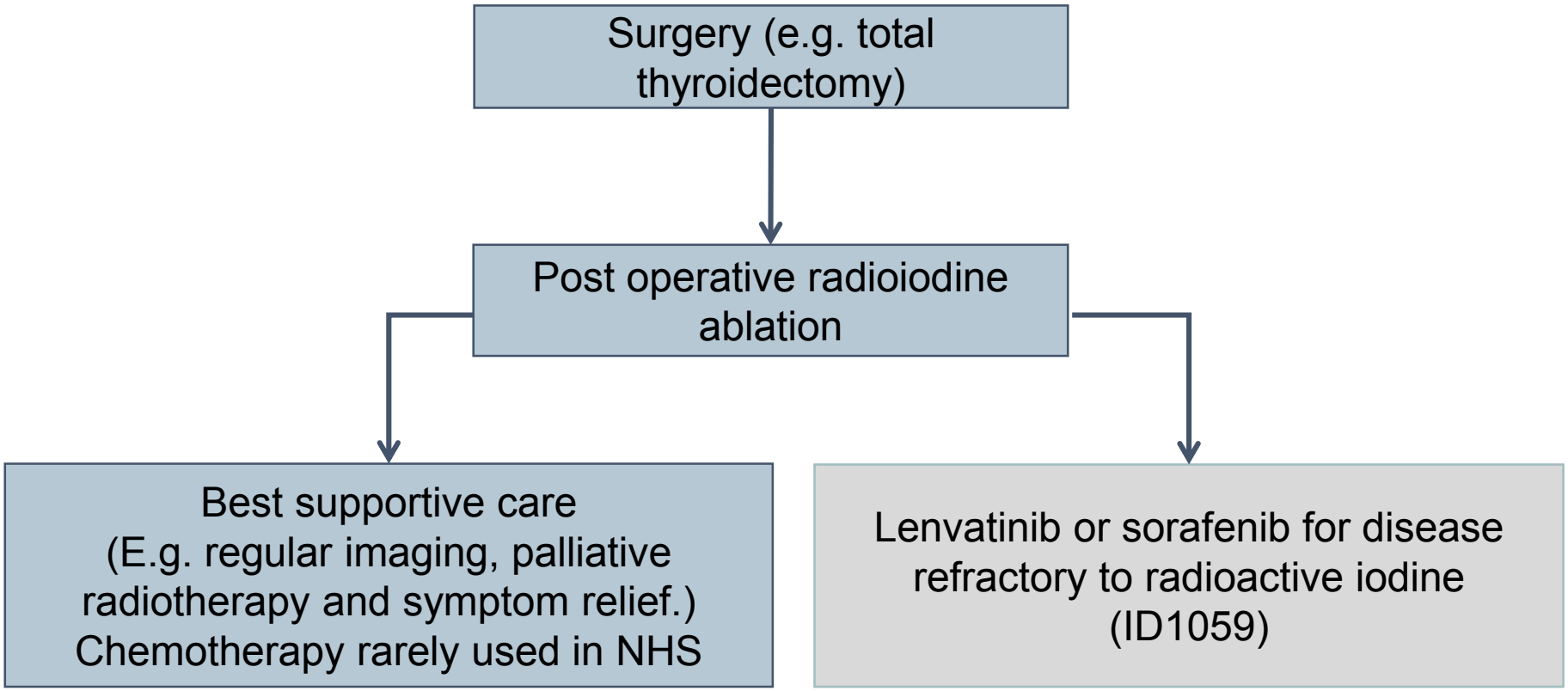
Key issues: clinical effectiveness

- 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
- 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)
  - Companies: indirect comparison included as part of base case
- 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)

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) ***

Patient perspectives

- Submissions from: Butterfly Thyroid Cancer Trust, The British Thyroid Foundation
- Thyroid cancer:
  - Rare (3200 new cases p.a. in the UK), good patient information and dedicated clinical nurse specialists often not available
  - 90-95% cure rate
  - Peaks of incidence in 20s and 60s, more common in women
- “Symptoms such as pain, swallowing difficulties and breathing difficulties, a reduction in activities of daily living and quality of life”
- “The psychological impact of this disease can also be substantial with low mood and fatigue commonly reported”
- “After three months of taking Sorafenib his quality of life was massively improved. Scans showed a large reduction in tumour size”
- “After two months on Lenvatinib... her seizures stopped and she is able to get out with her children and look after them properly”

Clinician perspectives (1)

- One submission from Royal College of Physicians
- “Best supportive care...may include palliative radiotherapy, locally ablative therapies, analgesia, bisphosphonates and/or denosumab, but none of these treatments is likely to impact survival”
- Currently Sorafenib available through CDF and Lenvatinib through compassionate access programme
- “All [oncologists] would recommend Sorafenib or Lenvatinib as standard of care for a patient with progressive and symptomatic (or imminently symptomatic) disease”
- The 2 published phase 3 clinical trials:
  - “do reflect current UK practice”
  - “demonstrated significant improvements in progression free survival”
  - “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”

Clinician perspectives (2)

- Implementation of Lenvatinib and Sorafenib in the NHS:
  - “Clinicians would be expected to follow the starting and stopping rules used in the clinical trials”
  - “Use within a specialist multidisciplinary thyroid cancer clinic for optimal care”
  - “Specialist nursing input, with expertise in managing the side effects of tyrosine kinase inhibitor”
  - “Both treatments do require additional clinical monitoring visits, especially early in the course of treatment”
  - “side-effects...monitored carefully...need not significantly affect quality of life”

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 companies 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%)

Source: Table 4 in Bayer submission, table 6 in Eisai submission and table 11 in AR

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 pazopanib and/or sorafenib in SELECT, but not reported for DECISION
*Various includes the following categories: other therapeutic radiopharmaceuticals; all other therapeutic products; diagnostic agents; diagnostic radiopharmaceuticals

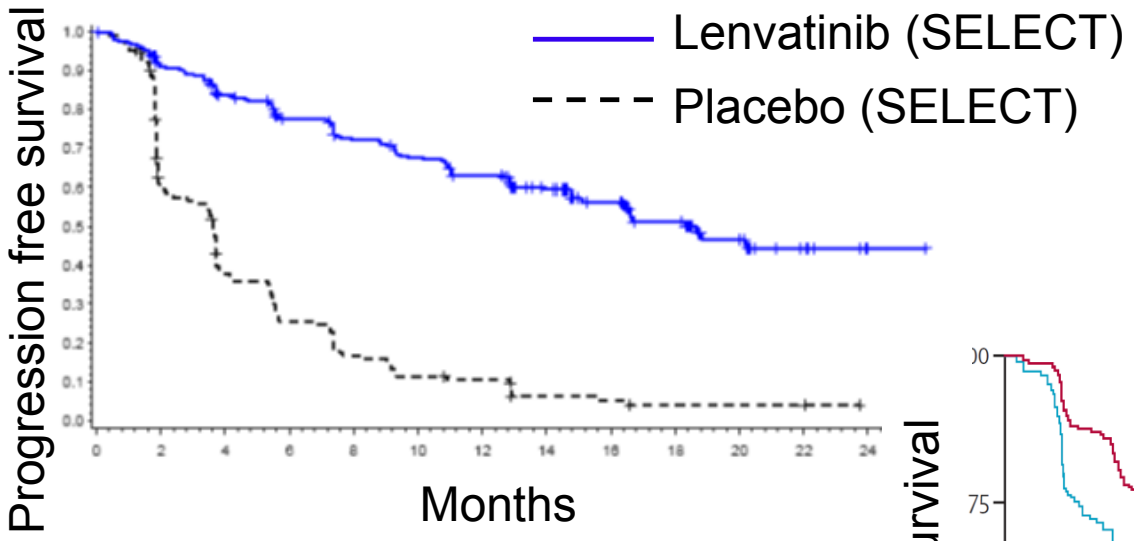
Source: Table 10 in AR

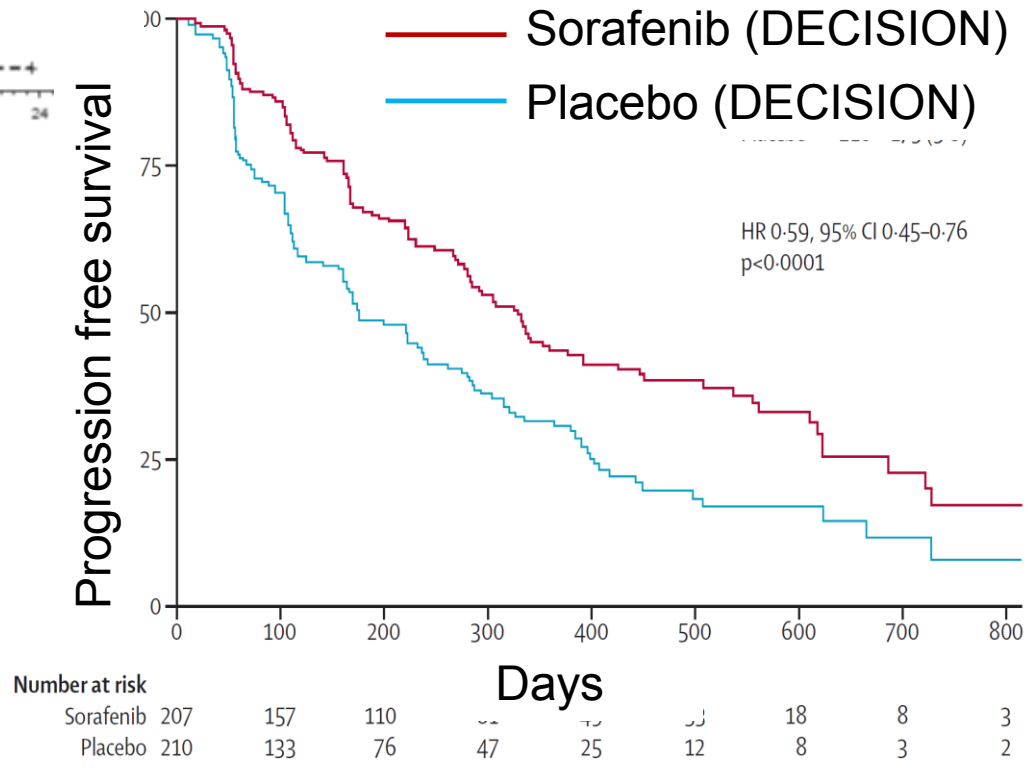
Summary of clinical effectiveness (1)

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)
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	3.	HR 0.84 (0.62 to 1.13)	HR 0.92 (0.71 to 1.21)
OS (RPSFTM)	3.	HR 0.54 (0.36 to 0.80)†	HR 0.77 (0.58 to 1.02)
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
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)
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 (PFS)

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)

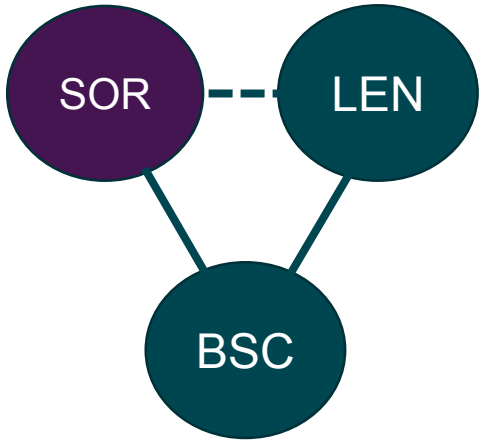
Summary of adverse events

- 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)



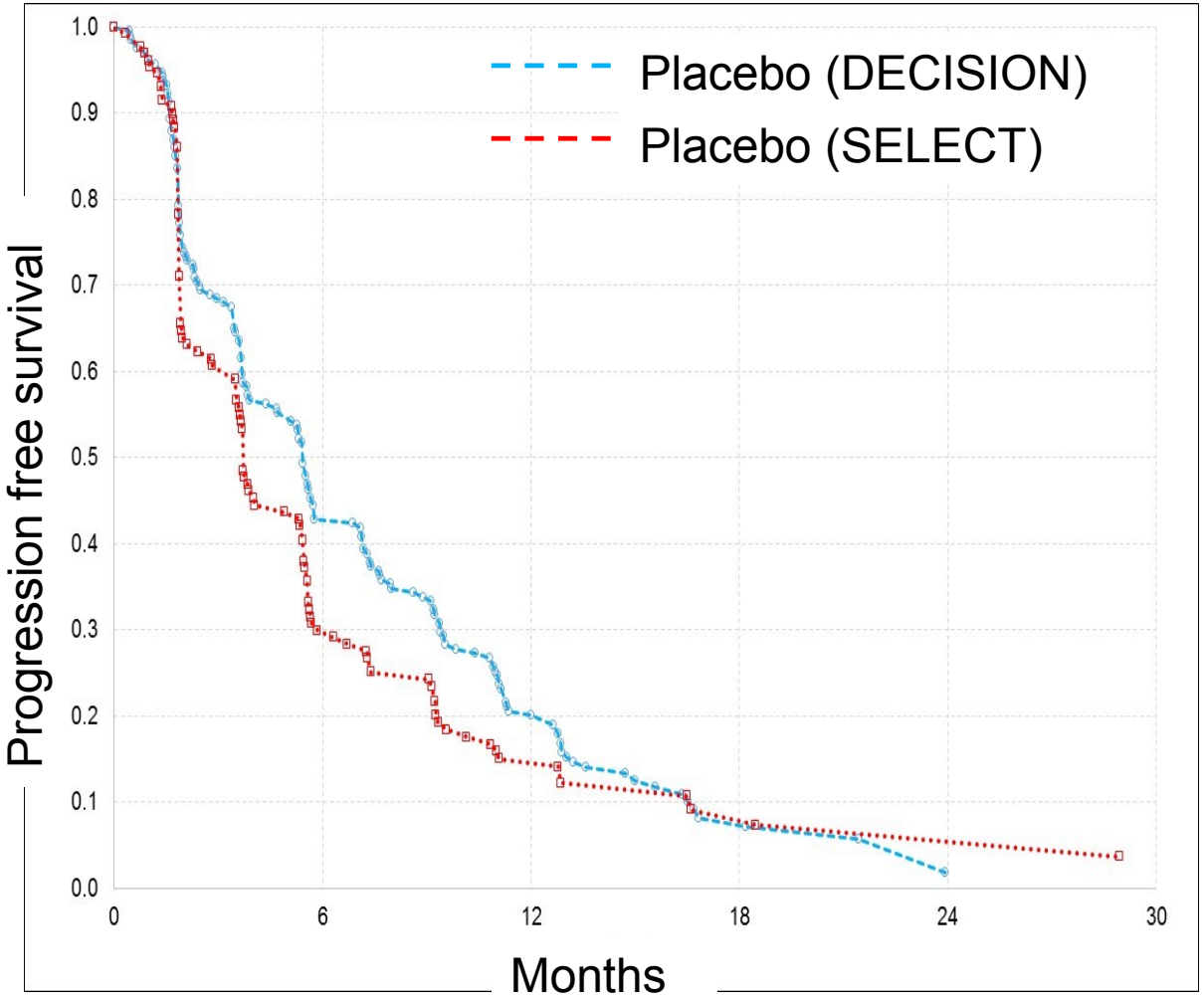
- No direct evidence for lenvatinib vs. sorafenib
- Both companies use indirect treatment comparison
- AG: ITC not appropriate because BSC arms in 2 trials not comparable

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.
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