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

Multiple Technology Appraisal

Cost Effectiveness

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1st meeting: 27 September 2017

Committee D

Slides for Committee, projector and public [noACIC]

NICE National Institute for Health and Care Excellence

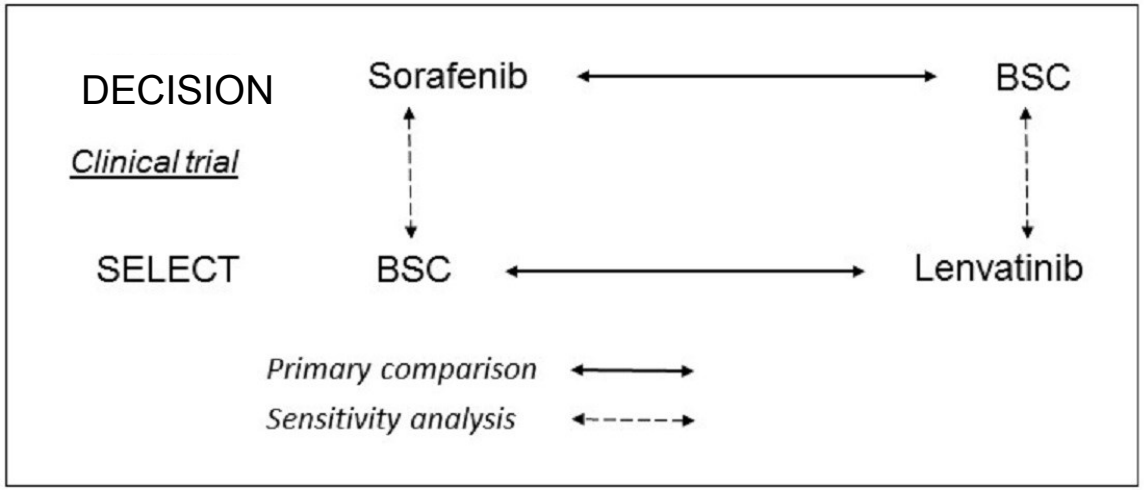
Key issues: cost-effectiveness

- 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?
- Any health-related benefits not captured for lenvatinib/sorafenib?
- Any potential equalities issues?

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 30 days for lenvatinib and 28 days for sorafenib)	
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 (direct comparisons compared with BSC also reported)		• Indirect comparison not appropriate • Each drug vs. own BSC arm (scenario: other BSC arm)
Extrapolation	• PFS: Piecewise gamma, • OS: Piecewise exponential	• PFS and OS: Fully parametric exponential	• PFS and OS: Piecewise exponential • Locally assessed PFS data from trials used (closer to clinical practice)
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

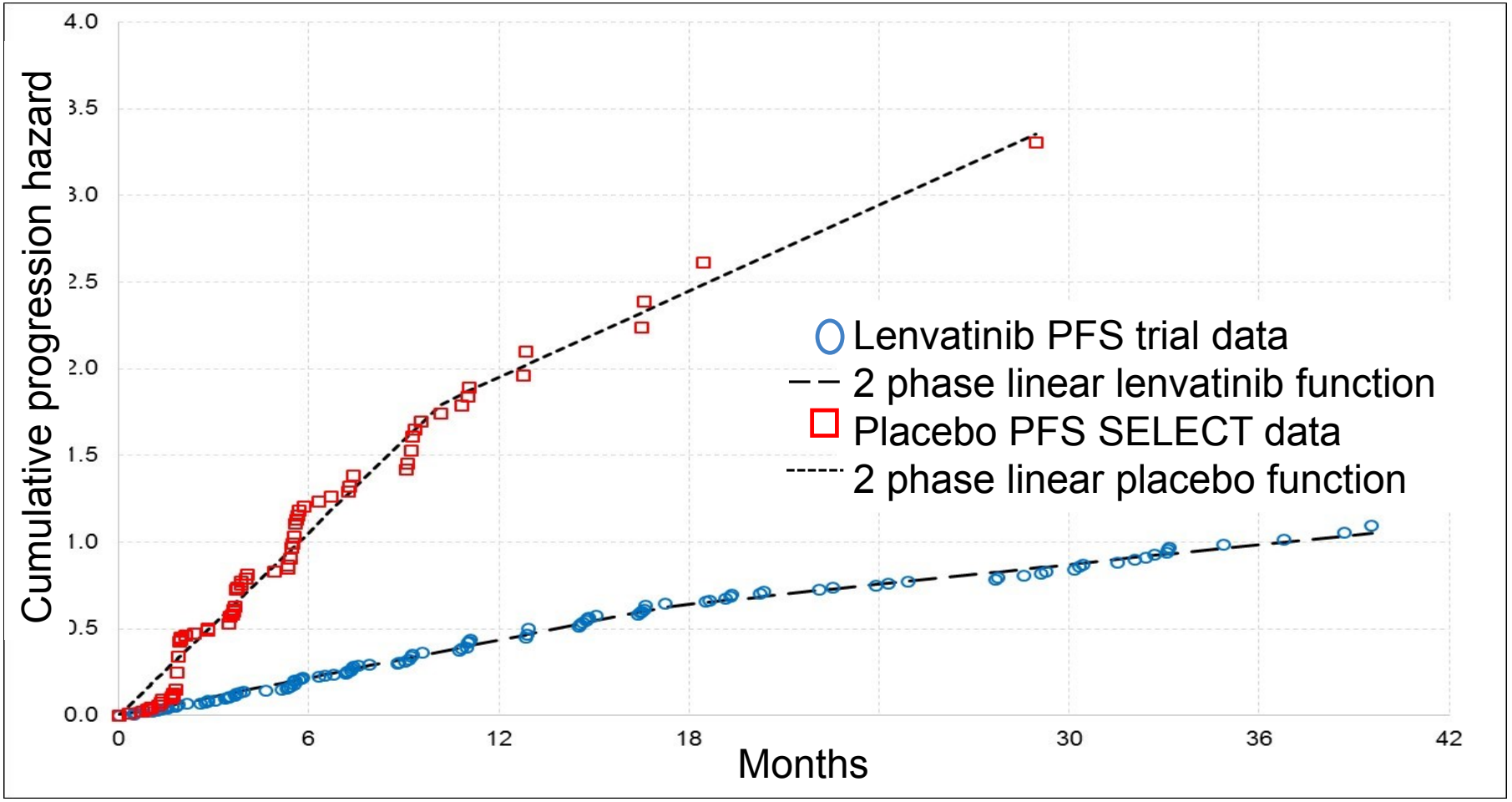
Extrapolations

- Companies use distributions based on measures of fit (as well as published epidemiological evidence and clinical advice)*
- 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			

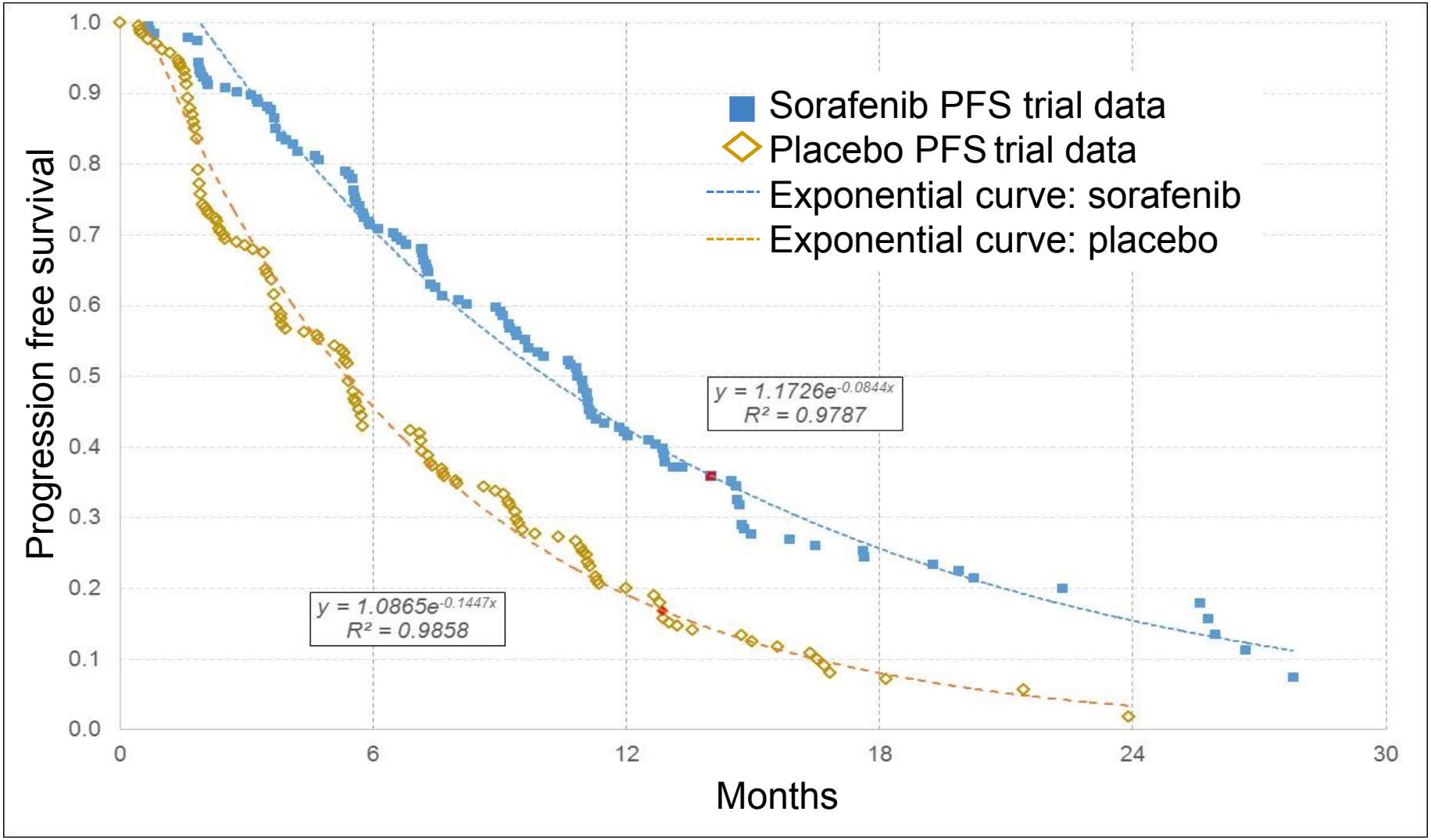
**Slide amended following the committee meeting*

PFS extrapolation-lenvatinib

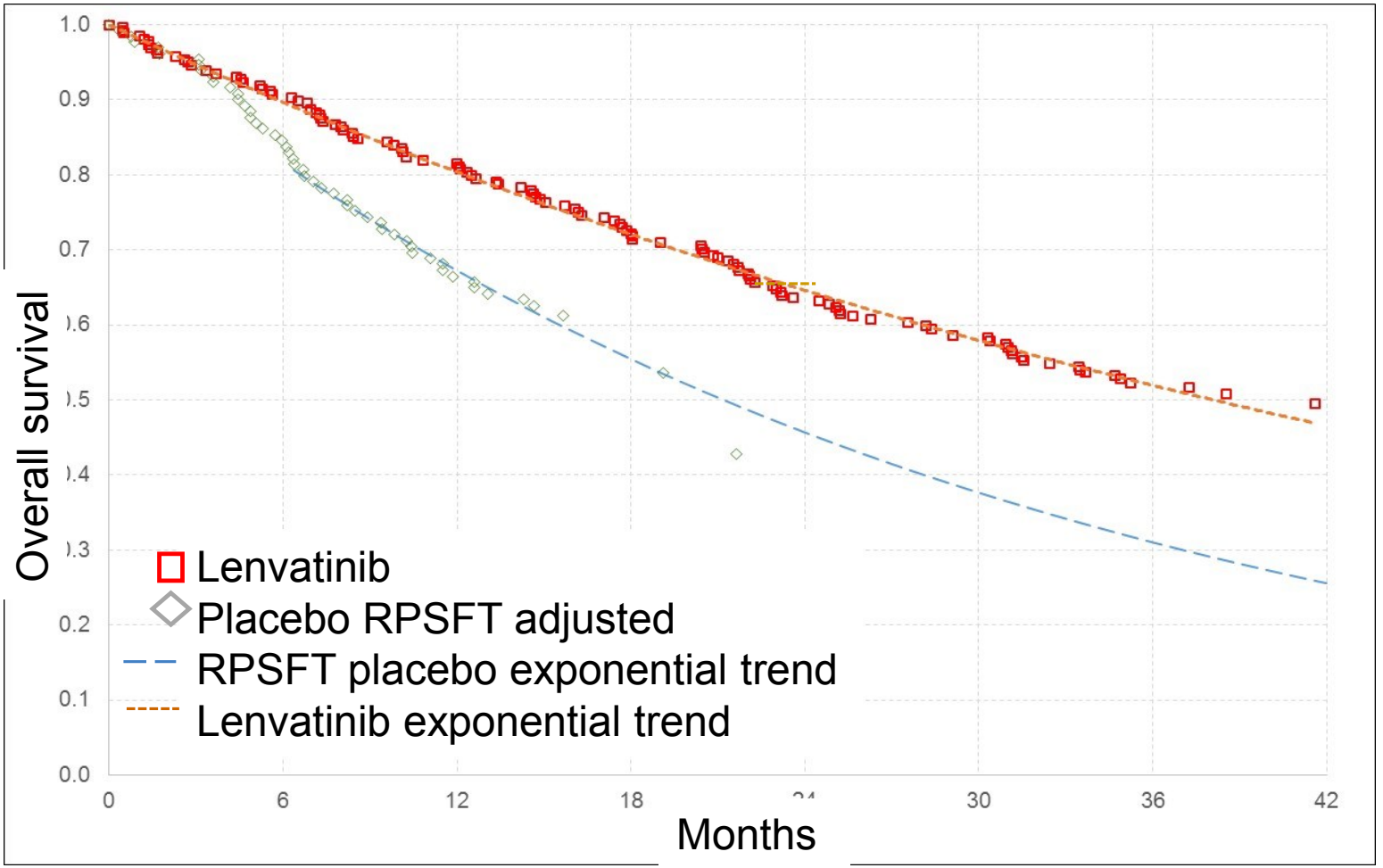


- SELECT trial data for PFS show more complex pattern in each arm. Cumulative hazard plot shows 2 distinct phases (both follow constant hazard)

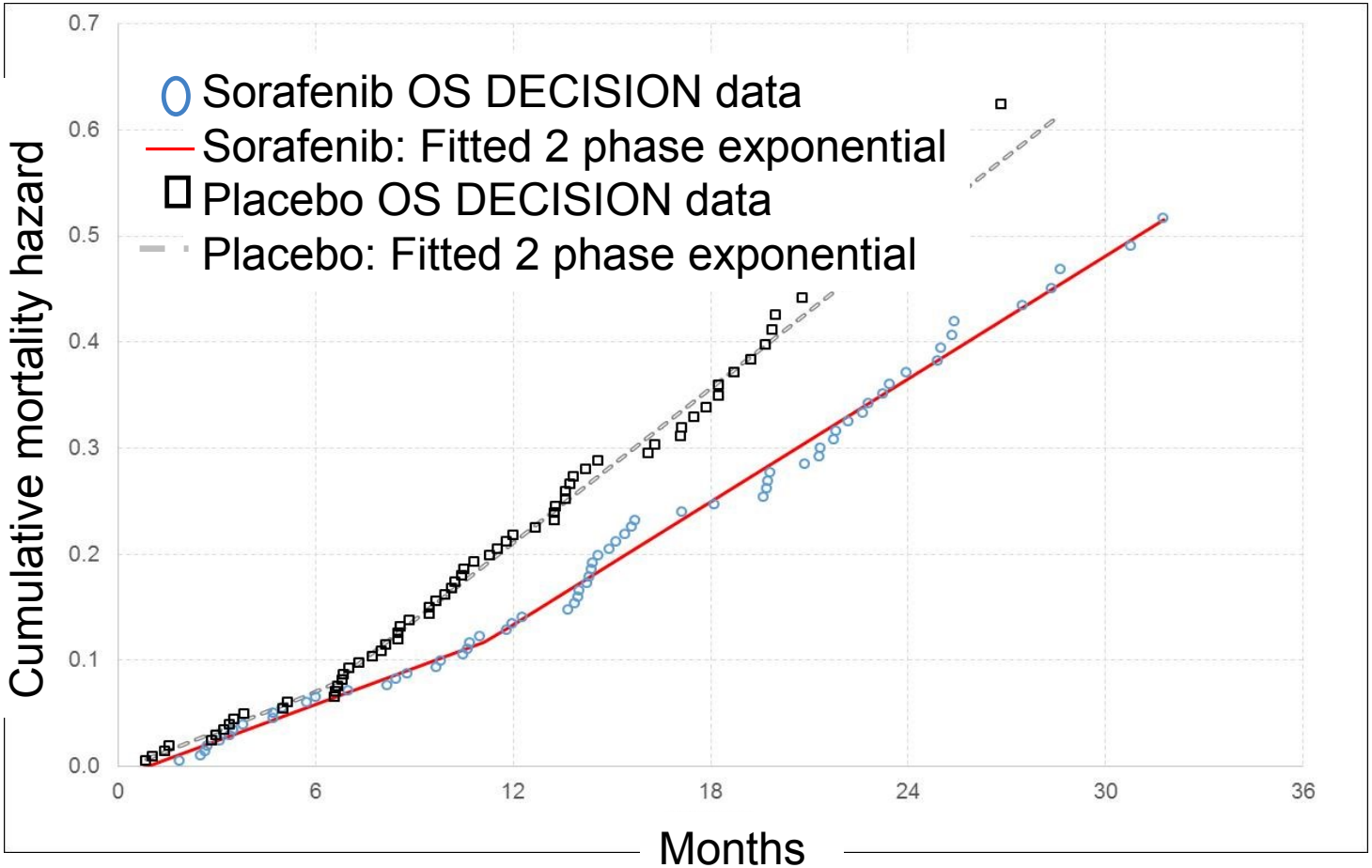
PFS extrapolation-sorafenib



OS extrapolation-lenvatinib



OS extrapolation-sorafenib



- OS data from the DECISION trial indicates patients in both treatment arms subject to a period of relatively low mortality hazard, followed by transition (11.2 months for SOR and 6.4 months for placebo) to a higher constant risk of death

Model estimates

Outcome	AG estimate	LEN gain	SOR gain
PFS	Lenvatinib: 41.0, Placebo: 6.9 Sorafenib: 13.8, Placebo: 7.6	*+34.1*	*+6.3*
OS (RPSFT)	Lenvatinib: 55.1, Placebo: 30.2 Sorafenib: 56.8, Placebo: 43.8	*+24.9*	*+13.0*
PPS	Lenvatinib: 14.1, Placebo: 23.3 Sorafenib: 42.9, Placebo: 36.2	*-9.2*	*+6.7*

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

Assessment group:

- main difference occurs in the PFS results where lenvatinib provides substantially greater benefit than sorafenib
- estimated OS results very similar (55 vs 57 months), and consequently estimated PPS reduced with lenvatinib treatment but increased for sorafenib
- 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

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: on balance data from DECISION trial should be used in base case (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	All: 064*	All: 0.64	

Source: Tables 18 and 27 in Eisai and Bayer submission

**Slide amended following committee meeting*

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. Treat with caution as some key outcome data not provided in form requested

Note: list price ICERs for Bayer are from table 50 in the AR

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	Lenvatinib model: placebo arm - 30.2* months Sorafenib model: placebo arm - 43.8* 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

Assessment group report consultation (1)

- Only received comments from companies (factual errors not presented here)

Theme	Comments	AG response
Indirect comparison	**Bayer**: agree differences in trial population and sorafenib vs. BSC provides most robust economic evaluation as taken from DECISION trial **Eisai**: trials similar enough for ITC	ITC not appropriate (see AR) MAIC may not address problem with risk profiles in placebo arm
Extrapolation	**Bayer**: AG choice not sufficiently supported, lacks face validity and underestimates values (treatment duration overestimated for sorafenib and underestimated for lenvatinib)- impacts on drug costs	AG show exponential fit to trial data (see response to consultation)*
Utility values	**Bayer**: inappropriate to use EQ-5D from DECISION for lenvatinib (differences in trial population and safety) **Eisai**: reasonable to assume utility values for lenvatinib should be higher than sorafenib	Pragmatic decision to use data from DECISION for both trials -best available source based on real-world evidence

**Slide amended following committee meeting*

Assessment group report consultation (2)

Theme	Comments	AG response
Resource use	**Eisai**: not clinically plausible to assume same level of resource use and cost pre and post-progression	Resource use based on clinical advice
Symptomatic and/or rapidly progressing disease	**Bayer and Eisai:** shouldn't restrict to symptomatic patients only because clinical benefit in asymptomatic	AG only suggest this group currently receives systemic treatment
End of life	**Bayer**: Both treatments should be considered EOL	Neither trial meet EOL as mean survival in placebo/BSC arm is substantially greater than 24 months
Safety profile	**Bayer**: Different safety profile for each treatment, choice would allow clinicians to account for co-morbidities and patient preference	Agree differences in the safety profiles of lenvatinib and sorafenib

Assessment group report consultation (3)

Theme	Comments	AG response
Sequencing	**Bayer**: No evidence on the efficacy of sorafenib, following treatment with lenvatinib	Agree no evidence on the efficacy of sorafenib, following lenvatinib
Generalisability	**Eisai**: SELECT study is generalisable to NHS clinical practice	Patients without clinically significant progressive disease may not be treated to avoid risk of side effects
Model structure	**Eisai**: disagree with AG for not including separate health state for response to treatment because it contradicts published evidence and advice from UK clinical experts	AG concluded vignette analysis did not yield sufficiently robust utility for a response state-single stable disease state with AE disutilities more credible
Adverse events	**Eisai**: not clinically plausible to assume treatment-emergent AEs unresolvable and persist beyond the cessation of treatment	AG amend model as AE costs over estimated - reduced ICER for LEN £2,000 and £3,000 for SOR

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