NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Eisai Ltd (company)
   - Bayer
   - Department of Health and Social Care – No comment

   Comments on the Appraisal Consultation Document from experts:
   - No comments received

   Comments on the Appraisal Consultation Document received through the NICE website
   - No comments received

3. **Company appendix of new evidence** – submitted by Eisai

4. **Evidence Review Group critique of company ACD comments –** prepared by BMJ Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Lenvatinib for untreated advanced hepatocellular carcinoma

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	Eisai	Eisai have received approval for a revised PAS discount: Eisai have revised the PAS discount as part of this ACD consultation and details of the revised PAS have been provided separately.	Thank you for your comment. The updated PAS discount was considered by the committee when making its decision.
2	Consultee	Eisai	Eisai have submitted a revised model which includes the committee's preferred assumptions as per Section 3.21 of the ACD. A table is presented in the accompanying appendix which demonstrates the impact of each of the committee's preferred assumptions on the cost, QALY, ICER and predicted mean overall survival benefit with lenvatinib, in comparison with the company's corrected base case. The table also presents results using the committee's preferred assumptions, assuming a sorafenib PAS discount ranging from [redacted]%. Eisai agrees that the full ITT population from REFLECT should be used and that this population is reflective of UK clinical practice. Eisai agrees that an adjusted analysis is appropriate, as imbalances in baseline characteristics which were potentially important prognostic factors may affect the treatment benefit seen with lenvatinib (as outlined in Section 3.6 of the ACD). Baseline imbalances of note in REFLECT included the proportion of patients with AFP levels ≥200 ng/mL (46.4% in the lenvatinib arm and 39.3% in the sorafenib arm) and the proportion of patients with an aetiology of HCV (19% in the lenvatinib arm (and 26.5% in the sorafenib arm). In the presence of imbalances for strong predictors of outcomes, adjustment for such covariates generally improves the precision and efficiency of the analysis and avoids conditional bias from chance covariate imbalance. Adjustments using the corrected group prognosis (CGP) method have been included in the revised model as per the committee's preference. Model results using the CGP method were included in the response to ERG clarification questions and had minimal impact on the ICER and on the predicted mean overall survival benefit (See Appendix Table 1, rows 1 and 4), thus providing reassurance and reducing uncertainty. The revised model also includes all events in the analysis and only censored if there were missing assessments or no disease progression at the patients' last assessment (EMA censoring approach) in line with the committee's preference, as the committee considered that the company approach (FDA censoring) to censoring would likely overestimate PFS gain in favour of lenvatinib (see Appendix Table 1,	Thank you for your comments and submission of additional evidence. The committee agreed that the updated approach for adjusting for baseline characteristics using the corrected group prognosis method was acceptable (see section 3.12 of the FAD). The committee also agreed that the updated approach to censoring of progression-free survival was appropriate (see section 3.8 of the FAD). The committee understood that the REFLECT trial did not capture all outcomes using the standard RECIST criteria, and considered the evidence presented (which included results captured using mRECIST). The committee concluded that both the lognormal and gamma extrapolations were a reasonable visual fit to the trial data (see section 3.15 of the FAD). The committee considered that it was acceptable to include both the costs and benefits of post-progression treatments in line with REFLECT (see sections 3.13 and 3.17 of the FAD) to mitigate any potential confounding of overall survival. The committee did recognise that it had not seen alterative statistical adjustments for progression-free survival, and that this introduced uncertainty into the analysis; the committee accounted for this when making its decision (see section 3.20 of the FAD). The committee concluded that the most plausible ICER

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			row 7). The Kaplan Meier curve for investigator assessed PFS using mRECIST is presented in the accompanying appendix (Figure 1). An investigator assessment of PFS using RECIST 1.1 was not performed in the REFLECT study. All efficacy endpoints conducted for the primary analyses in REFLECT (with the exception of OS) were based on tumour response evaluations as determined by the investigator according to mRECIST for HCC for hepatic lesions. mRECIST was used as it more appropriately reflects changes in intrahepatic lesions by measuring only the viable portion of the lesions. The revised model has also utilised a gamma distribution for the extrapolation of PFS as per the committee's preference (see Appendix Table 1, row 3). Adjusted Kaplan-Meier's for PFS using both the EMA and FDA censoring approaches, with gamma and log-normal distributions are presented in the accompanying appendix. In the company submission, the gamma distribution was not used as PFS for sorafenib exceeded that of lenvatinib (PFS with censoring according to the FDA approach; Figure 4 in the accompanying appendix), which was not considered a clinically plausible scenario. Using the committee's preferred approach to censoring, the difference between the gamma (Appendix Figure 2) and the log normal (Appendix Figure 3) distributions, based on comparison to adjusted Kaplan-Meier curves, are modest in terms of goodness-of-fit. Using all of the other committee's preferred assumptions and assuming a sorafenib discount of [redacted]%, the ICER with the gamma distribution is £[redacted] and the ICER with the log-normal distribution is £[redacted] As per Sections 3.13 and 3.18 of the ACD, the revised model includes the clinical benefit of post-progression therapies as per REFLECT, as well as the costs of all post-progression treatments and procedures (see Appendix Table 1, rows 5 and 6, respectively). In RELFECT 43.1% of patients in the lenvatinib arm compared with 51.1% of patients in the sorafenib arm received post-progression therapies. The committee agreed that there was an imbalance in post-progression therapies which favoured sorafenib. Therefore, by not adjusting for this imbalance, the mean OS benefit for lenvatinib of 3.0 months is likely to be conservative. There are currently no NICE-recommended second-line therapies for advanced HCC. In addition, the assessment group report concluded that the full trial population was not reflective of UK clinical practice with regards to the extent and type of subsequent treatments received. The statistical adjustment of post-treatment anti-cancer therapy use as a covariate within the economic analysis was intended as an exploratory analysis to illustrate the magnitude of effect that these imbalances may have in the estimation of cost-effectiveness for lenvatinib; after adjustment using this approach, the expected life extension associated with lenvatinib is increased to over 4 months. When all of the committee's preferred assumptions are included, the ICER for lenvatinib is [redacted] when using the sorafenib list price, and £[redacted] when assuming a PAS discount of [redacted]% for sorafenib.	falls within the range normally considered to be an acceptable used of NHS resources, and concluded that lenvatinib should be recommended for routine used (see section 3.20 of the FAD).
3	Consultee	Eisai	Eisai believes that lenvatinib meets the criteria for an end of life treatment	The committee considered whether lenvatinib meets

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			By including all of the committee's preferred assumptions, the mean OS benefit is almost unchanged from the company's original submission at 3.0 months and therefore Eisai believe that there is sufficient certainty for the EOL criteria to be met. Given that the committee's preferred base case does not include an adjustment for post progression therapies, which were considered by the committee to be imbalanced in favour of sorafenib, the mean OS benefit of 3 months is likely to be a conservative estimate.	the end of life criteria (see section 3.21 of the FAD). Based on the evidence it had seen, the committee concluded that lenvatinib meets the criterion for short life expectancy. However, it did not consider the evidence that lenvatinib extends life by 3 months to be sufficiently robust.
4	Consultee	Eisai	Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS: Eisai believe that it is important for both clinicians and patients to have access to lenvatinib to improve treatment choice, as the only NICE-recommended treatment option for patients with advanced HCC is sorafenib. As acknowledged by the Committee, sorafenib is not always effective, and many people cannot tolerate it because of side effects. In response to the ACD, Eisai have implemented all of the committee's preferred base case assumptions. Using the committee's preferred base case, lenvatinib is associated with an OS benefit of 3 months and is therefore considered to meet the criteria for an end of life treatment. Lenvatinib is a cost-effective treatment for HCC assuming a sorafenib PAS of [redacted]% and that end of life criteria is granted.	Comment noted. The recommendation made in the final appraisal document (FAD, section 1.1) is made in respect of the full evidence base.
5	Commentator	Bayer	We are concerned about the lack of transparency during this appraisal process. In particular the appraisal committee meeting was held without any opportunity for members of the public to attend.	Thank you for your comment. It is standard NICE process for meetings to be held without public observers if CHMP opinion has not been released and it is considered to be commercially sensitive. This is to protect the commercial interests of the manufacturer of the technology being appraised. NICE endeavours to keep the appraisals process as transparent as possible; documents from the first committee meeting are released when CHMP opinion is granted.
6	Commentator	Bayer	We are concerned about the lack of transparency during this appraisal process because no ICERs are reported in the ACD. [redacted]	Thank you for your comment. NICE highly values transparency. However, decision making ICERs could not be included in the ACD because of the presence of commercial arrangements for the comparator technology. The ERG recalculated the ICER estimates to incorporate these commercial arrangements; these ICERs were used by the committee to make its decision.
7	Commentator	Bayer	In the ACD, when discussing the recommendation the 3rd paragraph on page 3 states,"sorafenib is not always effective and many people cannot tolerate it because of side effects". We strongly believe that this statement gives a misleading impression because the way it is worded suggests that sorafenib is less well	Thank you for your comment. The FAD has been updated to reflect that sorafenib and lenvatinib have different side effect profiles, and that tolerance of each drug will differ for each patient (see section 3.2 of the

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			tolerated then lenvatinib. This is not a reasonable interpretation of the evidence given that, in the REFLECT trial drug withdrawal due to adverse events was higher in the lenvatinib arm compared to the sorafenib arm. Furthermore, there were more high grade and serious adverse events in the lenvatinib arm (vs sorafenib). In the REFLECT trial, treatment-related treatment-emergent adverse events led to lenvatinib drug withdrawal in 42 (9%) patients. In the sorafenib arm, treatment related treatment-emergent adverse events led to drug withdrawal in 34 (7%) patients. In the sorafenib pivotal study, the SHARP study, the rate of discontinuation of the study drug due to adverse events was similar in the active and placebo groups (38% sorafenib vs. 37% placebo) suggesting that sorafenib was well tolerated. We therefore request that this statement is amended to reflect that the drugs may have different side effect profiles.	FAD).
8	Commentator	Bayer	Regarding paragraph 3.2 (page 5). While we agree that hand-foot skin reactions can be inconvenient to patients, hypertension increases cardiovascular events risk which may not be more acceptable to patients and requires additional resources to manage. Furthermore, hand-foot skin reactions can be effectively managed by taking simple precautionary measures or dose titrations.	Thank you for your comment. The FAD has been updated to reflect that sorafenib and lenvatinib have different side effect profiles, and that tolerance of each drug will differ for each patient (see section 3.2 of the FAD).
9	Commentator	Bayer	Regarding paragraph 3.2 (page 5). In the REFLECT study, high grade adverse events and serious adverse events are higher in the lenvatinib arm compared to the sorafenib arm: Treatment-emergent adverse events of grade ≥3: 357 (75%) lenvatinib arm vs 316 (67%) sorafenib arm. Treatment-related treatment-emergent adverse events of grade ≥3: 270 (57%) lenvatinb arm vs 231 (49%) sorafenib arm. Serious treatment-emergent adverse events: 205 (43%) lenavitinb arm vs 144 (30%) sorafenib arm. Serious treatment-related treatment-emergent adverse events: 84 (18%) lenvatinb arm vs 48 (10%) sorafenib arm. Given that, in the REFLECT trial lenvatinib had a numerically worse side effect profile particularly with regard to grade 3/4 events and that drug withdrawal due to adverse events was higher in the lenvatinib arm compared to the sorafenib arm, we would challenge the Committees conclusion that lenvatinib would offer improved benefits for people with advanced unresectable hepatocellular carcinoma. Rather the different side effect profiles of the two products may be more or less acceptable to patients who should be offered a choice of product.	Thank you for your comment. The FAD has been updated to reflect that sorafenib and lenvatinib have different side effect profiles, and that tolerance of each drug will differ for each patient (see section 3.2 of the FAD).
10	Commentato	Bayer	Regarding the title of paragraph 3.2 (page 5). Given the above comments and that	Thank you for your comment. The summary sentence

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	r		both drugs have different side effects profiles but similar overall survival benefits, the title should reflect the need for patients' choice rather than particular benefits of one drug over the other.	section 3.2 of the FAD is 'Lenvatinib may offer benefits over current treatment options'. This reflects the evidence that the committee heard in the first committee meeting from the clinical and patient experts. The committee also considered clinical effectiveness evidence from the REFLECT trial during the appraisal.
11	Commentato r	Bayer	Paragraph 3.24, page 18. It is unclear which evidence was presented to the Committee however it is unlikely that "a survival benefit of over 3 months could be expected for lenvatinib compared with sorafenib". The OS KM curves (slide 17) overlap at 36 months, this is a trend reflected in the PFS KM curves which also overlap at 24 months (slide 19). This would suggest any survival benefit for lenvatinib is captured within the trial period and it is unclear how this could vastly exceed the difference in median OS of 1.3 months. The power of the REFLECT study to declare superiority of lenvatinib to sorafenib was approximately 82% using a superiority test with assumed true HR of 0. 80. Overall survival superiority over sorafenib was not achieved, as hazard ratio was 0·92 (95% CI 0·79–1·06).	Thank you for your comment. The committee considered overall survival evidence from the REFLECT trial and the mean survival benefit predicted by the model. It concluded that there was not sufficient evidence to indicate that lenvatinib offers an extension to life of more than three months compared with current NHS treatment (see section 3.21 of the FAD).
12	Commentato r	Bayer	It is not appropriate to adjust clinical data based on differences in post-progression treatment, as the treatments received differed by study group: • The trial protocol allowed for different post-progression treatment in each arm. Whilst a small number of sorafenib patients moved on to a second line therapy with regorafenib, many continued sorafenib treatment where clinical benefit following disease progression is not expected. All lenvatinib patients who continued treatment following progression switched to sorafenib. Sorafenib has not been studied in a second line setting in HCC, so clinical benefit is unknown. Sorafenib has a different mechanism of action and has shown clinical benefit following lenvatinib in other indications such as differentiated thyroid cancer. For this reason adjustment of clinical outcomes in favour of lenvatinib or sorafenib is inappropriate and not evidence based. Other issues in the ERG report include imbalance in post progression treatment in the REFLECT trial. 43.1% in the lenvatinib arm and 51.1% in the sorafenib arm had post-treatment anti-cancer therapy. 8% difference between both arms populations is not statistically significant and unlikely to lead to longer OS in sorafenib group compared to lenvatinib group.	Thank you for your comment. The committee considered that it was acceptable to for the model to include the costs and benefit of post-progression treatments, modelled in line with treatments used in the REFLECT trial (see sections 3.13 and 3.17 of the FAD).
13	Commentato r	Bayer	Wastage was treated differently in this appraisal compared to TA474. The ERG argue this is immaterial since it is dealt with similarly in both arms of the economic	Thank you for your comment. The ERG and appraisal committee were aware of the commercial

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			model. However it is not clear to Bayer whether this is truly the case [redacted]	arrangements for both lenvatinib and sorafenib. The ERG recalculated the ICER estimates to incorporate commercial arrangements for both lenvatinib and sorafenib; these ICERs were used by the committee to make its decision.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 30 August 2018 **via NICE Docs**

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eisai Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]
Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Eisai have received approval for a revised PAS discount** Eisai have revised the PAS discount as part of this ACD consultation and details of the revised PAS have been provided separately.
2	Eisai have submitted a revised model which includes the committee's preferred assumptions as per Section 3.21 of the ACD. A table is presented in the accompanying appendix which demonstrates the impact of each of the committee's preferred assumptions on the cost, QALY, ICER and predicted mean overall survival benefit with lenvatinib, in comparison with the company's corrected base case. The table also presents results using the committee's preferred assumptions, assuming a sorafenib PAS discount ranging from [redacted]%. Eisai agrees that the full ITT population from REFLECT should be used and that this population is reflective of UK clinical practice. Eisai agrees that an adjusted analysis is appropriate, as imbalances in baseline characteristics which were potentially important prognostic factors may affect the treatment benefit seen with lenvatinib (as outlined in Section 3.6 of the ACD). Baseline imbalances of note in REFLECT included the proportion of patients with AFP levels ≥200 ng/mL (46.4% in the lenvatinib arm and 39.3% in the sorafenib arm) and the proportion of patients with an aetiology of HCV (19% in the lenvatinib arm (and 26.5% in the sorafenib arm). In the presence of imbalances for strong predictors of outcomes, adjustment for such covariates generally improves the precision and efficiency of the analysis and avoids conditional bias from chance covariate imbalance. Adjustments using the corrected group prognosis (CGP) method have been included in the revised model as per the committee's preference. Model results using the CGP method were included in the response to ERG clarification questions and had minimal impact on the ICER and on the predicted mean overall survival benefit (See Appendix Table 1, rows 1 and 4), thus providing reassurance and reducing uncertainty. The revised model also includes all events in the analysis and only censored if there were missing assessments or no disease progression at the patients' last assessment (EMA censoring approach) in line with the committee's preference, as the committee considered that the company approach (FDA censoring) to censoring would likely overestimate PFS gain in favour of lenvatinib (see Appendix Table 1, row 7). The Kaplan Meier curve for investigator assessed PFS using mRECIST is presented in the accompanying appendix (Figure 1). An investigator assessment of PFS using RECIST 1.1 was not performed in the REFLECT study. All efficacy endpoints conducted for the primary analyses in REFLECT (with the exception of OS) were based on tumour response evaluations as determined by the investigator according to mRECIST for HCC for hepatic lesions. mRECIST was used as it more appropriately reflects changes in intrahepatic lesions by measuring only the viable portion of the lesions. The revised model has also utilised a gamma distribution for the extrapolation of PFS as per the committee's preference (see Appendix Table 1, row 3). Adjusted Kaplan-Meier's for PFS using both the EMA and FDA censoring approaches, with gamma and log-normal distributions are presented in the accompanying appendix. In the company submission, the gamma distribution was not used as PFS for sorafenib exceeded that of lenvatinib (PFS with censoring according to the FDA approach; Figure 4 in the accompanying appendix), which was not considered a clinically plausible scenario. Using the committee's preferred approach to censoring, the difference between the gamma (Appendix Figure 2) and the log normal (Appendix Figure 3) distributions, based on comparison to adjusted Kaplan-Meier curves, are modest in terms of goodness-of-fit. Using all of the other committee's preferred assumptions and assuming a sorafenib discount of [redacted]%, the ICER with the gamma distribution is £[redacted] and the ICER with the log-normal distribution is £[redacted]

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	As per Sections 3.13 and 3.18 of the ACD, the revised model includes the clinical benefit of post-progression therapies as per REFLECT, as well as the costs of all post-progression treatments and procedures (see Appendix Table 1, rows 5 and 6, respectively). In RELFECT 43.1% of patients in the lenvatinib arm compared with 51.1% of patients in the sorafenib arm received post-progression therapies. The committee agreed that there was an imbalance in post-progression therapies which favoured sorafenib. Therefore, by not adjusting for this imbalance, the mean OS benefit for lenvatinib of 3.0 months is likely to be conservative. There are currently no NICE-recommended second-line therapies for advanced HCC. In addition, the assessment group report concluded that the full trial population was not reflective of UK clinical practice with regards to the extent and type of subsequent treatments received. The statistical adjustment of post-treatment anti-cancer therapy use as a covariate within the economic analysis was intended as an exploratory analysis to illustrate the magnitude of effect that these imbalances may have in the estimation of cost-effectiveness for lenvatinib; after adjustment using this approach, the expected life extension associated with lenvatinib is increased to over 4 months. When all of the committee's preferred assumptions are included, the ICER for lenvatinib is [redacted] when using the sorafenib list price, and £[redacted] when assuming a PAS discount of [redacted]% for sorafenib.
3	**Eisai believes that lenvatinib meets the criteria for an end of life treatment** By including all of the committee's preferred assumptions, the mean OS benefit is almost unchanged from the company's original submission at 3.0 months and therefore Eisai believe that there is sufficient certainty for the EOL criteria to be met. Given that the committee's preferred base case does not include an adjustment for post progression therapies, which were considered by the committee to be imbalanced in favour of sorafenib, the mean OS benefit of 3 months is likely to be a conservative estimate.
4	**Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS** Eisai believe that it is important for both clinicians and patients to have access to lenvatinib to improve treatment choice, as the only NICE-recommended treatment option for patients with advanced HCC is sorafenib. As acknowledged by the Committee, sorafenib is not always effective, and many people cannot tolerate it because of side effects. In response to the ACD, Eisai have implemented all of **t**he committee's preferred base case assumptions. Using the committee's preferred base case, lenvatinib is associated with an OS benefit of 3 months and is therefore considered to meet the criteria for an end of life treatment. Lenvatinib is a cost-effective treatment for HCC assuming a sorafenib PAS of [redacted]% and that end of life criteria is granted.

Insert extra rows as needed

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Bayer plc**]

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** • In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned about the lack of transparency during this appraisal process. In particular the appraisal committee meeting was held without any opportunity for members of the public to attend.
2	We are concerned about the lack of transparency during this appraisal process because no ICERs are reported in the ACD. "academic / commercial in confidence information removed"
3	In the ACD, when discussing the recommendation the 3rd paragraph on page 3 states,"sorafenib is not always effective and many people cannot tolerate it because of side effects". We strongly believe that this statement gives a misleading impression because the way it is worded suggests that sorafenib is less well tolerated then lenvatinib. This is not a reasonable interpretation of the evidence given that, in the REFLECT trial drug withdrawal due to adverse events was higher in the lenvatinib arm compared to the sorafenib arm. Furthermore, there were more high grade and serious adverse events in the lenvatinib arm (vs sorafenib). In the REFLECT trial, treatment-related treatment-emergent adverse events led to lenvatinib drug withdrawal in 42 (9%) patients. In the sorafenib arm, treatment related treatment-emergent adverse events led to drug withdrawal in 34 (7%) patients. In the sorafenib pivotal study, the SHARP study, the rate of discontinuation of the study drug due to adverse events was similar in the active and placebo groups (38% sorafenib vs. 37% placebo) suggesting that sorafenib was well tolerated.

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	We therefore request that this statement is amended to reflect that the drugs may have different side effect profiles.
4	Regarding paragraph 3.2 (page 5). While we agree that hand-foot skin reactions can be inconvenient to patients, hypertension increases cardiovascular events risk which may not be more acceptable to patients and requires additional resources to manage. Furthermore, hand-foot skin reactions can be effectively managed by taking simple precautionary measures or dose titrations.
5	Regarding paragraph 3.2 (page 5). In the REFLECT study, high grade adverse events and serious adverse events are higher in the lenvatinib arm compared to the sorafenib arm: Treatment-emergent adverse events of grade ≥3: 357 (75%) lenvatinib arm vs 316 (67%) sorafenib arm. Treatment-related treatment-emergent adverse events of grade ≥3: 270 (57%) lenvatinb arm vs 231 (49%) sorafenib arm. Serious treatment-emergent adverse events: 205 (43%) lenavitinb arm vs 144 (30%) sorafenib arm. Serious treatment-related treatment-emergent adverse events: 84 (18%) lenvatinb arm vs 48 (10%) sorafenib arm. Given that, in the REFLECT trial lenvatinib had a numerically worse side effect profile particularly with regard to grade 3/4 events and that drug withdrawal due to adverse events was higher in the lenvatinib arm compared to the sorafenib arm, we would challenge the Committees conclusion that lenvatinib would offer improved benefits for people with advanced unresectable hepatocellular carcinoma. Rather the different side effect profiles of the two products may be more or less acceptable to patients who should be offered a choice of product.
6	Regarding the title of paragraph 3.2 (page 5). Given the above comments and that both drugs have different side effects profiles but similar overall survival benefits, the title should reflect the need for patients' choice rather than particular benefits of one drug over the other.
7	Paragraph 3.24, page 18. It is unclear which evidence was presented to the Committee however it is unlikely that "a survival benefit of over 3 months could be expected for lenvatinib compared with sorafenib". The OS KM curves (slide 17) overlap at 36 months, this is a trend reflected in the PFS KM curves which also overlap at 24 months (slide 19). This would suggest any survival benefit for lenvatinib is captured within the trial period and it is unclear how this could vastly exceed the difference in median OS of 1.3 months. The power of the REFLECT study to declare superiority of lenvatinib to sorafenib was approximately 82% using a superiority test with assumed true HR of 0. 80. Overall survival superiority over sorafenib was not achieved, as hazard ratio was 0·92 (95% CI 0·79–1·06).
8	It is not appropriate to adjust clinical data based on differences in post-progression treatment, as the treatments received differed by study group: • The trial protocol allowed for different post-progression treatment in each arm. Whilst a small number of sorafenib patients moved on to a second line therapy with regorafenib, many continued sorafenib treatment where clinical benefit following disease progression is not expected. All lenvatinib patients who continued treatment following progression switched to

	sorafenib. Sorafenib has not been studied in a second line setting in HCC, so clinical benefit is unknown. Sorafenib has a different mechanism of action and has shown clinical benefit following lenvatinib in other indications such as differentiated thyroid cancer. For this reason adjustment of clinical outcomes in favour of lenvatinib or sorafenib is inappropriate and not evidence based. Other issues in the ERG report include imbalance in post progression treatment in the REFLECT trial. 43.1% in the lenvatinib arm and 51.1% in the sorafenib arm had post-treatment anti-cancer therapy. 8% difference between both arms populations is not statistically significant and unlikely to lead to longer OS in sorafenib group compared to lenvatinib group.
9	Wastage was treated differently in this appraisal compared to TA474. The ERG argue this is immaterial since it is dealt with similarly in both arms of the economic model. However it is not clear to Bayer whether this is truly the case “academic / commercial in confidence information removed”

Insert extra rows as needed

Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma [ID1089] ACD response – appendix

1. Economic model results using the committee's preferred assumptions

Table 1: Economic model results

		Sorafenib list price analysis			Sorafenib [redacted] discount			Sorafenib [redacted] discount			Sorafenib [redacted] discount			Predicted mean overall survival benefit
#	Scenario	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	
1	Corrected company base-case (revised PAS - [redacted] discount)†	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	3.1
2	ERG base-case†	[redacted]	0.220	[redacted]	[redacted]	0.220	[redacted]	[redacted]	0.220	[redacted]	[redacted]	0.220	[redacted]	4.1
3	1 + gamma distribution to extrapolate PFS for lenvatinib and sorafenib†	[redacted]	0.164	[redacted]	[redacted]	0.164	[redacted]	[redacted]	0.164	[redacted]	[redacted]	0.164	[redacted]	3.1
4	1 + CGP prognosis method to adjust for imbalances in baseline characteristics†	[redacted]	0.167	[redacted]	[redacted]	0.167	[redacted]	[redacted]	0.167	[redacted]	[redacted]	0.167	[redacted]	3.0
5	1 + post-progression treatments in line with REFLECT†	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	3.1
6	5+ the costs of post-	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	[redacted]	0.176	[redacted]	3.1

#	Scenario	Sorafenib list price analysis			Sorafenib [redacted] discount			Sorafenib [redacted] discount			Sorafenib [redacted] discount			Predicted mean overall survival benefit
		Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	Δ Costs	Δ QALYs	ICER	
	progression treatments AND procedures†													
7	1 + censoring approach categorising all disease progression and deaths as events‡	[redacted]	0.171	[redacted]	[redacted]	0.171	[redacted]	[redacted]	0.171	[redacted]	[redacted]	0.171	[redacted]	3.1
8	Committee preferred base-case‡	[redacted]	0.159	[redacted]	[redacted]	0.159	[redacted]	[redacted]	0.159	[redacted]	[redacted]	0.159	[redacted]	3.0
9	Committee preferred base-case - log-normal distribution for PFS‡	[redacted]	0.163	[redacted]	[redacted]	0.163	[redacted]	[redacted]	0.163	[redacted]	[redacted]	0.163	[redacted]	3.0

† Based on 'ID1089 lenvatinib Eisai clarification CE model ERG v0.1 010518 AS [ACIC]' updated to include revised lenvatinib PAS; ‡ Based on 'ID1089 lenvatinib Eisai clarification CE model ERG v0.1 010518 AS [ACIC]' updated to include revised lenvatinib PAS and a censoring approach that categorises all disease progression and deaths as events.

Abbreviations: CGP, corrected group prognosis; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality adjusted life year.

2. Kaplan-Meier curves for progression-free survival using EMA censoring approach

Figure 1: Kaplan-Meier curves and analysis for EMA progression-free survival with stratification factors in IVRS per investigator review

Median was estimated with Kaplan-Meier method and 95% confidence interval was constructed with a generalised Brookmeyer and Crowley method. Hazard ratio is expressed as lenvatinib/sorafenib and was estimated from Cox proportional hazard model with treatment as independent variable and stratified by IVRS stratification factors. Efron method is used for ties. P-value is for superiority test (lenvatinib vs sorafenib) and is calculated using log-rank test stratified by IVRS stratification factors.
+ Censored observations
Abbreviations: CI, confidence interval; EMA, European Medicines Agency; HR, hazard ratio; IVRS, interactive voice response system.

2. Adjusted Kaplan-Meier curves

Note – curves presented in Figures 2-5 were adjusted for the same variables as in the company base-case.

Figure 2: PFS extrapolations using the EMA censoring approach (committee's preferred approach) – gamma

Abbreviations: EMA, European Medicines Agency; KM, Kaplan-Meier; LEN, lenvatinib; PFS, progression-free survival; SOR, sorafenib.

Figure 3: PFS extrapolations using the EMA censoring approach committee's preferred approach) – lognormal

Abbreviations: EMA, European Medicines Agency; KM, Kaplan-Meier; LEN, lenvatinib; PFS, progression-free survival; SOR, sorafenib.

Figure 4: PFS extrapolations using the FDA censoring approach (company base case) – gamma

Abbreviations: FDA, Food and Drug Administration; KM, Kaplan-Meier; LEN, lenvatinib; PFS, progression-free survival; SOR, sorafenib.

Figure 5: PFS extrapolations using the FDA censoring approach (company base case) – lognormal

Abbreviations: FDA, Food and Drug Administration; KM, Kaplan-Meier; LEN, lenvatinib; PFS, progression-free survival; SOR, sorafenib.

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

ERG REVIEW OF COMPANY'S RESPONSE TO THE ACD

September 2018

This report was commissioned by the NIHR HTA Programme as project number 16/58/18

BMJ Technology Assessment Group

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1 ERG REVIEW OF THE NEW EVIDENCE

The company submitted a response to address key uncertainties and preferences expressed by the Committee in the Appraisal Consultation Document (ACD). The ERG's review of the response and additional evidence provided by the company is provided under the following subheadings.

1.1 Company's additional analyses

The company's response included an updated model to provide an analysis that was in line with the Committee's preferred modelling assumptions, as outlined in the ACD. The key difference in this model was that it incorporated updated progression-free survival (PFS) models fitted to data with different censoring rules applied.

The data used to model PFS in the company's original submission were censored at the point of treatment discontinuation for patients who discontinued treatment before they had experienced disease progression (e.g., due to toxicity). However, the ERG considered this to potentially overestimate the benefit of lenvatinib compared with sorafenib, because more patients in the lenvatinib group discontinued for reasons other than disease progression. The Committee agreed and preferred an analysis based on data that only had censoring applied if there was no disease progression at the patients' last assessment or if data were missing, in line with European Medicines Agency (EMA) guidance.

The company re-fitted all the survival models that were used in the original submission and adjusted them using the Corrected Group Prognosis (CGP) method, as per the Committee's preference. However, the company did not provide an updated set of Akaike Information Criterion (AIC) or Bayesian Information Criterion (BIC) statistics to assess the best fitting model. The company also did not provide updated coefficients with p-values for each of the variables used in the adjustment, to assess the potential uncertainty in these models, which may differ from the models previously fitted to the censored data.

The company provided results of the Committee's preferred base case, which along with the aforementioned remodelling, used the gamma function to model PFS. It included all post-progression treatment costs in line with those received in the REFLECT trial and, therefore, the survival models used were not adjusted for post-progression treatment effects. The company's analyses were also updated with a new patient access scheme (PAS) for lenvatinib, as agreed between the company and the Department of Health and Social Care (DHSC). This increased the discount from [redacted] to [redacted].

1.2 ERG critique

1.2.1 Survival analysis (using uncensored data)

The company provided an analysis in line with the preferences that the Committee outlined in the ACD and this analysis appears to have been conducted correctly with no errors identified by the ERG in the company's updated model. Although the ERG considers the analyses likely to be sound, the company did not provide full details of all the updated analyses, making it difficult for the ERG to fully assess the analyses presented.

The company's comments lacked clarity with regard to goodness-of-fit and adjustments in the updated survival modelling for PFS. The company did not provide the AIC and BIC so the ERG could not fully assess whether the originally chosen best fitting model for PFS remained the best fitting once the censoring rules for treatment discontinuation had been removed. However, given the similarity of the Kaplan–Meier plots for the original and uncensored data (Figure 1 and Figure 2, respectively), the ERG considers it unlikely for an alternative model to be better fitting than the gamma, which was specified in the ACD as the committee's preferred choice.

Figure 1. Kaplan–Meier curve for investigator-assessed progression-free survival (reproduced from CS, Figure 4)

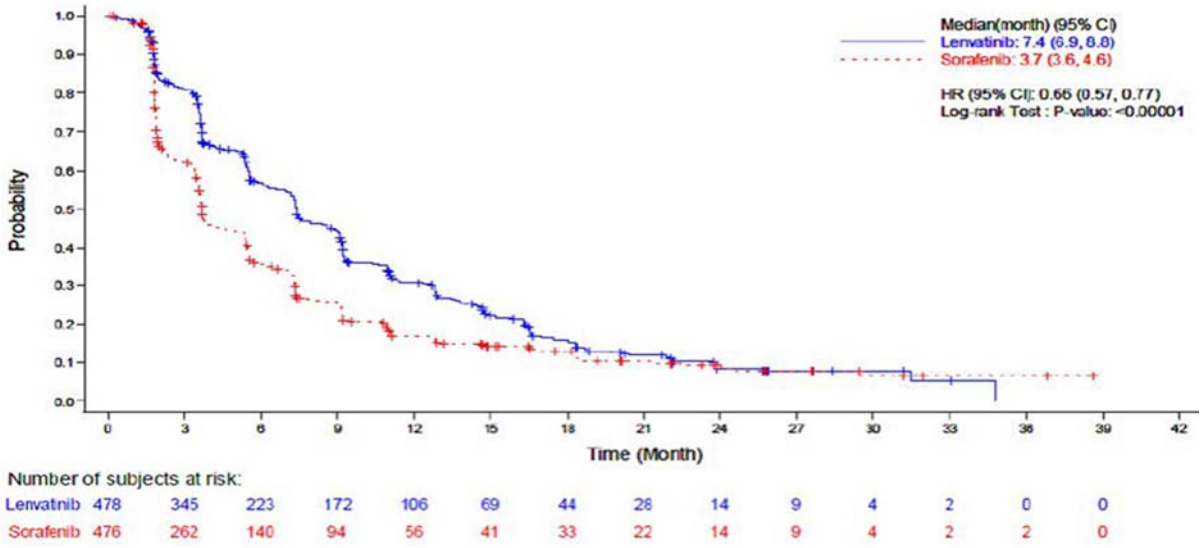

Figure 2. Kaplan–Meier curves for investigator assessed progression-free survival using EMA censoring approach (reproduced from Figure 1 in the appendix to the company's response to the ACD)

Redacted

The company also did not provide the p-values for each of the variables included in the adjusted models, which could have changed the selection after the censoring rules were changed. More importantly, the company appears to have adjusted the PFS models using the variables that were selected for the OS model as per the original submission. A variable selection procedure applied to the PFS data may have resulted in a different level of adjustment, so uncertainty remains in the PFS analysis that the company have provided.

1.2.2 Post progression treatments

Although the Committee stated a preference in the ACD that the modelling of post-progression treatment costs and effects should be in line with the REFLECT trial, the ERG considers this to be inappropriate. There were a number of different treatments received by patients in the REFLECT trial after the primary treatment that are not used in clinical practice and have not been recommended or assessed by NICE.

The list price of drugs that have not be approved by NICE for the second-line treatment of hepatocellular carcinoma (HCC) potentially represents a treatment strategy that is not cost effective, which could bias the results of the comparison of lenvatinib and sorafenib as a first-line treatment. If, for example, the post-progression treatments received by patients in the sorafenib group are ineffective but have a high price, the incremental cost will be reduced in favour of lenvatinib, hence, reducing the incremental cost effectiveness ratio (ICER).

The ERG notes that the adjusted OS models used in the ERG base case, used to avoid the need to apply appropriate costs, also involves a great degree of uncertainty given that the adjustments were made using a binary indicator variable. This means that the effectiveness of individual post-progression

treatments, or at least classes of treatment, have not explicitly been accounted for. However, the models were independently fitted to the lenvatinib and sorafenib groups, so the post-progression treatment effect is at least specific to the primary treatment and may account for imbalances in varying subsequent treatment effects to some extent.

The ERG agrees that the adjusted models cannot necessarily be considered a better alternative to addressing the issue of inappropriately imbalanced and non-recommended treatments post-progression. However, the ERG has concerns with the Committee's preferred approach and notes that there are imbalances in duration of treatment as well as in the proportion of patients receiving the drugs, which both have an impact on the costs applied.

The most commonly received drug post-progression in the REFLECT trial was sorafenib, and although it was received by more patients in the lenvatinib group ([redacted] compared to [redacted] in the sorafenib group), applying a potentially non-cost-effective price may in fact introduce bias in favour of sorafenib rather than lenvatinib. This could be the case if patients no longer receive a benefit from sorafenib post-progression after receiving sorafenib at first-line, hence the "cost-effective" price for sorafenib would be zero. If a benefit could still be gained post-lenvatinib treatment, then a positive cost should be applied for those patients. The ERG conducted a scenario analysis to illustrate the potential impact of this hypothetical situation by assuming those patients who continued with sorafenib post-progression would have the same survival without further sorafenib treatment, and hence, only the costs are removed. The results of this analysis are given in Section 3. Other imbalances in proportion of patients as well as treatment durations exist between the two treatment groups in the REFLECT trial, however, the direction of a potential bias is not clear.

1.2.3 End of Life

The Committee's preferred base case results for survival on sorafenib treatment is 1.73 years (undiscounted) and, therefore, fulfils the criteria for a short life expectancy. The incremental gain in survival for lenvatinib treatment is 3 months (undiscounted) and, therefore, also fulfils the criterion for a sufficient gain in survival.

Given that the increase in survival for the Committee's preferred base case is on the threshold, and there is still uncertainty remaining in the estimates of OS because of the differences in subsequent treatments, there is also, therefore, uncertainty of whether the criteria would be met.

The ERG notes that the OS modelling that was adjusted to account for imbalances in post-progression treatments increased this incremental survival benefit to over 4 months, so this may provide some reassurance to the Committee that the criteria would met. Consideration of the difference between the ICER and the threshold may also mitigate this uncertainty.

2 COMPANY'S UPDATED RESULTS

The company submitted an unrevised preferred base case analysis along with scenario analyses that changed each aspect that the Committee specified as their preferred analysis in the ACD. The company's base case and the Committee's preferred base case results are presented in Table 1 and Table 2, respectively, which are based on the updated PAS price for lenvatinib and the list price for sorafenib. The results of the incremental changes are provided in the appendix to the company's comments on the ACD.

Table 1. Company's corrected base case results (updated PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Sorafenib	£65,574	1.46	1.03	-	-	-	-
Lenvatinib	[redacted]	1.69	1.20	[redacted]	0.226	0.176	[redacted]
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

Table 2. Committee's preferred base case (updated PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Sorafenib	£68,589	1.60	1.13	-	-	-	-
Lenvatinib	[redacted]	1.81	1.29	[redacted]	0.214	0.159	[redacted]
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

3 ADDITIONAL WORK UNDERTAKEN BY THE ERG

The ERG conducted a scenario analysis around the Committee's preferred base case analysis, which removed the costs of post-progression sorafenib treatment in the sorafenib group only. The reasoning for this is that sorafenib may no longer be effective after progression on first-line sorafenib treatment, and as it is not a recommend treatment at second line, applying this cost with no associated benefit would bias the ICER in favour of lenvatinib. The results of this scenario are given in Table 3

Table 3. Committee's preferred base case with post-progression sorafenib cost removed for sorafenib group only

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Sorafenib	£67,413	1.60	1.13	-	-	-	-
Lenvatinib	[redacted]	1.81	1.29	[redacted]	0.214	0.159	[redacted]
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

The Committee were concerned about the potentially high utility for the post-progression state. The ERG, therefore, conducted a scenario to assess the impact of reducing the utility from [redacted] to 0.50. This reduction is arbitrary but demonstrates how sensitive the results are to this parameter. The results of this analysis are given in Table 4.

Table 4. Committee's preferred base case with utility for post-progression set to 0.50

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Sorafenib	£68,589	1.60	0.97	-	-	-	-
Lenvatinib	[redacted]	1.81	1.12	[redacted]	0.214	0.156	[redacted]
Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio.							

4 CONCLUSION

The company provided updated analyses using the assumptions and data that were preferred by the Committee, as stated in the ACD. Although the robustness of these analyses was not fully disclosed in terms of the statistics for goodness-of-fit and covariate adjustments, the analyses appear to have been generally performed well.

An exception to this is the covariate adjustment for the PFS models, which was based on a variable selection procedure applied only to the OS data. Applying a selection procedure to the PFS data may have resulted in a different model specification in terms of the variables adjusted for, which could impact the magnitude of the resulting benefit. The direction of the effect this could have is not clear but the ERG considers the impact likely to be less than the impact of changing from no adjustment to the company's adjustment. This difference increases the expected time in the progression-free state in Committee's preferred base case from 2.1 months to 2.4 months, so the ERG considers it unlikely to have a meaningful impact on the ICER.

The remaining uncertainty then lies with the estimates of OS, and in particular, the potential effect of the imbalances in post-progression treatments. The ERG is concerned with applying costs that do not reflect the current UK clinical pathway or treatments that have not been assessed as cost-effective in the post-progression setting. However, without the knowledge of whether the second-line treatments are cost-effective or not, this uncertainty cannot be reduced any further than the company's analyses have already attempted to do.

The end-of-life criteria appear to have been met in all of the key analyses presented by the company, although in the Committee's preferred base case analysis, the incremental survival benefit is on the threshold. Consideration of the magnitude of the ICER in comparison to the end-of-life threshold should be taken to potentially alleviate concerns around the uncertainty of this criteria being met.

Results of the company's and ERG analyses based on the Commercial Access Agreement (CAA) between the holder of the marketing authorisation for sorafenib and the DHSC (as well as the lenvatinib PAS), are provided in a separate confidential appendix.