Public observer slides – no confidential information

NICE National Institute for Health and Care Excellence

Lenvatinib for untreated advanced hepatocellular carcinoma

Chair's presentation

2nd appraisal committee meeting
Committee C
Lead team: Gail Coster, David Chandler and Natalie Hallas
ERG: BMJ
NICE technical team: Lucy Beggs and Alex Filby
Company: Eisai
27th September 2018

Key issues

- Modelling of committee's preferred assumptions from ACM1
- Gamma and log-normal distributions for PFS extrapolation
- End of Life criteria
- Most plausible ICER?

[redacted]

Lenvatinib (Eisai)

Expected marketing authorisation	Positive CHMP opinion granted July 2018: 'treatment of adult patients who have received no prior systemic therapy for HCC'
Administration & dose	• Oral capsules • Recommended daily dose: 8 mg (2 x 4 mg capsules) if body weight <60 kg and 12 mg (3 x 4 mg capsules) if body weight ≥60 kg.
Mechanism of action	Multi-kinase inhibitor and selectively inhibits the kinase activities of all vascular endothelial growth factor receptors, in addition to other proangiogenic and oncogenic pathways
List price & PAS discount	£1,437.00 per pack of 30 x 4 mg capsules Cost per cycle: £3,152 (dosing from REFLECT), Simple PAS discount (commercial in confidence)

[redacted]

Key results from REFLECT

- Open label RCT, lenvatinib vs sorafenib
- Population = people with Child-Pugh Class A HCC with ECOG PS 0 or 1

Outcome (months)	Lenvatinib median (range)	Sorafenib median (range)	Hazard ratio (95% CI)
Overall survival			
Unadjusted	13.6 (12.1 to 14.9)	12.3 (10.4 to 13.9)	0.92 (0.79 to 1.06)
Adjusted for post-progression treatment	–	–	[redacted]
Investigator-assessed progression-free survival			
Modified RECIST	7.4 (6.9 to 8.8)	3.7 (3.6 to 4.6)	0.66 (0.57 to 0.77)
Modified RECIST with updated censoring*	–	–	[redacted]
Independently assessed progression-free survival			
Modified RECIST	7.3 (5.6 to 7.5)	3.6 (3.6 to 3.7)	0.64 (0.55 to 0.75)
Standard RECIST	7.3 (5.6 to 7.5)	3.6 (3.6 to 3.9)	0.65 (0.56 to 0.77)

*Updated censoring = all deaths/progressions treated as events, no censoring at treatment discontinuation unless disease progression

[redacted]

Key committee considerations in ACD (1)

Issue	Committee consideration
Censoring	• Considered censoring people with no disease progression at treatment discontinuation to favour lenvatinib • Preferred to treat all disease progressions and deaths as events
Baseline imbalances	• Despite imbalances, accepted REFLECT as relevant to NHS • Company's adjustment for OS & PFS was based on covariates selected from OS data → uncertainty in PFS analysis • Preferred the corrected group prognosis method to mean of covariates approach • Did not see preferred adjusted analysis → uncertainty
OS in REFLECT	• Proportional hazards not met → interpret hazard ratios with caution • Overall survival with lenvatinib non-inferior to sorafenib
OS extrapolation	• Committee concluded log-logistic extrapolation appropriate as good fit to data for both arms
PFS in REFLECT	• Proportional hazards not met → interpret hazard ratios with caution • Evidence of PFS benefit but uncertainty about size of benefit due to issues with censoring and adjustment for baseline characteristics

[redacted]

Key committee considerations in ACD (2)

Issue	Committee consideration
PFS extrapolation	• Committee preferred gamma distribution (with adjustment to stop curves crossing) to lognormal as it was a better fit to data in both treatment arms
Post-progression treatment	• Company's model included clinical benefit of post-progression treatment (modelled in line with distribution of treatments used in REFLECT) • ERG highlighted that post-progression treatments may confound overall survival results (likely to favour sorafenib) • Committee accepted company's modelling of post-progression treatment benefit but preferred for model to also include costs of post-progression treatments (both in line with distribution of treatments used in REFLECT)
Most plausible ICER	• Did not see analyses including preferred assumptions (hence could not assess model fit) • Uncertainty → no 'most plausible' ICER for lenvatinib vs sorafenib
End of life	• Lenvatinib meets criterion for short life expectancy • Uncertainty about extension to life
Key conclusion	• Uncertainty as preferred modelling/statistical assumptions not explored • No 'most plausible' ICER but estimate likely to be higher than £20k-£30k p/QALY gained & does not meet end of life

[redacted]

ACD Preliminary Recommendation

Lenvatinib is not recommended within its anticipated marketing authorisation for untreated, advanced, unresectable hepatocellular carcinoma in adults.

[redacted]

ACD consultation responses

- Consultee comments from:
  – Eisai

- Commentator comments from:
  – Bayer (manufacturer of sorafenib)

- No web comments

[redacted]

Adverse events

Comments from Bayer (sorafenib manufacturer)

- Lay explanation in ACD: *'sorafenib is not always effective and many people cannot tolerate it because of side effects'*
- ACD section 3.2: *'**Lenvatinib may offer benefits over current treatment options**…', '…hand-foot syndrome is more common with sorafenib… unpleasant for patients' & '…side effects of lenvatinib, such as hypertension… may be more acceptable'*
- Comment that evidence from REFLECT does not show that sorafenib is less well tolerated than lenvatinib
- Comment suggesting that ACD should instead reflect that lenvatinib & sorafenib have different side effect profiles

[redacted]

Post-progression treatment

- ACM1: ERG identified imbalance between post-progression treatment in REFLECT treatment arms
- Committee accepted modelling of post-progression treatment costs & benefit in line with REFLECT

Comments from Bayer (comparator manufacturer):

- *'all lenvatinib patients who continued treatment following progression switched to sorafenib'*
- *'many [sorafenib patients] continued sorafenib treatment where clinical benefit following disease progression is not expected.'*
- Sorafenib has not been studied as 2L treatment for HCC → *'clinical benefit is unknown'*
- *'It is not appropriate to adjust clinical data based on differences in post-progression treatment…'*

ERG comment:

- ERG disagrees with committee → modelling post-progression treatment costs & benefits in line with REFLECT not appropriate because…
  - Distribution/duration of post-progression treatment differs between treatment arms
  - Not all post-progression treatments in REFLECT used in clinical practice/ NICE recommended
- ERG explored hypothetical scenario where post-progression treatment with sorafenib improves outcomes after lenvatinib, but not after sorafenib (ie. clinical benefits in sorafenib arm are the same regardless of post-progression sorafenib)
- In this scenario, assumed that patients in sorafenib arm would not receive post-progression sorafenib → costs taken out (explored in hypothetical scenario: slide 16)

[redacted]

Committee preferences and company's new analysis

Committee preference:	Did company include?
All disease progressions & deaths treated as events (censoring)	✓
Baseline characteristic imbalances adjusted using corrected group prognosis method	✓
Survival curves and Kaplan-Meier data adjusted for baseline characteristics	✓
PFS extrapolation using gamma distribution	✓
Post-progression treatment distribution in line with REFLECT	✓
Include costs & benefits of all post-progression interventions used in REFLECT	✓

Company also submitted a revised Patient Access Scheme discount

[redacted]

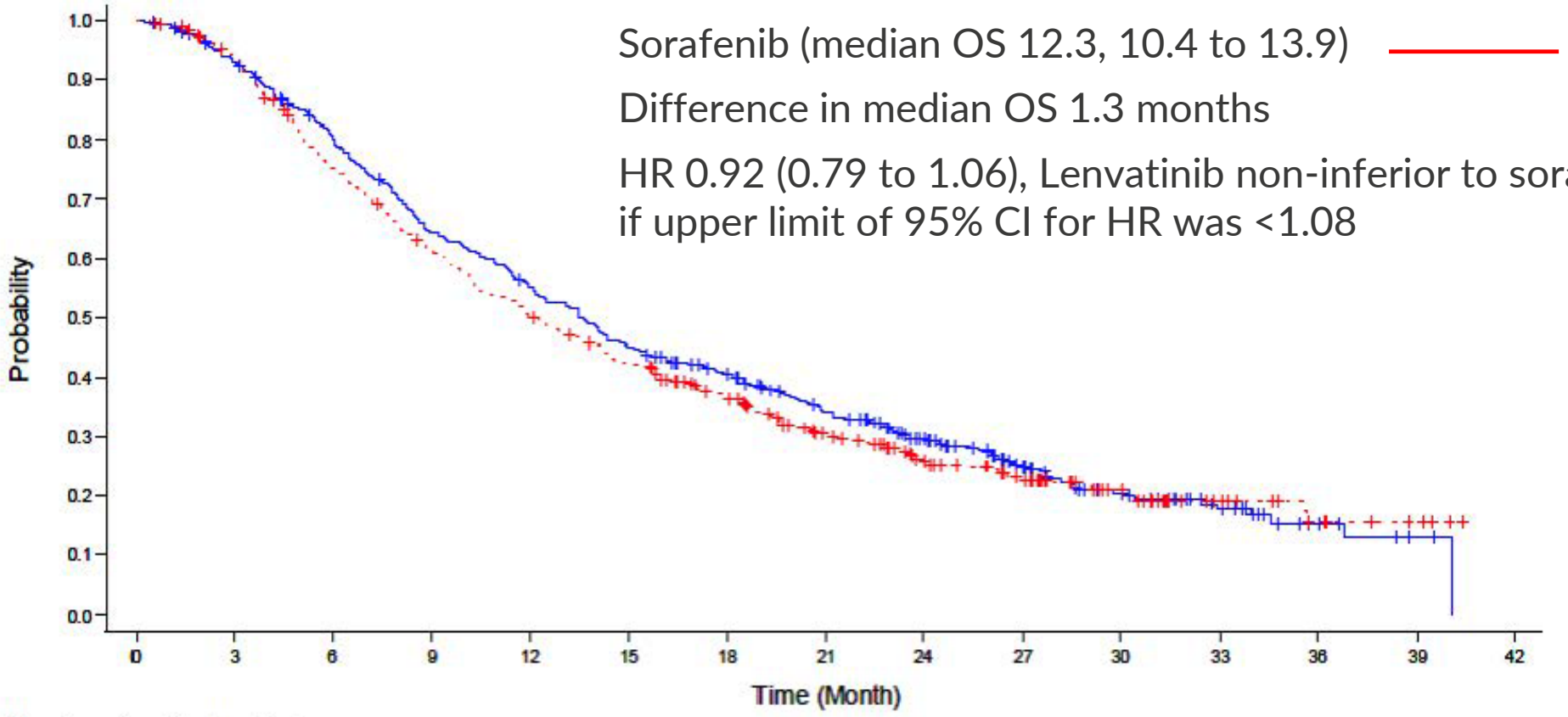
Overall survival in REFLECT (recap from ACM1)

Lenvatinib (median OS 13.6, 12.1 to 14.9)

Sorafenib (median OS 12.3, 10.4 to 13.9)

Difference in median OS 1.3 months

HR 0.92 (0.79 to 1.06), Lenvatinib non-inferior to sorafenib if upper limit of 95% CI for HR was <1.08

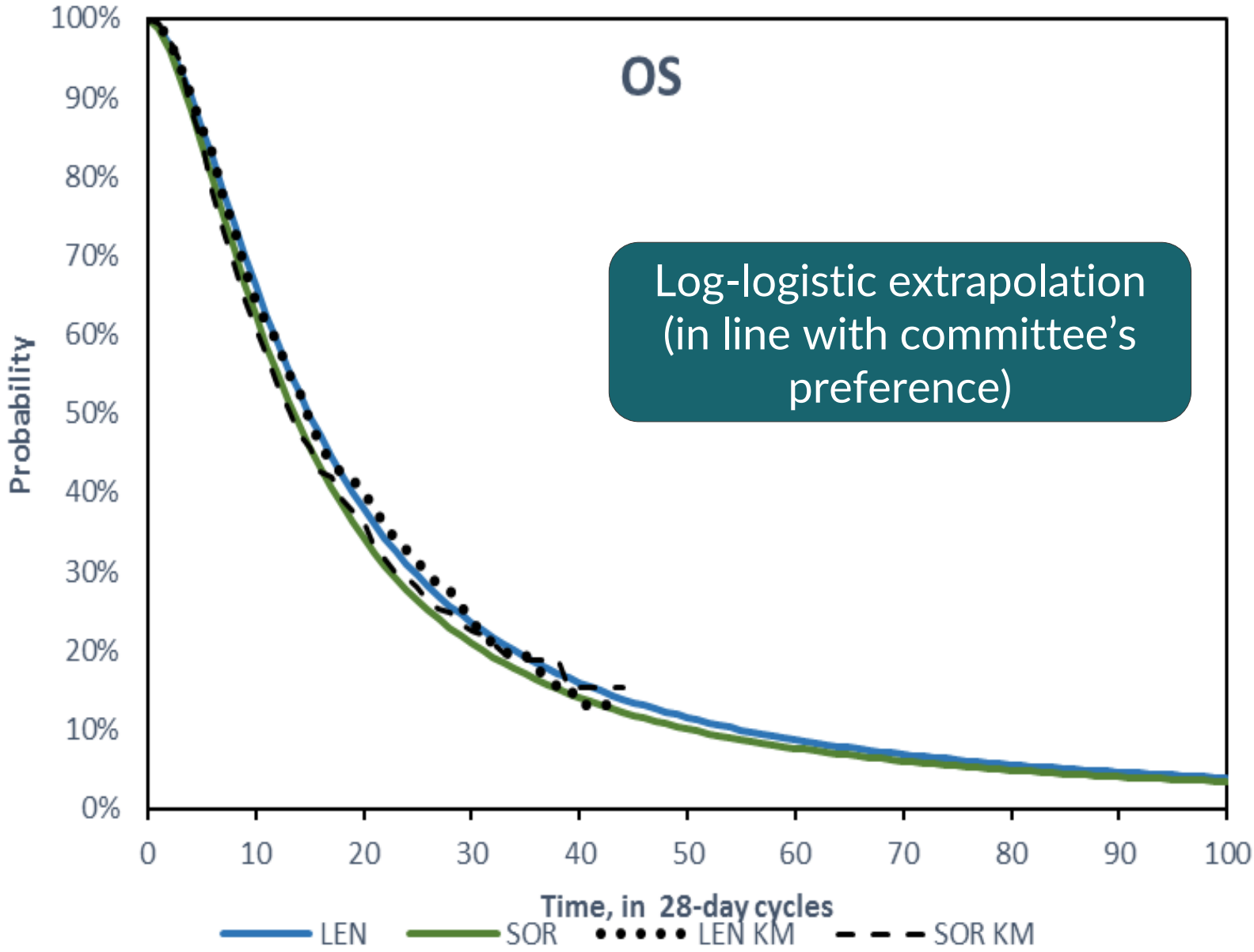


Number of subjects at risk:

Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

[redacted]

Overall survival extrapolation (recap from ACM1)



[redacted]

Updated censoring of PFS (new analysis)

- Company's revised model includes all events in PFS analysis (only censors missing assessments or patients with no progression at last assessment)
- Investigator assessed PFS using 'standard' RECIST 1.1 not captured in REFLECT → PFS analyses based on mRECIST

Kaplan-Meier curves for REFLECT PFS with updated censoring

[redacted]

PFS extrapolations (new analysis)

- Company model now adjusts for imbalances in baseline characteristics using the corrected group prognosis method
- Extrapolations based on adjusted Kaplan-Meier's for PFS using updated censoring approach

Academic in confidence

ERG comment:

- ERG: analysis appears to have been conducted correctly & analyses likely to be sound
- New analyses similar to original KM curves → gamma likely to remain best fit
- Company did not indicate significance of coefficients in updated adjustment set
- Adjustment set based on OS rather than PFS model → uncertainty in PFS analysis
- Did not provide AIC/BIC statistics to assess model fit

[redacted]

Company results & scenario analyses

- Lenvatinib price with updated PAS discount vs sorafenib list price
- Final column shows mean OS benefit predicted from model
- Survival gain is consequence of modelling assumptions used in each scenario → trial results, choice of censoring approach, survival extrapolations, post-progression treatment benefit & lifetime horizon all inform model's predicted mean OS benefit

Scenario		Δ Costs	Δ QALYs	ICER	Predicted mean OS benefit
1	Corrected company base-case from ACM1	[redacted]	0.176	[redacted]	3.1 months
2	ERG base-case from ACM1	[redacted]	0.220	[redacted]	4.1 months
3	Company base-case + PFS gamma extrapolation	[redacted]	0.164	[redacted]	3.1 months
4	Company base-case + corrected group prognosis	[redacted]	0.167	[redacted]	3.0 months
5	Company base-case + post-progression tx distributions & costs in line with REFLECT	[redacted]	0.176	[redacted]	3.1 months
6	Company base-case + updated censoring	[redacted]	0.171	[redacted]	3.1 months
7	Committee preferred base-case*	[redacted]	0.159	[redacted]	3.0 months
8	Committee preferred base-case with log-normal PFS extrapolation	[redacted]	0.163	[redacted]	3.0 months

[redacted]

**Includes updated censoring, PFS gamma extrapolation, corrected group prognosis adjustment, costs & benefits of post-progression in line with REFLECT*

Additional ERG scenario analyses

- Lenvatinib price with updated PAS discount vs sorafenib list price
- ERG Scenario 1 = removed costs of post-progression sorafenib in sorafenib arm (because sorafenib may no longer be effective after prior sorafenib)
- ERG Scenario 2 = in ACM1 committee considered progressed disease utility value may be too high (although concluded not a key driver of the ICER) → scenario exploring change from [redacted] to 0.50

	Scenario	Δ Costs	Δ QALYs	ICER	Predicted mean OS benefit
Committee preferred base-case		[redacted]	0.159	[redacted]	3.0 months
1	Committee preferred base-case with post-progression sorafenib cost removed for sorafenib arm only	[redacted]	0.159	[redacted]	3.0 months
2	Committee preferred base-case progressed disease utility value = 0.50	[redacted]	0.156	[redacted]	3.0 months

[redacted]

End of life considerations

- ACM1: committee concluded lenvatinib meets short life expectancy criterion but identified uncertainty about extension to life
- Company: all scenarios predict mean OS benefit >3.0 months (slide 15)
- Company: committee's preferred base case does not adjust for post progression therapies → imbalance likely to favour sorafenib (ACD section 3.9)
- REFLECT = non-inferiority study design → lenvatinib had non-inferior overall survival to sorafenib (HR: 0.92, 95% CI: 0.79, 1.06)
- Bayer (sorafenib manufacturer): >3 month survival benefit of lenvatinib over sorafenib *'unlikely'*

ERG comment:

- Using committee's preferred base-case, lenvatinib survival gain = 3 months (undiscounted)
- Uncertainty in OS modelling due to uncertainty in post-progression treatments
- However, survival >4 months when OS modelling adjusted for post-progression imbalances

[redacted]

Other consultee comments

- Procedural question about NICE processes
- Comment checking incorporation of sorafenib commercial access agreement details into modelling of drug wastage

[redacted]

Key issues

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- End of Life criteria
- Most plausible ICER?

[redacted]