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

Multiple Technology Appraisal

2nd meeting: 9 January 2018

Committee D

Slides for public observers [redacted]

NICE National Institute for Health and Care Excellence

Key issues

- Most appropriate economic analysis for decision-making:
  - 3-state model or 4-state response-based model
- Preferred extrapolation for PFS and OS
- Does the committee accept other model changes, including
  - lower average dose of lenvatinib, alternative estimation of AE duration and correction of discounting error *(revised AG base case based on company comments)*
  - alternative values for resource use based on 4 UK clinical experts *(AG sensitivity analysis based on company comments)*
- Is end of life criterion for short life expectancy (<24 months) met?
- Most plausible ICER
- Other ACD comments
  - Inequality in access across the UK

Lenvatinib and sorafenib

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	
Patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	

ACD: preliminary recommendation

- Committee did not recommend lenvatinib or sorafenib
- The cost effectiveness estimates are higher than acceptable, end-of-life criteria does not apply and CDF is not suitable
  - Committee would have preferred to have seen overall survival extrapolations that used both piecewise and fully parametric curves and a range of alternative statistical distributions

ACD summary

ACD (section)	Committee conclusion
Trial evidence (3.2)	• Trial populations are very similar to people having treatment in clinical practice (that is, people with progressive disease that is symptomatic or that will become symptomatic very quickly) • Both treatments have a marketing authorisation for progressive disease, this is not restricted to symptomatic disease
ITC (3.5)	An indirect treatment comparison is not appropriate to compare lenvatinib and sorafenib because of differences in the trials
Clinical effectiveness (3.3 and 3.4)	• Both treatments improve PFS compared with placebo but lenvatinib shows a larger benefit • Lenvatinib improves OS but the magnitude of benefit for sorafenib is less convincing

	PFS	OS
Lenvatinib	HR 0.24 (0.16 to 0.35)	RPSFT HR 0.54, (0.36 to 0.80)*
Sorafenib	HR 0.49 (0.39 to 0.61)	RPSFT HR 0.77 (0.58 to 1.02)
*confidence interval from bootstrapping		

ACD summary

ACD (section)	Committee conclusion
Economic models (3.7)	In the absence of a 4-state model that modelled response appropriately, the committee used AG 3-state model (comparing each treatment with BSC) for decision-making
Extrapolation of OS (3.8)	No sufficient justification to favour one approach (AG and Eisai: piecewise exponential, Bayer: fully parametric exponential)
Uncaptured benefits (3.11)	There may be some health related benefits from response to treatment that are not captured in AG analyses (AG model does not include response state) which could reduce ICERs but no evidence for this
End of life (3.12 and 3.13)	• Both drugs meet criterion for extension to life but neither meet criterion for short life expectancy as mean OS>24 months in AG model • Committee debated whether it could apply flexibility when interpreting the end-of-life criteria but recognised that a high degree of certainty is needed and this could be resolved by further information on overall survival

ACD consultation (1)

- Received comments from Eisai, Bayer, RCP and 25 web comments

Theme	Comments
Correction of errors	**Eisai**: Identified errors in mean dose of lenvatinib and formula for AE in AG model
Uncaptured benefit from response to treatment	**Eisai**: Agree health related benefits from response is not captured in preferred analyses. To clarify, proportion of responders and non responders from SELECT for each visit used to inform the pre-progression responder and pre-progression non response states in model. Therefore, duration of response implicitly captured **Bayer**: No evidence to support uncaptured benefit: • SAE, grade 3+ AE and discontinuations were all higher for lenvatinib in SELECT compared with sorafenib in DECISION (expected to influence QoL estimates) • Clinical advisers disagreed whether response was a meaningful health state in model. Response measured differently in trials (RECIST 1.0 and 1.1) and are not directly comparable

ACD consultation (2)

Theme	Comments
Indirect comparison	**Bayer**: ACD states indirect comparison inappropriate, but comparative statements are made all through the ACD • naïve cross-trial comparisons not in line with conclusion on trial comparability
EOL	**Bayer**: Committee conclusion that benefit with sorafenib is less convincing does not reflect evidence. Life extension with sorafenib is clinically meaningful • Survival gain vs. BSC in AG model – 12.9 months • OS results from trial – HR 0.77 (95% CI 0.58 to 1.02) due to crossover adjustment
Individual preference	**Bayer**: Availability of both treatments would be most appropriate
Extrapolation of survival	**Bayer**: Outstanding issues with AG extrapolation (new evidence submitted) and cost of post progression treatment
AE and resource use does not reflect UK clinical practice	**Eisai**: Not reasonable to assume AE costs would continue for entire length of treatment duration. Resource use not in line with clinical advice

ACD consultation (3)

Theme	Comments
Inequality in access	**Web comments and RCP:** Rare cancer and drugs effective in delaying progression. Available in Scotland and Wales so should be available in England. No alternative disease modifying treatment.

- Different methods and processes for Wales and Scotland and different confidential discounts may be in place
- NICE guidance officially for England. NICE Social value judgement states NICE should evaluate drugs for rare disease in same way as any other treatment

New evidence (Eisai): Dose and AE

- Correct average dose for 2015 data cut is 16.3 mg (not 17.4mg)
- Not reasonable to assume AE cost would continue for entire length of treatment duration: **AG approach not plausible**
  - Mean treatment duration in SELECT 13.8 months and all AE durations substantially shorter
  - Eisai use mean AE duration to model AE
- Corrected error: AE results not being discounted
- AG resource use estimates not consistent with clinical advice from 4 UK clinical experts
  - for treating hypertension, monthly oncology visits, hospitalisation, MRI and bone scans

AG revised base case:

- Corrected average dose for lenvatinib - ✓
- New estimation method for AE based on new evidence of AE duration from Eisai - ✓
- Correction of discounting error for AE - ✓
- No changes to resource use in base case (Eisai model uses costs based on multi-national survey but this may not be applicable to UK clinical practice) - x
  - AG sensitivity analyses only

New evidence (Eisai): End of life criteria

Eisai	Assessment Group
Eisai identified additional references: • Survival for patients with RAI-refractory DTC and distant metastases is around 2.5 to 3.5 years (Durante 2006, Robbins 2006, Worden 2014) • Death from thyroid cancer within 3 years is common (Pfister 2008) • Consistent with clinical expert at ACM1 (at least 50% of patients will not live longer than 2 years) After applying flexibility around EOL criteria, it is reasonable to conclude lenvatinib can meet criterion for short life expectancy	AG: no reliable evidence life expectancy is <24 months: • Durante (2006) fitting 2 phase exponential model median survival 26.66 months and mean OS 62.5 months • Robbins (2006) median survival >40 months in 400 metastatic thyroid cancer patients • Worden (2014) and Pfister (2008) clinical reviews and do not contain any new evidence

Lenvatinib vs BSC: List price

Changes	ICER Lenvatinib vs. BSC	
	Eisai	**AG**
Base case (ACM1)	**£48,569**	**£62,802***
AG model with lenvatinib mean dose of 16.3mg	£59,247	£59,247
AE cost revision	N/A	£60,208
AG model with discounting error corrected (AG agree)	£62,736	£62,736
AG model & 1 additional GP contact for hypertension	£60,411	N/A
AG model with Eisai hospitalisations estimate	£57,754	N/A
AG model assuming monthly oncologist visits	£62,207	N/A
AG model assuming 7.5% MRI and 9% bone scans	£60,438	N/A
AG model using mean AE duration to model AEs	£60,692	N/A
Revised base case	**£48,607****	**£56,653**
Sensitivity analyses	N/A	**£54,713†**
* AG corrected base case, ** based on all changes, † based on all changes (GP hypertension treatment, no bone scans, fewer MRIs, more frequent oncologist visits)		

ICERs using confidential discount for lenvatinib to be discussed in part 2

New evidence (Bayer): survival modelling

1) Survival curves in AG erratum do not match those in AG model
2) AG's survival curve extrapolation lack face validity:
   - artificial drop in extrapolated portion unlikely to reflect clinical practice and underestimates long term survival outcomes
   - fitted PFS curves do not start at 1 (AG model: KM data for initial time period)
3) Clinical plausibility of extrapolations

Figure 1. PFS extrapolation in AG erratum

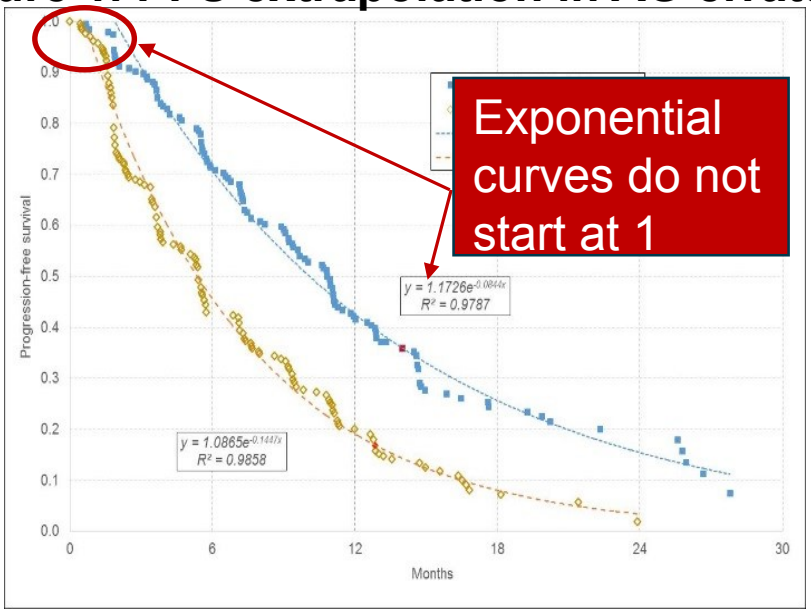
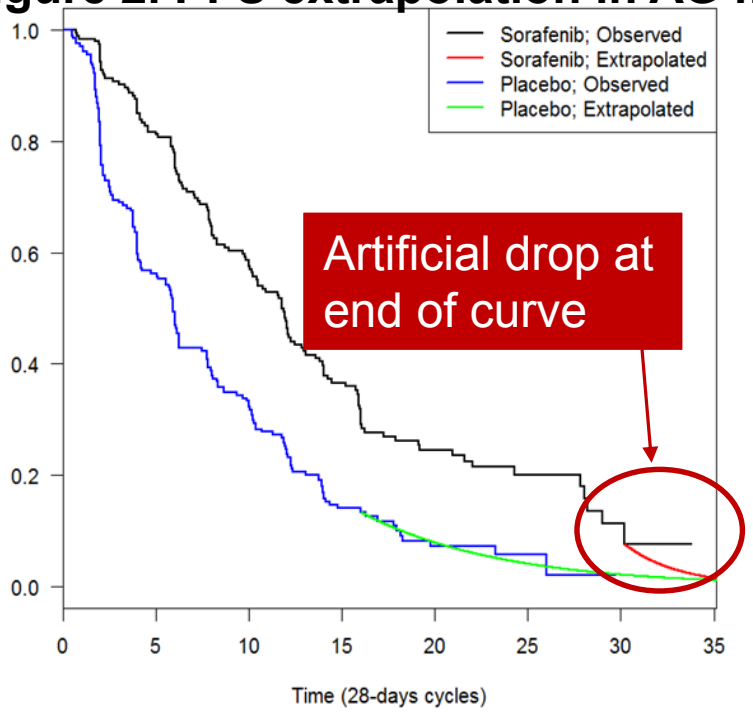


Figure 2. PFS extrapolation in AG model

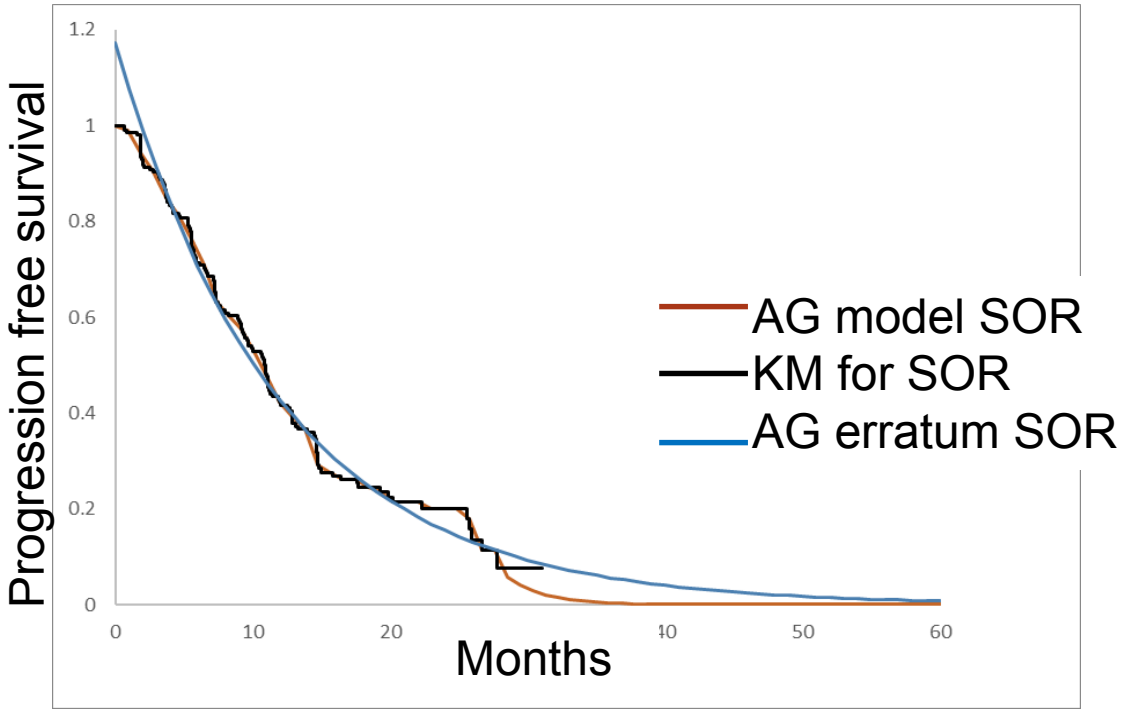


1. Survival curves in AG model needs revision

- Time cut off for switching between KM data and extrapolation in AG report/erratum differs compared with AG model. Bayer correct this and ICER is reduced by [redacted] compared with the AG base case (CAA analyses)

ICER

Time cut for using KM	AG model	AG report/ erratum
PFS time cut (months)	SOR: 27.8, BSC: 14.7	SOR: 25, BSC: 16.5
OS time cut (months)	SOR: 31.8, BSC: 25.4	SOR: 11.96, BSC: 6.4

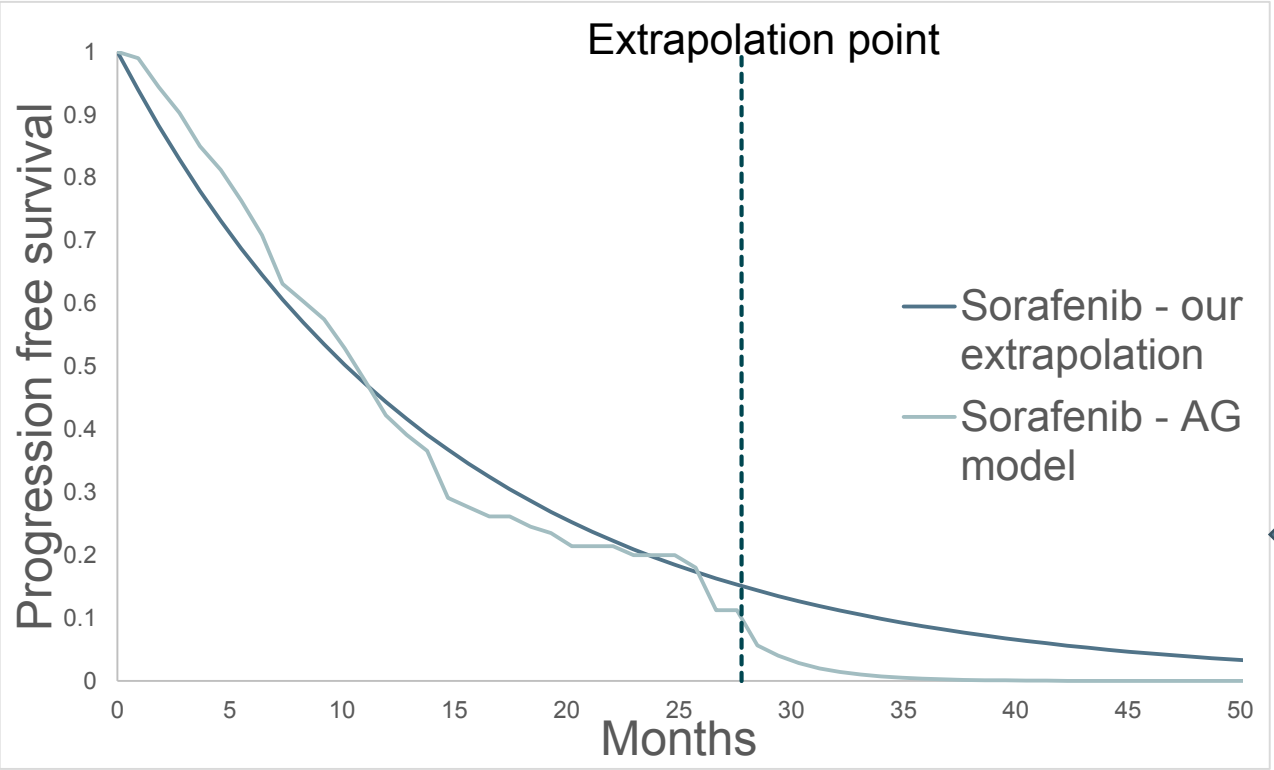


Bayer correction:
OS: use AG erratum for time cut off (piecewise model)
PFS: use AG report/erratum for time cut-off (single exponential)
NB: time cuts from AG report identified approx. when OS hazard changed

2. AG's survival curves lack face validity

- Bayer carry out scenario analyses with different extrapolations but suggest **single fully parametric curve** does not have face validity issues and best fits:
  - observed data (DECISION)
  - long term estimates (clinical experts)

ICER



AG curve uses KM data until extrapolation point

3. Clinical plausibility of survival extrapolations

- Different extrapolation methods are similarly plausible, results should be seen as range of plausible ICERs (not single ICER)
- Single exponential approach fits range of survival estimates provided by UK clinical experts slightly better (greater clinical plausibility compared with AG approach)

	Long-term survival according to:				
Survival	Clinical Experts (n=7)	Published Studies*	Bayer single Exponential distribution	AG's piecewise Exponential distribution	Corrected piecewise (in line with AG specification)
5 year	20-30%	-	30%	28%	24%
10 year	10-15%	10 and 12%	9.5%	5%	5%
15 year	5-10%	-	3%	1%	1%

* Durante et al (2006) and Shoup et al (2003)

AG response: Initial PFS

- Standard parametric curves rarely pass through initial time point of clinical trial unless constrained to do so
  - Trial start involves inclusion/exclusion and ensures risk of very early event artificially supressed (screened out)
  - PFS data, most early events take place *after* an initial interval between baseline and the first scheduled clinic visit for assessment
  - Little change in initial period followed by shift in data trend to right
  - Fixing modelled curve to pass through 100% survival results in artificial distortion of fitted model (underestimate PFS and overestimates OS)
  - AG model more accurate in short and long term (confirmed by goodness of fit statistics)

AG response: PFS tail

1. Sharp decline in PFS	• Sudden increased risk in final phase typical of informative right-censoring (no re-analyses from Bayer so can't rule this out)
2. Late patient assessment	• Appropriate to include data for long-term data fitting. Similar to Bayer approach (mean PFS 15.39 months)
3. Final phase increased risk	• **AG approach**: may expect to continue beyond trial period. Requires fitting appropriate projective function only to this final data segment (mean PFS 12.77 months)
4. Assume last 6 patients progress	• After final recorded PFS event, only 6/207 remained at risk (KM wide confidence interval). Assume remaining patents likely to progress/die shortly after (mean PFS 12.63 months)
AG prefer option 3	• Option 1 (most generous) to 4 (most conservative) • Option 3 is pragmatic and maximises the direct use of KM data and close fit to the final anomalous events. Neither unduly generous nor excessively conservative.

AG revised base case: No change to PFS (single exponential extrapolation fitted to final data segment). Extrapolation used when minimal difference between observed and extrapolated data (placebo: 12.8, sorafenib: 14.0 months)

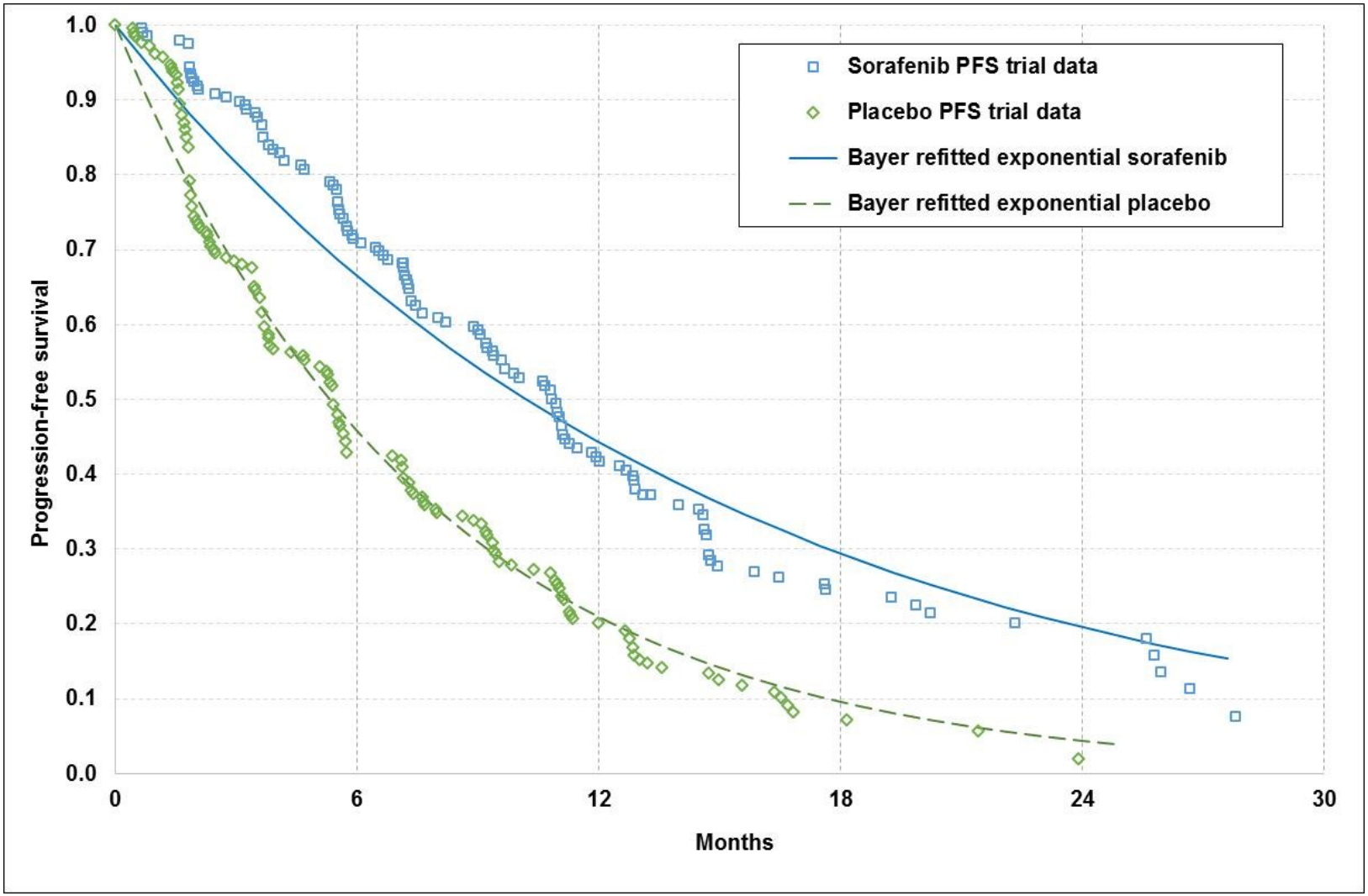
AG response: Bayer's alternative PFS analyses

PFS modelling approach	Sorafenib	Placebo	Net Gain
Assessment Group (K-M then exponential)	13.84	7.56	+ 6.28
1. Bayer simple exponential	16.49	8.85	+ 7.64
2. Bayer K-M data + piecewise extrapolation	16.02	9.44	+ 6.58
3. Bayer K-M data + exponential extrapolation	16.63	8.87	+ 7.77

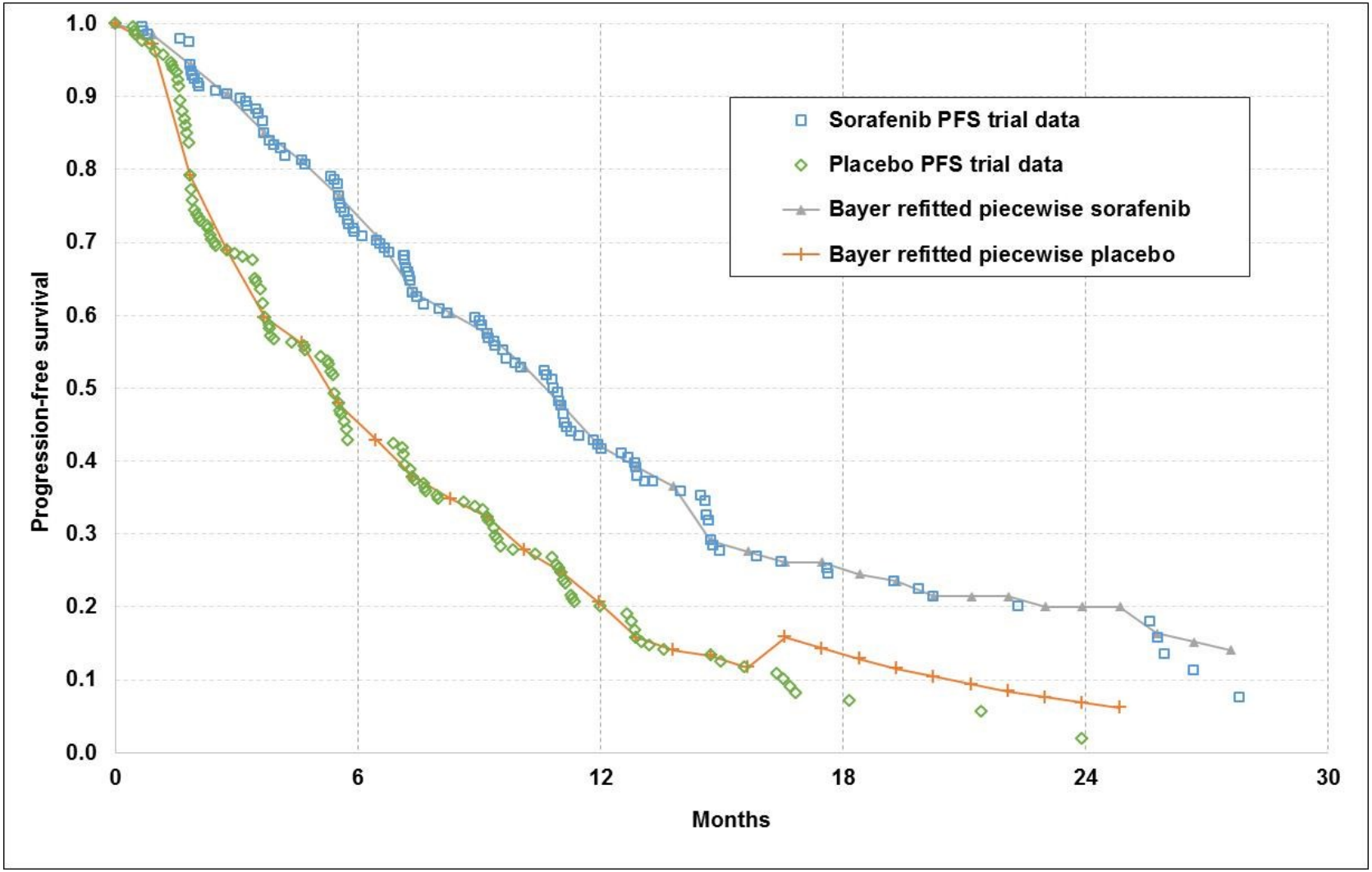
AG comments on Bayer's alternative analyses:

1. Bayer's simple exponential model underestimates PFS in sorafenib arm for 11 months and then consistently over-estimates for remaining 18 months. Lifetime projection: around 2 additional months of net PFS benefit in favour sorafenib.
2. Bayer's K-M and piecewise extrapolation follows trial data for 16 months then appends piecewise long-term exponential trend. However there is serious flaw in the implementation of the extrapolation in the placebo arm (PFS unexpectedly increases at month 16 by about 35% and this is sustained). Time-to-event analysis can never increase (only decrease or stay level over time).
3. Bayer's K-M and exponential extrapolation uses K-M data for first 16 months placebo and 25 months sorafenib, followed by simple exponential curve. However in the final 2 to 3 months there is sudden decrease in PFS (sorafenib) from 18% to 7.5% and this is not accounted for.

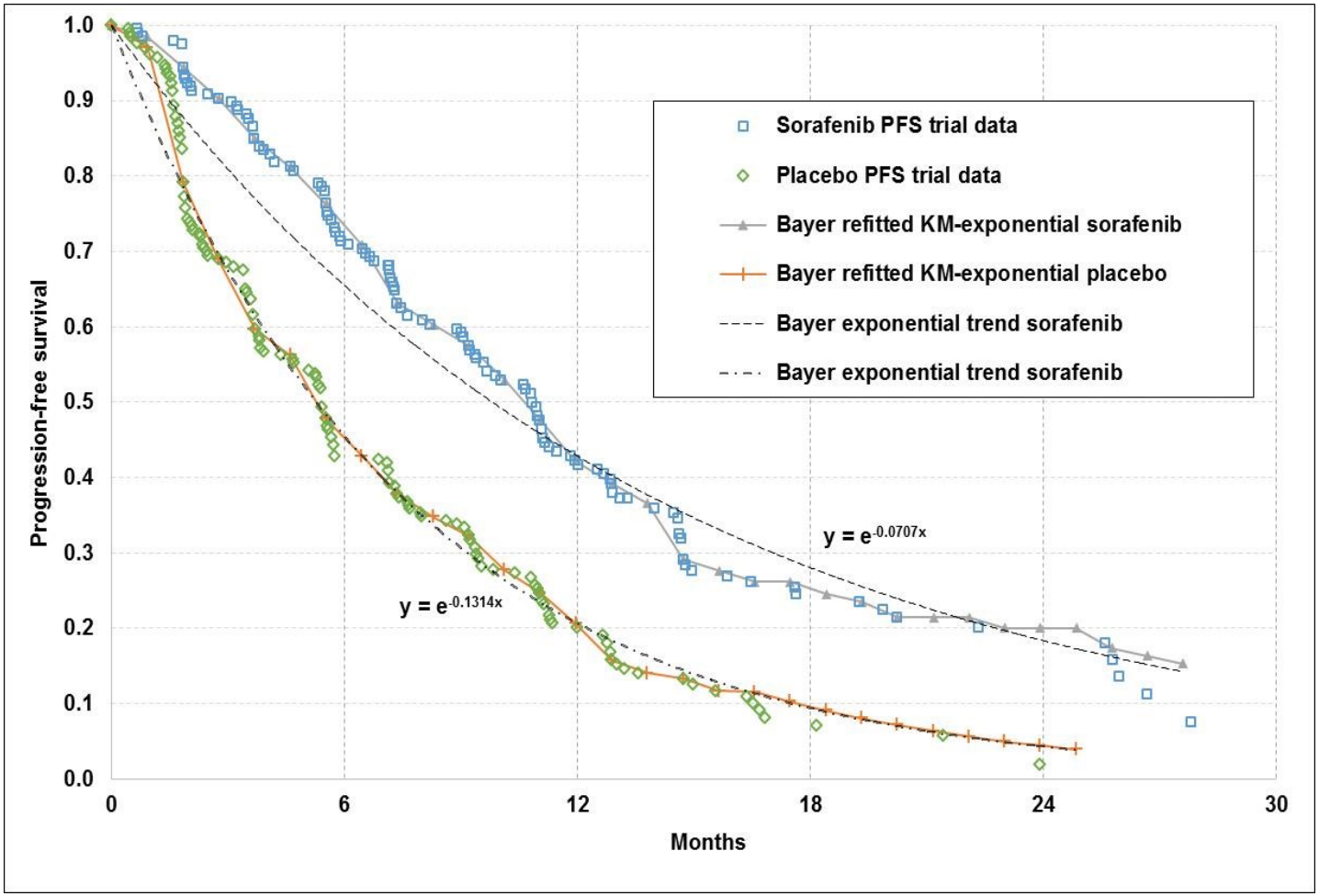
1. PFS with fitted constrained exponential trends



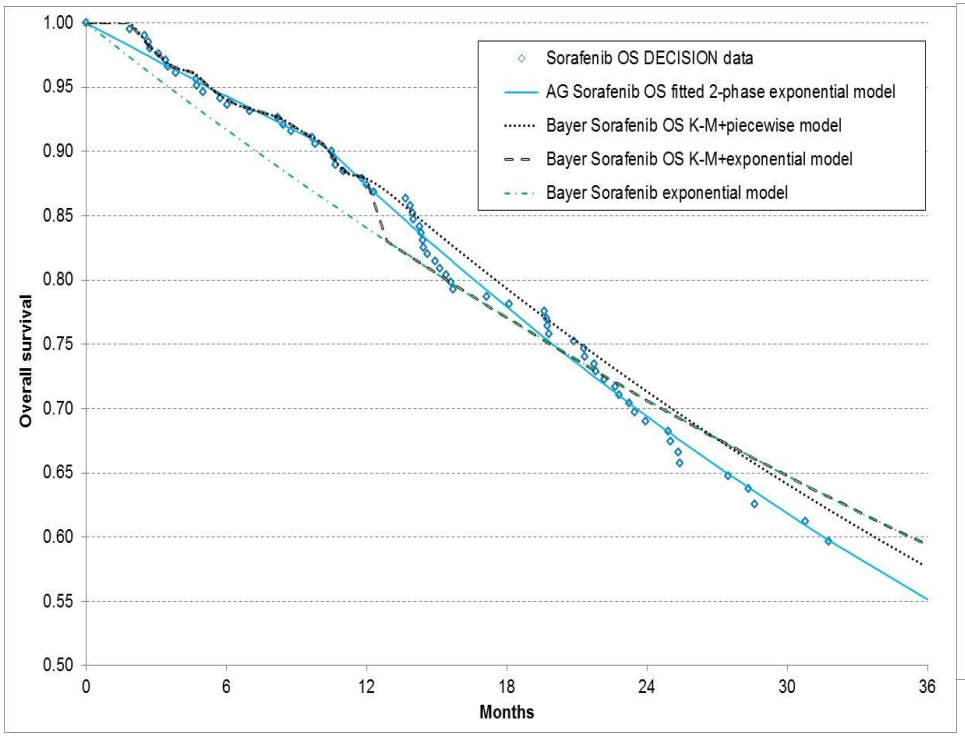
2. PFS with fitted piecewise trends

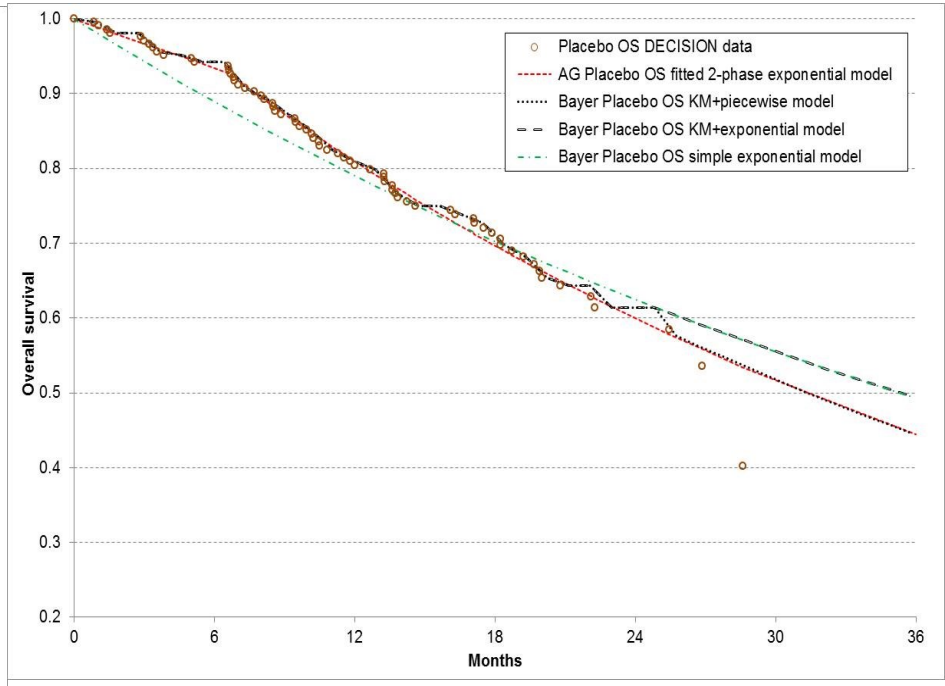


3. PFS with refitted KM exponential trends



AG response: Bayer's alternative OS analyses





- AG prefer 2-phase exponential method to extrapolate OS.
- All 3 alternative analyses from Bayer show clear long-term trends which result in increasing bias towards over-estimating OS in the sorafenib arm compared to trial data and AG model.
- 2 of the 3 proposed models for placebo also show long-term over-estimation.

New evidence (Bayer): Time on treatment

- Inconsistencies around implementation of treatment discontinuation:
  1) Patients receive TKI treatment until progression (UK clinical practice)
  2) Patients can receive TKI treatment post-progression (DECISION and SELECT trials)
  3) Patients continue receiving TKI treatment after progression with sorafenib but not with lenvatinib (AG model)

Not plausible (inconsistent with trials and UK clinical practice)

- In both SELECT and DECISION, a proportion continue treatment with TKI after progression
  - DECISION: continued treatment with sorafenib (27%)
  - SELECT: continued treatment with other TKIs, not lenvatinib
    - Therefore post progression treatment with other TKI (e.g. sorafenib) not costed, though clinical benefit likely to be comparable
    - 16% in lenvatinib arm and 12% in placebo arm received anti-cancer treatments after progression

ICER

Bayer scenario: no sorafenib after progression gives lower ICERs for sorafenib vs BSC

AG response: Time on treatment

Company and AG model do not explicitly include post-progression active treatment costs (only routine care). No sufficient data on post progression treatment duration.

AG model offers 3 options for costing treatment

1) Treatment duration governed by estimated PFS (treatment stops on disease progression or death)
2) **AG preferred:** Treatment duration governed by estimated Time on Treatment (treatment may extend beyond progression in trials)
3) AG Sensitivity analysis: Treatment duration estimated as the minimum number of patients on treatment at each time point by either PFS or recorded time on treatment.

- AG model relied solely on trial data supplied by companies.
  - Sorafenib: treatment stopped after cycle 40 (complete treatment data)
  - Lenvatinib: only 8% still on treatment after cycle 48 (minor extrapolation to estimate treatment up to cycle 50)

AG revised base case: No changes to time on treatment (option 2: fully consistent with the trial outcomes used to calibrate all other model results.)

AG scenario for treatment duration

1) No cost for post progression sorafenib
   - Same as using PFS (rather than TTD) for treatment duration
   - In DECISION there is very little difference between PFS and TTD patient numbers
   - Small impact on sorafenib ICER
   - Large impact on lenvatinib ICER when using PFS instead of TTD

2) Include cost of post progression TKI in lenvatinib arm
   - No reliable mean to estimate post progression treatments
   - Can highlight 19.5% in lenvatinib arms and 16% in BSC arm in SELECT previously received TKI therapy (mainly sorafenib), therefore unlikely to receive again

New evidence (Bayer): EOL

1. Life expectancy for **symptomatic** patients <24 months
   - Subgroup of patients symptomatic at start of therapy in BSC arm of DECISION (21%). Median OS = 15.72 months, Mean OS = 22.05 months (not adjusted for treatment cross over)
2. Small patient population (<60 per year)
   - In UK there is a very small number of people with disease that is refractory to radioactive iodine
3. Extension to life vs. life expectancy trade-off
   - Plausible that people eligible for treatment in UK (symptomatic and progressive disease) have lower life expectancy than trial population but still likely to receive substantial survival benefit
4. Social value judgements and innovation
   - Disease that is refractory to radioactive iodine is terminal
   - Need to consider the lack of alternative active treatment options when assessing patient's valuation of an available treatment as uncaptured benefit
   - Sorafenib is innovative and created true step change in therapy

This slide has been amended following the second committee meeting

AG response: EOL in symptomatic subgroup

- AG reproduced company estimates in symptomatic subgroup using data extracted from KM plots provided by digitizing timing of individual events
- Analysis based on small proportion of patients (21%) in placebo group and no evidence to justify applying results to whole trial population
- Difference between AG and Bayer survival estimates
  - AG: where available data largely complete, mean survival preferable measure. Wide confidence intervals around median and mean values. No strong evidence that survival without sorafenib <24 months

	Median survival (months)	Mean survival (months)
Bayer*	15.72	22.05
AG (re-analysis using data from KM)	18.92 (95% CI 9.51 to 28.34)	23.97 (95% CI 18.41 to 29.52)
AG (alternative extrapolation using simple exponential model)	N/A	29.95

**Bayer accepted the AG values in its response to NICE questions*

OS data from AG addendum: BSC arms

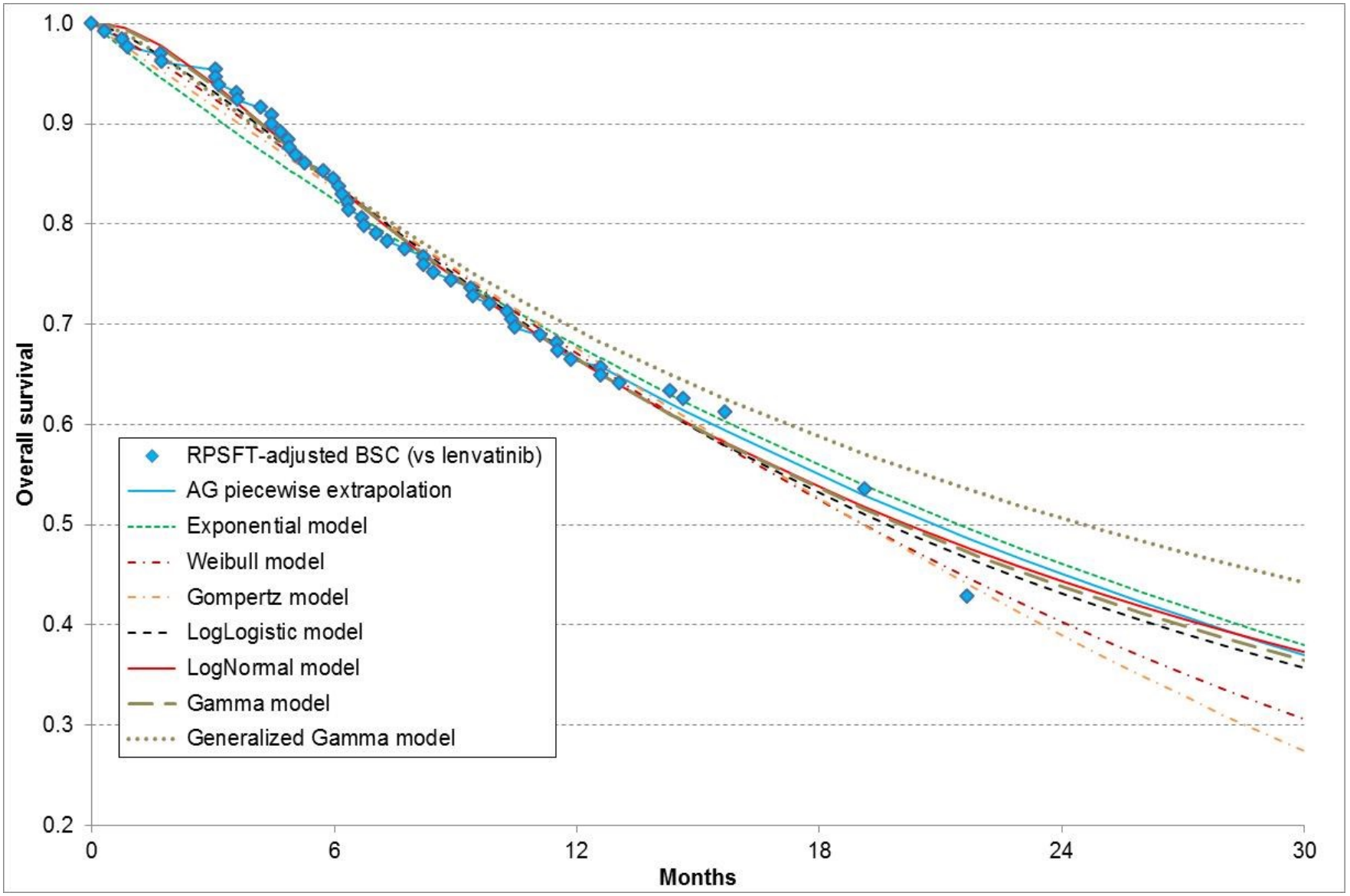
OS extrapolation (ranked by AIC fit)	SELECT mean OS*	OS extrapolation (ranked by AIC fit)	DECISION mean OS*
1. Piecewise exponential**	30.25	1. Gompertz	27.95
2. Log-normal	34.45	2. Weibull	33.57
3. Gamma	33.04	3. Log-Logistic	42.12
4. Log-logistic	33.56	3. Piecewise exponential**	40.64
5. Weibull	25.05	4. Generalized Gamma	38.25
6. Gompertz	22.09	5. Gamma	42.57
7. Exponential	30.85	6. Log-Normal	43.74
8. Generalised Gamma	41.41	7. Exponential	47.54
*Mean overall survival in months at 10 years, ** AG preferred model			

OS data from AG addendum: Intervention arms

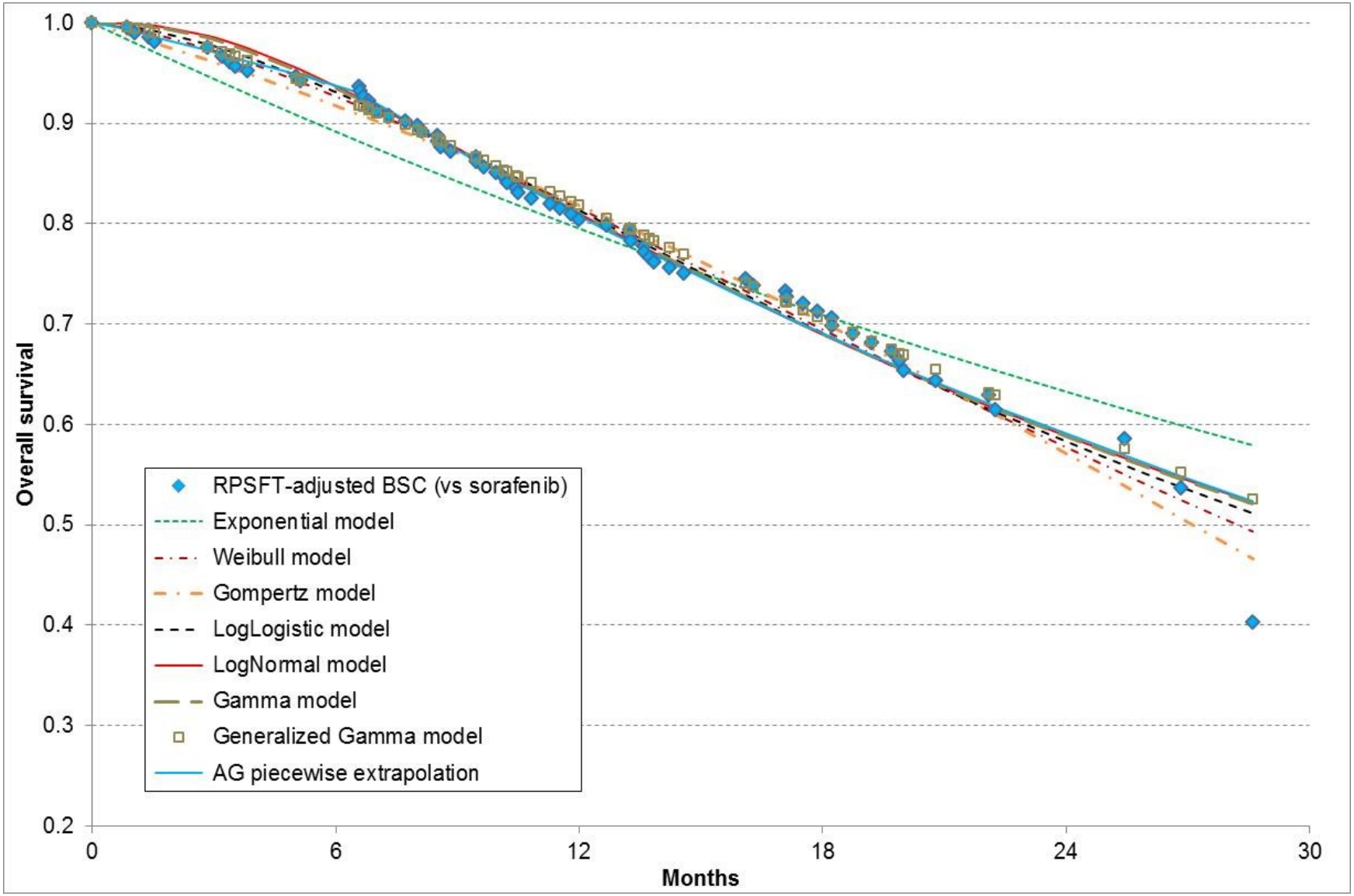
OS extrapolation (ranked by AIC fit)	SELECT mean OS* lenvatinib	OS extrapolation (ranked by AIC fit)	DECISION mean OS* sorafenib
1. Weibull	48.65	1. AG piecewise/exponential**	51.44
2. Exponential**	49.18	2. Weibull	45.88
3. Log-Logistic	54.02	3. Log-Logistic	53.68
4. Gompertz	49.42	4. Gompertz	37.45
5. Generalized Gamma	53.98	5. Gamma	55.11
6. Gamma	54.63	6. Log-Normal	56.17
7. Log-Normal	55.30	7. Exponential	58.29
		8. Generalized Gamma	NC

Abbreviations: NC generalized gamma algorithm did not converge to a meaningful survival model (not monotonically decreasing); OS, overall survival
*Mean overall survival in months at 10 years, ** AG preferred model

OS extrapolation (BSC from SELECT)



OS extrapolation (BSC from DECISION)



This slide has been amended following the second committee meeting

Revised base case for sorafenib vs BSC

- Bayer do not clearly state revised base case but make following changes:

Change in model	Bayer	AG
Correction following ACM1	Yes	Yes
Corrected discounting error (costs of treating AE for both drugs were not discounted in previous model)	No	Yes
Mean AE duration to model AE	No	Yes*
PFS: KM curve then single exponential (unconstrained) OS: KM curve then fitted 2 phase exponential trend	N/A	Yes
Bayer's revised AG scenario (PFS: KM then single fitted exponential, OS: KM then revised piecewise exponential)	Yes (scenario)	No
PFS and OS extrapolation: KM curve then single fully parametric exponential	Yes (scenario)	No
PFS and OS extrapolation: single fully parametric exponential in line with Bayer's clinical expert estimates (no KM data used)	Yes (scenario)	No

*alternative method to estimate AE duration using new evidence from Eisai

Sorafenib vs. BSC (list price)

Changes	ICER SOR vs. BSC	
	Bayer	**AG**
Base case at ACM 1	**£56,417**	**£83,590[a]**
AE cost revision	N/A	£82,721
Discounting error	N/A	£83,508
1. Bayer's revised AG scenario (PFS: KM then single fitted exponential, OS: KM then revised piecewise exponential)	£50,731‡ £61,167*	£59,496 to £68,648**
2. PFS and OS extrapolation: KM curve then single fully parametric exponential	£62,910‡ £52,159*	£61,166 to £70,595**
3. PFS and OS extrapolation: single fully parametric exponential in line with Bayer's clinical expert estimates (no KM data used)	£63,757‡ £52,844*	£61,661 to £70,913**
Revised base case	NR	**£82,721**
Sensitivity analyses	N/A	**£80,446[b]**

[a]AG corrected base case, [b] based on all changes (GP hypertension treatment, no bone scans, fewer MRIs, more frequent oncologist visits), ‡ TTD only, * TTD or PFS, ** TTD, PFS or PFS/TTD for treatment duration. *ICERs using confidential discount for sorafenib to be discussed in part 2*

Key issues

- Most appropriate economic analysis for decision-making:
  - 3-state model or 4-state response-based model
- Preferred extrapolation for PFS and OS
- Does the committee accept other model changes, including
  - lower average dose of lenvatinib, alternative estimation of AE duration and correction of discounting error *(revised AG base case based on company comments)*
  - alternative values for resource use based on 4 UK clinical experts *(AG sensitivity analysis based on company comments)*
- Is end of life criterion for short life expectancy (<24 months) met?
- Most plausible ICER
- Other ACD comments
  - Inequality in access across the UK