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# Lead team presentation

# Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma [ID1089]

Clinical effectiveness

1st Appraisal Committee meeting

Committee C

Lead team: Gail Coster, David Chandler and Natalie Hallas

Evidence Review Group: BMJ

NICE technical team: Abi Senthinathan, Alex Filby

Company: Eisai

30th May 2018

**Slides for Committee and projector [ACIC]**

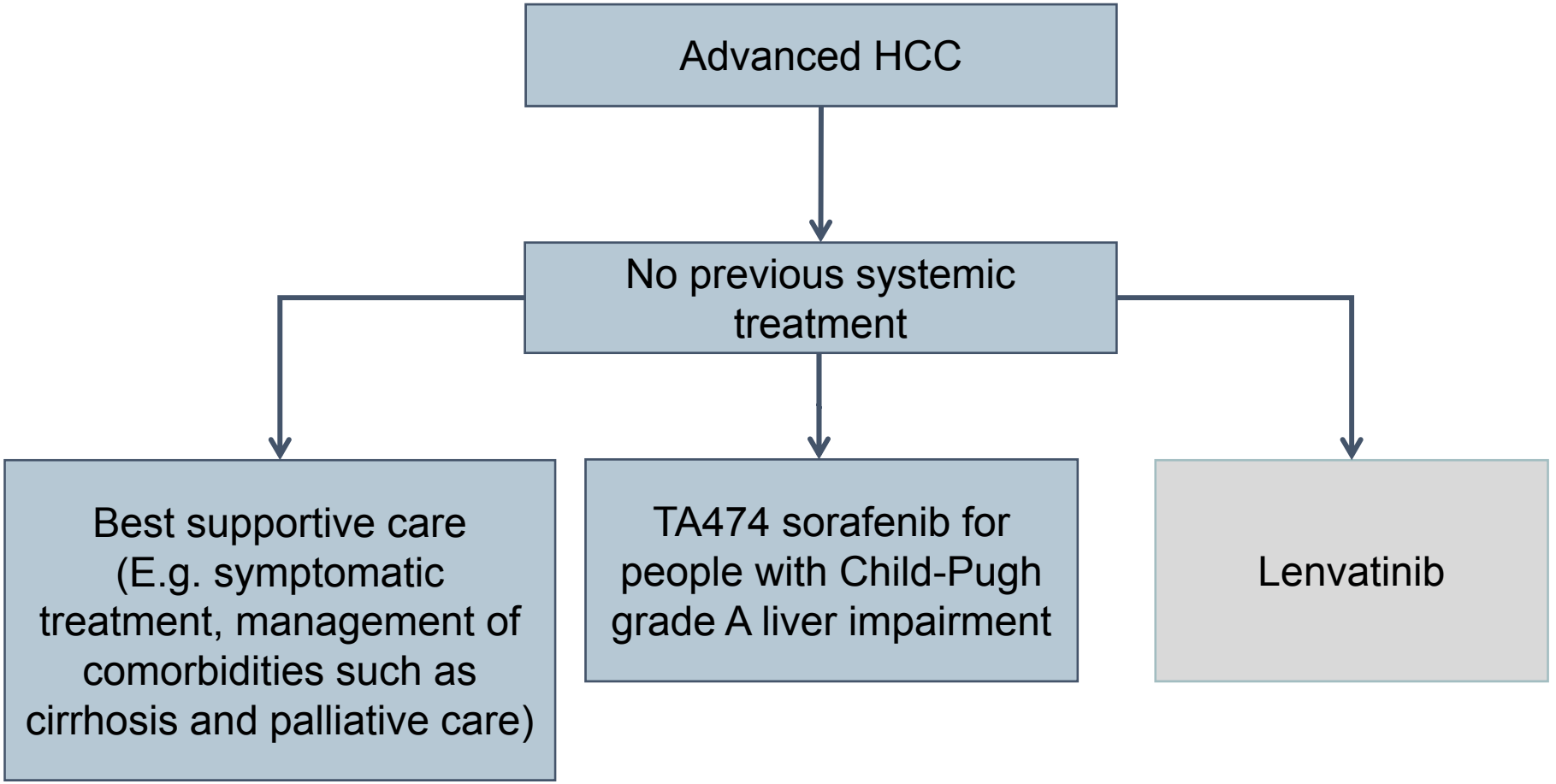
# Key issues – clinical effectiveness

- The company have positioned lenvatinib as a potential treatment for people with Child-Pugh Class A liver function, is this appropriate?
- Is it appropriate to exclude BSC as a comparator?
- Is the REFLECT trial generalisable to clinical practice in the NHS?
  - Post progression anti-cancer treatments were received in both arms
  - Trial population had stage B or C HCC, Child-Pugh class A and ECOG PS 0 or 1
- Is it appropriate to use results from the full population (rather than Western subgroup)?
- What censoring rules are most appropriate?
- Have the results of the REFLECT trial showed non-inferiority compared with sorafenib?

# Hepatocellular carcinoma (HCC)

- HCC is the most common type of primary liver cancer in England with 2,456 cases diagnosed in 2015.
- It is commonly associated with cirrhosis (scarring of the liver), which can be caused by excessive alcohol intake, viral infections such as hepatitis B or C, or other conditions.
- Early stage HCC may be treated with potentially curative surgery (hepatic resection), or percutaneous radiofrequency/thermal ablation in patients with well-preserved liver function, or liver transplantation for those with impaired liver function.
- In the UK, only about 30% of patients with HCC are suitable for curative therapy such as liver transplantation, local resection or radiofrequency ablation or palliative chemoembolization.
- Treatment is palliative rather than curative for people with more advanced disease (include interventional procedures such as transarterial chemoembolisation or selective internal radiation therapy, and external beam radiotherapy).
- TA474 recommends sorafenib as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment.

# Treatment pathway for HCC




Recreated using section 1.3 of company submission

# Patient and carer views
## Submission from The Hepatitis C Trust

- Poor prognosis and a fatal condition
- Often diagnosed late –
  - for some people it may be the first sign they have hepatitis C
- People also often think that curing their hepatitis C will cure their cancer or remove entirely the risk of cancer
  - *" …agonising mentally, both for patients and carers"*
- Physical symptoms include:
  - digestive problems
  - weight loss
  - pain
  - increasingly feeling unwell.

# Patient, professional & expert views
## Current treatments

- Submissions from The Hepatitis C Trust, BSG Liver Section, NHS England and 2 clinical experts
- Currently, the only approved treatment for advanced HCC other than supportive care, is sorafenib which has a low response rate and toxicity
  - With up to 25% patients discontinuing therapy
- Lenvatinib would improve first line systemic therapy
- Both sorafenib and lenvatinib are administered in the outpatient setting and require outpatient monitoring
- Later onset of cancer symptoms (role function, pain, diarrhoea, nutrition and body image) deterioration compared with sorafenib.
- Common adverse events of lenvatinib were hypertension, diarrhoea, fatigue, decreased appetite and weight decrease.
- Lenvatinib also has a different side effect profile than sorafenib and that choice may be beneficial for patients.

# NHS England

- If NICE recommends lenvatinib in this indication, NHS England treatment criteria will reflect trial eligibility criteria (Child-Pugh A status and also of ECOG performance score of 0 or 1).
- Use of sorafenib after disease progression on sorafenib is not commissioned by NHS England.
- There is no clinical evidence to justify a survival gain in the economic model of almost 3 months (based on median survivals in REFLECT).
- Lenvatinib has a higher response rate of 24% versus 9% for sorafenib. For patients who are symptomatic of bulky disease (for example liver pain or the consequences of compression of large blood vessels).
- If recommended by NICE as a treatment option for previously untreated patients with HCC, NHS England would commission the use of **either** lenvatinib **or** sorafenib as systemic TKI treatment options.
  - It would allow switching from one drug to the other **only** if there were unacceptable side-effects **and** documented evidence that disease progression had not occurred at the time of switching.

# NICE scope and decision problem

| | NICE scope | Company |
|---|---|---|
| **Population** | Within the marketing authorisation for adults with unresectable hepatocellular carcinoma who have not previously received systemic treatment | Submission covers **Child-Pugh Class A liver function**, in line with REFLECT trial. Also consistent with TA474 sorafenib |
| **Intervention** | Lenvatinib | |
| **Comparators** | • Sorafenib<br>• Best supportive care (BSC) | Company do not consider BSC to be a relevant comparator because clinical input suggests this is a small proportion of the population (<5%). In the overall population, almost all people will be eligible for systemic therapy. |
| **Outcomes** | Overall survival, progression-free survival, response rate, adverse effects of treatment, health-related quality of life | |

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# Lenvatinib (Eisai)

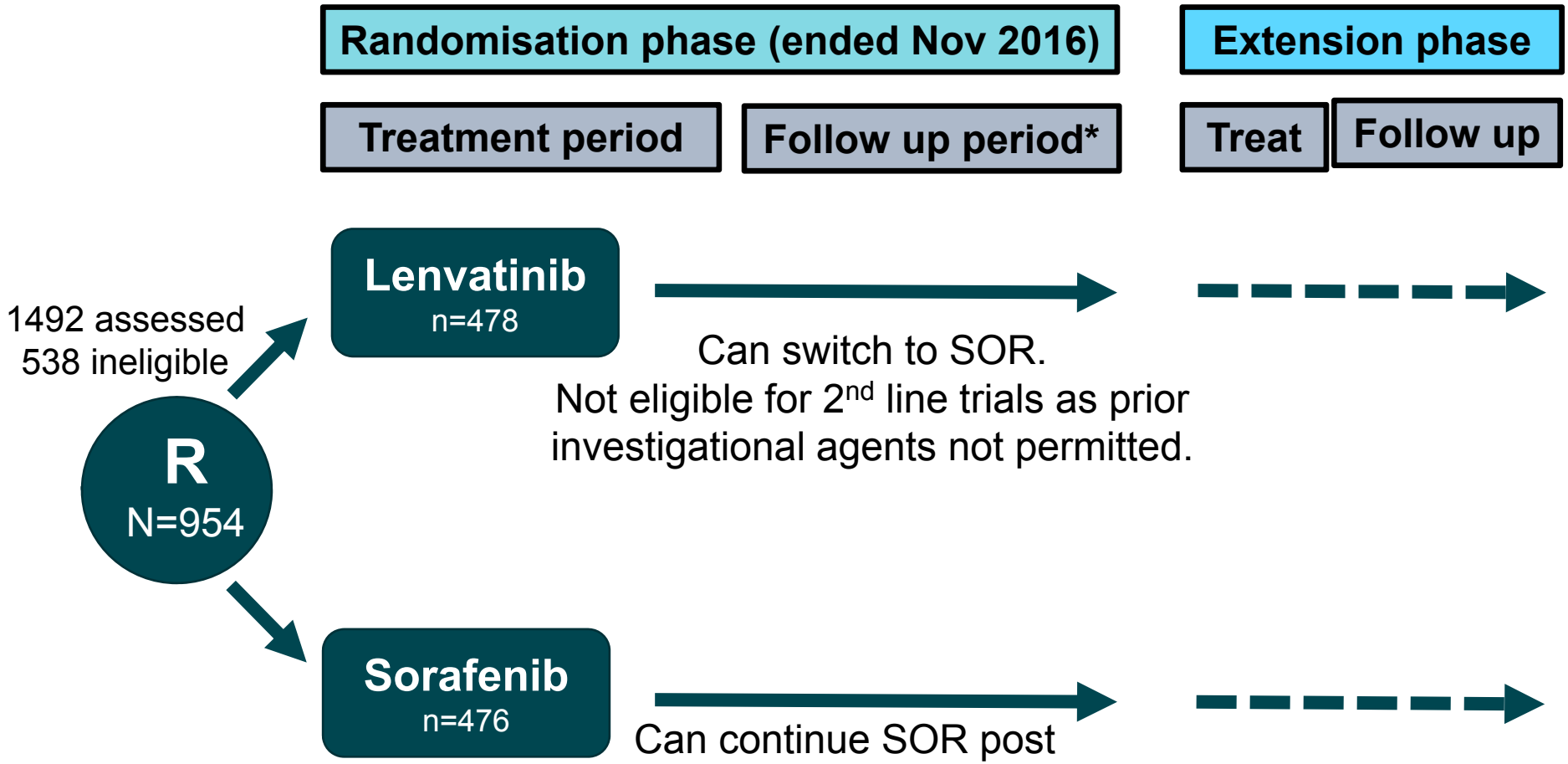
| | |
|---|---|
| **New marketing authorisation [ID1089]** | • Positive CHMP expected July 2018: 'treatment of adult patients who have received no prior systemic therapy for HCC' |
| **Mechanism of action** | Multi-kinase inhibitor and selectively inhibits the kinase activities of all vascular endothelial growth factor receptors, in addition to other proangiogenic and oncogenic pathways |
| **Administration and dosage** | • Oral capsules<br>• 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. |
| **List price & PAS discount** | £1,437.00 per pack of 30 x 4 mg capsules<br>Cost per cycle: £3,152 (dosing from REFLECT),<br>Annual cost: [redacted] (estimated by NICE)*<br>Average cost of a course of treatment (including PAS): [redacted]<br>Simple discount (magnitude: commercial in confidence) |
| *£3,152 x (8.2 months) mean treatment duration for lenvatinib in REFLECT | |

*Note: This slide has been amended following the appraisal committee meeting*

# REFLECT trial
## Summary

| | REFLECT |
|---|---|
| **Study design** | International, multicentre, randomised, open-label, phase 3 study (non-inferiority) |
| **Population** | 954 adults with histologically or cytologically confirmed diagnosis of unresectable HCC or clinically confirmed diagnosis of HCC, Child-Pugh class A, ECOG PS 0 or 1, stage B or C (based on BCLC staging system) with no previous systemic anti-cancer therapy. |
| **Intervention** | Lenvatinib (12 mg or 8 mg once daily), n=478 |
| **Comparator** | Sorafenib (400 mg twice daily), n=476 |
| **Concomitant medicines** | The following were **not** allowed during trial: surgery or radiotherapy for the treatment of HCC, systemic therapy, antiplatelet agents and anticoagulants that required monitoring (e.g. warfarin) |
| **Subgroups** | Pre-specified analyses based on age (≤65, ≥65 to <75 years and ≥75 years), sex and aetiology (Hepatitis B, Hepatitis C and alcohol). |
| **Location** | 20 countries including 20 patients from UK |

# REFLECT trial
## Study design




**Some patients received other post-progression therapies (only sorafenib and regorafenib licensed treatments for HCC)*

Source: adapted from figure 2 in company submission

# REFLECT post-progression treatment
## Regional subgroups and full population

- Fewer people in lenvatinib arm had post-progression treatment (43% vs. 51%). Longer OS with post-progression treatment (may bias OS in favour of sorafenib). More imbalance in post-progression treatment in Western subgroup.

| | Lenvatinib | | | Sorafenib | | |
|---|---|---|---|---|---|---|
| **Treatment during follow-up** | Western (N=157) | Asia-Pacific (N=321) | Total (N=478) | Western (N=157) | Asia-Pacific (N=319) | Total (N=476) |
| **Any anti-cancer therapy** | 44 (28.0) | 162 (50.5) | 206 (43.1) | 71 (45.2) | 172 (53.9) | 243 (51.1) |
| **Any anti-cancer medication*** | 41 (26.1) | 115 (35.8) | 156 (32.6) | 61 (38.9) | 123 (38.6) | 184 (38.7) |
| **Any anti-cancer procedure** | 11 (7.0) | 111 (34.6) | 122 (25.5) | 18 (11.5) | 112 (35.1) | 130 (27.3) |
| **Targeted therapy†** | [redacted] | NR | [redacted] | [redacted] | NR | [redacted] |
| **Sorafenib‡** | [redacted] | NR | [redacted] | [redacted] | NR | [redacted] |
| **Regorafenib** | [redacted] | NR | [redacted] | [redacted] | NR | [redacted] |

All data reported are n (%) *not given for a procedure †any antineoplastic & immunomodulating agent ‡ In sorafenib arm, patients continued sorafenib after progression.



Source: Table 12 in company submission, tables 4 & 5 in clarification response

# REFLECT baseline characteristics
## Full population

| Characteristic | Lenvatinib (n=478) | Sorafenib (n=476) |
|---|---|---|
| Age, mean (SD) | 61.3 (11.7) | 61.2 (12.0) |
| ECOG PS 0** | 304 (63.6) | 301 (63.2) |
| Child-Pugh score 5 (Class A)† | 368 (77.0) | 357 (75.0) |
| Child-Pugh score 6 (Class A) † | 107 (22.4) | 114 (23.9) |
| Concomitant systemic antiviral therapy for hepatitis B or C | 163 (34.1) | 149 (31.3) |
| Any previous radiotherapy | 49 (10.3) | 60 (12.6) |
| Prior anti-cancer procedures* | 327 (68.4) | 344 (72.3) |
| AFP levels ≥200 ng/mL | 222 (46.4) | 187 (39.3) |
| Aetiology of HCC-Hepatitis B | 251 (52.5) | 228 (47.9) |
| Aetiology of HCC-Hepatitis C | 91 (19.0) | 126 (26.5) |
| Aetiology of HCC-Alcohol | 36 (7.5) | 21 (4.4) |

All data reported are n (%) unless otherwise stated, *including radiotherapy **all remaining EGOG PS 1 †all remaining Child-Pugh score 7 or 8 (Class B)
Abbreviations: AFP, alpha-fetoprotein. Red box = company highlighted imbalances

# REFLECT baseline characteristics
## Geographical region

| Characteristic | Lenvatinib (n=478) | | Sorafenib (n=476) | |
|---|---|---|---|---|
| | Asia-Pacific | Western | Asia-Pacific | Western |
| Age, mean (SD) | 60.0 (11.76) | 63.8 (11.15) | 60.2 (11.87) | 63.3 (12.06) |
| ECOG PS 0 | 206 (64.2) | 98 (62.4) | 204 (63.9) | 97 (61.8) |
| AFP levels ≥200 ng/mL | 157 (48.9) | 65 (41.4) | 137 (42.9) | 50 (31.8) |
| Aetiology of HCC-Hepatitis B | 212 (66.0) | 39 (24.8) | 197 (61.8) | 31 (19.7) |
| Aetiology of HCC-Hepatitis C | 50 (15.6) | 41 (26.1) | 70 (21.9) | 56 (35.7) |
| Aetiology of HCC-Alcohol | 17 (5.3) | 19 (12.1) | 8 (2.5) | 13 (8.3) |

All data reported are n (%) unless otherwise stated, *including radiotherapy
Abbreviations: AFP, alpha-fetoprotein. Red box = company highlighted imbalances (these were not pre-specified randomisation stratification factors)

Source: Table 8 in ERG report

# REFLECT trial results
## Full population

| Outcome | LEN (n=478) | SOR (n=476) | Result (95% CI) |
|---|---|---|---|
| OS* (months) | Median 13.6 (12.1 to 14.9) | Median 12.3 (10.4 to 13.9) | HR 0.92 (0.79 to 1.06) |
| Adjusted OS** | - | - | [redacted] |
| PFS* (months) investigator-assessed | Median 7.4 (6.9 to 8.8) | Median 3.7 (3.6 to 4.6) | HR 0.66 (0.57 to 0.77)‡ |
| mRECIST & amended censoring† | - | - | [redacted] |
| PFS* (months) independent review | Median 7.3 (5.6 to 7.5) | Median 3.6 (3.6 to 3.7) | - |
| mRECIST | - | - | HR 0.64 (0.55 to 0.75) |
| RECIST v1.1 | - | - | HR 0.65 (0.56 to 0.77) |

*Stratified by region (Asia–Pacific; Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg). **Adjusted by post-treatment anti-cancer treatment (post-hoc analyses). ‡From stratified cox model and censored if discontinued treatment for any reason other than progression. †not censored at treatment discontinuation if no disease progression

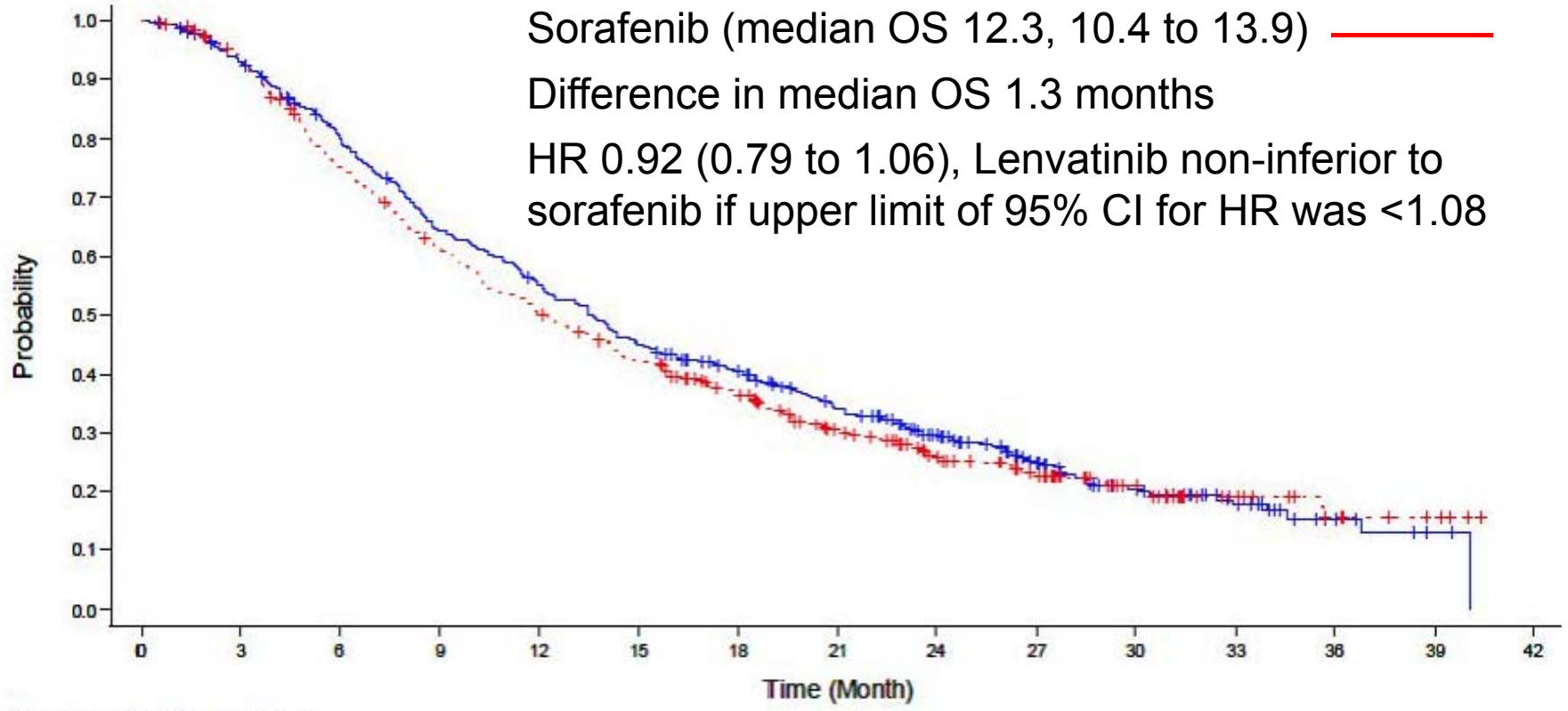
# REFLECT
## OS (not adjusted for post-progression treatment)

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




Source: Figure 3 in company submission

# ERG report
## Survival censoring

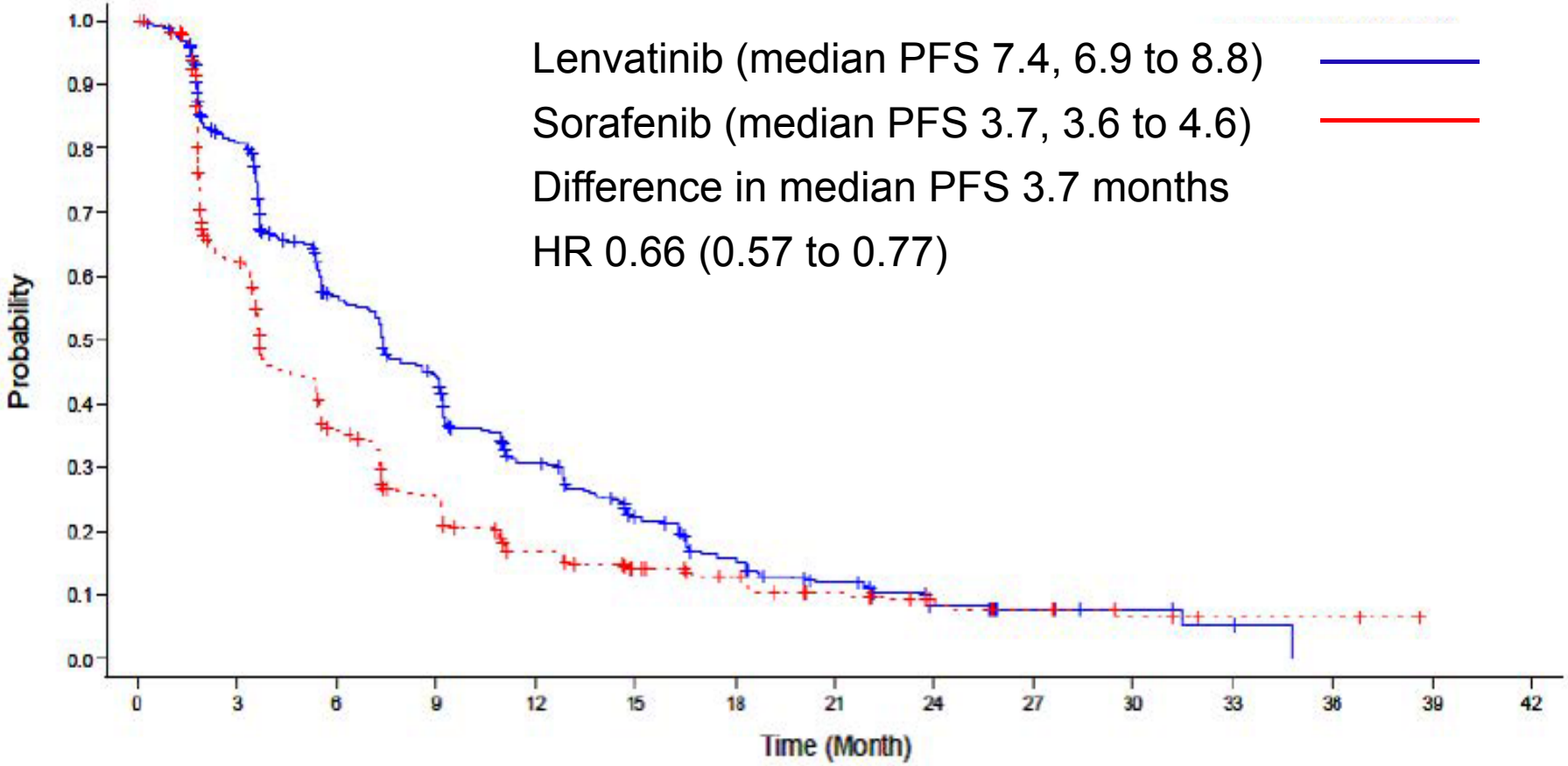
- Censoring in primary analyses (PFS and TTP) at treatment discontinuation if no disease progression.
  - likely to favour lenvatinib because treatment discontinuation for reasons other than progression (that is, due to TEAEs or patient choice) more common in lenvatinib group than sorafenib group.
  - At clarification company reported sensitivity analyses with censoring in line with EMA guidance
- ERG: consistency in direction of effect provides robust evidence of PFS benefit with lenvatinib, although rules for censoring mean extent of benefit may be [redacted]

| Outcome | Lenvatinib | Sorafenib | Lenvatinib vs. sorafenib |
|---|---|---|---|
| PFS (months) using FDA* | Median 7.4 | Median 3.7 | HR 0.66 (0.57 to 0.77) |
| PFS (months) using EMA** | Median [redacted] | Median [redacted] | [redacted] |

*Censor at treatment discontinuation if no disease progression **included all progressions and deaths as events (not censored at treatment discontinuation if no disease progression).
Abbreviations: HR, hazard ratio

# REFLECT

## Investigator-assessed PFS, censor at treatment discontinuation if no disease progression




Source: Figure 4 in company submission

# Secondary outcomes from REFLECT
## Full population

| Outcome | LEN (n=478) | SOR (n=476) | Result (95% CI) |
|---|---|---|---|
| Disease progression | [redacted] | [redacted] | P-value not reported |
| Median time to progression (months) | 8.9 (7.4, 9.2) | 3.7 (3.6, 5.4) | P-value not reported |
| ORR | 115 (24.1) | 44 (9.2) | OR 3.13 (2.15 to 4.56) |
| EQ-5D (HUI or VAS) | Not reported | Not reported | no statistically significant differences in HUI or VAS scores between groups at Cycles 3, 6, 9, 12, 15, or 18 (p>0.05) |

Abbreviations: LEN Lenvatinib; HUI, health utility index; OR odds ratio; ORR objective response rate; SOR sorafenib; VAS, visual analogue scale

- Quality of life (QoL) broadly same across both treatments for majority of function and symptom areas
- Clinically meaningful delay in worsening of QoL for lenvatinib compared with sorafenib across several EORTC measures:
  - role functioning (HR 0.83, 0.71 to 0.97), pain (HR 0.82, 0.70 to 0.95), diarrhoea (HR 0.53, 0.45 to 0.63), body image (HR 0.79, 0.68 to 0.93), nutrition (HR0.81, 0.68 to 0.95)

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# REFLECT trial
# Adverse events

Draft SPC states:

- [redacted]

- [redacted]

# REFLECT trial
## Adverse events

| Outcome | Lenvatinib (n=476) | Sorafenib (n=475) |
|---|---|---|
| Mean treatment duration, months (SD) | 8.2 (7.04) | 6.0 (6.47) |
| Mean dose intensity, mg/day/patient (SD) | 9.4 (5.71) | 663.8 (173.15) |
| Any TEAE, n (%) | 470 (98.7) | 472 (99.4) |
| Hypertension | 201 (42.2) | 144 (30.3) |
| Diarrhoea | 184 (38.7) | 220 (46.3) |
| Decreased appetite | 162 (34.0) | 127 (26.7) |
| Weight decreased | 147 (30.9) | 106 (22.3) |
| Fatigue | 141 (29.6) | 119 (25.1) |
| Palmar-plantar erythrodysaesthesia syndrome (hand-foot syndrome) | 128 (26.9) | 249 (52.4) |
| TEAE ≥Grade 3 | 357 (75.0) | 316 (66.5) |
| Any serious AE | 205 (43.1) | 144 (30.3) |
| TEAEs leading to withdrawal | 94 (19.7) | 69 (14.5) |
| TEAEs leading to dose reduction | 184 (38.7) | 185 (38.9) |

Abbreviations: TEAE treatment emergent adverse event

# REFLECT trial results

## pre-planned subgroups

| Outcome | Hazard ratio (95% CI) |
|---|---|
| OS* | Western: 1.08 (0.82 to 1.42)*, [redacted]<br>Asia-Pacific: 0.86 (0.72 to 1.02)*, [redacted] |
| OS* with additional covariates | Baseline AFP (<200 or ≥200 ng/mL): 0.86 (0.74 to 1.00) |
| | Region: 0.92 (0.79 to 1.06)** |
| | Aetiology of HCC (hepatitis B, hepatitis C, alcohol): 0.86 (0.72 to 1.01) |
| Median PFS (months) investigator -assessed | Western: 0.81 (0.61 to 1.08)<br>Asia-Pacific: 0.61 (0.51 to 0.73) |
| | Baseline AFP <200 ng/mL: 0.68 (0.55 to 0.83)<br>Baseline AFP ≥200 ng/mL: 0.59 (0.47 to 0.75) |
| | Aetiology hepatitis B: 0.62 (0.50 to 0.75), hepatitis C: 0.78 (0.56 to 1.09), Alcohol: 0.27 (0.11 to 0.66) |

*Stratified by region (Asia–Pacific; Western), macroscopic portal vein invasion or extrahepatic spread or both (yes, no), ECOG PS (0, 1) and body weight (<60 kg, ≥60 kg). **status of subsequent anti-cancer therapy (yes/no) used as an additional covariate factor. Abbreviations: AFP, alpha-fetoprotein; LEN Lenvatinib; OS overall survival; PFS progression free survival; SOR sorafenib

Source: section B2.6.1.1.2 (page 38) of company submission and table 21 in company submission appendix, tables 11 and 57 in ERG report

# Summary of ERG comments (1)

| | |
|---|---|
| BSC comparator | • Agree BSC only used if systemic treatment not appropriate |
| Baseline imbalance | • Imbalance in baseline characteristics but may not necessarily impact relative treatment effects<br>• OS similar between Western subgroup and full population when both were adjusted for subsequent treatment<br>• Agree AFP is prognostic factor but no clinical rationale to dichotomise (AFP≥200 ng/ml) |

# Summary of ERG comments (2)

**Western subgroup**

- REFLECT population from Asia-Pacific may not be generalisable to UK but no evidence Western subgroup more applicable given loss in precision

**Other bias**

- Independent imaging review assessments considered less biased (similar results)
- Censoring rules (PFS and TTP) may favour lenvatinib (more patients stopped treatment for reasons other than progression)
- Interpret HRs for PFS and OS with caution as proportional hazards assumption does not hold

# Key issues – clinical effectiveness

- The company have positioned lenvatinib as a potential treatment for people with Child-Pugh Class A liver function, is this appropriate?
- Is it appropriate to exclude BSC as a comparator?
- Is the REFLECT trial generalisable to clinical practice in the NHS?
  - Post progression anti-cancer treatments were received in both arms
  - Trial population had stage B or C HCC, Child-Pugh class A and ECOG PS 0 or 1
- Is it appropriate to use results from the full population (rather than Western subgroup)?
- What censoring rules are most appropriate?
- Have the results of the REFLECT trial showed non-inferiority compared with sorafenib?

Contains AIC and CIC

# Lead team presentation

# Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma [ID1089]

Cost effectiveness

1st Appraisal Committee meeting

Committee C

Lead team: Gail Coster, David Chandler and Natalie Hallas

Evidence Review Group: BMJ

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Company: Eisai

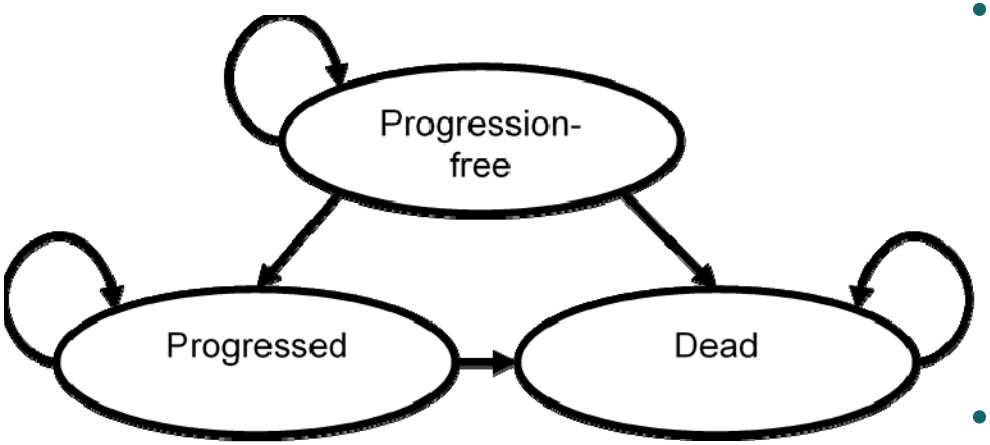
30th May 2018

**Slides for Committee and projector [ACIC]**

# Key issues – cost-effectiveness

- Is the company's covariate adjustment of survival models appropriate?
- Is progression-free survival (PFS) likely to be overestimated when FDA censoring method is applied?
- What parametric curve should be used to extrapolate PFS?
- Should drug wastage be included and how?
  - 7 day wastage or ERG scenario using planned daily number of capsules
- More patients in sorafenib arm received post-progression anti-cancer treatment in REFLECT
  - In UK clinical practice, would post-progression treatments be used?
  - Should adjustments be made to overall survival?
- Is end of life criteria met?
- Most plausible ICER?
- Equality issues?

# Company model
## Model structure

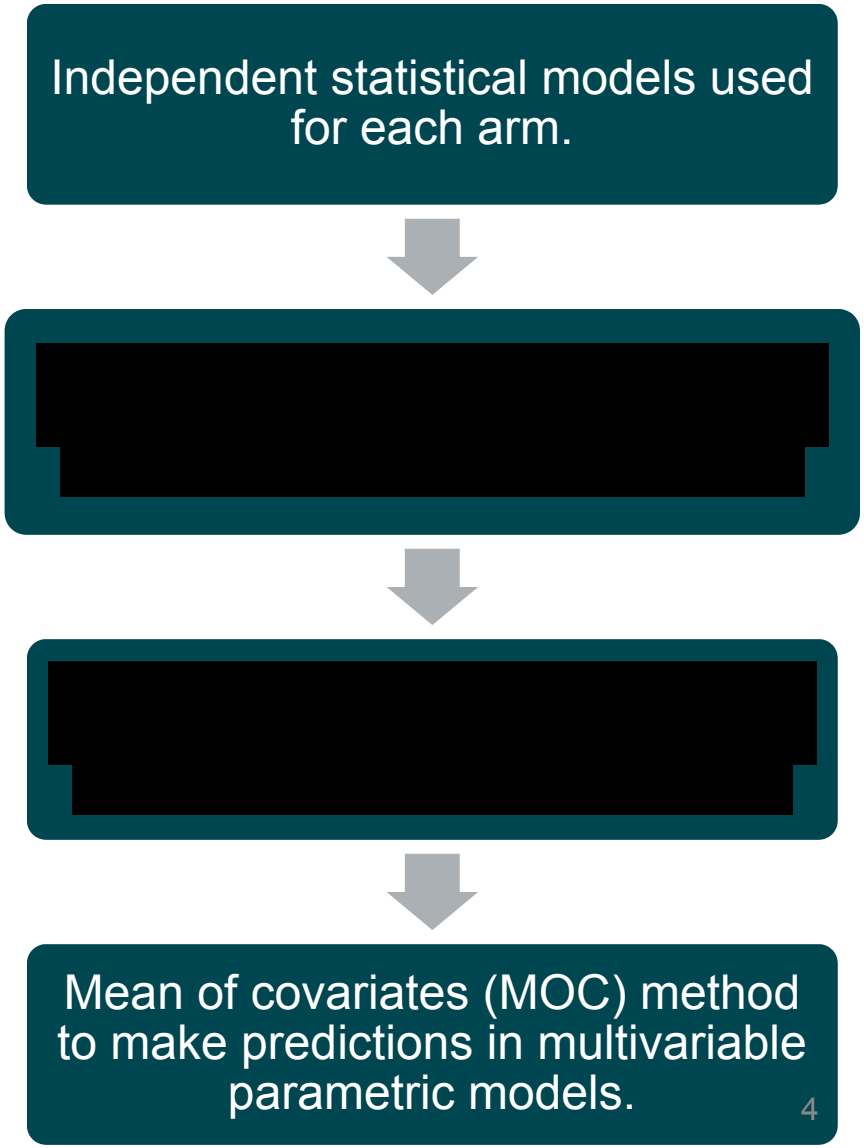



- Partitioned survival model
  - distribution of patients across all health states at each cycle is modelled, defined by overall survival (OS) and progression-free survival (PFS) curves.
- Uses patient-level data from RELECT, lifetime horizon, half-cycle correction and 3.5% discount rate.
- REFLECT provides relatively complete observed PFS & OS
  - 64.4% in the lenvatinib arm had experienced disease progression
  - 73.4% died at the end of trial (data cut-off Nov 2016).

**ERG comments:**
- Model structure and approach appropriate.
- Inconsistency in application of half-cycle correction to costs - corrected in ERG's preferred base case.

# Company model
## Adjustment of baseline characteristics

- Company base case adjusts for imbalance in baseline characteristics using multivariable adjustments to the PFS and OS curves
  - scenario 1: unadjusted parametric models
  - scenario 2: adjusts for AFP and stratification factors only




Abbreviations: AFP, alpha-fetoprotein

# Adjustment of baseline characteristics
## ERG comments

- Should have included all variables in adjustment for both PFS & OS then made selection on each parametric model.
- Adjusted PFS model potentially more unreliable than OS model - Cox PH only applied to OS data.
- Each variable assumed to have relative effect on hazard ratio (PH not assessed for all variables).
- Company approach adds uncertainty but with RCT data (only some imbalances), provides some reassurance that adjustment is sufficient.

# Company model
## Survival extrapolation

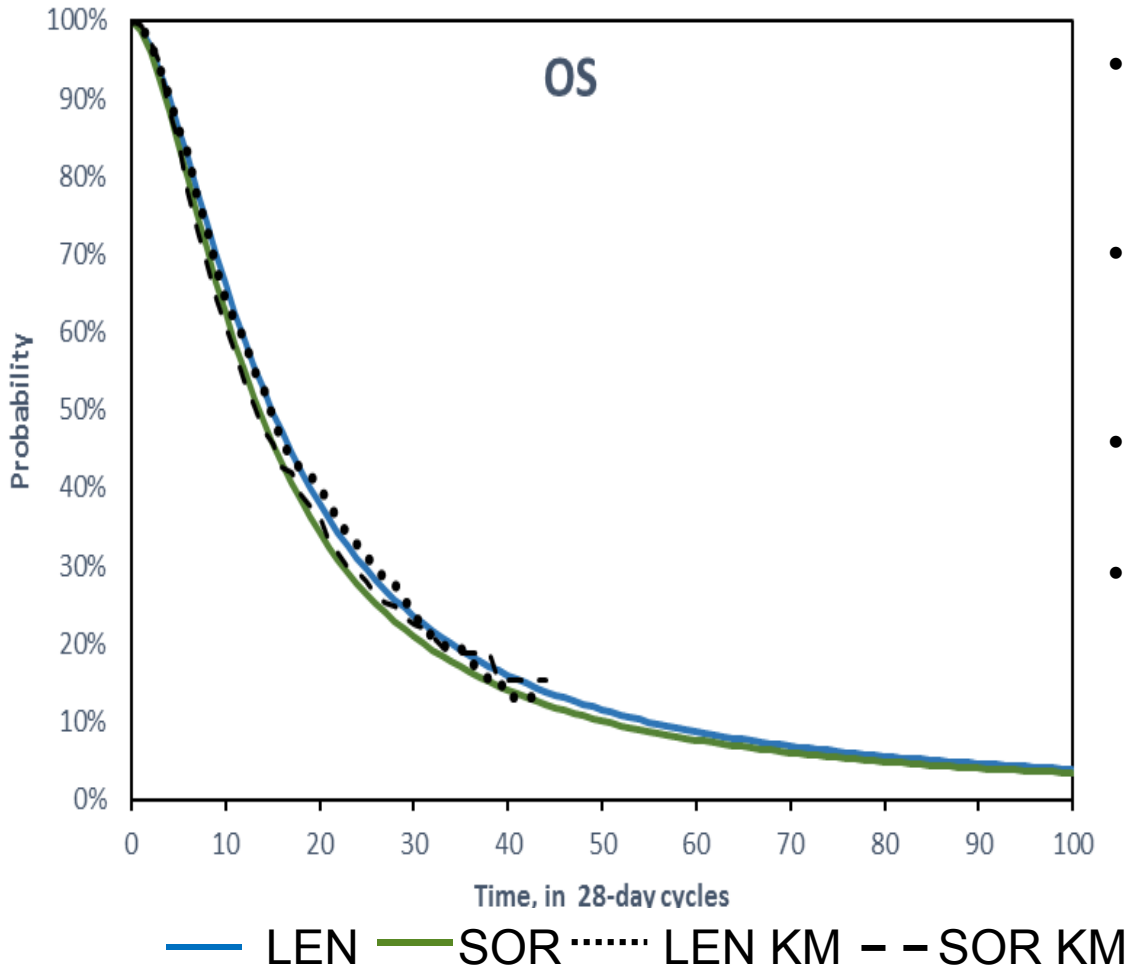
| Outcome | Extrapolation | Distribution in base case |
|---|---|---|
| PFS | • Extrapolation needed<br>• Survival for sorafenib was 6% at last observed data point (Kaplan-Meier [KM] curve) | log-normal** |
| OS | • Extrapolation needed<br>• 73% in lenvatinib and 74% in sorafenib arm died at last observed data point | log-logistic* |
| TTD | • KM curve used<br>• data almost complete 0% lenvatinib and 4% sorafenib and assume 4% stopped treatment at end of follow up | N/A |

*Note: Weibull, exponential, log-logistic, log-normal, gamma and Gompertz distributions investigated for all outcomes (scenario analyses for all listed distributions).*

*company: consistent with the 2016 sorafenib reconsideration (2 real-world data sources showed small proportion survive for extended period of time, indicating log-normal curve is better fit than Weibull), as for certain ranges of the parameters, the shape of the log-normal and log-logistic hazard functions can be very similar.

**gamma distribution preferred for sorafenib arm but this led to extrapolations in which PFS for sorafenib exceeded that of lenvatinib (not clinically plausible, so not considered further).

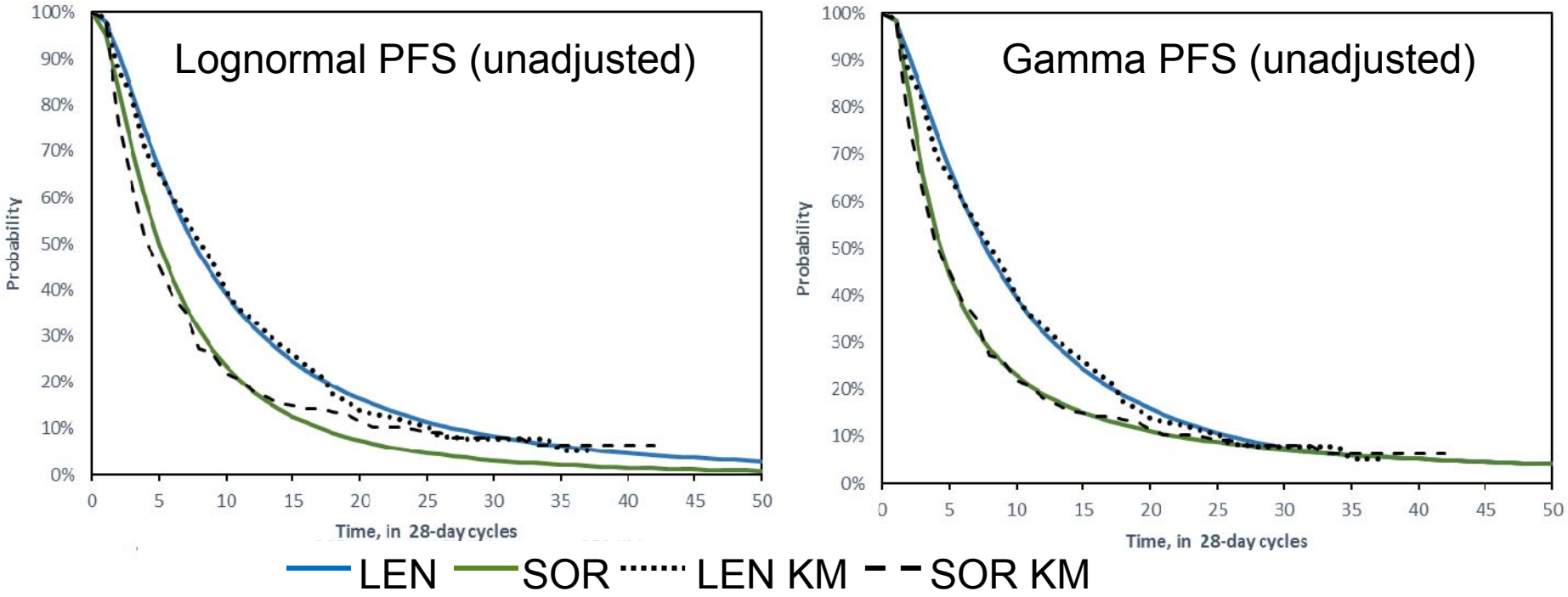
# OS extrapolation
## ERG comments




- Clinical expert advice to ERG: 10 year plausible max OS for untreated advanced HCC
- Extrapolated curved in line with this (approx. 1-2% alive in each group at 10 years)
- No changes to company OS extrapolation in ERG base case
- ERG scenario: Gamma curve because it was a similarly well fitted curve but with a slightly more conservative extrapolation

**ERG base case:** use log-logistic distribution to extrapolate OS (no change)
**ERG scenario:** use gamma distribution to extrapolate OS

# Progression-free survival extrapolation
## ERG comments




- Lognormal not a good fit for SOR. Company should have assessed unadjusted models against KM data.
- ERG's agrees with using same functional form across treatment groups but reasonable fit should be considered in both groups.
- Gamma model the best statistical fit in terms of AIC and BIC & good fit for lenvatinib.

**ERG base case:** use gamma model for PFS (not log-normal) and prevent curves from crossing over

# Adverse events (AEs)
## ERG comments

| Company approach | ERG comments |
|---|---|
| Model all grade 3 or 4 TEAEs with incidence >5%:<br>1. Hypertension (LEN 23% vs. SOR 14%)<br>2. Weight loss (8% vs. 3%)<br>3. Blood bilirubin ↑ (7% vs. 5%)<br>4. Proteinuria (6% vs. 2%)<br>5. Gamma-glutamyltransferase ↑ (6% vs. 4%)<br>6. Platelets ↓ (6% vs. 3%)<br>7. Aspartate aminotransferase ↑ (5% vs. 4%)<br>8. Diarrhoea* (4% both arms)<br>9. Fatigue* (4% both arms)<br>10. Hand-foot syndrome (3% vs. 11%)<br>11. Asthenia* (3% vs. 2% | • ERG's clinical experts confirmed all relevant AEs included. Company's approach reasonable but excluded grade 5 AE (avoid double counting mortality cost.)<br>• **Company scenarios**:<br>– apply cost of 1 hospitalisation to 12.8% in LEN and 7.6% in SOR arm with grade 5 AE (minimal impact on ICER).<br>– Western subgroup analysis using AE data from full population – inconsistent.<br>• **ERG scenario:** Western AE data correctly used (minimal impact on ICER).<br>• AEs associated with post-progression anti-cancer interventions not included - unlikely to have large impact on ICER. |

*occurred in <5% of patients, but company's clinical experts expected those AEs to have significant clinical/economic impacts. Abbreviations: TEAE, treatment emergent adverse event

# Company model
## Health related quality of life (HRQoL)

- EQ-5D-3L collected in REFLECT
- Adjusted mean utility values for progression-free and progressed health states similar between the lenvatinib and sorafenib arms
  - **Company base case**: utility values in full REFLECT population for both arms
  - **Company scenario**: committee preferred in TA474 sorafenib and TA514 regorafenib because base case may not capture reduced HRQoL after disease progression.
- [illegible]

| Health state | Utility value: mean (standard error) |
|---|---|
| **Progression-free** | 0.745 (0.0079) |
| **Progressed** | 0.678 (0.0118) |

Source: Table 33 in company submission

Small difference between progression-free and progressed utility values may be due to close post-progression measurement after disease progression

Clinical experts: post-progression estimate higher than expected, as significant impact on well-being

# Company model
## Treatment costs

- Drug costs based on mean observed dose in trials but drug wastage not included.
  - **Company scenario:** Discontinuation of treatment was associated with wastage of 7 days' worth of drug costs in line with TA474 sorafenib. ERG considers this arbitrary (no rationale in either submission) and associated with significant uncertainty.

**ERG scenario:** drug costs based on the planned number of daily capsules

- No administration or monitoring costs for LEN or SOR:
  - Outpatient administration (costs captured in background medical management)
  - Clinical expert: in practice, monitoring requirements same for both treatments (also in line with AG model for ID1059 for thyroid cancer)
- One-off acquisition cost of subsequent anti-cancer medication based on REFLECT:

| Use of post-progression therapy | Proportion leaving progression-free state | | Mean duration of post-progression therapy (days) | |
|---|---|---|---|---|
| | LEN | SOR | LEN | SOR |
| Sorafenib† | [redacted] | [redacted] | [redacted] | [redacted] |
| Regorafenib‡ | [redacted] | [redacted] | [redacted] | [redacted] |

† mean dose 663.8mg assumed to be the same as first line; ‡mean dose 144 mg taken from the RESORCE trial. Abbreviations: LEN lenvatinib; SOR sorafenib

# Company model
## Health state costs

- Resource use based on two pooled surveys (TA189 & updated in TA474 sorafenib for HCC).
  - Original: new unit costs applied
  - Updated: costs uplifted to 2016/17
  - Weighted average cost based on number of clinicians responding to each survey

| Weighted average cost per cycle | Progression-free | Progressed |
|---|---|---|
| Physician visits | £159.63 | £384.40 |
| Laboratory tests | £161.78 | £135.56 |
| Radiological tests | £30.04 | £27.25 |
| Hospitalisation | £91.52 | £196.78 |
| Hospital follow-up* | £168.50 | £726.26 |
| Social care* | £21.19 | £1,066.07 |
| **Total** | **£632.67** | **£2,536.32** |

**based only on survey results presented in the original sorafenib submission to NICE.*

**ERG comments**

- Potential double counting of post-progression management (minimal ICER impact)
- ERG's clinical expert: patients in UK would not receive post-progression treatment, (regorafenib not recommended by NICE & counterintuitive to offer regorafenib/sorafenib after failure on same drug class).
- Post-progression drug costs applied to 'newly progressed' patients but company overestimate this. **ERG scenario:** mortality adjustment for newly progressed

# Other ERG comments

| Company | ERG comments |
|---|---|
| Imbalance in post-progression treatment in REFLECT trial | • Greater proportion of post-progression treatment in sorafenib group likely to lead to longer OS.<br>• Company use crude adjustment but this scenario preferable to company's base case - avoids the need to offset potential benefits from these treatments by applying costs (no subsequent treatments recommended beyond 2nd line in UK). |
| Base case uses full population (not Western subgroup) | • Lower sample size in subgroup (954 to 314) so less robust.<br>• OS in lenvatinib subgroup worse than sorafenib group (not significant). After adjusting for imbalances in post-progression anti-cancer therapies results similar to full population. |
| Data censored if no progression at treatment discontinuation | • Using this approach PFS potentially overestimated (company's scenario included all progressed disease events).<br>• Both analyses unreliable as PH assumption not met<br>• ERG scenarios: diminish the treatment effect for PFS. |

**ERG base case:** use OS adjusted for post-progression anti-cancer treatment and remove post progression treatment costs
**ERG base case:** use full population (no change from company base case)
**ERG scenario:** lower PFS treatment effect

# Company base case and ERG assumptions

| | Company | ERG |
|---|---|---|
| Clinical effectiveness | • Adjust for imbalance in baseline characteristics (but not post-progression treatment & exclude post-progression AE)<br>• Independent models for each arm (PH assumption not supported)<br>• Censor at discontinuation if no progression | Use OS adjusted for post-progression treatment *(scenarios: ↓ PFS treatment effect to assess censoring)* |
| Extrapolation | PFS: log-normal, OS: log-logistic, TTD: none (data almost complete) | PFS: gamma *(scenario: OS gamma)* |
| HRQoL | • No difference between LEN and SOR<br>• Disutilities for AEs not explicitly modelled | No changes |
| Costs | Resource use costs same for LEN and SOR in progression-free and progressed state. Drug wastage not included | Correct half-cycle error *(scenarios: full drug cost & no AE cost)* |
| Post-progression treatment | One-off cost and only sorafenib & regorafenib costs included | Remove post-progression costs *(scenarios: include post progression procedures & mortality adjustment)* |

# Company's base case results

## After clarification (PAS for lenvatinib, list price sorafenib)

- Company's base case amended at clarification:
  - categorised Child–Pugh class as categorical variable (A vs B) rather than continuous (multivariate analyses were re-estimated)
  - corrected end of life care costs

| | Total | | | Incremental | | | |
|---|---|---|---|---|---|---|---|
| **Drug** | Costs (£) | LYG | QALYs | Costs | LYG | QALYs | **ICER** |
| Deterministic | | | | | | | |
| **SOR** | £65,592 | 1.46 | 1.03 | - | - | - | - |
| **LEN** | [redacted] | 1.69 | [redacted] | [redacted] | 0.23 | [redacted] | Dominant |
| Probabilistic sensitivity analysis | | | | | | | |
| **SOR** | £65,688 | - | 1.03 | - | - | - | - |
| **LEN** | [redacted] | - | [redacted] | [redacted] | - | [redacted] | Dominant |

- Most influential parameters:
  - Baseline hazard for PFS and OS
  - Proportion of patients randomised to lenvatinib but used sorafenib as a post-progression treatment
  - Duration of post-progression sorafenib use after lenvatinib

Source: Tables 43 and 45 in ERG report

# Company's scenario analyses

1) Include drug wastage (in line with TA474)
2) Exclude mortality costs
3) Exclude covariate adjustment
4) Adjust for AFP and stratification factors only
5) Alternative OS distribution
6) Alternative PFS distribution
7) Change resource costs (halved and doubled)
8) Target dose assumed
9) 1.5% discount rate
10) Time horizon: 1, 2 or 5 years
11) Use sorafenib (TA474) or regorafenib (TA514) utility data
12) Post progression utility 0.5
13) Assume discount for sorafenib*

In all scenario analyses lenvatinib was dominant compared with sorafenib (*except using assumed 60% discount for sorafenib)

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# ERG scenario analyses

## Lenvatinib vs. sorafenib (PAS for lenvatinib, list price sorafenib)

| Scenario | Incremental | | | ICER |
|---|---|---|---|---|
| | Cost | LY | QALY | |
| Company's corrected base case | [redacted] | 0.23 | [redacted] | Dominant |
| 1. Adjusted OS for post-progression anti-cancer intervention & no post-progression treatment cost | [redacted] | 0.30 | [redacted] | Dominant |
| 2. PFS: gamma (prevention of curves crossing) | [redacted] | 0.23 | [redacted] | Dominant |
| 3. OS: gamma (prevention of curves crossing) | [redacted] | 0.18 | [redacted] | Dominant |
| 4. Mortality adjustment for newly progressed patients | [redacted] | 0.23 | [redacted] | Dominant |
| 5. All post-progression intervention costs (including procedures) | [redacted] | 0.23 | [redacted] | Dominant |
| 6. Scenario 4 and 5 | [redacted] | 0.23 | [redacted] | Dominant |
| 7. Scenario 1 with Western subgroup with Western subgroup AEs | [redacted] | 0.11 | [redacted] | Dominant |
| 8. Full costs of drugs (no dose reductions) | [redacted] | 0.23 | [redacted] | Dominant |
| 9. Removal of AEs | [redacted] | 0.23 | [redacted] | Dominant |

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# ERG's base case results

## Lenvatinib vs. sorafenib (PAS for lenvatinib, list price sorafenib)

| | Total | | Incremental | | ICER | |
|---|---|---|---|---|---|---|
| **Drug** | Costs (£) | QALYs | Costs | QALYs | vs. base case | All changes |
| **1. Company's corrected base case** | | | | | | |
| **SOR** | £65,574 | 1.03 | - | - | - | - |
| **LEN** | [redacted] | [redacted] | [redacted] | [redacted] | Dominant | Dominant |
| **2. Post-progression adjustment to OS and no post progression therapy costs** | | | | | | |
| **SOR** | £60,243 | 0.95 | - | - | - | - |
| **LEN** | [redacted] | [redacted] | [redacted] | [redacted] | Dominant | Dominant |
| **3. Gamma distribution for PFS (with prevention of curves crossing)** | | | | | | |
| **SOR** | £56,237 | 0.96 | - | - | - | - |
| **LEN** | [redacted] | [redacted] | [redacted] | [redacted] | Dominant | Dominant |
| **ERG base case (1 to 3)** | | | | | | **Dominant** |

- ERG unable to incorporate uncertainty around its preferred survival models in PSA (covariance matrices not provided).
- No PSA conducted as ERG considered results without this uncertainty to be unreliable and potentially misleading.

*Note: ICERs with comparator CAA discount to be presented in part 2 slides*

Source: Table 48 in ERG report

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# ERG's base case scenario analyses

## Lenvatinib vs. sorafenib (PAS for lenvatinib, list price sorafenib)

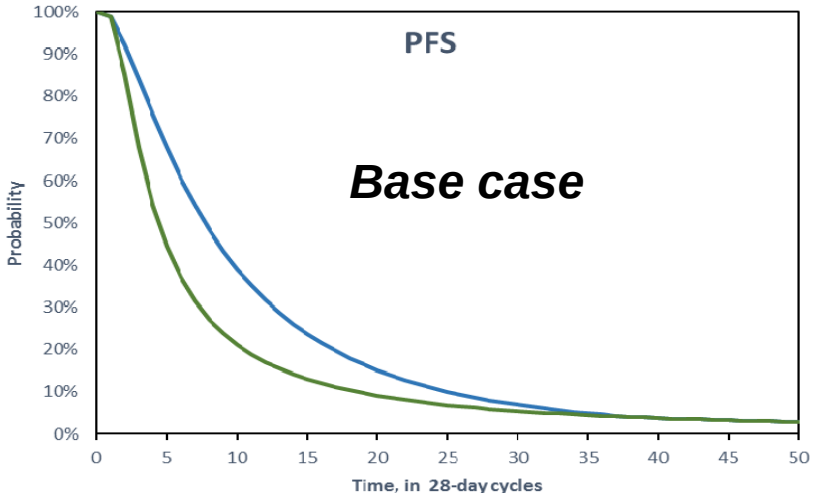
| Scenario | Incremental | | | ICER vs. base case |
|---|---|---|---|---|
| | Cost | LY | QALY | |
| ERG base case | [redacted] | 0.30 | [redacted] | Dominant |
| 1. Reduce scale of gamma PFS function by 5% | [redacted] | 0.30 | [redacted] | £2,085 |
| 2. Reduce scale of gamma PFS function by 10% | [redacted] | 0.30 | [redacted] | £8,490 |
| 3. Reduce scale of gamma PFS function by 15% | [redacted] | 0.30 | [redacted] | £14,024 |
| 4. Gamma distribution for OS (with prevention of curves crossing) | [redacted] | 0.24 | [redacted] | Dominant |

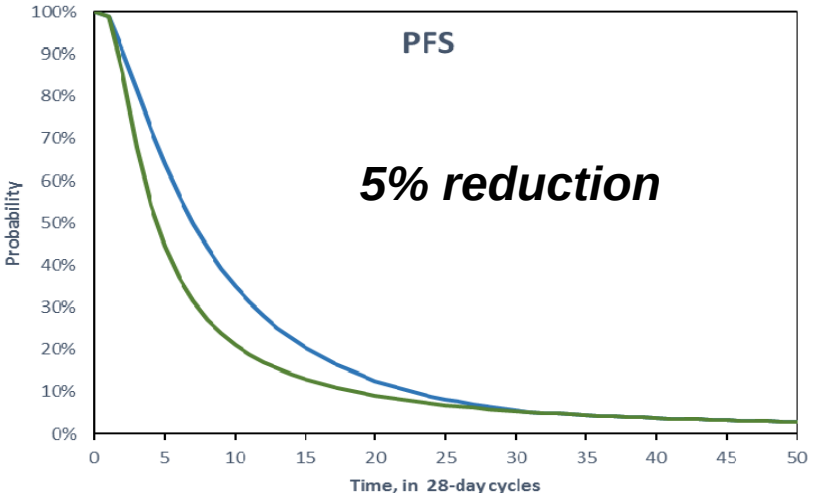
Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.

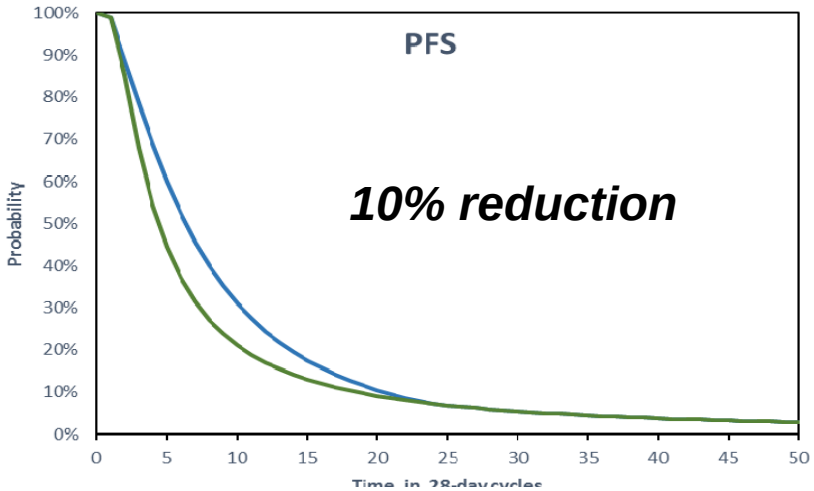
Source: Table 49 in ERG report

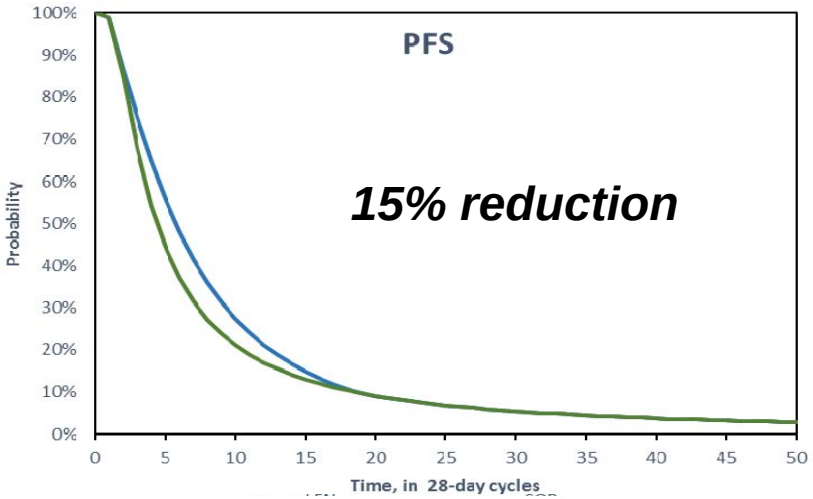
# ERG base case scenario

## PFS gamma curves with reduction in scale parameters




Key: LEN SOR

# End of life
## Short life expectancy

| Company | ERG |
| --- | --- |
| Yes, median survival for patients with advanced HCC is <1 year; 4 to 8 months if untreated and 6 to 11 months with sorafenib. | ESMO-ESDO guidelines give median OS based on natural history as 4 to 8 months, and 6 to 11 months with sorafenib, for people with BCLC Stage C HCC.<br>From the company submission:<br>• Sorafenib median OS in REFLECT (primary analysis) = 12.3 months (upper quartile 25.4 months).<br>• Sorafenib mean OS = 17.5 months (company base case), 16.2 months (ERG's base case). |

Source: Table 50 in ERG report

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# End of life
## Extension to life

| Criterion | Company | ERG |
|---|---|---|
| **Met criterion?** | Yes, mean OS benefit for lenvatinib of 3.1 months compared with sorafenib (page 67 in company submission) | Incremental mean OS benefit from the company's economic model:<br>• Company base case at clarification = 3.1 months<br>• ERG base case = 4.1 months. |
| **LY gain** | 0.22 (company submission)<br>0.23 (after clarification stage) | 0.33 (ERG preferred base case) |
| **Treatment effect** | **Lenvatinib**: Median 13.6 (12.1 to 14.9 months)<br>**Sorafenib**: Median 12.3 (10.4 to 13.9 months)<br>Unadjusted HR 0.92 (0.79 to 1.06)<br>Adjusted for post-progression treatment HR [redacted] | |

Source: Table 50 in ERG report

# Innovation and equality

**Innovation**

- Company consider lenvatinib innovative because it is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that inhibits the kinase activities of VEGF and FGF receptors in addition to other proangiogenic and oncogenic pathway-related RTKs involved in tumour proliferation.
- Sorafenib currently the only available systemic treatment option for patients with advanced HCC and there is a clear unmet need for new treatments which delay progression and improve survival without negatively impacting patients' quality of life.

**Equality**

- Company state no known equality issues
  - Clinical expert statement: "HCC is much more common in men and this was reflect in the trial population in which 85% were male."
  - Hep C trust: "Liver cancer disproportionately affects men (though not women) living in deprived areas in England. It also disproportionately affects Asian and Black people."

# Key issues – cost-effectiveness

- Is the company's covariate adjustment of survival models appropriate?
- Is progression-free survival (PFS) likely to be overestimated when FDA censoring method is applied?
- What parametric curve should be used to extrapolate PFS?
- Should drug wastage be included and how?
  - 7 day wastage or ERG scenario using planned daily number of capsules
- More patients in sorafenib arm received post-progression anti-cancer treatment in REFLECT
  - In UK clinical practice, would post-progression treatments be used?
  - Should adjustments be made to overall survival?
- Is end of life criteria met?
- Most plausible ICER?
- Equality issues?