NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

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

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:
   - Bayer
   - Eisai
   - National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians and the Royal College of Radiologists – joint response

   A 'no comment' response was received from the Department of Health
   There were no comments from patient or clinical experts

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **New evidence submitted by companies:**
   - **Bayer**
     - Additional information following NICE request
   - **Eisai**

5. **Assessment Group response to consultation comments,** produced by Liverpool Reviews and Implementation Group (LRIG)

6. **Assessment Group addendum,** produced by Liverpool Reviews and Implementation Group (LRIG)

7. **Assessment Group response to clarification questions posed by NICE,** produced by Liverpool Reviews and Implementation Group (LRIG)

8. **Assessment Group annex,** produced by Liverpool Reviews and Implementation Group (LRIG)

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

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

Multiple 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 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 determination (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, 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	Company	Bayer	Both Assessment Group and Appraisal Committee agreed that it was inappropriate to compare results of the sorafenib and lenvatinib trials via an indirect comparison due to differences in the trials. However in multiple sections of the ACD comparative statements are made. These are based on naïve cross-trial comparisons and are not in keeping with the Committee's conclusions regarding trial comparability.	Thank you for your comment. At both committee meetings, the clinical experts emphasised the increased response rate with lenvatinib. At the second meeting the clinical expert also confirmed that there is very little clinical difference between the RECIST1.0 and 1.1 criteria.
2	Company	Bayer	The ACD notes that "survival benefit with sorafenib is less convincing". The Assessment Group model estimates sorafenib to extend life by an average of 12.9 months versus BSC. Sorafenib is associated with an overall survival hazard ratio versus BSC of 0.77 (95% CI 0.58 to 1.02). This wide confidence interval is driven by the adjustment for treatment cross over and whilst this does cross 1 (1.02) there is equal downwards uncertainty associated with this adjustment (0.58). Extension of life to an average patient of over one year is clinically meaningful, and seldom seen with oncology treatments. On this basis the Committee's conclusion that survival benefit is less convincing does not reflect the evidence considered. This conclusion is reflected in 3.12 of the ACD where "the committee recognised it was likely that both treatments provided a substantial overall survival gain compared with best-supportive care"	Thank you for your comment. Issues relating to the overall survival results from the trials are discussed in section 3.4 of the FAD. This section has been amended to clarify that the overall survival results are uncertain due to crossover adjustment and the use of anticancer treatment after disease progression.
3	Company	Bayer	Bayer welcomes the committee's conclusion that the decision to use lenvatinib or sorafenib is based on individual circumstances and careful consideration of risks and benefits. Differences in mechanism of action and safety profiles have been highlighted throughout the appraisal. Availability of both treatments would provide the most appropriate treatment for each patient and maximise patient outcomes for this small patient group.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
4	Company	Bayer	The ACD states that the company (Bayer) commented that the "Assessment Group's approach (to extrapolation) lacked face validity and overestimated the treatment duration for sorafenib, while underestimating that for lenvatinib". There are outstanding issues with AG extrapolations (these are addressed in	Thank you for your comment. Issues relating to extrapolation and post progression treatment are discussed and resolved in sections 3.9, 3.10 and 3.13 of the FAD.

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			Section 1 of the response) and this also applies to the lenvatinib extrapolation of treatment duration. The time to treatment discontinuation curve for sorafenib is complete. The cited overestimation of treatment costs for sorafenib relate to both treatments allowing TKI treatment after progression. In DECISION sorafenib patients could continue treatment with sorafenib (this is costed for), in SELECT some lenvatinib patients switched to sorafenib (and other TKIs on progression) this is not costed for.	
5	Company	Bayer	The ACD states that the Committee 'recognised that utility values from DECISION did not adequately capture the different side effects to treatment and the different response to treatment and this may have underestimated utility values for lenvatinib' There is no evidence to support the statement: • SAEs, grade >3 AEs and discontinuations were higher for lenvatinib in the SELECT trial than sorafenib in the DECISION trial; these would be expected to influence quality-of-life estimates. Clinical advisors (ERG/AC representatives) disagreed on whether response to treatment was a meaningful health state in the model. Response rates are measured using different criteria in each trial (RECIST 1.0 and RECIST 1.1) and are not directly comparable.	Thank you for your comment. At both committee meetings, the clinical experts emphasised the increased response rate with lenvatinib. At the second meeting the clinical expert also confirmed that there is very little clinical difference between the RECIST1.0 and 1.1 criteria. No changes to the FAD.
6	Company	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.
7	Company	Eisai	Eisai do not agree that the summary of the cost effectiveness evidence is a reasonable interpretation of the evidence for the reasons cited below: **The assessment group's model does not include the correct mean dose of lenvatinib (16.3mg), which was provided in the company response to the AG report, as below:** Eisai have identified an error in the average dose reported in the company submission and as a result in the AG report. The average dose 17.4mg is from the first datacut (November 2013). The updated correct average dose for the August 2015 datacut is 16.3mg. The revised ICER using the list price is: **£59,247.**	Thank you for your comment. Section 3.14 of the FAD has been amended to reflect this change.
8	Company	Eisai	**Eisai do not agree with the methodology of calculating adverse event costs in the assessment group model as it is not reflective of UK clinical practice.** As stated by the clinical expert at the committee meeting, it is not reasonable to	Thank you for your comment. Section 3.14 of the FAD has been amended to reflect this change.

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			assume that the adverse event costs would continue for the entire length of treatment duration. Eisai have submitted additional evidence on the duration of adverse events from the SELECT trial. Further detail is provided in Appendix 1.	
9	Company	Eisai	**Eisai do not agree with the resource use data used in the assessment group model as it is not reflective of UK clinical practice.** Eisai do not agree with the data used by the AG to estimate resource use in the model as it is not consistent with clinical advice received by 4 UK clinical experts experienced in treating RAI-refractory DTC. Eisai have submitted additional evidence on resource use data. Further detail is provided in Appendix 1.	Thank you for your comment. Section 3.12 and 3.13 has been added to the FAD to describe scenario analyses using alternative resource use.
10	Company	Eisai	Correction of an error in the AG formula for AEs which meant off-treatment AE costs were not being discounted results in an ICER for lenvatinib vs BSC of **£62,736** at list price.	Thank you for your comment. Section 3.14 of the FAD has been amended to reflect this change.
11	Company	Eisai	**Eisai agree that there are some health-related benefits from response to treatment that are not captured in the preferred analyses, which would reduce the ICER and have provided some additional information/clarification below:** **Eisai would like to clarify the implementation of the response state within the Eisai submitted electronic model.** The ACD states: "The committee also understood that Eisai's model did not incorporate the duration of response appropriately and therefore questioned the validity of the model." To clarify, response is included within the model as a separate partition. Where oncology models commonly include states for pre- and post-progression, and death, our model effectively includes pre-progression responder, pre-progression non-response, post-progression, and death. In order to inform membership of the pre-progression response state, patient-level data from SELECT were analysed and for each visit (corresponding to cycles in the economic model) the proportion of subjects who were considered responders were calculated. These proportions are then used directly in the model for lenvatinib and BSC. Thus, loss of response (and therefore duration of response) are reflected in the lower proportions seen within the pre-progression responder state over time. Duration of response is therefore contained implicitly within this data and the analysis.	Thank you for your comment. Section 3.8 of the FAD highlights the assessment group's concerns with the response state used in the Eisai model and the committee's conclusion on the most appropriate model for decision-making.
12	Company	Eisai	**End of life criteria** Eisai appreciate that the committee indicated that it could show flexibility around the end-of-life-criteria and it could accept a longer life expectancy of more than 24	Thank you for your comment. Based on the evidence presented to it, the committee concluded that neither lenvatinib nor sorafenib met the criterion for short life expectancy and therefore the end-of-life criteria did not

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			months because of the substantial survival benefit shown by lenvatinib, but needed further information on overall survival to do so. Further detail is provided in Appendix 1.	apply. (section 3.19 of the FAD)
13	Company	Eisai	**Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS.** At the committee meeting, the patient expert explained that patients with radioiodine refractory differentiated thyroid cancer experience debilitating symptoms such as pain and fatigue and this can impact severely on their quality of life. This is a small group of patients and the clinical expert highlighted that the only alternative is best supportive which has minimal impact on the underlying disease. As highlighted in the ACD, there is therefore a need for active treatment options for disease that does not respond to radioactive iodine. Lenvatinib has been licensed in this group of patients for more than two years, since June 2015, but has yet to be made available routinely to English patients on the NHS. It was approved by the EMA on the basis of its outstanding results in progression free survival and tumour shrinkage, including complete response in a few patients in the Phase III SELECT study. Lenvatinib was approved for use on the NHS in Scotland more than a year ago in September 2016 and 11 patients have been treated to date. In Wales, AMWSG have approved its use (based on the same cost effectiveness model as submitted to NICE) very recently on the 18th October. Currently, 50 patients in England have restricted access to lenvatinib through a compassionate access program. The AG model has been updated to include the changes highlighted above and is included separately as part of this response. At list price, the combined additional changes presented above result in an ICER of **£48,607**. When the revised confidential discount is applied, the ICER for lenvatinib versus BSC is well within the required cost effectiveness threshold and Eisai urges NICE to approve lenvatinib without further delay to address the inequality in access for UK patients.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
14	Consultee	NCRI-ACP-RCR-RCR	We note the appraisal committee recognises that: 1. lenvatinib and sorafenib are the only treatment options for progressive, locally advanced or metastatic differentiated thyroid cancer after surgery and radioactive iodine. 2. both lenvatinib and sorafenib are effective in delaying disease progression 3. following adjustment for cross-over in the trials, lenvatinib prolongs survival In view of these findings we strongly urge the committee to reconsider their initial	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.

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			decision not to recommend either lenvatinib or sorafenib for treatment of this population of patients with advanced thyroid cancer. This would create an inequality in access to these drugs for patients in England in contrast to those in Scotland, Wales, other countries in Europe and around the world. Patients in England will have best supportive care only with no disease modifying treatment options.	
15	Web comment	Carer	Please can you reconsider approving the use of Lenvatenib and Sorafenib for the treatment of advanced Thyroid cancer. My daughter had Thyroid cancer at age 16 years, she also has learning difficulties. We always live in the fear that her cancer could return. For all the people living with advanced cancer who need this treatment, please consider that they have hopes and dreams, families and lives to live. The treatment is available, please don't block its use because this cancer is rare. A rare cancer does not make it any less important than a well known cancer, that discrimination is unfair. Every life matters. Please don't take away the hope from those who desperately need this treatment.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
16	Web comment	Patient	I am writing to you to vent my frustration, I have just been informed that NICE have not approved these drugs for use on patients with advanced thyroid cancer. I myself have advanced non avid thyroid cancer and these drugs where my only hope at living a long life. I feel it is so wrong that all money is thrown at the breast cancer, colon, Prostrate cancer etc. Because thyroid cancer is rare and normally highly treatable we are forgotten about. Yes the majority of thyroid cancer case are highly treatable/ curable. But recent statistics show that this is no longer the case in many patients. The only treatment that has been available for thyroid cancer patients for decades is RAI. Like myself many patients are classed as refractory (Non Avid) and drugs like sorefanib and lenvatinib are our only life long for slowing the progression of the cancer. I feel that you making this decision you are putting all thyroid cancer patients who need these drugs on the scrap heap, with no alternative treatments you are basically handing us a death sentence needlessly. You are discriminating against patients with thyroid cancer just because you havenâ€™t made the neccessary arrangements for rare cancers to be included.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
17	Web comment	Patient	As a thyroid cancer patient, I am absolutely shocked and extremely disappointed to hear the news that you have decided not to approve Sorafenib or Lenvatenib for patients with thyroid cancer, furthermore that are recommending against access via the CDF. Both Wales and Scotland have approved this and it is truly disgraceful that NICE have gone against recommendations from professionals. For patients with advanced thyroid cancer, this will have a devastating effect on their lives. I urge the panel to reconsider and overturn this decision.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.

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18	Web comment	Patient	As a patient currently living with thyroid cancer I am radio active insensitive, I am 35 years old with two young children dependant on me. Any chance you can give to people Ike me or any other patients with this cancer to successfully treat it would be a dream come true. To have the power to give just one person hope, hope not to die hope to see their kids grow up. Take this power and use it to allow thyroid cancer patients to have access to this drug. Scotland and Wales have access to it, so why can't we. Please give us a chance. Praying for approval for this drug.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
19	Web comment	Patient	A frustrating outcome on the decision from a patient point of view regarding the decision on Lenvatinib. currently i am taking Lenvatinib, which has created stability in my disease, Differentiated Follicular Tyroid cancer. Overall i would describe the report interesting & full of controdictions. On one hand you clearly state Lenvatinib is effective & delays progressions (which I am experiencing) on the other hand the drug is marginally higher in cost than you would like to be beneficial enough to life.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
20	Web comment	Carer	Health care and access to drugs should not depend on your location within Great Britain We have nationalised health care and should be entitled to receive appropriate treatment regardless of postcode. This treatment has been accepted as beneficial in Wales and Scotland, and must therefore be made available to those living in England too. To make the decision to shorten someone's life because of where they live is amoral.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
21	Web comment	Patient	lenvatinib can be acquired for a discount (which is not disclosed as it is commercially sensitive). This drug is available in Scotland and soon to be in Wales. Why does living in England make it too expensive? Further more, if Thyroid cancer is rare. Why would it not be available?	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
22	Web comment	Public	Please reconsider the decision re. availability of Sorafenib and Lenvatenib for thyroid cancer patients. People's lives are the most precious thing on this earth, not money. Thank you.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
23	Web comment	Patient	There is evidence that the drugs work to prolong life, as such they are being used to treat thyroid cancer in other contries. It seems the value of life is less in this country. I can only conclude from this decision that a) people with rare cancer are being deacriminated against, and b) thyroid cancer affects more women than men and this decision therefore seemingly discriminates against women. I urge the committee to reconsider their decision. The treatment works. If this treatment is not approved there will be people in this country suffering the psychological effects of knowing there is a drug available that prolongs life, but because they have been	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.

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			born in this country they will not be treated. Have the psychological effects of this been considered in the cost benefit analysis?	
24	Web comment	Public	It seems strange that NICE reaches different conclusions from two of the UK's devolved regions, compounding the lack of consistency in treatment across the UK. I would urge you to reconsider.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
25	Web comment	Patient	This is grossly unfair, perhaps we shall have to move to Scotland or Wales to get the treatment which will help us. Not everyone has a private income to be able to afford the drugs which will help. Please think again.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
26	Web comment	Patient	I just wanted to reach out and express my disappointment at this decision. Reading that the lives of thyroid cancer patients are worth less than these drugs cost is very upsetting. At the moment, my thyroid cancer metasteses are taking up iodine. However there may come a time when they become non avid. To see that this drug, that could extend my life and make it better, would be denied to me because of where I live and because money is worth more than my life - is unconscionable. Thyroid cancer is a rare cancer, and within that group, for people to be non avid is even more rare. So the cost of accepting these drugs would not be that great to the NHSin the grand scheme of things. This decision is descriminating against people, based on their geography. If you happen to live in England, we will have no access. But in Scotland and Wales, we would. Healthcare should not be based on where you live, and it is sad to see that this might be the case.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
27	Web comment	Patient	When a medication is proven in research to prolong the life of those with a cancer, the best form of support NHS could give is to allow the medication. Wordy explanations as to why this is not the best course of action serve no good purpose to the sufferers.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
28	Web comment	Public	If something will help prolong the lives of young people then it should be made available to them	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond

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				to radioactive iodine.
29	Web comment	Public	It has come to my attention that one of the treatment options discussed here (Lenvatinib) has been approved in other regions of the UK. While I do not have a medical background, the proximity of Wales and Scotland to England suggest that the circumstances in all three regions are likely to be similar. As a result of this, the specific circumstances that led to a different recommendation in England require explanation.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
30	Web comment	Patient	I speak as a patient with non iodine avid follicular thyroid cancer which has metastasised to my sternum and lungs. I have this summer taken part in the SELIMETRY trial of Selumetinib - it wasn't successful in kicking my tumours back into iodine take up. Sorafenib and Lenvatinib are currently the only two drugs that could there for me when I reach a point that the tumours in my lungs have grown to the extent that my quality of life is seriously affected. I now have nothing as a safety net and am reeling from the shock of learning that my two chances of respite are going to be taken away from me. Kate at Butterfly Thyroid Cancer Trust hits nail on head: â€œit's time that NICE made some parameters for rare diseases instead of making all diseases the same.â€□ There might only about 200 people who could benefit from these two drugs, not thousands. It feels like we are being set up to fail as we canâ€™t meet the required amount of data from research trials as we simply don't have the patient numbers. Can you say why your decision for patents in England is different that that recently announced for Wales and Scotland?	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
31	Web comment	Public	It is imperative that these are available in England. Patients should not be forced to re-locate in order to survive this condition.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
32	Web comment	Public	The decision not to offer this drug in England discriminates against people with rare forms of cancer. It means that my wonderful friend will have to seriously consider moving to Wales or Scotland at a time when he will particularly need support from	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic,

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			established networks of friends around him. People like him would just be abandoned. Please approve the drugs for use in England as they have done in the rest of the UK.	differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
33	Web comment	Public	This is a disgrace. A rare cancer with treatment approved in both Wales and Scotland - hang your heads in shame. What happened to United Kingdom - rapidly becoming divided Kingdom with people living in England yet again losing out/becoming second class citizens.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
34	Web comment	Public	I believe that treatment should be available across the UK and no-one should have to consider relocating to access neccessary drugs.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
35	Web comment	Patient	If NICE are proposing to withdraw these drugs that to some are last resort treatments, what are they replacing them with? Supportive care sounds like a palliative approach - but with these drugs life is extended. As a thyroid cancer patient who is RAI resistant I have expected to try these drugs to blast my cancer. If I lived in Wales or Scotland I could still receive them but unless I relocate my options are limited. Having worked within the NHS and seen the waste of money on epic scales, I feel that life is not sacrosanct but a monetary figure. I would ask that a person centred approach be used not an accountancy programme. Please reconsider we have lives that need to be lived and that we are valued members of society.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
36	Web comment	Close family member of a person likely to need the treatment in future	The cost of this medication should be irrelevant due to the low number of people likely to be prescribed. If it is available in Scotland and Wales it should also be available in England. A close family member is likely to need this medication in future, he has always lived in England and should not feel it necesary to uproot himself to live in Scotland or Wales to receive treatment. His continuing care in hospitals in the London area has been excellent and he will definitely want to continue with that.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
37	Web comment	Public	To remove the only drugs available to help this small number of people seems grossly unfair. How can 2 other organisations approve the use and yet NICE fail to see sufficient benefit?	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.

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38	Web comment	Public	Please fund this drug, everybody deserves the right to survive cancer, regardless of where you live. Also because your cancer is a rare type it should not make your outcome less valuable.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.
39	Web comment	Carer	Please can you reconsider approving the use of Lenvatenib and Sorafenib for the treatment of advanced Thyroid cancer. My daughter had Thyroid cancer at age 16 years, she also has learning difficulties. We always live in the fear that her cancer could return. For all the people living with advanced cancer who need this treatment, please consider that they have hopes and dreams, families and lives to live. The treatment is available, please don't block its use because this cancer is rare. A rare cancer does not make it any less important than a well known cancer, that discrimination is unfair. Every life matters. Please don't take away the hope from those who desperately need this treatment.	Thank you for your comment. The FAD recommends both lenvatinib and sorafenib as treatment options for progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

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

Appendix to Response by Bayer

Date of response: 10th November 2017

Contains confidential information

AIC: Academic in confidence is marked in yellow

CIC: Commercial in confidence is marked in blue

Appendix to Company Response to ACD

The appendices presented provide further detail and evidence to support the key technical issues discussed in the main body of this response.

Appendix 1: Response to ACD by statement

Appendix 1: Response to ACD by statement

Page number	Response to statement in the ACD
3, 7	Both Assessment Group and Appraisal Committee agreed that it was inappropriate to compare results of the sorafenib and lenvatinib trials via an indirect comparison due to differences in the trials. However in multiple sections of the ACD comparative statements are made. These are based on naïve cross-trial comparisons and are not in keeping with the Committee's conclusions regarding trial comparability.
3	The ACD notes that "survival benefit with sorafenib is less convincing". The Assessment Group model estimates sorafenib to extend life by an average of 12.9 months versus BSC. Sorafenib is associated with an overall survival hazard ratio versus BSC of 0.77 (95% CI 0.58 to 1.02). This wide confidence interval is driven by the adjustment for treatment cross over and whilst this does cross 1 (1.02) there is equal downwards uncertainty associated with this adjustment (0.58). Extension of life to an average patient of over one year is clinically meaningful, and seldom seen with oncology treatments. On this basis the Committee's conclusion that survival benefit is less convincing does not reflect the evidence considered. This conclusion is reflected in 3.12 of the ACD where "the committee recognised it was likely that both treatments provided a substantial overall survival gain compared with best-supportive care"
9	Bayer welcomes the committee's conclusion that the decision to use lenvatinib or sorafenib is based on individual circumstances and careful consideration of risks and benefits. Differences in mechanism of action and safety profiles have been highlighted throughout the appraisal. Availability of both treatments would provide the most appropriate treatment for each patient and maximise patient outcomes for this small patient group.
11	The ACD states that the company (Bayer) commented that the "Assessment Group's approach (to extrapolation) lacked face validity and overestimated the treatment duration for sorafenib, while underestimating that for lenvatinib". There are outstanding issues with AG extrapolations (these are addressed in Section 1 of the response) and this also applies to the lenvatinib extrapolation of treatment duration. The time to treatment discontinuation curve for sorafenib is complete. The cited overestimation of treatment costs for sorafenib relate to both treatments allowing TKI treatment after progression. In DECISION sorafenib patients could continue treatment with sorafenib (this is costed for), in SELECT some lenvatinib patients switched to sorafenib (and other TKIs on progression) this is not costed for.
12	The ACD states that the Committee 'recognised that utility values from DECISION did not adequately capture the different side effects to treatment and the different response to treatment and this may have underestimated utility values for lenvatinib'

	There is no evidence to support the statement: • SAEs, grade >3 AEs and discontinuations were higher for lenvatinib in the SELECT trial than sorafenib in the DECISION trial; these would be expected to influence quality-of-life estimates. • Clinical advisors (ERG/AC representatives) disagreed on whether response to treatment was a meaningful health state in the model. Response rates are measured using different criteria in each trial (RECIST 1.0 and RECIST 1.1) and are not directly comparable.

Appendix 2: Technical Issues with AG methods

The method employed by the AG uses two time points, one which determines where the shape of the exponential survival curve changes and one to determine when to switch from using the KM curves to the extrapolation.

For the second time point the AG responses to Company's questions on the methodology states that the time point for switching from the KM curves to the exponential extrapolation is determined by "generally selecting the maximum limit for direct K-M data use to coincide as far as possible with an event time where the difference between the K-M value and the modelled estimate is minimized."

There are a number of inconsistencies between the AG report (and associated erratum document) and the values in the model for the time for switching between the KM curves and the extrapolation.

a) Time cut for using KM:

PFS

- In the report it states KM values used until 16.5 months (BSC) and 25 months (sorafenib)
- In the model the KM values are used until 14.7 months (BSC) and 27.8 months (sorafenib)

OS

- In the erratum to the report it states KM values used until 6.4 months (BSC) and 11.96 months (sorafenib)
- In the model the KM values used until 25.4 months (BSC) and 31.8 months (sorafenib)

Therefore, for almost all outcomes and arms of the trial the KM curves are used for longer than reported by the AG. In the response to company's questions on the methodology the AG state that the KM curve is used "until the K-M data are no longer available, or are too unstable (due to small numbers of patients at risk and/or events), when parametric functions can be applied for extrapolation". Most notably for OS the KM curves are used for much longer than stated, into times where the number of patients at risks are low and therefore unstable. In the updated model scenarios the reported time point is used, not that used in the AG model.

b) Lenvatinib time to treatment duration

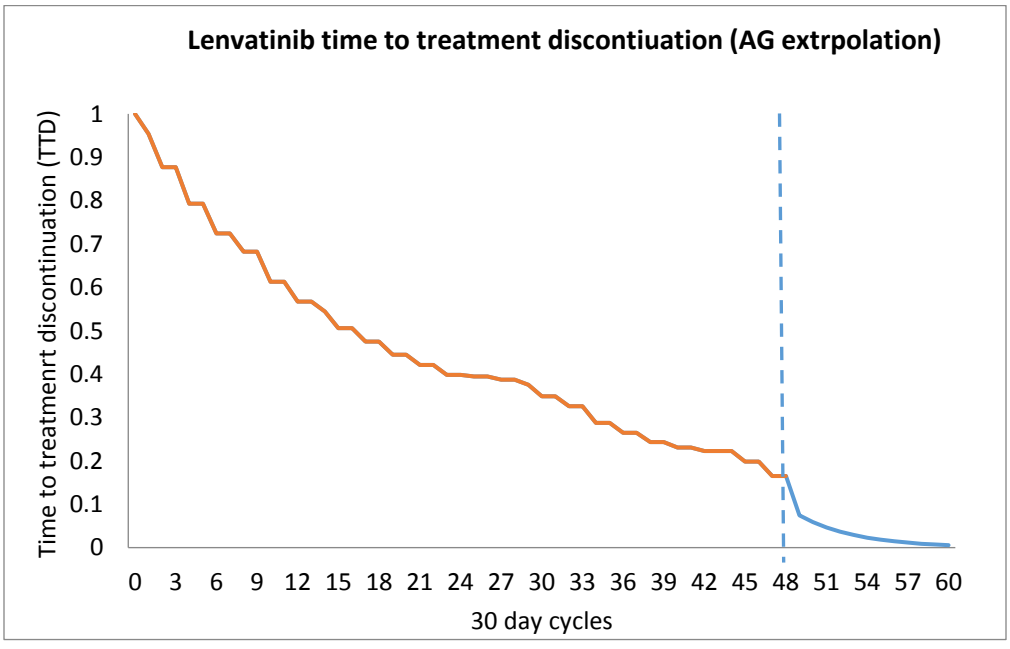
The Assessment Group report stated that the 'SELECT trial data are virtually complete for the cycles of lenvatinib dispensed during the trial' (11). In the model data up to cycle 48 is marked 'academic in confidence' indicating data is this is taken from the trial, with data following extrapolated.

In the cycle following the extrapolation we see a large decline that is not in keeping with the trends before or after the exploration point (Table 1). In keeping with the sorafenib PFS extrapolation there is no clinical rational for this sudden decline and the result is an underestimation of time to event outcomes. This is presented graphically in Figure 1.

Table 1: Assessment Group extrapolation of time to event data

Cycle no.	Percentage on treatment
44	[redacted]
45	[redacted]
46	[redacted]
47	[redacted]
48	[redacted]
49	7.45%
50	5.89%
51	4.66%

Figure 1: Lenvatinib time to treatment extrapolation: Assessment Group extrapolation



c) Correction to AG calculation

The Company attempted to replicate the analysis reported by the AG in initial report and the erratum.

These issues and inconsistencies not only make it difficult for a stakeholder to replicate the analysis but also reduce confidence in the methodology and reporting of the implementation. For this reason the company refitted the piecewise exponential for OS and used the single exponential for PFS.

Following the description of the methodology provided by the AG, a piecewise exponential distribution was fitted to the OS empirical data. The time cuts were taken directly from the AG report that identified approximately where the OS hazard changed. The two parameters (hazards) for the piecewise exponential distribution were estimated using likelihood maximization (parameters shown in Table 2).

Table 2: Re-estimated parameters for piecewise exponential distribution

	OS	**OS**
Treatment	sorafenib	BSC
Time cut (months)	11.2	6.4
Time cut (cycles)	12.175	6.957143
Hazard #1	0.009918	0.008649
Hazard #2	0.016315	0.023522
Start value	0.894863	0.946151

Observed versus predicted survival (Figure 2) and cumulative hazard curves (Figure 3) were generated to visually assess the goodness of fit. These show that the piecewise exponential refitted by the company give a good fit to the observed data.

Figure 2: Observed versus predicted OS using refitted piecewise exponential curves

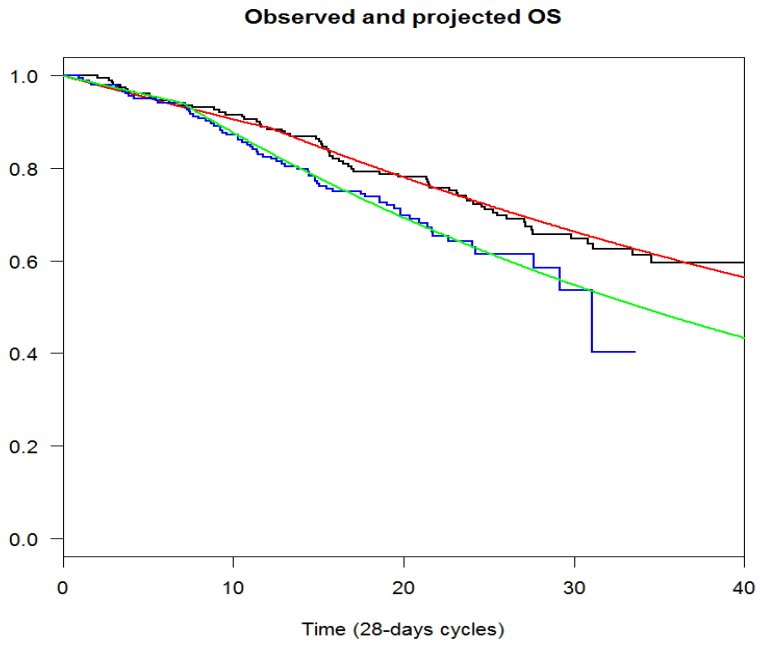
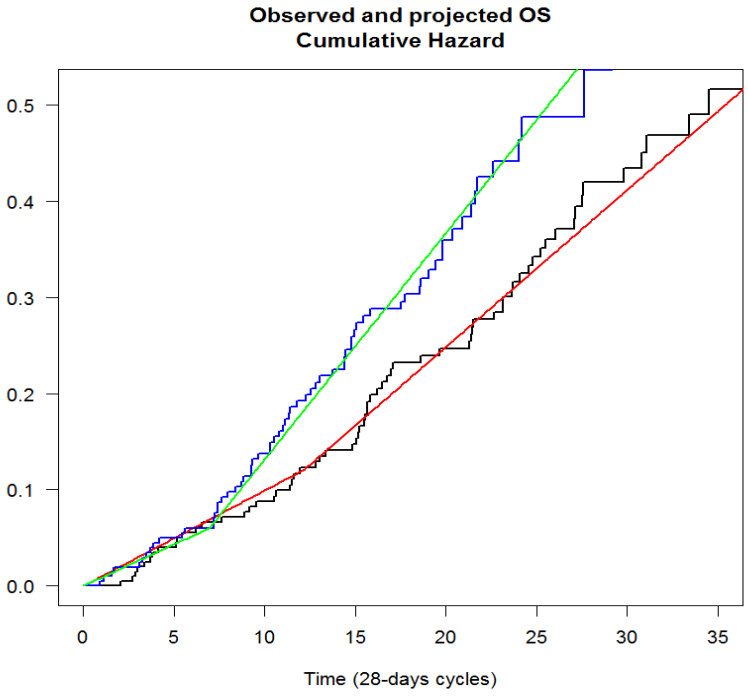


Figure 3: Cumulative hazard plot for refitted piecewise exponential curves



Fitting of single parametric models

The AG states that single parametric distributions do not fit well to the data but do not provide any evidence to support this statement. Bayer presented extensive information on single parametric

extrapolations fitted to DECISION trial data in the original submission. This information demonstrates that good fits to the trial data are possible with single parametric distributions. Please see original appendix for details.

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 10 November 2017 through NICE Docs.

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.	[**N/A**]
Name of commentator person completing form:	[redacted]

Comment number	Comments
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.	
Eisai do not agree that the summary of the cost effectiveness evidence is a reasonable interpretation of the evidence for the reasons cited below:	
1	**The assessment group's model does not include the correct mean dose of lenvatinib (16.3mg), which was provided in the company response to the AG report, as below:** Eisai have identified an error in the average dose reported in the company submission and as a result in the AG report. The average dose 17.4mg is from the first datacut (November 2013). The updated correct average dose for the August 2015 datacut is 16.3mg. The revised ICER using the list price is: **£59,247.**
2	**Eisai do not agree with the methodology of calculating adverse event costs in the assessment group model as it is not reflective of UK clinical practice.** As stated by the clinical expert at the committee meeting, it is not reasonable to assume that the adverse event costs would continue for the entire length of treatment duration. Eisai have submitted additional evidence on the duration of adverse events from the SELECT trial. Further detail is provided in Appendix 1.

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3	**Eisai do not agree with the resource use data used in the assessment group model as it is not reflective of UK clinical practice.** Eisai do not agree with the data used by the AG to estimate resource use in the model as it is not consistent with clinical advice received by 4 UK clinical experts experienced in treating RAI-refractory DTC. Eisai have submitted additional evidence on resource use data. Further detail is provided in Appendix 1.
4	Correction of an error in the AG formula for AEs which meant off-treatment AE costs were not being discounted results in an ICER for lenvatinib vs BSC of **£62,736** at list price.
Eisai agree that there are some health-related benefits from response to treatment that are not captured in the preferred analyses, which would reduce the ICER and have provided some additional information/clarification below:	
5	**Eisai would like to clarify the implementation of the response state within the Eisai submitted electronic model.** The ACD states: "The committee also understood that Eisai's model did not incorporate the duration of response appropriately and therefore questioned the validity of the model." To clarify, response is included within the model as a separate partition. Where oncology models commonly include states for pre- and post-progression, and death, our model effectively includes pre-progression responder, pre-progression non-response, post-progression, and death. In order to inform membership of the pre-progression response state, patient-level data from SELECT were analysed and for each visit (corresponding to cycles in the economic model) the proportion of subjects who were considered responders were calculated. These proportions are then used directly in the model for lenvatinib and BSC. Thus, loss of response (and therefore duration of response) are reflected in the lower proportions seen within the pre-progression responder state over time. Duration of response is therefore contained implicitly within this data and the analysis.
End of life criteria Eisai appreciate that the committee indicated that it could show flexibility around the end-of-life-criteria and it could accept a longer life expectancy of more than 24 months because of the substantial survival benefit shown by lenvatinib, but needed further information on overall survival to do so. Further detail is provided in Appendix 1.	
Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS. At the committee meeting, the patient expert explained that patients with radioiodine refractory differentiated thyroid cancer experience debilitating symptoms such as pain and fatigue and this can impact severely on their quality of life. This is a small group of patients and the clinical expert highlighted that the only alternative is best supportive which has minimal impact on the underlying disease. As highlighted in the ACD, there is therefore a need for active treatment options for disease that does not respond to radioactive iodine. Lenvatinib has been licensed in this group of patients for more than two years, since June 2015, but has yet to be made available routinely to English patients on the NHS. It was approved by the EMA on the basis of its outstanding results in progression free survival and tumour shrinkage, including complete response in a few patients in the Phase III SELECT study.	

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Lenvatinib was approved for use on the NHS in Scotland more than a year ago in September 2016 and 11 patients have been treated to date. In Wales, AMWSG have approved its use (based on the same cost effectiveness model as submitted to NICE) very recently on the 18th October. Currently, 50 patients in England have restricted access to lenvatinib through a compassionate access program. The AG model has been updated to include the changes highlighted above and is included separately as part of this response. At list price, the combined additional changes presented above result in a revised company base case ICER of **£48,607**. Further detail is provided in Appendix 1. When the revised confidential discount is applied, the ICER for lenvatinib versus BSC is well within the required cost effectiveness threshold and Eisai urges NICE to approve lenvatinib without further delay to address the inequality in access for UK patients.

Insert extra rows as needed

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Consultation on the appraisal consultation document – deadline for comments 5pm on 10 November 2017 through NICE Docs.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCR-RCR
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
	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.
1	We note the appraisal committee recognises that: 1. lenvatinib and sorafenib are the only treatment options for progressive, locally advanced or metastatic differentiated thyroid cancer after surgery and radioactive iodine. 2. both lenvatinib and sorafenib are effective in delaying disease progression 3. following adjustment for cross-over in the trials, lenvatinib prolongs survival In view of these findings we strongly urge the committee to reconsider their initial decision not to recommend either lenvatinib or sorafenib for treatment of this population of patients with advanced thyroid cancer. This would create an inequality in access to these drugs for patients in England in contrast to those in Scotland, Wales, other countries in Europe and around the world. Patients in England will have best supportive care only with no disease modifying treatment options.

Insert extra rows as needed

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Please can you reconsider approving the use of Lenvatenib and Sorafenib for the treatment of advanced Thyroid cancer. My daughter had Thyroid cancer at age 16 years, she also has learning difficulties. We always live in the fear that her cancer could return. For all the people living with advanced cancer who need this treatment, please consider that they have hopes and dreams, families and lives to live. The treatment is available, please don't block its use because this cancer is rare. A rare cancer does not make it any less important than a well known cancer, that discrimination is unfair. Every life matters. Please don't take away the hope from those who desperately need this treatment.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am writing to you to vent my frustration, I have just been informed that NICE have not approved these drugs for use on patients with advanced thyroid cancer. I myself have advanced non avid thyroid cancer and these drugs where my only hope at living a long life. I feel it is so wrong that all money is thrown at the breast cancer, colon, Prostrate cancer etc. Because thyroid cancer is rare and normally highly treatable we are forgotten about. Yes the majority of thyroid cancer case are highly treatable/ curable.

	But recent statistics show that this is no longer the case in many patients. The only treatment that has been available for thyroid cancer patients for decades is RAI. Like myself many patients are classed as refractory (Non Avid) and drugs like sorefanib and lenvatinib are our only life long for slowing the progression of the cancer. I feel that you making this decision you are putting all thyroid cancer patients who need these drugs on the scrap heap, with no alternative treatments you are basically handing us a death sentence needlessly. You are discriminating against patients with thyroid cancer just because you haven't made the neccessary arrangements for rare cancers to be included.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a thyroid cancer patient, I am absolutely shocked and extremely disappointed to hear the news that you have decided not to approve Sorafenib or Lenvatenib for patients with thyroid cancer, furthermore that are recommending against access via the CDF. Both Wales and Scotland have approved this and it is truly disgraceful that NICE have gone against recommendations from professionals. For patients with advanced thyroid cancer, this will have a devastating effect on their lives. I urge the panel to reconsider and overturn this decision. *[In disclosure section]* Yes, I have thyroid cancer and understand it's devastating effects for patients unable to have this medication.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	

Section 1 (Appraisal Committee's preliminary recommendations)	As a patient currently living with thyroid cancer I am radio active insensitive, I am 35 years old with two young children dependant on me. Any chance you can give to people Ike me or any other patients with this cancer to successfully treat it would be a dream come true. To have the power to give just one person hope, hope not to die hope to see their kids grow up. Take this power and use it to allow thyroid cancer patients to have access to this drug. Scotland and Wales have access to it, so why can't we. Please give us a chance. Praying for approval for this drug.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	A frustrating outcome on the decision from a patient point of view regarding the decision on Lenvatinib. currently i am taking Lenvatinib, which has created stability in my disease, Differentiated Follicular Tyroid cancer. Overall i would describe the report interesting & full of controdictions. On one hand you clearly state Lenvatinib is effective & delays progressions (which I am experiencing) on the other hand the drug is marginally higher in cost than you would like to be beneficial enough to life.

Name	[redacted]
Role	Carer
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Health care and access to drugs should not depend on your location within Great Britain We have nationalised health care and should be entitled to receive appropriate treatment regardless of postcode. This treatment has been accepted as beneficial in Wales and Scotland, and must therefore be made available to those living in England too. To make the decision to shorten someone's life because of where they live is amoral.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	lenvatinib can be acquired for a discount (which is not disclosed as it is commercially sensitive). This drug is available in Scotland and soon to be in Wales. Why does living in England make it too expensive? Further more, if Thyroid cancer is rare. Why would it not be available? *[In disclosure section]* Lenvatinib is proven to help these cancers. It is available in Scotland and soon to be Wales. It can also be acquired under an undisclosed discount making it much more affordable. Why then does England believe it's not affordable?

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Please reconsider the decision re. availability of Sorafenib and Lenvatenib for thyroid cancer patients. People's lives are the most precious thing on this earth, not money. Thank you.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's	There is evidence that the drugs work to prolong life, as such they are being used to treat thyroid cancer in other contries. It seems the value of life is less in this country. I can only conclude from this decision that a) people with rare cancer are

preliminary recommendations)	being deacriminated against, and b) thyroid cancer affects more women than men and this decision therefore seemingly discriminates against women. I urge the committee to reconsider their decision. The treatment works. If this treatment is not approved there will be people in this country suffering the psychological effects of knowing there is a drug available that prolongs life, but because they have been born in this country they will not be treated. Have the psychological effects of this been considered in the cost benefit analysis?

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It seems strange that NICE reaches different conclusions from two of the UK's devolved regions, compounding the lack of consistency in treatment across the UK. I would urge you to reconsider. *[In disclosure section]* A close relative living in England suffers from this condition and will be denied treatment to which I, also living in the UK, would be entitled were I similarly afflicted.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This is grossly unfair, perhaps we shall have to move to Scotland or Wales to get the treatment which will help us. Not everyone has a private income to be able to afford the drugs which will help. Please think again. *[In disclosure section]* No, apart from having worked in the NHS all my life I am appalled at the way it is being dragged down and mishandled.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I just wanted to reach out and express my disappointment at this decision. Reading that the lives of thyroid cancer patients are worth less than these drugs cost is very upsetting. At the moment, my thyroid cancer metasteses are taking up iodine. However there may come a time when they become non avid. To see that this drug, that could extend my life and make it better, would be denied to me because of where I live and because money is worth more than my life - is unconscionable. Thyroid cancer is a rare cancer, and within that group, for people to be non avid is even more rare. So the cost of accepting these drugs would not be that great to the NHSin the grand scheme of things. This decision is descriminating against people, based on their geography. If you happen to live in England, we will have no access. But in Scotland and Wales, we would. Healthcare should not be based on where you live, and it is sad to see that this might be the case.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	When a medication is proven in research to prolong the life of those with a cancer, the best form of support NHS could give is to allow the medication. Wordy explanations as to why this is not the best course of action serve no good purpose to the sufferers.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD:	

Section 1 (Appraisal Committee's preliminary recommendations)	If something will help prolong the lives of young people then it should be made available to them

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It has come to my attention that one of the treatment options discussed here (Lenvatinib) has been approved in other regions of the UK. While I do not have a medical background, the proximity of Wales and Scotland to England suggest that the circumstances in all three regions are likely to be similar. As a result of this, the specific circumstances that led to a different recommendation in England require explanation.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I speak as a patient with non iodine avid follicular thyroid cancer which has metastasised to my sternum and lungs. I have this summer taken part in the SELIMETRY trial of Selumetinib - it wasn't successful in kicking my tumours back into iodine take up. Sorafenib and Lenvatinib are currently the only two drugs that could there for me when I reach a point that the tumours in my lungs have grown to the extent that my quality of life is seriously affected. I now have nothing as a safety net and am reeling from the shock of learning that my two chances of respite are going to be taken away from me. Kate at Butterfly Thyroid Cancer Trust hits nail on head: “it's time that NICE made some parameters for rare diseases instead of making all diseases the same.”

	There might only about 200 people who could benefit from these two drugs, not thousands. It feels like we are being set up to fail as we can't meet the required amount of data from research trials as we simply don't have the patient numbers. Can you say why your decision for patents in England is different that that recently announced for Wales and Scotland?

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is imperative that these are available in England. Patients should not be forced to re-locate in order to survive this condition.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The decision not to offer this drug in England discriminates against people with rare forms of cancer. It means that my wonderful friend will have to seriously consider moving to Wales or Scotland at a time when he will particularly need support from established networks of friends around him. People like him would just be abandoned. Please approve the drugs for use in England as they have done in the rest of the UK.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	

Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This is a disgrace. A rare cancer with treatment approved in both Wales and Scotland - hang your heads in shame. What happened to United Kingdom - rapidly becoming divided Kingdom with people living in England yet again losing out/becoming second class citizens. *[In disclosure section]* Nothing relevant other than having loved ones affected by your disgraceful decision

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I believe that treatment should be available across the UK and no-one should have to consider relocating to access neccessary drugs.

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	If NICE are proposing to withdraw these drugs that to some are last resort treatments, what are they replacing them with? Supportive care sounds like a palliative approach - but with these drugs life is extended. As a thyroid cancer patient who is RAI resistant I have expected to try these drugs to blast my cancer. If I lived in Wales or Scotland I could still receive them but unless I relocate my options are limited. Having worked within the NHS and seen the waste of money on epic scales, I feel that life is not sacrosanct but a monetary figure. I would ask that a person centred approach be used not an accountancy programme. Please reconsider we have lives that need to be lived and that we are valued members of society.

Name	[redacted]
Role	Close family member of a person likely to need the treatment in future
Other role	
Organisation	
Location	Scotland
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The cost of this medication should be irrelevant due to the low number of people likely to be prescribed. If it is available in Scotland and Wales it should also be available in England. A close family member is likely to need this medication in future, he has always lived in England and should not feel it necesary to uproot himself to live in Scotland or Wales to receive treatment. His continuing care in hospitals in the London area has been excellent and he will definitely want to continue with that.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	To remove the only drugs available to help this small number of people seems grossly unfair. How can 2 other organisations approve the use and yet NICE fail to see sufficient benefit?

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Please fund this drug, everybody deserves the right to survive cancer, regardless of where you live. Also because your cancer is a rare type it should not make your outcome less valuable.

Name	[redacted]
Role	Public
Other role	
Organisation	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	This treatment should be made available for anyone who has this disease throughout the UK. A rare condition is just that so take-up figures would be low but it would save lives.

Name	[redacted]
Role	NHS Professional
Other role	
Organisation	Thyroid Cancer sub group of NCRI Head and Neck clinical studies group
Location	England
Conflict	Disclosure: I have been on Speakers Bureau and Advisory boards for both Eisai and Bayer
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	We note that the appraisal committee recognises that: 1. lenvatinib and sorafenib are the only treatment options for progressive, locally advanced or metastatic differentiated thyroid cancer after surgery and radioactive iodine. 2. Both lenvatinib and sorafenib are effective in delaying disease progression 3. Following adjustment for cross-over in the trials, lenvatinib prolongs survival In view of these findings we strongly urge the committee to reconsider the initial decision not to recommend either lenvatinib or sorafenib for treatment of this population of patients with advanced thyroid cancer. This would create an inequality in access to these drugs for patients in England in contrast to those in Scotland, Wales, other countries in Europe and around the world. Patients in England will have best supportive care only with no disease modifying treatment options.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

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

Response by Bayer

Date of response: 10th November 2017

Contains confidential information

AIC: Academic in confidence is marked in yellow

CIC: Commercial in confidence is marked in blue

Executive summary

Bayer's response to the ACD focuses on two critical areas of uncertainty highlighted by the Appraisal Committee:

1. **Inappropriate implementation of survival modelling underestimates clinical benefit in the AG model**

- A number of technical issues identified with the implementation of survival curves in the AG model underestimate the clinical benefit of sorafenib. Correcting for these, whilst retaining the AG's preferred methods results in an ICER of £[redacted]/QALY, a reduction of [redacted]%.

- With regard to the use of a single parametric or piecewise extrapolation, the Committee acknowledged in the ACD there was 'no sufficient justification to favour one approach (Bayer/AG) over the other'. The Company therefore compared extrapolations to published estimates and the assessment of 7 UK clinical experts. Results suggest the single exponential approach (£[redacted]/QALY) offers greater clinically plausibility than the approach currently employed and fall in a close range despite differing approaches.

- The company challenge inconsistencies in the incorporation of post-progression TKI treatment in the AG model. These inconsistencies relate to differences in how this assumption is applied across treatments (sorafenib and lenvatinib) and its relevance to UK clinical practice. Aligning this assumption with that currently used for lenvatinib results in ICERs of £[redacted]/QALY for the single exponential extrapolation and £[redacted]/QALY for the corrected AG model.

2. **End-of-life criteria: Symptomatic patients have a life expectancy of less than 24 months**

- The ACD states in the UK 'best supportive care is offered until disease starts to progress and symptoms occur'. A new analysis is therefore presented showing that survival for symptomatic patients in the BSC arm of the DECISON trial was less than 24 months (15.75 months (median) and 22.05 months (mean). This is in line with the estimate of the NICE clinical expert, who reported that in the UK 'at least 50% of patients will not live longer than 2 years'

- Sorafenib was the first licensed therapy and resulted in a step-wise change in treatment. Innovation has not been considered to date in this appraisal. RAI-R DTC is a terminal condition with currently no available active treatment options. The value to patients of receiving active treatment as opposed to palliative care is an additional uncaptured benefit.

- In the ACD the NICE clinical expert reported 'at least 50% of patients will not live longer than 2 years' an estimate in keeping with the end-of-life criteria. The company present a pragmatic analysis considering a potential trade-off in survival benefit and life expectancy showing that treatment commencing at a life expectancy of 24 months would deliver survival gains far exceeding 3 months, meeting the end-of-life criteria.

- Evidence is available to suggest sorafenib can be considered an end-of-life treatment:
    - Small treated patient population: 50-60 per year (CDF notifications)
    - Large survival benefit: 13 months versus BSC (4 x criteria requirement)
    - Life expectancy of symptomatic patients: 22.05 months (mean) or 15.75 months (median)

3. **Conclusion: Under all scenarios ICERs fall in a tight range around £30,000/QALY**

- Evidence presented focuses around two key uncertainties highlighted by the Appraisal Committee
- Both treatments should be considered under the end-of-life criteria
- Keeping all the Appraisal Committee's preferred assumptions, and varying for only uncertainties discussed in this response results in a range of ICERs from £[redacted]- £[redacted] per QALY. ICERs show cost-effectiveness across a very tight range, and across all discussed assumptions indicating low uncertainty, with scenarios reflecting UK clinical practice resulting in ICERs less than £30,000/QALY

Area of uncertainty 1: Uncertainty in the implementation of survival modelling and treatment assumptions in the Assessment Group model

1. The implementation of the survival curves by the Assessment Group requires revision

Survival curves presented in the AG Report Erratum and those incorporated in the AG model (Figure 1) require revision to address the following issues:

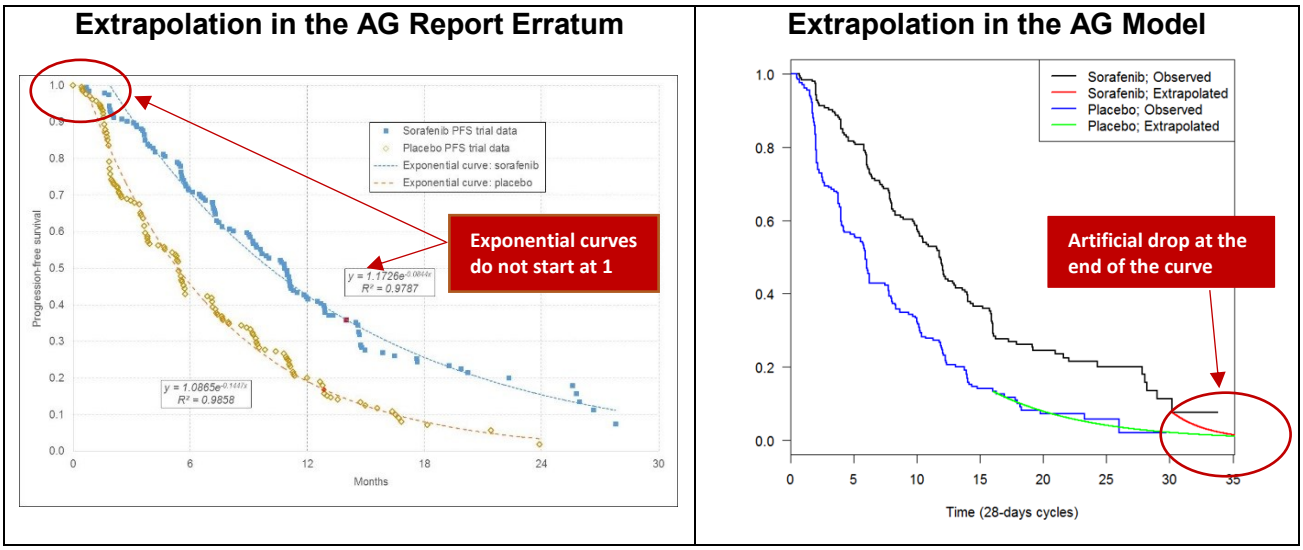
1. Fitted PFS curves in the AG Report Erratum show that the probability of being survival free at the initial time point is 1.17 for those treated with sorafenib and 1.08 with best-supportive care (Figure 1). While the model does not use the fitted curve for the initial time period, only the Kaplan-Meier estimates, this suggest the AG's extrapolation fitted (independently of the time point) lacks face validity.

2. The survival curves presented in the erratum by the AG for the sorafenib vs. BSC comparison do not match the curves incorporated in the AG model (Figure 2). On this basis it is unclear if the correct PFS curve was implemented in the AG model.

3. Survival curves in the AG model lack face validity with an artificial drop in the extrapolated portion of the curve due to extrapolation from the tail of the KM which is unlikely to reflect clinical practice (Figure 1). In some cases this underestimates long term survival outcomes not only compared to observed data from the DECISION trial, but also compared to clinical experts' estimates and published data (Table 1).

These points demonstrate that the implementation of survival curves by the AG require revision. The company has therefore revised the analysis implemented by the AG. These issues are explored further in Section 1a.

Figure 1: Comparison of extrapolations shown in AG Report Erratum and in AG Model



a) Technical issues with the implementation of survival models

The Assessment Group appears to have followed an unorthodox approach of extrapolating survival curves by attaching the exponential distribution to the last Kaplan-Meier estimate (Figure 1 and Figure 3). Due to the few patients at risk in the tails of Kaplan-Meier curves, this is a highly uncertain approach (1, 2). In these cases where there is a sharp decrease in the Kaplan-Meier curve at the last estimate this approach underestimates the long-term outcomes.

In extrapolating sorafenib PFS, the single exponential distribution submitted by Bayer follows the Kaplan-Meier curve initially used in the AG model. However in the AG model the curve switches to the extrapolated portion at the end of the KM with a drop in the curve at the extrapolation point resulting in a rapid decline underestimating PFS. This is unlikely to be representative of what is seen in clinical practice. A further example of this can be seen with the extrapolation of overall survival and lenvatinib treatment duration (Appendix 2).

Following a previous request for clarification from the Company, details of the extrapolation approach were provided in the AG erratum. However PFS curves presented in this erratum do not appear to correspond to those in the model. In Figure 2 the parameters for the curves reported in the erratum (Figure 1) are replotted against the curve used in the model. This demonstrates that the values in the model deviate from those reported and demonstrate the artificial drop in the curve after the switch from the KM curve to the exponential. The time cuts used in the model also vary those reported in the erratum (Appendix 2). The Company corrects for above technical issues, whilst keeping AG's preferred method and assumptions in the following section (1b).

Figure 2: Comparison of the exponential reported in the erratum and the curve actually used in the model for sorafenib PFS

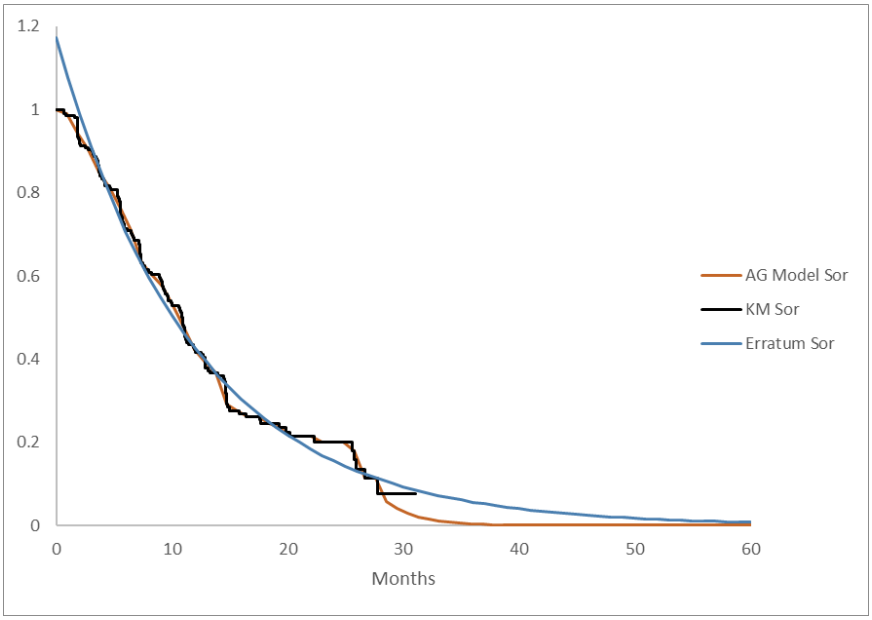
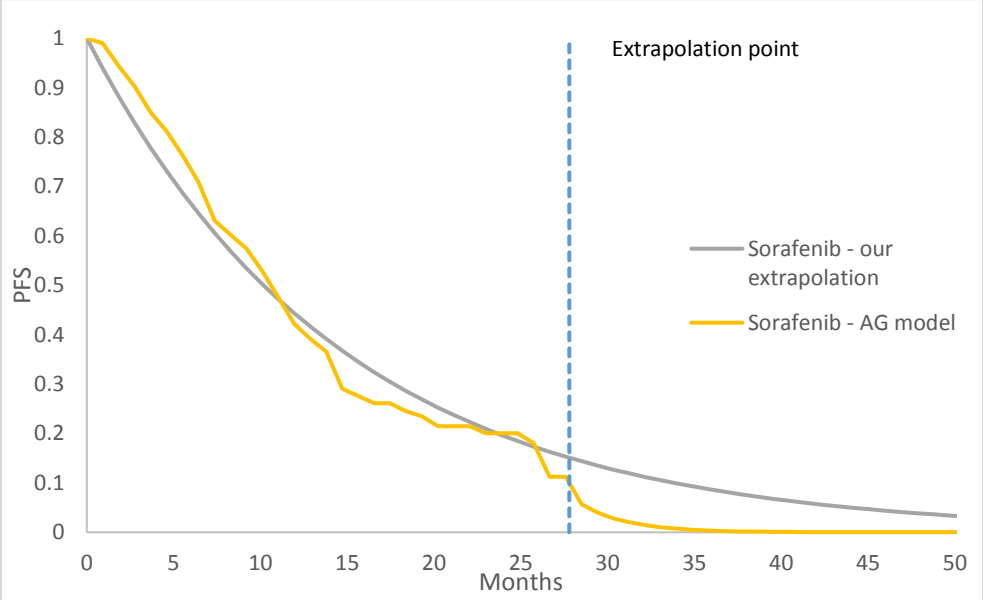


Figure 3: Comparison of AG model and Bayer extrapolation for sorafenib PFS (the AG curve corresponds to the Kaplan-Meier curve up to the extrapolation point)



b) Correction to AG implementation of survival models

The Company has revised the AG extrapolation in the model by using the Kaplan-Meier estimates until the time point preferred by the AG, and has fitted the piecewise exponential curves as preferred by the AG using the same split time reported in the AG Erratum for overall survival, and a single exponential for PFS. These curves were implemented in the latest version of the AG Corrected Model[1]. The resulting revised curves fit the observed data (DECISION trial) and the long-term survival estimates (clinical experts assessment (n=7) and published data) better and do not have face validity issues (probability of the extrapolated curves exceeding 1, sharp unexplained drop) (Table 1). (Please see Appendix 1 for further information on the revised curves).

With revision of the extrapolations using the method and time points (split time) reported by the AG, the ICER is reduced substantially, showing that health benefits with sorafenib were underestimated. Using the sorafenib CMU price, the revised fits resulted in an ICER of £[redacted]/QALY compared to the AG estimate of [redacted], a reduction of [redacted]%.

[1] (ID1059 thyroid cancer AG model final corrected 181017AS [AIC].xlsm

c) Single vs. piecewise extrapolation: There are different, similarly plausible extrapolation methods resulting in a range of ICERs for the sorafenib vs. BSC comparison

The company agrees with the Committee's assessment, that there is a degree of uncertainty in the approach for extrapolating outcomes in terms of fitting a piecewise or conventional single parametric exponential distribution. The ACD concluded there is "no sufficient justification to favour one approach over the other"(3).

The Company incorporated in the original submission and economic model, all commonly used parametric curves and assessed their fit to the trial data as per the DSU Technical Support Document (4). This is a pre-specified process using statistical criteria, visual comparison of observed and fitted curves, and clinical plausibility.

In accordance with the DSU guidance, "it is of even greater importance to justify the plausibility of the extrapolated portion of the survival model chosen, as this is likely to have a very large influence on the estimated mean survival. This is difficult, but may be achieved using external data sources, biological plausibility, or clinical expert opinion" (4). As the SEER database population used by the AG differs from the trial populations, e.g. is not restricted to iodine refractory patients, the Company used published survival information and UK clinical expert opinion through a clinician survey (n=7) for the original submission (Company Submission Appendices 7.10) to assess biological plausibility[3].

While all approaches resulted in similar survival at five years, according to published data for this population and clinical experts' estimates, the approach implemented in the AG model underestimates the long-term survival of this patient population (Table 1).

With no strong justification for choosing between methods, and the single exponential approaches fitting the ranges provided by UK clinical experts slightly better, further consideration of these fits are required. These methods are all plausible and the results should be looked at not as a single ICER, but a range of plausible ICERs. Results suggest the single exponential approach undertaken by the Company (£[redacted]/QALY), offers greater clinically plausibility than the approach currently employed. Despite the differences in approaches employed both methods offer very close estimates.

Table 1: Biological plausibility of the long-term survival estimates using the single exponential distribution and the piecewise fit implemented by the AG

	Survival according to:				
Survival	**Clinical Experts (n=7)**	**Published Studies (5, 6)**	**Bayer Single Exponential distribution**	**AG's Piecewise Exponential distribution**	**Corrected Piecewise distribution (according to AG specification)**
5 year	20-30%	-	30%	28%	24%
10 year	10-15%	10 and 12%	9.5%	5%	5%
15 year	5-10%	-	3%	1%	1%

d) Treatment assumptions in the AG model are inconsistent across treatments and with UK clinical practice

There are also inconsistencies around the implementation of treatment discontinuation. Three different scenarios can be implemented in the model:

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

The last scenario as implemented in the AG model is inconsistent with both the trials and UK clinical practice, and is not considered plausible. In both SELECT and DECISION a proportion of patients continue TKI treatment after progression. Whilst in DECISION this reflects continued treatment with sorafenib, in SELECT a trial rule stipulates this cannot be the study drug (lenvatinib). As a result TKI use following progression is with other TKIs such as sorafenib and is not costed, though clinical benefit is likely to be comparable. Aligning this assumption with that currently used for lenvatinib, results in close estimates of cost-effectiveness of £[redacted]/QALY for the single exponential extrapolation and [redacted]/QALY for the corrected AG model.

In terms of UK clinical practice, the license for sorafenib recommends that “treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs”(7). This is consistent with clinical practice, where sorafenib use stops after progression. It is also in line with the finding of a recent study, which shows only a negligible proportion of patients receive sorafenib in subsequent lines of treatment (4.5%) in the EU5 (8). This approach provides alignment between both treatments, and UK clinical practice. Cost-effectiveness results including this scenario are presented in the table of plausible ICERs (Table 2).

Updated cost-effectiveness results

The ICER can be assumed to be between the worst-case scenario, i.e. the revised implementation of the piecewise fit of the AG model assuming patients continue TKI treatment past progression, and the best case plausible scenario, the use of single exponential distribution (also considered plausible by the Committee) with patients discontinuing sorafenib treatment latest at progression according to clinical practice. This results in an ICER between a tight range of £[redacted]/QALY and £[redacted]/QALY, which is around the upper end of the range normally considered cost-effective for non-end-of-life treatments.

Results in Table 2 use all the Appraisal Committees preferred assumptions, varying for only areas of uncertainty highlighted by the Committee and discussed in this response:

1) **Extrapolation of OS:**
    - Scenario 1: Piecewise
    - Scenario 2 and 3: Single parametric curves

2) **DECISION trial data:**
    - Scenario 1 and 2: Direct use of observed Kaplan-Meier estimates until the time point from AG report (not AG model)
    - Scenario 3: Fitted parametric curves throughout the time horizon

3) **Time on treatment:**
    - UK clinical practice (maximum until progression)
    - Total clinical trial cost (some patients allowed to continue TKI treatment after progression)

Varying these areas of uncertainty results in the following scenarios:

Scenario 1	PFS: KM curve until time reported by AG followed by corrected implementation of single exponential OS: KM curve until time reported by AG followed by refitted piecewise
Scenario 2	PFS: KM curve until time reported by AG followed by corrected implementation of single exponential OS: KM curve until time reported by AG followed by RPSFT adjusted separately fitted single exponential
Scenario 3	PFS: Single exponential OS: RPSFT adjusted separately fitted single exponential

Table 2: Results using the sorafenib price with the CMU discount

	Approach to extrapolating PFS	Approach to extrapolating OS	Approach to extrapolating treatment duration	Incremental costs	Incremental QALYs	ICER
Incorrect scenario	**Extrapolation:** Incorrect Implementation (**AG scenario**)	**Extrapolation:** Incorrect Piecewise (**AG scenario)**	TTD only	[redacted]	0.528	[redacted]
Scenario 1: Revised AG scenario	**Extrapolation:** KM curve then single fitted exponential curve	**Extrapolation:** KM curve then revised piecewise exponential curve (AG scenario)	TTD only	[redacted]	**0.736**	[redacted]
			TTD or PFS	[redacted]	**0.736**	[redacted]
Scenario 2: Mixture of Revised AG and Single exponentials	**Extrapolation:** KM curve then single fitted exponential curve	**Extrapolation:** KM curve then single fitted exponential curve	TTD only	[redacted]	**0.715**	[redacted]
			TTD or PFS	[redacted]	**0.715**	[redacted]
Scenario 3: Single exponentials (best long-term fit as per clinical experts' estimates)	**Extrapolation:** Single fitted exponential curve	**Extrapolation:** Single fitted exponential curve	TTD only	[redacted]	**0.705**	[redacted]
			TTD or PFS	[redacted]	**0.705**	[redacted]

KM: Kaplan-Meier, TTD: time to treatment discontinuation, PFS: progression-free survival, AG: Assessment Group

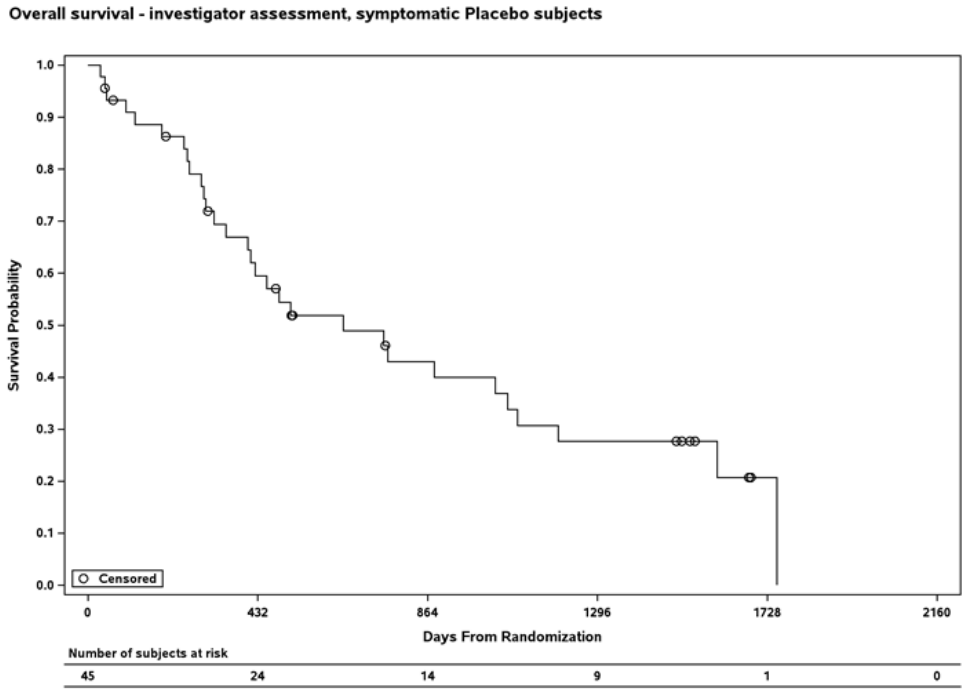
Area of uncertainty 2: End-of-life criteria

a) Life expectancy for symptomatic patients is less than 24 months

The ACD stated that in UK clinical practice *'best supportive care is offered until disease starts to progress and symptoms occur'*. In the DECISON trial a sub-group of patients were identified who were symptomatic at the commencement of therapy.

Following a request from the committee for additional evidence on the life expectancy of the treated population, estimates were calculated for this subgroup of symptomatic and progressive BSC patients. Median and mean overall survival for this population was 15.72 months and 22.05 months respectively. This aligns closely with estimates provided by the NICE clinical expert in the previous meeting that *'at least 50% of patients will not live longer than 2 years*'. These estimates have not been adjusted for treatment crossover, which would lower both mean and median life expectancy estimates.

Figure 4: Overall survival progressive and symptomatic patients in the DECISION trial (BSC)



In line with recent NICE appraisals (9) it is the median that sets the expectation of the average patient's survival and hence their valuation of life years whilst they are gained. Whilst median overall survival for patients treated with best-supportive care (adjusted for cross-over) in the DECISION trial was 34 months, exceeding the 24 month life expectancy criteria by 10 months, (10) there is uncertainty in this estimate due to statistical methods required to adjust for treatment crossover.

The Assessment Group highlighted survival estimates from Canada of 2.5-3.5 years (11) however upon inspection of the source it is not clear this source relates specifically to patients who are radioactive iodine refractory. If this is the case, these estimates would likely be lower and in line with those of the NICE clinical expert.

Given this evidence, in addition to estimates in the literature previously cited by the company, it is likely that progressive and symptomatic patients treated in UK clinical practice have a life expectancy of less than 24 months.

b) Small patient population

In the UK a very small number of patients suffer from RAI-R DTC. CDF notifications show between July 2014 and June 2016, during which sorafenib was the only treatment option, between 50 to 55 patients per year were considered eligible for treatment. This is in line with current patient estimates, and substantially smaller than the 7,000 patient limit historically applied when considering end-of-life conditions.

c) Extension of life vs. life expectancy trade-off

Whilst life expectancy for some patients may exceed 24 months, the average extension of life was 13 months in the AG model, exceeding end-of-life criteria by 10 months. The possibility of a trade-off in criteria was considered by the committee but no assessment was made in this respect.

Life expectancy and extension of life criteria relate to the date at which treatment commences. With the ACD citing committee discussion around the treated UK population being symptomatic and progressive, and UK clinical practice where *'at least 50% of patients will not live longer than 2 years'* it is plausible and that patients when seen as eligible for treatment in the UK may have a lower life expectancy than in the trials.

If we assume that patients are treated later in UK clinical practice (at an average expectancy of 24 months) they are still likely to receive a substantial survival benefit from treatment. Whilst it is assumed that treatment initiation in the UK seeks to maximise survival and therefore there would be no reason to decrease this survival benefit. If we were to conservatively assume the ratio of life expectancy and extension remains constant (i.e. reduction results in a reduction in survival of the same magnitude) an adjustment factor of 0.706 applied to both life expectancy and life extension, meets the expectancy criteria (24 months), with the extension of life of over 9 months.

Whilst this approach is novel it provides a helpful framework to consider the likely trade-off, when aligning treatment to that seen in UK clinical practice and that it is likely that treatment would meet end-of-life criteria if given at 24 months.

Scenario 1: DECISION trial (median overall survival)

BSC	Life expectancy (34 months)	
Sorafenib	Life expectancy (34 months)	Extension of life (12.9 months)

Scenario 2: DECISION trial (application to UK clinical practice)

BSC	Life expectancy (24 months)	
Sorafenib	Life expectancy (24 months)	Extension of life (9.1months)

d) Social value judgements and innovation

NICE apply end-of-life criteria to account for society's valuation that QALYs achieved in the later stages of terminal diseases are provided greater weight. Patients with RAI-R DTC have a terminal disease and unlike in other cancers there is not the opportunity for further or alternative lines of treatment. This absence of an active treatment option should be considered when assessing a patient's valuation of an available treatment as an uncaptured benefit.

NICE also has the responsibility to recognise innovation and the long-term benefits to the NHS of this innovation. Sorafenib was the first licensed treatment made available for this patient group and created a true step change in therapy.

Conclusion: Under all scenarios ICERs fall in a tight range around £30,000/QALY reflecting low uncertainty

Evidence presented in this response is focused around two key uncertainties highlighted by the Appraisal Committee, the implementation of survival modelling by the AG and whether treatments meet the NICE end-of-life criteria.

Issues with the face validity of survival modelling in the AG model have been highlighted (including probabilities >1, discrepancies between curves in model and AG report, and extrapolations driven by few events). These underestimate the clinical outcomes for sorafenib. Correcting for these issues produces very similar estimates of cost-effectiveness to other extrapolations considered by the committee.

Evidence has been presented highlighting that patients with progressive and symptomatic disease have a life expectancy of less than 24 months (median: 15.72 months and mean: 22.05 months). This is supports statements made by the NICE clinical expert in the ACD.

Keeping <u>all</u> the Appraisal Committee's preferred assumptions, and varying for only uncertainties discussed in this response results in a tight range of ICERs from £[redacted] - £[redacted] per QALY. ICERs show cost-effectiveness across a very tight range and across all discussed assumptions indicating low uncertainty, with scenarios reflecting UK clinical practice resulting in ICERs less than £30,000/QALY

References

1. Altman DG. Practical statistics for medical research: CRC press; 1990.
2. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. The Lancet. 2002;359(9318):1686-9.
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10. Bayer plc. Clinical study report: 14.2.2 Overall survival - with cross over correction by RPFST method: descriptive statistics. (Data on file).
11. Liverpool Reviews and Implementation Group. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine,. 2017.

Dear Kate,

Thank you for the request dated 15th December 2017 regarding the ongoing appraisal of sorafenib for the treatment of differentiated thyroid cancer after radioactive iodine.

Please find responses from the company below. Please contact the company if further clarification is required.

1. Please fill in tables 1 and 2 below relating to the goodness of fit and mean overall survival predictions for alternative OS extrapolations and indicate which model(s) are preferred by Bayer

Please see below the requested tables. The preferred extrapolations are those presented by the company in the ACD response, the ICERs for which are presented in tables 3 and 4.

Table 1: Goodness of fit results for comparator arm in DECISION

Time point of extrapolation	Model type (RPSFT Adjusted)	Sum of squared residuals*	Number of parameters estimated	AIC	-2*log likelihood	Rank by AIC	Mean OS (months) at 10 years**
0	Weibull	0.074739	3	357.830	353.830	4	0.7%
0	Log-normal	0.025497	2	355.611	351.611	1	15.7%
0	Log-logistic	0.04802	2	356.492	352.492	2	11.1%
0	Exponential	0.033787	1	361.701	359.701	6	9.5%
0	Generalized gamma	0.062072	3	357.600	351.600	3	2.5%
0	Gompertz	0.110059	2	361.365	357.365	5	0%
6.4 Months	KM curve then Piecewise Exponential	0.047509	2	α	α		5.2%
6.4 Months	KM Curve then single exponential	0.028169	1	α	α		9.5%

* Using the ordinary least squares (OLS) method to estimate distributional parameters and associated standard errors for time-to-event data can be problematic. The OLS method does not account for the timing of the events/censors. This can introduce bias in the standard error estimates. It also does not account for low numbers of patients in the tail and gives equal weight to all points on the curve. Therefore the goodness-of-fit statistic sum-of-squared residuals (SSR) can in turn be biased. The OLS approach is not recommended for time-to-event data analysis.

The most appropriate method for analysing time-to-event data is the maximum likelihood estimation (presented in the table). However, as the SSR does allow comparison of all extrapolations, unlike the AIC or log-likelihood these have been presented for all extrapolations.

** – Clinical experts predicted 10-15% survival at 10 years, published studies[1,2] predicted between 10-12% survival at 10 years in the BSC arm

α: Likelihood data is not presented for the piecewise extrapolation as the observed KM is used

Table 2: Goodness of fit results for sorafenib arm in DECISION

Time point of extrapolation	Model type (RPSFT Adjusted)	Sum of squared residuals*	Number of parameters estimated	AIC	-2*log likelihood	Rank by AIC	Mean OS (months) at 10 years
0	Weibull	0.004833	3	360.856	356.856	1	5.6%
0	Log-normal	0.005483	2	362.879	358.879	4	22.3%
0	Log-logistic	0.003411	2	360.922	356.922	2	17.8%
0	Exponential	0.021268	1	366.965	364.965	6	17.6%
0	Generalized gamma	0.005148	3	362.749	356.749	3	21.3%
0	Gompertz	0.008418	2	363.060	359.060	5	0.4%
11.96 Months	KM curve then Piecewise Exponential	0.006176	2	α	α		12.9%
11.96 Months	KM Curve then single exponential	0.009427	1	α	α		17.6%

For * and α - Please see notes on table 1

2. Please fill in table 3 below relating to cost effectiveness results for sorafenib vs. BSC for Bayer's alternative overall survival scenarios. Please include list price and CAA results in separate tables.

Table 3: Cost effectiveness results for sorafenib vs. BSC – list price

	Cost per patient		QALYs per patient		Life-years per patient		Incremental			ICER (£ per QALY gained)
Scenario	Sorafenib	BSC	Sorafenib	BSC	Sorafenib	BSC	Cost	QALY	Life-years	
1– TTD Only	[redacted]	£17,844	2.94	2.20	5.09	3.60	[redacted]	0.74	1.49	£61,167
1 -TTD or PFS	[redacted]	£17,844	2.94	2.20	5.09	3.60	[redacted]	0.74	1.49	£50,731
2 – TTD Only	[redacted]	£19,312	3.23	2.52	5.78	4.27	[redacted]	0.72	1.51	£62,910
2 - TTD or PFS	[redacted]	£19,312	3.23	2.52	5.78	4.27	[redacted]	0.72	1.51	£52,159
3 – TTD Only	[redacted]	£19,191	3.21	2.51	5.75	4.25	[redacted]	0.70	1.50	£63,757
3 - TTD or PFS	[redacted]	£19,191	3.21	2.51	5.75	4.25	[redacted]	0.70	1.50	£52,844

Scenario 1 – PFS = KM curve then single exponential, OS = KM curve then revised piecewise exponential
Scenario 2- PFS = KM curve then single exponential, OS = KM curve then single exponential
Scenario 3 – PFS = Single exponential, OS = Single exponential

Table 4: Cost effectiveness results for sorafenib vs. BSC – CAA Price

	Cost per patient		QALYs per patient		Life-years per patient		Incremental			ICER (£ per QALY gained)
Scenario	Sorafenib	BSC	Sorafenib	BSC	Sorafenib	BSC	Cost	QALY	Life-years	
1– TTD Only	[redacted]	£17,844	2.94	2.20	5.09	3.60	[redacted]	0.74	1.49	[redacted]
1 -TTD or PFS	[redacted]	£17,844	2.94	2.20	5.09	3.60	[redacted]	0.74	1.49	[redacted]
2 – TTD Only	[redacted]	£19,312	3.23	2.52	5.78	4.27	[redacted]	0.72	1.51	[redacted]
2 - TTD or PFS	[redacted]	£19,312	3.23	2.52	5.78	4.27	[redacted]	0.72	1.51	[redacted]
3 – TTD Only	[redacted]	£19,191	3.21	2.51	5.75	4.25	[redacted]	0.70	1.50	[redacted]
3 - TTD or PFS	[redacted]	£19,191	3.21	2.51	5.75	4.25	[redacted]	0.70	1.50	[redacted]

Scenario 1 – PFS = KM curve then single exponential, OS = KM curve then revised piecewise exponential
Scenario 2- PFS = KM curve then single exponential, OS = KM curve then single exponential
Scenario 3 – PFS = Single exponential, OS = Single exponential

References:

1. Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli J, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. The Journal of Clinical Endocrinology & Metabolism. 2006;91(8):2892-9.

2. Shoup M, Stojadinovic A, Nissan A, Ghossein RA, Freedman S, Brennan MF, et al. Prognostic indicators of outcomes in patients with distant metastases from differentiated thyroid carcinoma. Journal of the American College of Surgeons. 2003;197(2):191-7.

Dear Abi,

Thank you for the request dated 3rd January 2018 regarding the ongoing appraisal of sorafenib for the treatment of differentiated thyroid cancer after radioactive iodine. Please find clarification from the company below. Please contact the company if any further clarification is required.

Please find the requested data presented on the following pages for the following sub-groups:

a) Symptomatic patients in the Placebo arm (n=45);
b) Non-symptomatic patients in the Placebo arm (n=165);

a) Symptomatic patients in the Placebo arm (n=45);

Figure 1 Overall survival with RPSFT adjustment - symptomatic Placebo subjects

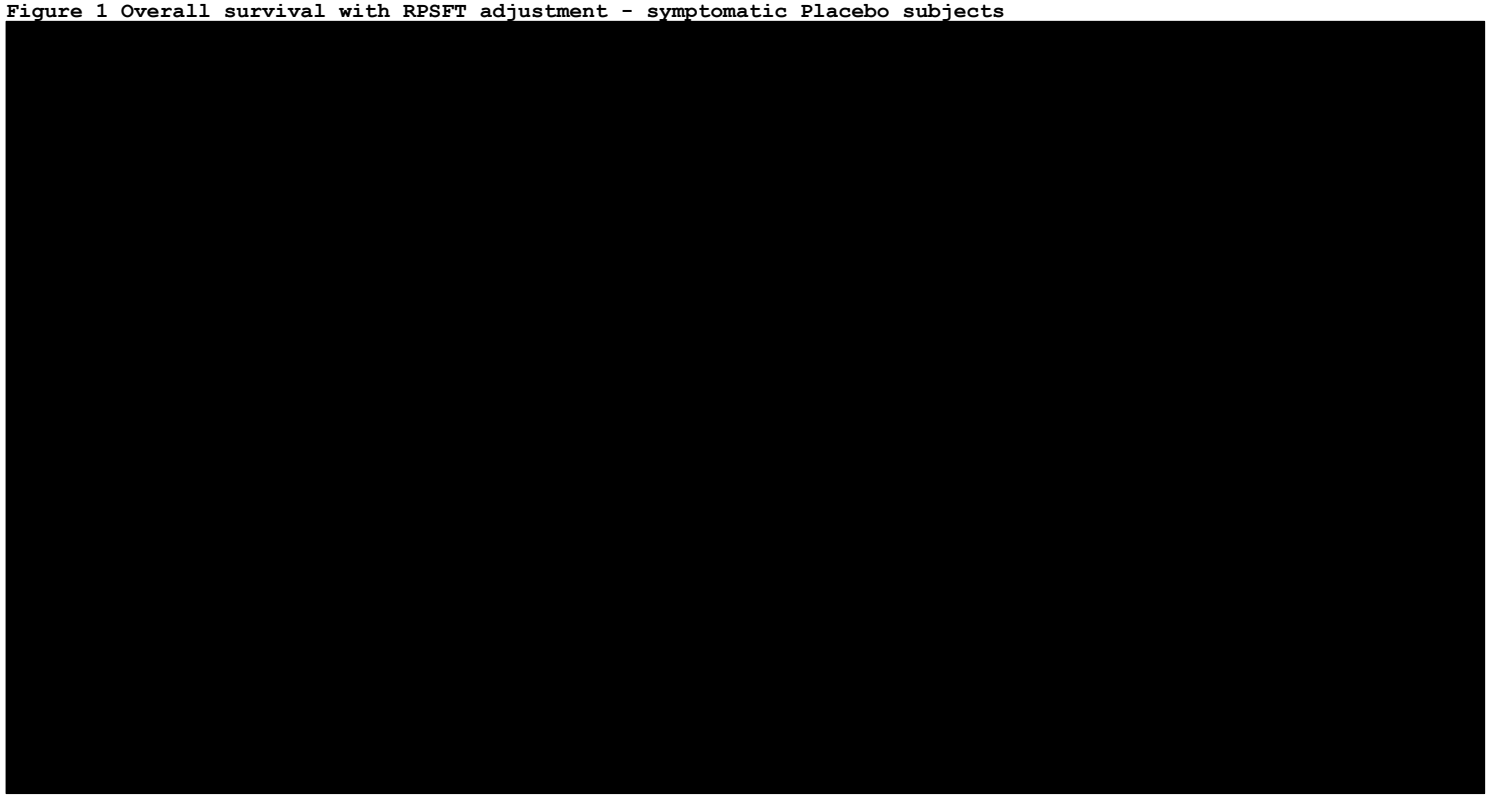

Table 1 / 1: Descriptive statistics for overall survival with RPSFT adjustment using Kaplan-Meier estimates - symptomatic Placebo subjects

Statistics	Units	Value
N		45 (100.0 %)
Number (%) of subjects with event		[redacted]
Number (%) of subjects censored		
Mean (until last event)	(days)	
Mean (until last observation)	(days)	
25th percentile [95% CI]	(days)	
Median [95% CI]	(days)	
75th percentile [95% CI]	(days)	
Range (including censored values)	(days)	
Range (without censored values)	(days)	[redacted]
Survival rate at	3 months [95 % CI]	
Survival rate at	6 months [95 % CI]	
Survival rate at	9 months [95 % CI]	
Survival rate at	12 months [95 % CI]	
Survival rate at	18 months [95 % CI]	
Survival rate at	24 months [95 % CI]	

** censored observation
A: Value cannot be estimated due to censored data
Median, percentile and 95 % CIs computed using Kaplan-Meier estimates
Bayer: /by-sasp/patdb/projects/439006/14295/stat/test_query36/pgms/tf_os_updates_km_rpsft_mean.sas enqlq 04JAN2018 7:33
End of table

b) Non-symptomatic patients in the Placebo arm (n=165)

Figure 2: Overall survival with RPSFT adjustment - non-symptomatic Placebo subjects

Table 2 / 1: Descriptive statistics for overall survival with RPSFT adjustment using Kaplan-Meier estimates - non-symptomatic Placebo subjects

Statistics	Units	Value
N		165 (100.0 %)
Number (%) of subjects with event		[redacted]
Number (%) of subjects censored		[redacted]
Mean (until last event)	(days)	[redacted]
Mean (until last observation)	(days)	[redacted]
25th percentile [95% CI]	(days)	[redacted]
Median [95% CI]	(days)	[redacted]
75th percentile [95% CI]	(days)	[redacted]
Range (including censored values)	(days)	[redacted]
Range (without censored values)	(days)	[redacted]
Survival rate at	3 months [95 % CI]	[redacted]
Survival rate at	6 months [95 % CI]	[redacted]
Survival rate at	9 months [95 % CI]	[redacted]
Survival rate at	12 months [95 % CI]	[redacted]
Survival rate at	18 months [95 % CI]	[redacted]
Survival rate at	24 months [95 % CI]	[redacted]

** censored observation
A: Value cannot be estimated due to censored data
Median, percentile and 95 % CIs computed using Kaplan-Meier estimates
Bayer: /by-sasp/patdb/projects/439006/14295/stat/test_query36/pgms/tf_os_updates_km_rpsft_mean.sas enqlq 04JAN2018 7:33
End of table

Appendix 1: Additional evidence submitted in response to ACD [ID1059]

1. Amended adverse event costs to incorporate duration of adverse event

Eisai have obtained further information from the SELECT trial on the median duration of adverse event episodes included in the AG model i.e. hypertension, proteinuria, and hand-foot syndrome, which are 4.8, 6.1, and 14.4 weeks, respectively, for subjects in the lenvatinib arm. This was based on any grade adverse events to be conservative. This is substantially shorter than the median treatment duration of lenvatinib from the SELECT study which is 13.8 months and further supports the fact that the AG's approach is not plausible.

A scenario combining these adverse event duration data with incidence rates from SELECT has been included in the AG model and this changes the ICER for lenvatinib vs BSC at list price to £60,571.

2. Amended resource use costs to more accurately reflect UK clinical expert advice

Eisai do not agree with the data used by the AG to estimate resource use in the model as it is not consistent with clinical advice received by 4 UK clinical experts experienced in treating RAI-refractory DTC.

In particular, the following assumptions are not clinically plausible:

- Assuming the same level of resource use and costs for the pre and post-progression states, an assumption which directly contradicts the expert clinical advice received by Eisai and published evidence. In a scenario exploring resource use in the AG model; using the AG estimates but adding in the Eisai estimates for hospitalisations pre-progression and post-progression, the ICER for lenvatinib vs BSC using the list price is: £57,754
- Assuming that treating hypertension will require two additional oncology visits. Clinical advice from 4 UK clinical experts experienced in treating RAI-refractory DTC and using lenvatinib is that hypertension is adequately managed within primary care and would require one additional GP contact per month. In a scenario incorporating this revised resource use in the AG model, the ICER for lenvatinib vs BSC using the list price is: £60,411

The above assumptions were originally included in the cost effectiveness model which Eisai submitted to NICE.

In addition, recent feedback received by one of the above UK clinical experts on the resource use data in the assessment group model is that oncologists would see patients with stable disease and progressed disease more frequently than only every 3 months, bone scans are not used and MRI scans are only used in a very small proportion of patients.

As a result, the following scenarios have been included in the AG model:

- monthly oncologist visits applied to pre- and post-progression states. The ICER for lenvatinib vs BSC using the list price is: £62,207
- 7.5% and 0% of pts receiving MRI and bone scans per 3 month, respectively. The ICER for lenvatinib vs BSC using the list price is: £60,438

3. End of life criteria

A range of lifetime parametric survival extrapolations were included in the cost effectiveness model which Eisai submitted. We have subsequently identified a number of additional references which indicates that survival for patients with RAI-refractory DTC and distant metastases is around 2.5–3.5 years (Durante 2006, Robbins 2006, Worden 2014) and death from thyroid cancer within 3 years under these circumstances is common (Pfister 2008). This is consistent with the information provided by the clinical expert at the committee meeting, ie that at least 50% of patients will not live longer than 2 years. There are a small proportion of patients with indolent disease who may live longer, but these represent a minority of patients.

As such, after applying some flexibility around the criteria, it is reasonable to conclude that lenvatinib can meet the criterion for short life expectancy and the end-of-life-criteria do apply in this orphan disease setting.

References:

Durante C et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006 Aug;91(8):2892-9

Robbins et al. Real-time prognosis for metastatic thyroid carcinoma based on 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography scanning. J Clin Endocrinol Metab. 2006 Feb;91(2):498-505

Worden F. Treatment strategies for radioactive iodine-refractory differentiated thyroid cancer. Ther Adv Med Oncol 2014; 6(6): 267-279

Pfister DG, et al. Refractory Thyroid Cancer: A Paradigm Shift in Treatment is Not Far Off. J Clin Oncol 2008; 26(29): 4701-4704

4. Revised company base case

	ICER Lenvatinib vs BSC
AG base case	**£62,802**
AG model with updated lenvatinib mean dose of 16.3mg	£59,247
AG model assuming 1 GP contact for hypertension	£60,411
AG model with Eisai hospitalisations estimate	£57,754
AG model assuming monthly oncologist visits	£62,207
AG model assuming 7.5% MRI and 9% bone scans	£60,438
AG model using mean AE duration to model AEs	£60,692
AG model with discounting error corrected	£62,736
AG model with all changes (new Eisai base case)	**£48,607**

Response to ACD Comments

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (ID1059)

Response to Company Comments on ACD

This response is part of a project commissioned by the NIHR HTA Programme as project number 16/51/20

30 November 2017

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

1 INTRODUCTION

This document has been prepared by the Assessment Group (AG) supporting the NICE appraisal of lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine, in response to detailed comments received from the sponsoring companies concerning the AG's report and economic model.

As far as possible, we have addressed all of the specific issues raised, and prepared revised cost-effectiveness results to assist further consideration of the topic by the Appraisal Committee.

2 RESPONSE TO COMMENTS FROM EISAI

Following consideration of the NICE Committee ACD (Appraisal Consultation Document) for this appraisal, Eisai (the company supporting the introduction of lenvatinib for treating differentiated thyroid cancer after radioactive iodine) provided a response in the form of five specific comments relating to the AG's decision model, and citing several academic papers to support the case that NICE should exercise the 'End of Life' provisions. In addition, Eisai has proposed a reduced NHS Patient Access Scheme (PAS) discounted price for lenvatinib.

The AG has given careful consideration to the points raised as follows:

2.1 Comment 1: Average dose of lenvatinib

Eisai point out that the average dose used in the AG model for calculating the cost of treatment with lenvatinib (17.4 mg) is incorrect and relates to an early data-cut of the SELECT trial. This should have been replaced by the more recent value of 16.3 mg, but this change was overlooked by the AG. The AG accepts this correction, and has amended their model appropriately. This change results in a reduction in the AG base case scenario incremental cost-effectiveness ratio (ICER) for lenvatinib of £3,555 per QALY gained.

2.2 Comment 2: Duration of adverse events

Eisai consider that the costing of adverse events (AEs) in the AG model is overstated as it assumes that patients experiencing an event will require treatment indefinitely. The AG requested information from Eisai concerning the duration of the main AEs as recorded in the SELECT trial, and has developed an alternative estimation method based on the new evidence. This reduces the absolute and incremental costs of treating AEs for both the

lenvatinib and sorafenib models. Applying this modification reduces the AG base case ICER using the list prices of drugs by £5,664 per QALY gained for lenvatinib and by £2,899 per QALY gained for sorafenib.

2.3 Comment 3: Resource use assumptions

Eisai considers that patients are routinely seen by an oncologist more frequently than quarterly, that bone scans are no longer used for these patients, and that MRI scans are only used for a small proportion of patients. In addition, Eisai point out that treatment for hypertension would not normally require regular input from an oncologist, but can be managed with monthly reviews by a GP.

The AG has carried out sensitivity analyses to estimate the importance of each of these issues to model results (see Section 5 below).

Eisai criticised the AG model for excluding consideration of variations in medical costs (especially hospital admissions) attributable to patient health state. The Eisai model bases its costing of thyroid cancer care solely on a multi-national survey published by Georghiou et al [1]. However, this study should be treated with caution as there are multiple reasons to question the applicability of its findings to UK clinical practice for the specific population of this appraisal including:

- Only 57% of patients surveyed suffered from Stage IV disease compared to 95% to 100% in the DECISION and SELECT trials;

- Only 14 UK patients in the survey were being treated with a multi-kinase inhibitor (sorafenib, n=10);

- The resource use tables in the paper are not split by country of origin, so it is not possible to determine how the UK pattern may differ from that of other countries (especially the US, which accounts for most of the cases reviewed);

- The final table compares six types of resource use by health state (objective tumour response versus stable disease versus progressive disease). Of these, only three show the highest resource use in the progressive disease category for all hospitalisations, while the other three show resource use that is higher in non-progressive states.

The AG concludes that this single source is not an adequate or reliable basis on which to introduce large estimates of medical costs in the UK calibrated to yield substantial cost

differentials between health states, and consequently to risk exaggerating minor differences in health state estimates into substantial differences in relative costs and ICERs between treatments.

2.4 Comment 4: Discounting error

Eisai point out a coding error in the AG model in which the costs of treating AEs arising for patients treated with lenvatinib are not discounted. In fact, this omission affects both lenvatinib and sorafenib. When this is corrected, the estimated mean cost of care is reduced by a small amount, and the estimated ICERs are reduced by £66 per QALY gained for lenvatinib and by £82 per QALY gained for sorafenib.

2.5 Comment 5: Duration of response to treatment

Eisai point out that the duration of response to treatment in the lenvatinib arm of the Eisai model is incorporated in their model and is sourced directly from the SELECT trial. However, in the absence of equivalent data from the DECISION trial, the patient numbers in the response state of the sorafenib arm of the Eisai model is based on a single aggregate ratio, which excludes any difference in either the timing or duration of response in the DECISION trial, affecting relative utility estimates. This limitation is the key ground for the AG's concern about the adoption of an extra 'response' health state in the Eisai model.

2.6 End of Life criteria

Eisai have cited four academic articles in support of their belief that lenvatinib should be subject to restrictive consideration on the ground that patients in the target population have a life expectancy of less than 24 months. The AG has examined these papers carefully and observes as follows:

- The Durante et al paper [2] reports on 444 patients treated for metastatic papillary and follicular thyroid carcinoma over a period of more than 40 years. Figure 1 provides the overall survival trend for patients without radioactive iodine take-up. Fitting a 2-phase exponential function to these data indicates that the median survival of these patients was 26.66 months and the long-term mean overall survival was 62.5 years.

- Robbins et al [3] reported on the prognosis of 400 metastatic thyroid cancer patients following positron emission tomography (PET) scanning. They chart the survival of these patients for over 8 years, and in all analyses relating to a range of patient characteristics, the median survival exceeds 40 months.

- Both Worden [4] and Pfister and Fagin [5] are clinical reviews and contain no new evidence.

In addition, we note that the principal paper reporting results from the SELECT trial (Schlumberger et al 2015 [6], Table 2) indicates that a straightforward exponential (constant hazard) relationship is present in the comparator arm after adjustment for crossover yielding a mean estimated overall survival of 37.2 months.

We are therefore not aware of any reliable evidence supporting the suggestion by Eisai that the life expectancy of this population is less than 24 months.

3 RESPONSE TO COMMENTS FROM BAYER

The comments received from Bayer relate to two broad areas: the modelling and implementation of time-to-event data used in the AG model, and establishing a basis for claiming the application of the NICE End of Life criteria in respect of treatment with sorafenib.

3.1 PFS modelling and implementation

a) Bayer comments on the AG modelling of PFS data from the DECISION trial, arguing that the fitted exponential trends do not pass through the initial time point of the data (i.e. 100% progression-free at randomisations), and therefore are not plausible.

   This comment indicates that Bayer do not appreciate that standard parametric curves rarely conform to the constraint of passing through the initial time point of a clinical trial unless constrained to do so. This is because the initial conditions of a typical clinical trial involve inclusion/exclusion limitations which ensure that the risk of a very early event (death or progression) is artificially suppressed (candidates in poor condition are frequently screened out). In addition, for PFS data, most early events take place *after* an initial interval between baseline and the first scheduled clinic visit for assessment (i.e. there are very, few mostly, symptomatic early events recorded, and then larger numbers of detected progressions discovered at each subsequent assessment). As a result, in the initial period little change occurs, but thereafter there is an apparent shift in the data trend to the right. Fixing the modelled curve to pass through the 100% survival/zero time point results in an artificial distortion of the fitted model, frequently biasing any extrapolation to understate early PFS estimates compared to trial data, and then overstates long-term event-free estimates. The AG method is therefore more accurate in both the short-term and the long-term, as confirmed by goodness of fit statistics.

b) Bayer question whether the 'correct' PFS model was used in the AG model. The apparent difference in different versions of the AG report and subsequent revisions arose from a complex chain of events and consequent reconsideration of earlier versions of the model.

As described in the AG report, Bayer chose not to respond to a request at the beginning of the MTA process to provide analyses of the latest time-to-event trial data using a common set of analytic rules, in order to ensure consistency between data from the two separate trials available to the AG. This request was prompted by strong evidence in the published results of the SELECT trial of a systematic bias arising from the analysis of data from censored patients. As Bayer did not respond to our request, it was necessary to include a caveat in our report that there may remain inconsistencies between the key data sources.

At a very late date in the development of the AG model and report, we noticed important differences in the time-to-event data from the DECISION trial, which were incorporated into the Bayer decision model (the only source of these data then available to us) and other available statistics. We raised the issue with Bayer, who informed us that the model data were out of date and provided a new data set. As a result, we were obliged to revisit all the analyses of DECISION trial data which we had already carried out, and make last minute alterations to the model and the final report.

At this stage we were already aware the Bayer were questioning the AG use of exponential modelling (as described in (a) above). We therefore decided to reduce as far as possible reliance on extrapolation and instead maximise direct use of the trial Kaplan-Meier data. However, there remained the question of how to treat the final segment of the trial for which several options were available.

The PFS data for the sorafenib arm showed a final sequence of five events beyond 25 months follow-up where estimated PFS declined more rapidly than occurred in the preceding 10 months. Several possible scenarios were considered which might explain this phenomenon and provide a basis for estimating PFS in the decision model:

{1} A sharp decline in PFS (equivalent to a sudden increase in risk) in the final phase of the data set is typical of informative right-censoring in clinical trials. In the absence of the re-analyses of the survival data initially requested by the AG, it was not

possible to rule out this explanation which would then require exclusion of the final sequence of biased events before fitting a long-term trend to the remaining data for life-time extrapolation of PFS.

{2} This effect could also be generated from a very late round of patient assessments. In this case it would be more appropriate to include these data in a long-term data-fitting exercise, using the resulting model to extrapolate beyond the available trial data.

{3} The effect could represent a final phase of increased risk of progression or death which might be expected to continue beyond the trial period. This requires fitting an appropriate projective function only to this final data segment as a basis for extrapolating beyond the available data. This yields a mean PFS estimated mean of 12.77 months.

{4} It was observed that following the final recorded PFS event in the sorafenib arm, only six patients of the original 207 remained at risk (less than 3%). At this point the Kaplan-Meier confidence interval would be wide and probably close to encompassing zero. In this context a simple solution would be to assume that these few remaining patients were likely to suffer progression or death shortly afterwards and therefore that the truncated mean PFS estimate obtained as the simple area under the curve at the time of the final recorded event would provide a good approximation to the true mean survival. This yields a value of 12.63 months.

In terms of estimated long-term mean PFS, these four options range from the most generous {1} to the most conservative {4}. The ERG did not consider that in the absence of the requested additional analyses it could justify supporting option {1} as reliable. Option {2} is similar to the approach taken by Bayer, and yielded an estimate for mean PFS of 15.39 months. From options {2} to {4}, the AG chose to proceed with option {3} on the basis that it maximises the direct use of trial Kaplan-Meier data, and provides a close fit to the final anomalous sequence of events. In addition, it is neither unduly generous nor excessively conservative.

Interpreting and projecting incomplete clinical trial results is not an exact mechanistic process, but requires a pragmatic approach recognising as far as possible the particular design and practical aspects of the restricted information available to the analyst. The option adopted by the AG for estimating long-term PFS is both pragmatic and reflective of the uncertainties attached to the data made available by Bayer.

3.2 Time on treatment

Bayer has misrepresented the approach taken by the AG in costing the active treatments (sorafenib and lenvatinib). For both cases the AG relied solely on the trial data supplied by the respective companies. Sorafenib treatment ceased altogether after cycle 40 (1 cycle = 28 days) so that treatment data are complete. For lenvatinib only 8% of patients were still on treatment after cycle 48 (1 cycle = 30 days), requiring only a minor extrapolation to estimate final treatments up to cycle 50.

The AG model offers three options for costing these treatments:

- Treatment duration governed by estimated PFS (i.e. treatment ceases on disease progression or death)
- Treatment duration governed by estimated Time on Treatment (i.e. treatment may extend beyond progression as recorded in the respective trials)
- Treatment duration estimated as the minimum number of patients on treatment at each time point by either PFS or recorded time on treatment.

The third option is included as a sensitivity analysis of the minimum possible treatment cost combining both approaches. (NB Bayer suggest that this option was only applied to sorafenib, and not to lenvatinib. This is incorrect as the same logic applies to both versions of the model).

The AG's preferred option is to use Time on Treatment, as that alone is fully consistent with the trial outcomes used to calibrate all other model results.

It should be borne in mind that directly aligning the results of a model populated with unique trial data with hypothetical 'real-life' scenarios subject to non-trial guidelines and restrictions is not realistic. No model can generate error-proof results for aspirational environments.

3.3 'End of Life' criteria

For both treatments, satisfying the NICE 'End of Life' criteria is an important requirement to achieve a positive NICE recommendation. Bayer seeks to focus attention on a phrase occurring in Section 3.1 of the ACD relating to evidence given verbally by a clinical expert at the Appraisal Committee meeting in September 2017 that *'best supportive care is offered until disease starts to progress and symptoms occur'*. Based on this comment, survival data are presented for the subgroup of patients in the placebo arm of the DECISION trial, who were recorded to be symptomatic at the time of enrolment. Bayer claims that these data

indicate that survival (median and mean) for this group is less than 2 years. On this basis the company implies that this provides a justification for invoking 'End of Life' provisions for the whole population considered in this appraisal.

However, there are several issues of concern with this line of argument:

Firstly, the quotation from the ACD is incomplete and does not justify limiting consideration to the suggested subgroup. In full it reads:

"In clinical practice, best supportive care is offered until disease starts to progress and symptoms occur, or there is rapid progression that is likely to become symptomatic."

The selected subgroup involves only a small proportion of the patients in the placebo arm (45 patients from a total of 210, i.e. 21.4%). No evidence is offered to justify applying results from this subgroup to the whole trial population.

The AG wished to assess the validity of the survival figures quoted by the company, and requested further information. Bayer has provided detailed results from Kaplan-Meier survival analyses for two patient subgroups (those symptomatic and non-symptomatic at randomisation) for each arm of the DECISION trial (treated with sorafenib or placebo) with survival plots for each subgroup as well as summary statistics. The results for the placebo arm have been adjusted to take account of treatment crossover in the placebo arm using the RPSFT method.

The AG has attempted to reproduce the company survival estimates shown of page 10 of Bayer's response to the ACD, using data extracted from the charts provided by digitizing the timing of individual events (deaths) and censoring.

The AG's estimates of survival are markedly different from those given by Bayer for symptomatic patients in the placebo trial arm. Bayer report the median survival time as 15.72 months, and the mean as 22.05 months. Re-analysing these data using the Kaplan-Meier method (SPSS 22), results in an estimated mean survival time of 23.97 months (95% confidence interval 18.41 to 29.52), and estimated median survival of 18.92 months (95% confidence interval 9.51 to 28.34). As the most recent survival plot terminates at zero with no patients remaining at risk, these results represent the best survival estimates available. However, it could be argued that the clustering of right-censored records (i.e. patients still at risk at the time of data cut) after 33 months may mean that the final segment of the survival chart is not reliable. The AG explored an alternative approach using extrapolation modelling and was able to achieve a satisfactory match to the trial data using a simple exponential

(constant risk) model. The resulting long-term estimated mean survival for initially symptomatic patients in the placebo arm is then 29.95 months.

In situations where the available data are largely complete, the mean survival is the preferable measure of longevity since it uses the whole of the available data, and is compatible with the methods of calculation required for a cost-effectiveness model.

Bayer claim that in this small selected subgroup of trial patients, the mean and median survival estimates are less than the 24 months, and therefore treatment with sorafenib meets the 'End of Life' criterion of expected survival less than 2 years. The AG analysis does not support this claim: from its analysis the most credible mean value for survival is almost exactly 24 months with an 11 month wide confidence interval, and the estimated median (about 19 months) has an even wider confidence range of plus or minus 9.5 months. This is a weak position from which to argue that survival without sorafenib treatment is less than 24 months.

The position is much clearer for patients without disease symptoms at the beginning of the trial and who were randomised to the comparator arm. The median survival for this sub-group is 37.65 months, and the restricted mean is 34.37 months with 37% of patients still alive.

Since no patient subgroups, other than subgroups based on previous treatment with tyrosine kinase inhibitors, were indicated for separate consideration in the appraisal scoping document, it seems likely that, regardless of any specific survival estimates suggested by Bayer, this approach falls outside the current remit and could not be used to support invoking the NICE 'End of Life' procedure for the whole patient population.

4 SUMMARY OF CHANGES TO AG BASE CASE ANALYSIS

Tables 1 and 2 summarise the main changes made to the AG model results over the course of this appraisal. The "original AG Base Case" provides results shown in the AG report as first submitted. The "Corrected Base Case" shows results following formal error-checking as presented at the first Appraisal Committee meeting. The "Revised Base Case" includes three additional corrections consequent on issues raised by Eisai (Section 2 above).

Table 1 Effect of additional model amendments from comments received on the ACD: lenvatinib vs BSC (full list price of lenvatinib)

Scenario/ model change	*Cost per patient*		*QALYs per patient*		*Life-years per patient*		*Incremental*			*ICER*	
	Lenvatinib	*BSC*	*Lenvatinib*	*BSC*	*Lenvatinib*	*BSC*	*Cost*	*QALYs*	*Life-years*	*£/QALY*	*Change*
Original AG Base Case	£95,102	£15,195	2.815	1.602	4.584	2.532	£79,907	1.213	2.052	£65,872	-
Corrected Base Case	**£91,377**	**£15,195**	**2.815**	**1.602**	**4.584**	**2.532**	**£76,182**	**1.213**	**2.052**	**£62,802**	**-**
Lenvatinib dose	£87,065	£15,195	2.815	1.602	4.584	2.532	£71,870	1.213	2.052	£59,247	-£3,555
AE costs revision	£87,857	£14,822	2.815	1.602	4.584	2.532	£73,036	1.213	2.052	£60,208	-£2,594
Discounting error	£91,297	£15,195	2.815	1.602	4.584	2.532	£76,103	1.213	2.052	£62,736	-£66
Revised Base Case	**£83,545**	**£14,822**	**2.815**	**1.602**	**4.584**	**2.532**	**£68,723**	**1.213**	**2.052**	**£56,653**	

BSC = Best Supportive Care, QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio, AE = adverse event

Table 2 Effect of additional model amendments arising from comments received on the ACD: sorafenib vs BSC (full list price of sorafenib)

Scenario/ model change	*Cost per patient*		*QALYs per patient*		*Life-years per patient*		*Incremental*			*ICER*	
	Sorafenib	*BSC*	*Sorafenib*	*BSC*	*Sorafenib*	*BSC*	*Cost*	*QALYs*	*Life-years*	*£/QALY*	*Change*
Original AG Base case	£63,188	£17,954	2.752	2.224	4.725	3.649	£45,234	0.528	1.076	£85,644	-
Corrected Base case	**£62,103**	**£17,954**	**2.752**	**2.224**	**4.725**	**3.649**	**£44,149**	**0.528**	**1.076**	**£83,590**	**-**
Lenvatinib dose	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
AE costs revision	£61,377	£17,686	2.752	2.224	4.725	3.649	£43,690	0.528	1.076	£82,721	-£869
Discounting error	£62,060	£17,954	2.752	2.224	4.725	3.649	£44,106	0.528	1.076	£83,508	-£82
Revised Base case	**£61,377**	**£17,686**	**2.752**	**2.224**	**4.725**	**3.649**	**£43,690**	**0.528**	**1.076**	**£82,721**	

5 SENSITIVITY ANALYSES

The four resource use parameters in the AG model described above (page 3), which were identified by Eisai as potentially significant deviations from UK clinical practice, have been explored by the AG to assess their influence on model outcomes. All four variables relate only to treatment costs, and have no impact on survival or patient utility.

Table 3 Effect of varying four resource use parameters on estimated ICERs

	Lenvatinib vs BSC			*Sorafenib vs BSC*		
	IC	*ICER*	*Change*	*IC*	*ICER*	*Change*
AG Revised base case	**£68,723**	**£56,653**	**-**	**£43,690**	**£82,721**	**-**
GP hypertension Tx	£68,664	£56,604	-£49	£43,671	£82,684	-£37
No bone scans	£67,113	£55,325	-£1,328	£42,861	£81,150	-£571
Fewer MRIs	£67,449	£55,644	-£1,009	£43,060	£81,527	-£1,194
More frequent oncologist visits	£69,264	£57,098	+£445	£43,969	£83,248	+£473
All changes	**£66,371**	**£54,713**	**-£1,941**	**£42,489**	**£80,446**	**-£2,275**

BSC = Best Supportive Care, IC = incremental cost per patient, ICER = incremental cost-effectiveness ratio, MRI = Magnetic Resonance Imaging; Tx = treatment; GP consultation costed as £36 per visit (PSSRU 2016)

It is clear that, individually and together, these suggested variations on model parameter values only reduce the ICERs by less than £2,000 per QALY gained.

6 CONCLUSION

The two companies have adopted different emphases in their responses to the ACD: Bayer have focussed predominantly on challenging the AG's approach to analysis of trial time-to-event data in populating their model and Eisai have concentrated on how resources are estimated and costed. This report has set out in detail how and why the AG adopted its approach to converting clinical trial evidence to populate their model, and why we see no valid reason to make any alterations in this respect. Eisai have pointed out some genuine errors, which have been corrected, and suggested several issues we feel it appropriate to explore through sensitivity analysis. Finally, Bayer's appeal to evidence from a small post-hoc subgroup of patients as a basis for attracting 'End of Life' consideration does not appear to be justified for either the whole trial population, or for the small subgroup highlighted.

7 REFERENCES

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Addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (ID1059)

Addendum

This report was commissioned by the NIHR HTA Programme as project number 16/51/20

18 October 2017

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

Additional survival analyses requested by Appraisal Committee

Following the first Appraisal Committee (AC) consideration of evidence submitted by the sponsoring companies for lenvatinib and sorafenib and the report from the independent Assessment Group (AG - Liverpool Reviews and Implementation Group [LRiG], University of Liverpool), the AG was requested to carry out additional analyses in order to inform two issues:

1) Which methods of parametric extrapolation are most appropriate for estimating extended overall survival (OS) in both the intervention and comparator arms of the key clinical trials (DECISION and SELECT trials);

2) Whether the estimated mean OS in the comparator arms of the key clinical trials is most likely to be greater or less than 24 months.

It is anticipated that the additional analyses will inform the decision of the AC as to whether either treatment conforms to the NICE criteria governing the application of the 'End of Life' cost-utility threshold in determining the cost-effectiveness of the two treatments.

A full set of analyses has been carried out covering seven standard parametric functions across data from both the intervention and comparator arms of the full trial data sets available: Exponential, Weibull, Gompertz, Log-Normal, Log-Logistic, Gamma and Generalized Gamma.

In addition, the piecewise/exponential method preferred by the AG for three of the four data sets (excluding the intervention arm of the SELECT trial where the AG preferred the exponential model) are also reported.

The relative 'goodness of fit' of the contending formulations are compared and ranked on the basis of their respective Akaike Information Criterion (AIC) scores.

The estimated restricted mean OS has been estimated in each case using the area-under-curve method to 10 years from randomisation.

Results

The results of the requested analyses are set out in Tables 1 to 4 below, in descending order (rank) of relative goodness of fit, with the best fitting formulation represented by the largest negative AIC value. Differences in AIC of less than 5 between models are not generally considered important.

In two of the four trial arms (Tables 1 and 4) the AG's piecewise/exponential model is the best-fitting option. In Table 2 the AG's preferred function (Exponential) is ranked second, though the fit is similar to that of the Weibull model ranked first. In Table 3, the Gompertz and Weibull are the best fitting models. Thus, there is no single formulation which shows a clear advantage over the other candidates.

It did not prove possible to fit a curve consistent with a survival model (monotonically decreasing function) for the Generalized Gamma function in Table 4.

Examination of the restricted mean survival across both sets of best supportive care (BSC) models indicates that only one combination of trial and model type yields an estimated mean survival time at 10 years of less than 24 months (Gompertz model in the SELECT trial), while the best-fitting models in Tables 1 and 3 yield estimated mean survival at 10 years of approximately 30 and 28 months respectively. This suggests a very low probability that the mean survival in untreated (BSC) patients in either trial is less than 24 months.

Figures 1 and 2 confirm that the general pattern is different when comparing OS data between the two trial populations – tending to flatten-out over time in the SELECT trial, but suggesting a steepening decline in the DECISION trial. However, it is worthy of comment that the final fatal event in each trial appears to move more sharply downward than might be expected from the preceding event data. This appears to influence the fitted curves more strongly for the Gompertz, Weibull, and Log-Logistic models than the other functions. However, there is no similar anomaly in the intervention arms of the two trials.

One possible explanation is that it is a consequence of the crossover correction procedure (rank preserving structural failure time method [RPSFT]) applied to patients switching to the active treatment from BSC. It may be that the calibration of the crossover adjustment is most strongly influenced by patients switching early in the trial, with the result that applying the same correction at much later times may over-compensate for the switch for those still at risk late in the trial. If speculation can be confirmed, then it would warrant omitting later events from consideration during model-fitting.

Table 1: Goodness of fit results for the comparator arm of the SELECT clinical trial

Trial	Arm	Model type	Sum of Squared Residuals	Number of parameters estimated	AIC	Rank by AIC	Mean OS (months) at 10 years
SELECT	BSC	**AG piecewise/exponential**	**0.0042**	**2**	**-275.1**	**1**	**30.25**
		Log-Normal	0.0081	2	-241.4	2	34.45
		Gamma	0.0082	3	-239.0	3	33.04
		Log-Logistic	0.0092	2	-235.1	4	33.56
		Weibull	0.0116	2	-223.3	5	25.05
		Gompertz	0.0155	2	-208.5	6	22.09
		Exponential	0.0254	1	-185.3	7	30.85
		Generalized Gamma	0.0300	3	-172.8	8	41.41

AIC=Akaike Information Criterion; BSC=best supportive care; OS=overall survival

Table 2: Goodness of fit results for the intervention arm of the SELECT clinical trial

Trial	Arm	Model type	Sum of Squared Residuals	Number of parameters estimated	AIC	Rank by AIC	Mean OS (months) at 10 years
SELECT	Lenvatinib	**Weibull**	**0.0061**	**2**	**-593.5**	**1**	**48.65**
		Exponential (AG preferred)	0.0064	1	-589.3	2	49.18
		Log-Logistic	0.0073	2	-571.6	3	54.02
		Gompertz	0.0075	2	-567.9	4	49.42
		Generalized Gamma	0.0112	3	-519.9	5	53.98
		Gamma	0.0124	3	-507.9	6	54.63
		Log-Normal	0.0143	2	-492.9	7	55.30

AIC=Akaike Information Criterion; OS=overall survival

Table 3: Goodness of fit results for the comparator arm of the DECISION clinical trial

Trial	Arm	Model type	Sum of Squared Residuals	Number of parameters estimated	AIC	Rank by AIC	Mean OS (months) at 10 years
DECISION	BSC	**Gompertz**	**0.0151**	**2**	**-277.0**	**1**	**27.95**
		Weibull	0.0156	2	-274.7	2	33.57
		Log-Logistic	0.0190	2	-261.6	3	42.12
		AG piecewise/exponential	0.0200	3	-256.0	4	40.64
		Generalized Gamma	0.0214	3	-251.5	5	38.25
		Gamma	0.0216	3	-251.0	6	42.57
		Log-Normal	0.0229	2	-249.2	7	43.74
		Exponential	0.0758	1	-170.9	8	47.54

AIC=Akaike Information Criterion; BSC=best supportive care; OS=overall survival

Table 4: Goodness of fit results for the intervention arm of the DECISION clinical trial

Trial	Arm	Model type	Sum of Squared Residuals	Number of parameters estimated	AIC	Rank by AIC	Mean OS (months) at 10 years
DECISION	Sorafenib	**AG piecewise/exponential**	**0.0050**	**3**	**-344.0**	**1**	**51.44**
		Weibull	0.0056	2	-338.6	2	45.88
		Log-Logistic	0.0061	2	-332.9	3	53.68
		Gompertz	0.0074	2	-319.9	4	37.45
		Gamma	0.0083	3	-310.3	5	55.11
		Log-Normal	0.0091	2	-306.3	6	56.17
		Exponential	0.0371	1	-215.4	7	58.29
		Generalized Gamma	NC	NC	NC	NC	NC

AIC=Akaike Information Criterion; NC=generalized gamma algorithm did not converge to a meaningful survival model (not monotonically decreasing); OS=overall survival

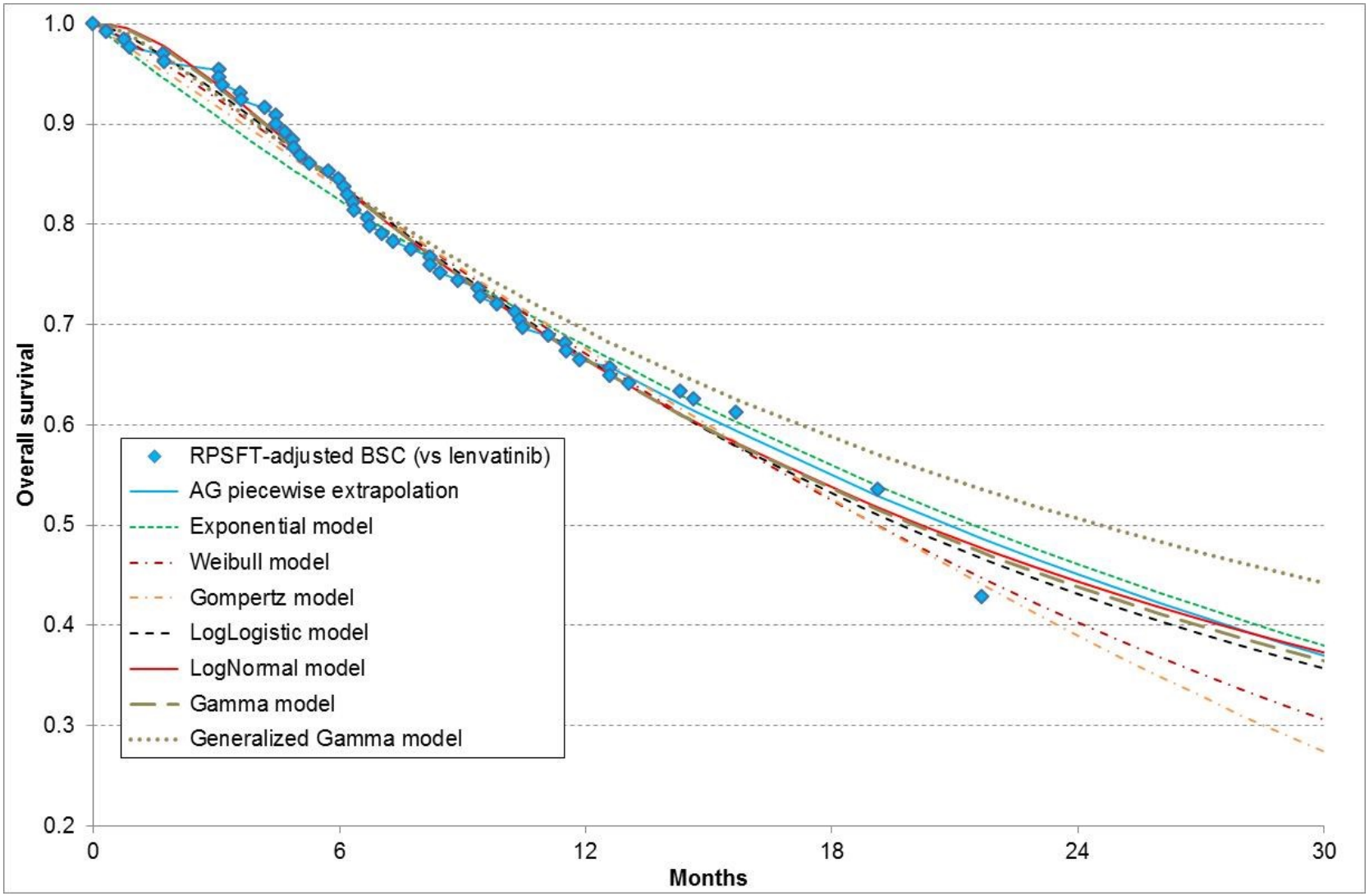

Figure 1: Comparison of fitted OS models for the BSC arm of the SELECT trial

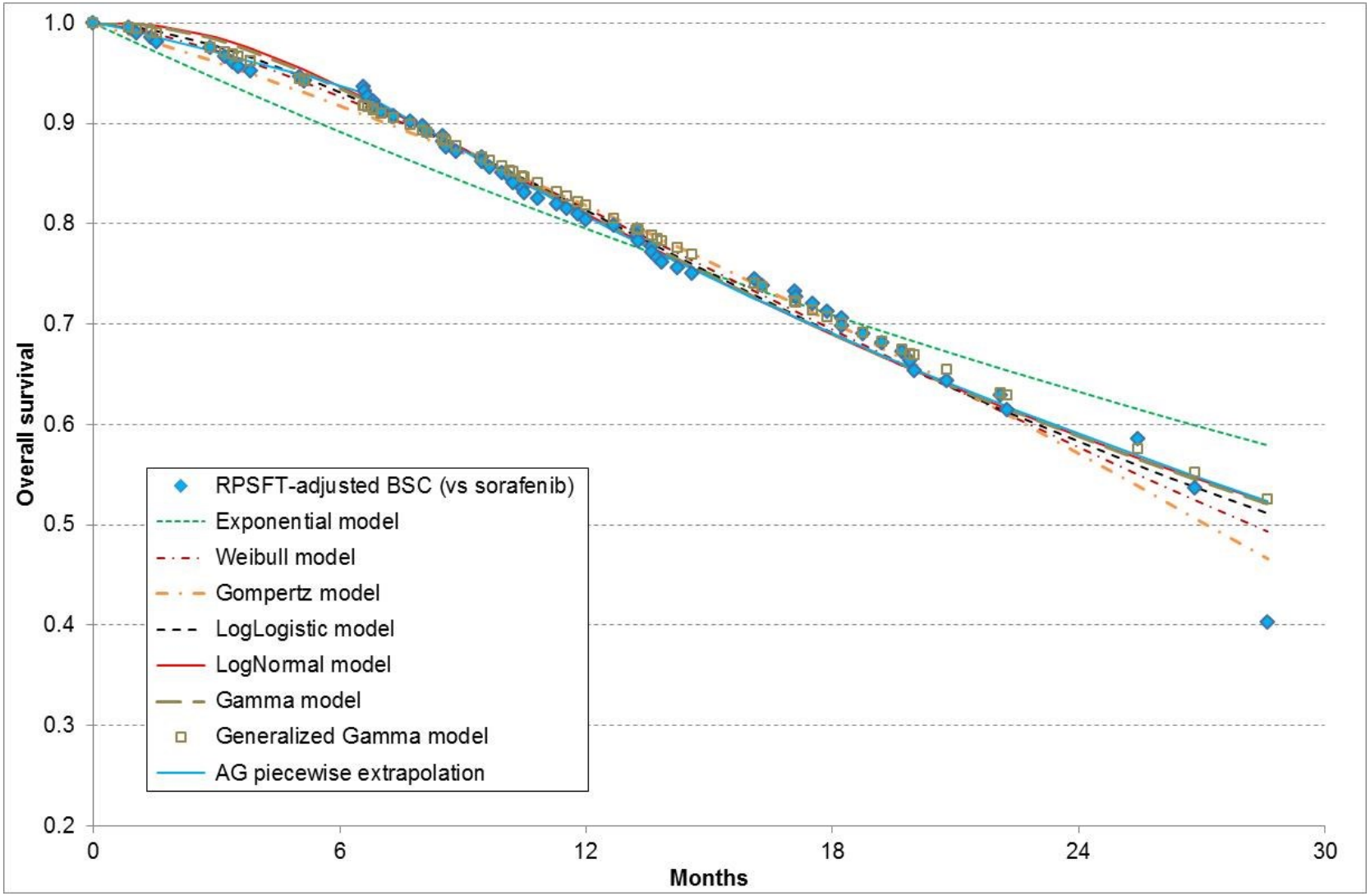

Figure 2: Comparison of fitted OS models for the BSC arm of the DECISION trial

This document is the Assessment Group (AG) response to clarification questions posed by NICE via email (15 December 2017, 13:49).

1. *Please clarify whether the revised AG base case used a piecewise exponential extrapolation for overall survival for all treatment arms? Currently the AG addendum suggests the AG preferred a* ***fully parametric exponential*** *extrapolation for the* ***lenvatinib*** *arm (see table 2 of AG addendum)*

    a. *Is this a change from the original AG base case?*

The AG revised base case has nothing at all to do with overall survival (OS) estimation. As set out in Tables 1 and 2 of the AG confidential appendix, it differs from the corrected base case only by changes to lenvatinib average dose, a specific discounting error and revisions to AE costs. Similarly, the corrected base case includes only those acknowledged problems identified by the companies prior to the first AC meeting. Throughout this process, the AG has made no changes at all to its modelling of time-to-event trial data, including OS.

There is a minor error in Table 2 of the AG confidential appendix, which may have caused confusion. The number of parameters estimated for the AG preferred option (Kaplan-Meier [K-M] / exponential extrapolation) should be 2 instead of 1 (i.e. the start time of the extrapolation and the exponential coefficient) and the AIC should be -587.3 and not -589.3. This has no material effect on the conclusions of the analysis.

2. *Please clarify whether the revised AG base case used a* ***fully parametric exponential*** *extrapolation for PFS (fitted to final data segment), and whether this was for all treatment arms*

    a. *Is this a change from the original AG base case?*

There is no change from the original AG base case for progression-free survival (PFS). For both trial arms, unconstrained exponential trends were fitted (i.e. not constrained to pass through the origin, therefore with two parameters not one). The direct trial K-M data were used in the model up to the point of minimum difference between the K-M estimate and the fitted unconstrained exponential trend, after which the exponential trend was used until the model time horizon.

3. *Following the pre-meeting this week please could you explore the following:*

    a. *No cost for post progression sorafenib (please could you confirm Bayer's ICERs using the company preferred extrapolation time points point and model and ICERs using the AG revised base case)*

    b. *Include cost of post progression TKI in lenvatinib arm (is this possible or is there a lack of data on TKI use and its duration?)*

Neither company provided follow-up data from their trial regarding the number of patients receiving any post-progression treatments, or the duration of such treatment. Therefore, it is not possible for the AG to consider any hypothetical scenarios about costs and effects which may have occurred under different circumstances. This is why the AG did not include any post-progression treatment costs in its model design.

It should be noted that neither of the company models nor the AG model explicitly includes any post-progression active treatment costs. The only costs which are estimated post-progression are the 'routine care' elements of supportive monitoring and care provided to all patients both before and after disease progression.

Scenario 3a. This scenario is equivalent to using PFS in place of time to treatment discontinuation (TTD) to represent drug use. However, in the DECISION trial there is very little difference between PFS and TTD patient numbers (see Figure 1). Applying this assumption to the AG model results in a net increase in the estimated cost per sorafenib-treated patient of [redacted], and an increase [redacted] in the estimated ICER. By contrast, using PFS in place of TTD for lenvatinib-treated patients in the SELECT trial increases the cost per patient [redacted], and the ICER by [redacted] per QALY gained.

Figure 1 Comparison of PFS and TTD for the DECISION and SELECT trials

Table 2 of the Bayer response to the ACD included cost-effectiveness results comparing the AG preferred model assumptions and parameters to three alternative scenarios focussed on different assumptions. These relate to methods proposed by Bayer in place of the AG preferred approach for extrapolation of outcome data (PFS and OS) from the DECISION clinical trial, as well as different options available for estimation of patients' average time on active treatment.

Unfortunately, these results are based on a version of the AG model which has subsequently been amended to accommodate various comments made by both companies in response to the ACD document. In order to obtain consistent and up-to-date cost-effectiveness estimates it has been necessary for the AG to incorporate the more recent amendments into the version of the AG model used by the company. The table below provides a comprehensive results summary including incremental cost-effectiveness ratios (ICERs) for sorafenib versus best supportive care (BSC), for both the list and NHS Commercial Medicines Unit acquisition prices for sorafenib.

It should be noted that the method used by Bayer for estimating treatment duration, based on the minimum of PFS and TTD, has not been correctly calculated and applied in the amended model. Therefore, the AG has reverted to the original correct method in preparing the results shown here.

Table 1: Results summary

Scenario	PFS	OS	Treatment duration	Sorafenib price	Incremental costs	Incremental QALYs	ICER
AG model	AG method	AG method	TTD	List	£43,690	0.528	**£82,721**
				[redacted]	[redacted]	[redacted]	[redacted]
AG model	AG method	AG method	PFS	List	£43,780	0.528	**£82,891**
				[redacted]	[redacted]	[redacted]	[redacted]
AG model	AG method	AG method	PFS/TTD	List	£42,344	0.528	**£80,154**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 1	KM -> fitted exponential	K-M-> piecewise exponential	TTD	List	£44,583	0.737	**£60,499**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 1	KM -> fitted exponential	K-M-> piecewise exponential	PFS	List	£50,589	0.737	**£68,648**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 1	KM -> fitted exponential	K-M-> piecewise exponential	PFS/TTD	List	£43,844	0.737	**£59,496**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 2	KM -> fitted exponential	KM -> fitted exponential	TTD	List	£44,493	0.715	**£62,200**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 2	KM -> fitted exponential	KM -> fitted exponential	PFS	List	£50,498	0.715	**£70,595**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 2	KM -> fitted exponential	KM -> fitted exponential	PFS/TTD	List	£43,753	0.715	**£61,166**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 3	Single fitted exponential	Single fitted exponential	TTD	List	£44,421	0.705	**£63,038**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 3	Single fitted exponential	Single fitted exponential	PFS	List	£49,971	0.705	**£70,913**
				[redacted]	[redacted]	[redacted]	[redacted]
Bayer Scenario 3	Single fitted exponential	Single fitted exponential	PFS/TTD	List	£42,451	0.705	**£61,661**
				[redacted]	[redacted]	[redacted]	[redacted]

PFS = progression-free survival; OS = overall survival; TTD = time to treatment discontinuation; PFS/TTD minimum of PFS and TTD; QALY = quality adjusted life year; ICER = Incremental cost-effectiveness ratio
K-M=Kaplan-Meier trial results; List = published company list price; CMU = NHS Commercial Medicines Unit agreed price

Scenario 3b. As explained above, there is no reliable means to estimate such hypothetical post-progression treatment costs without any credible basis for such calculations. It is only possible to highlight that 19.5% of lenvatinib treated patients and 16% of BSC patients in the SELECT trial had previously received TKI therapy (mainly sorafenib), and therefore would be unlikely to do so again.

Annex to Assessment Group report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (ID1059)

Assessment Group commentary on Bayer alternative time-to-event extrapolations of data from the DECISION trial

This annex is part of a project commissioned by the NIHR HTA Programme as project number 16/51/20

18 December 2017

Contains academic in confidence information

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Assessment Group commentary on Bayer alternative time-to-event extrapolations of data from the DECISION trial

As part of the formal response of Bayer to the NICE ACD document issued following the first consideration of evidence by the appraisal committee, the company put forward the results of remodelling of trial data undertaken to support estimation of a lower incremental cost-effectiveness ratio (ICER), than that obtained with the Assessment Group (AG) decision model.

The document summarises consideration by the AG of this additional evidence submitted by Bayer, relating specifically to the modelling and extrapolation of time-to-event data – overall survival (OS) and progression-free survival (PFS).

1 PROGRESSION-FREE SURVIVAL

1.1 Assessment Group analyses of PFS data

The AG reviewed the cumulative hazard trends for the latest data cut from the DECISION trial (Figure 1), and concluded that in both trial arms a simple linear trend with non-zero intercept was the optimal characterisation of the available data. This is equivalent to a simple exponential (i.e. constant hazard) model with a short initial event-free period (18 days in the placebo arm and 57 days in the sorafenib arm).

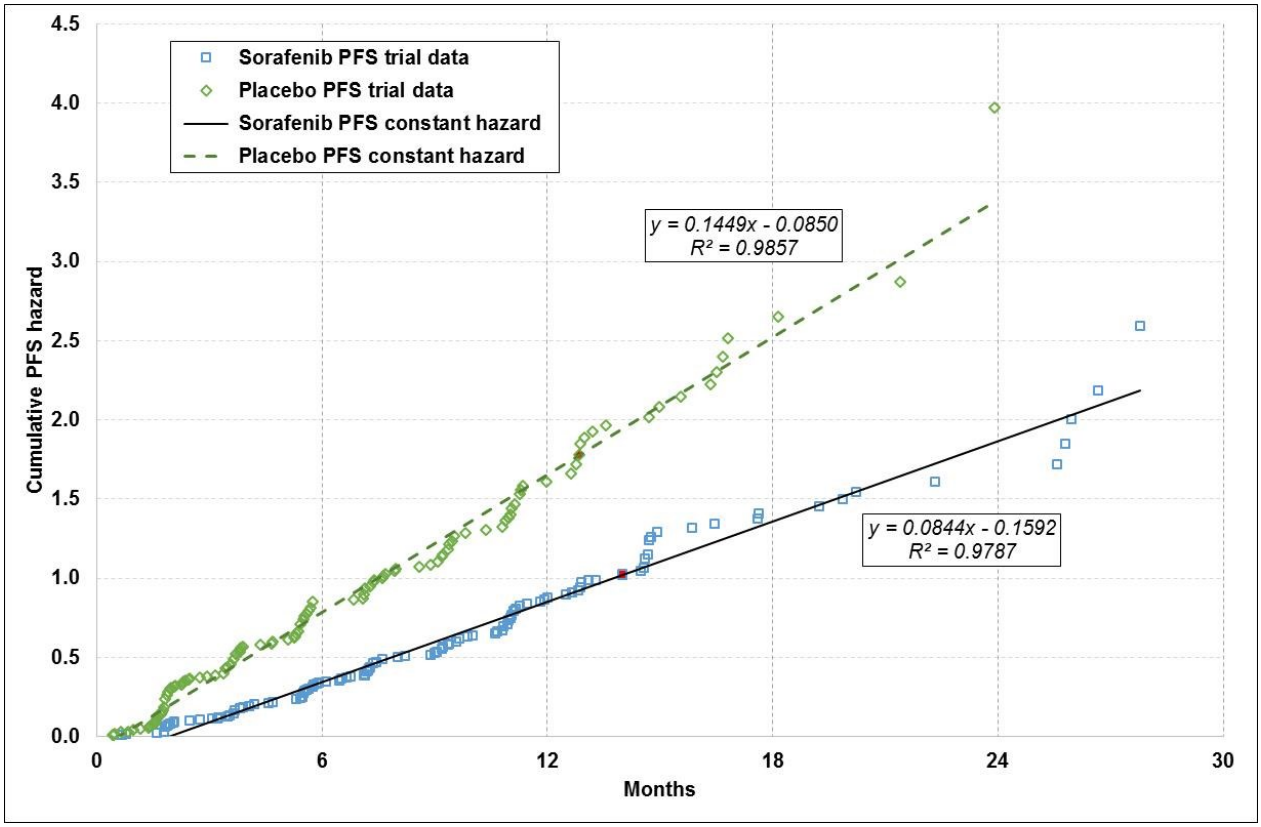

Figure 1: Cumulative hazard of disease progression or death in the DECISION trial, with fitted unconstrained exponential trends (transition from K-M data to exponential trend at data points filled red)

In order to represent data from the early phase of the trial, the unadjusted Kaplan-Meier (K-M) data were used in the decision model from time zero for at least 12 months, followed by an exponential extrapolation following the estimated trendline for each treatment arm. The switch from K-M data to extrapolation was determined by selecting the observed event time with the minimum residual difference between K-M data and the corresponding exponential trend at the same time. This occurred after 12.846 months for placebo-treated patients, and 13.996 months for sorafenib-treated patients.

The best estimate of mean PFS in the initial period prior to applying exponential extrapolation is obtained from the calculated area under the K-M curve from randomisation to the switching time. Thereafter, the addition progression-free time is easily calculated from the PFS value at the switch time and the estimation exponential trend parameter. This approach simultaneously optimises direct use of

trial K-M data in the initial period when most patients are still at risk, and preserves the long-term exponential trend calibrated on the whole of the available trial data.

For the sorafenib arm of the DECISION trial, mean PFS is estimated as 9.58 months (AUC K-M data) plus 4.26 months (exponential extrapolation), giving an overall mean of 13.84 months. The corresponding figures for the placebo arm are 6.39 months plus 1.17 months extrapolation giving an overall mean PFS of 7.56 months, indicating an overall PFS gain attributable to sorafenib of 6.28 months.

1.2 Bayer alternative analyses of PFS data

Bayer have prepared 3 alternative approaches to estimating long-term PFS:

a) *Simple exponential model*

This calibrates a one-parameter exponential function constrained to pass directly through the origin. Figure 2 shows how these models compare with the K-M trial results. In the placebo arm, the constrained exponential model is generally similar to the K-M results (with the exception of the initial 8 weeks). However, in the fitted sorafenib model the estimated PFS is seriously under-estimated for 11 months and then consistently over-estimated for the remaining 18 months. When projected over the full lifetime of the remaining patients this imbalance results in approximately 2 additional months of net PFS benefit in favour sorafenib.

b) *K-M data followed by piecewise extrapolation*

Initially this approach follows the K-M trial data closely for the first 16 months, and then appends a piecewise long-term exponential trend for extrapolation (Figure 3). Unfortunately, there is a serious flaw in the implementation of the extrapolation in the placebo arm, so that the estimate of PFS unexpectedly increases at month 16 by about 35% and sustains this increase in the subsequent life-time period. Time-to-event analysis can only decrease or remain level over time – they can never increase. The effect of this serious mistake is to understate the long-term PFS benefit attributable to sorafenib, with consequent errors in estimates of cost-effectiveness.

c) *K-M data followed by exponential extrapolation*

This method uses K-M data for the initial period (16 months in the placebo arm and 25 months in the sorafenib arm) followed by a simple exponential curve calibrated from the full K-M data thereafter (Figure 4). Here there is an issue with the final 2 to 3 months relating to the sorafenib arm which shows a sudden downturn in PFS from 18% to 7.5%. This sudden change is not reflected in this Bayer method, which suggests that the long-term exponential extrapolation may overstate significantly the PFS benefit attributable to sorafenib.

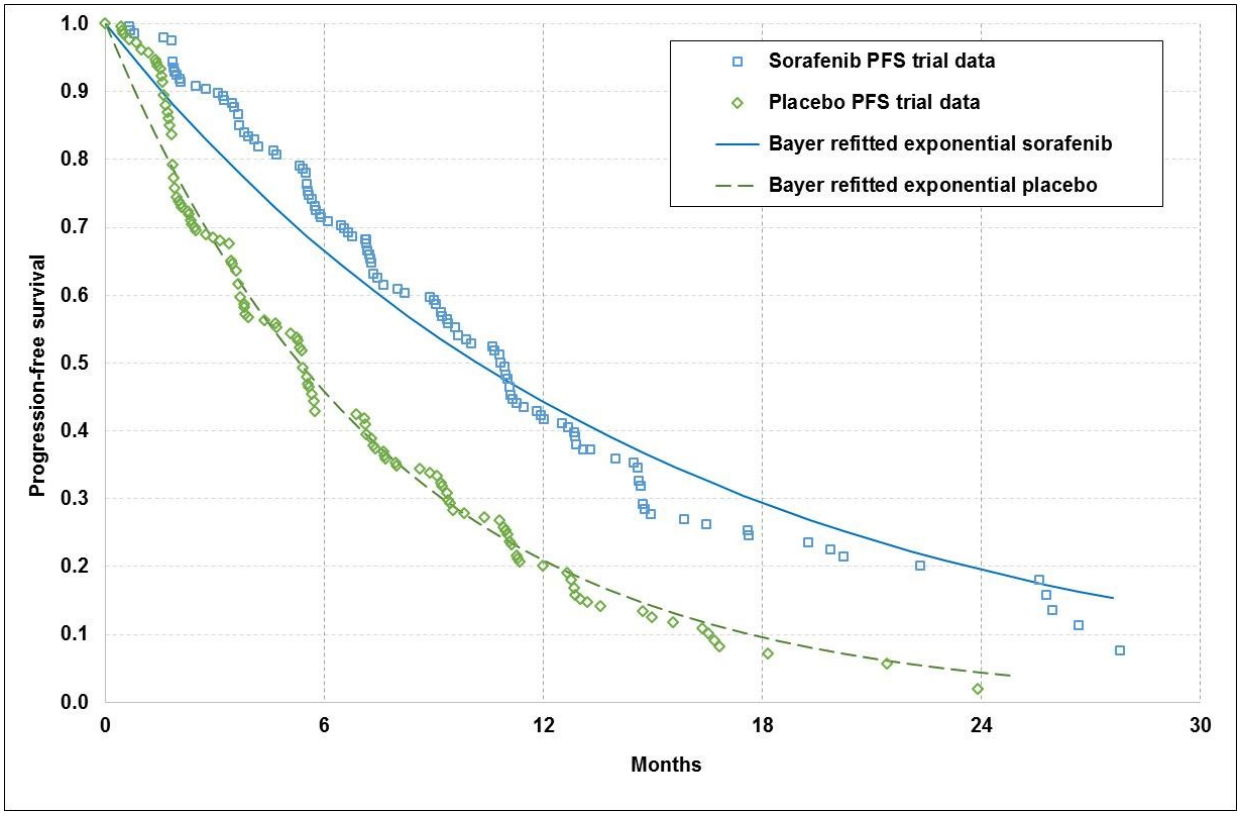

Figure 2: Progression-free survival in the DECISION trial, with fitted constrained exponential trends

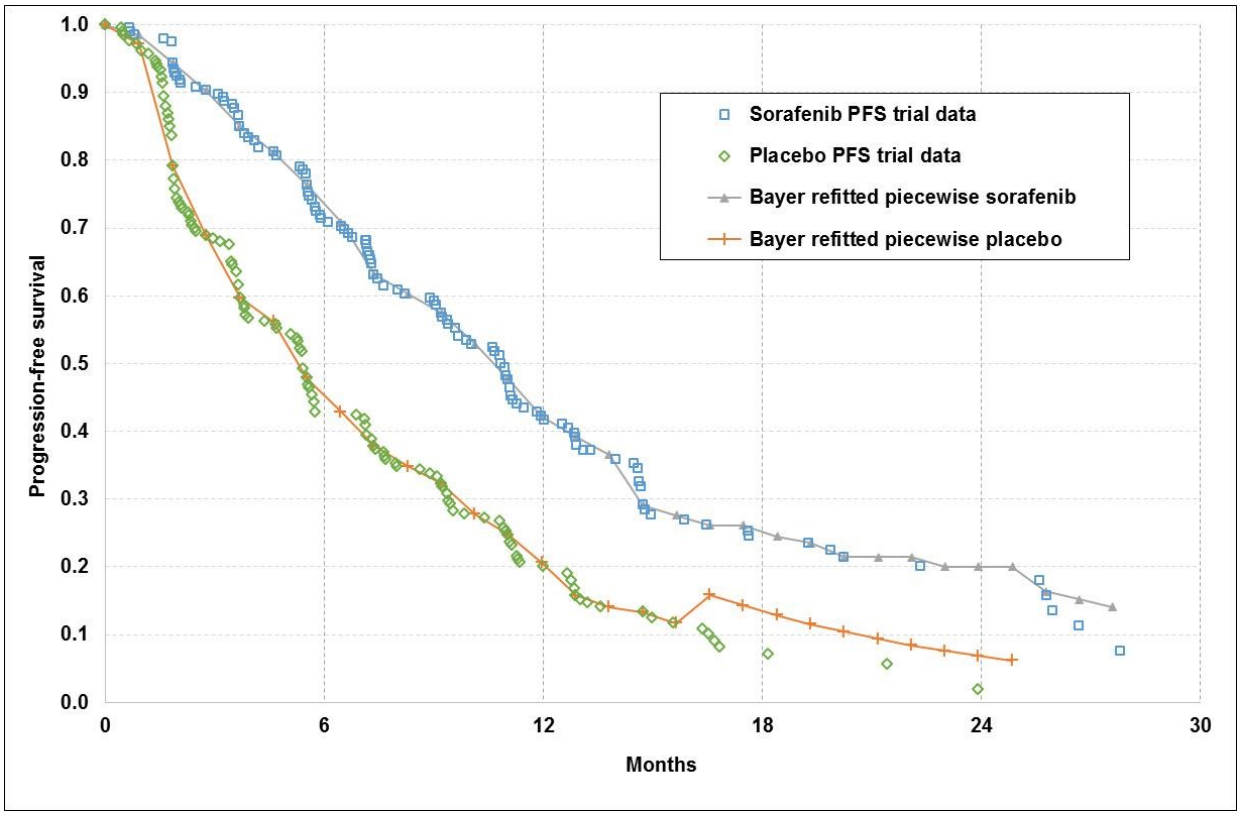

Figure 3: Progression-free survival in the DECISION trial, with fitted piecewise trends

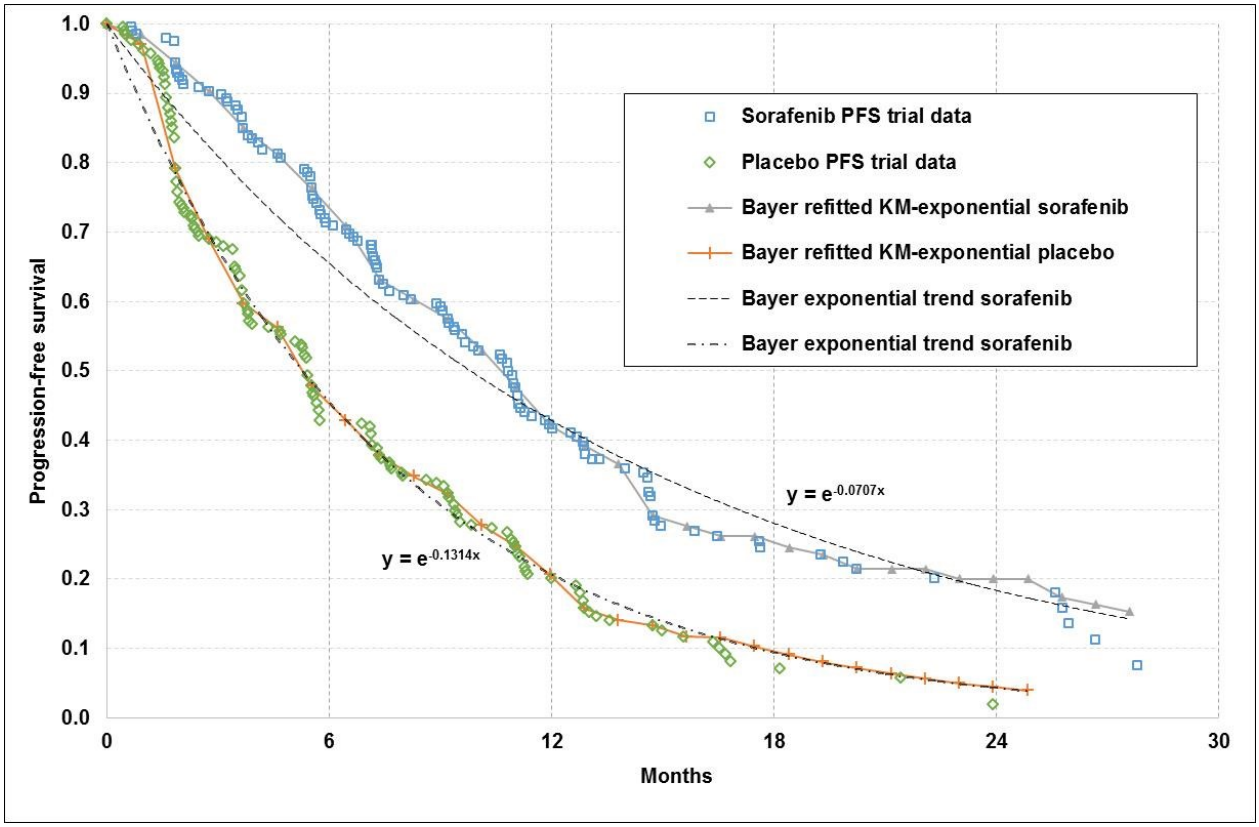

Figure 4: Progression-free survival in the DECISION trial, with refitted KM-exponential trends

1.3 PFS summary

Estimated values of mean PFS comparing the AG preferred approach to extrapolation with the three alternatives suggested by Bayer are shown in Table 1.

Table 1: Estimated mean PFS using the AG model and three alternative methods proposed by Bayer

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

2 OVERALL SURVIVAL

2.1 Assessment Group analyses of OS data

The AG used the latest version of overall survival trial data supplied by Bayer late in the development phase of the appraisal, following a query raised by the AG.

Figures 5 and 6 display the cumulative hazard and overall survival Kaplan-Meier results, together with the 2-phase exponential models fitted independently to the two trial arms. The Kaplan-Meier values were used to populate the AG model directly from the time of randomisation until the data point in each

arm with the minimum discrepancy between the trial data and the fitted model (indicated in Figures 5 and 6). This occurred after 25.436 months for placebo-treated patients, and 28.353 months for sorafenib-treated patients. Thereafter the fitted model values were applied for extrapolation.

The best estimate of mean OS in the initial period prior to applying exponential extrapolation is obtained from the calculated area under the K-M curve from randomisation to the switching time. Thereafter, the addition OS time is easily calculated from the OS value at the switch time and the estimation exponential trend parameter. This approach simultaneously optimises direct use of trial K-M data in the initial period when most patients are still at risk, and preserves the long-term exponential trend calibrated on the whole of the available trial data.

For the sorafenib arm of the DECISION trial, mean OS is estimated as 10.64 months (area under the K-M curve data) plus 46.03 months (exponential extrapolation), giving an overall mean of 56.66 months. The corresponding figures for the RPFST-adjusted placebo arm are 20.41 months plus 23.38 months extrapolation giving a total of 43.79 months, indicating an OS gain attributable to sorafenib of 12.88 months.

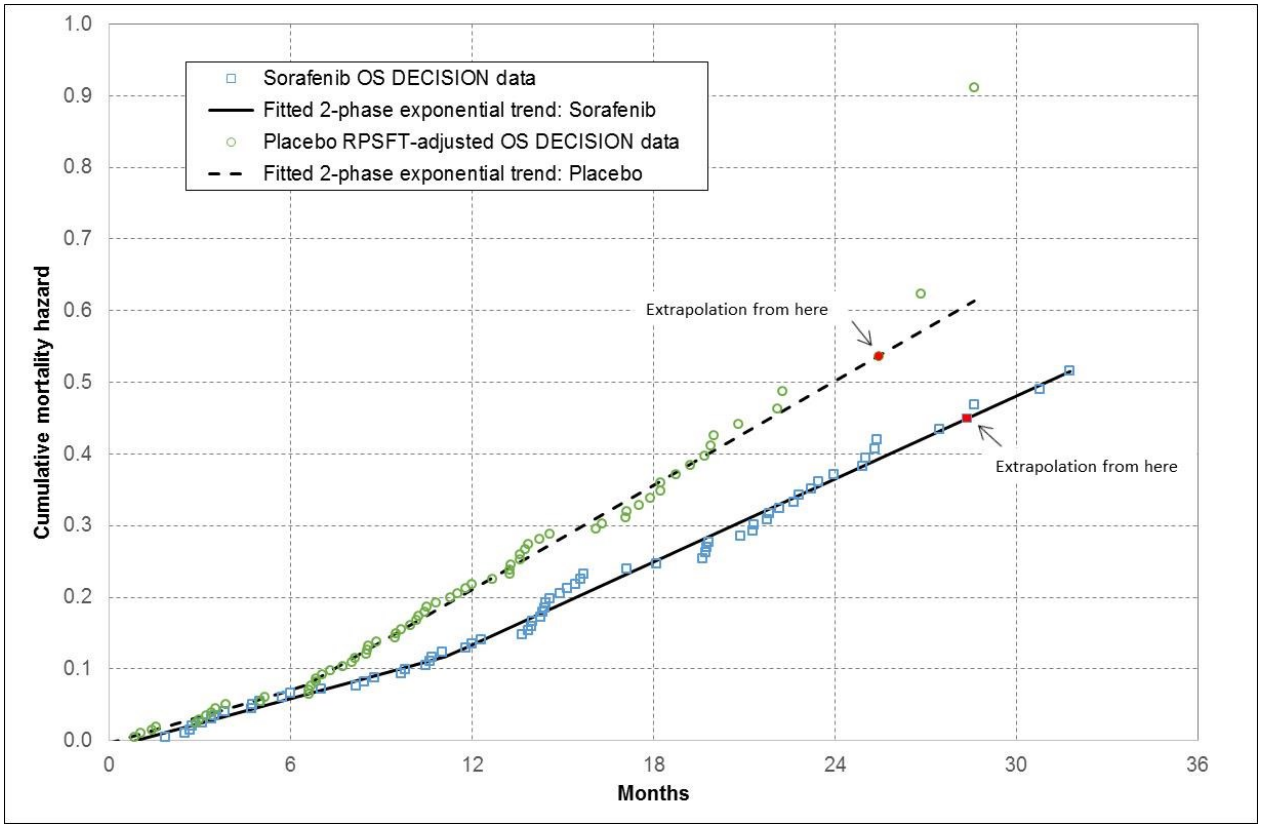

Figure 5: Cumulative hazard of death in the DECISION trial, with fitted unconstrained 2-phase exponential trends (transition from K-M data to exponential extrapolation at data points indicated)

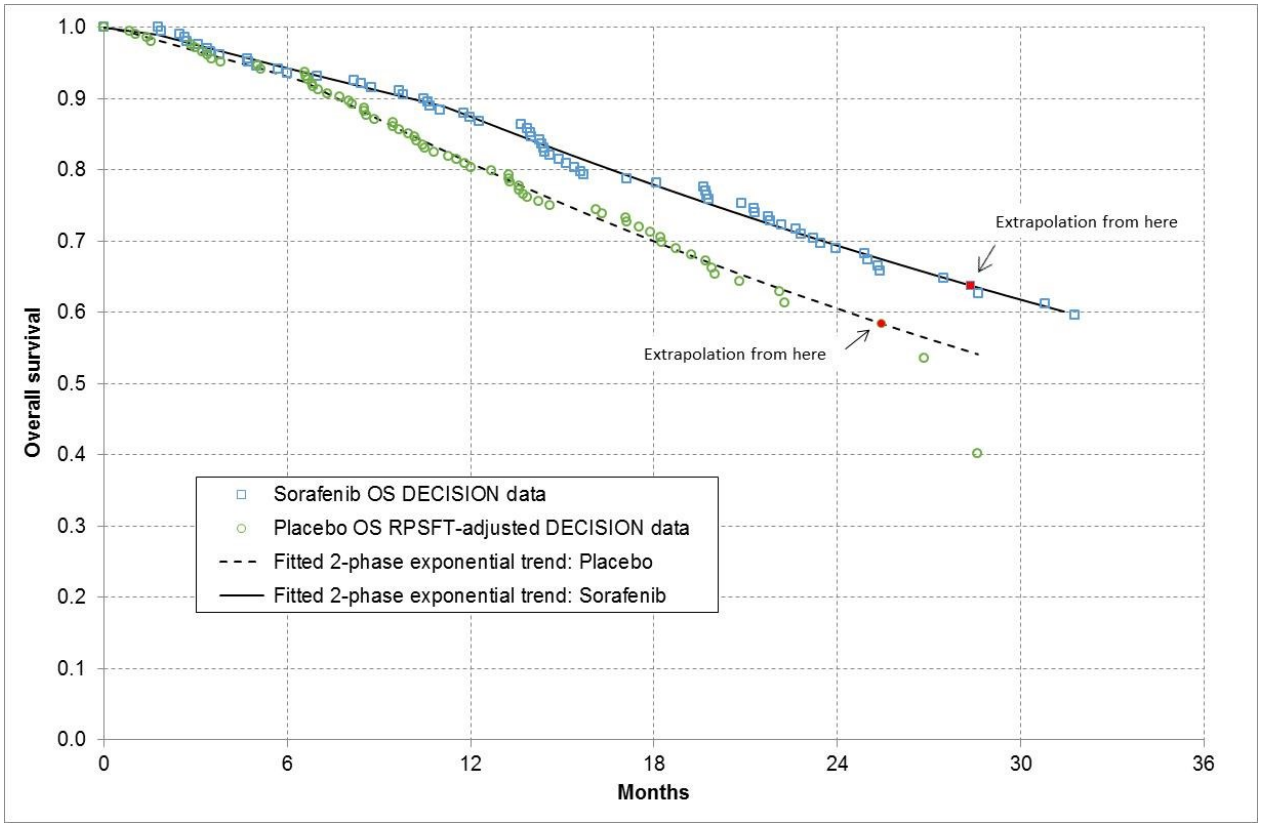

Figure 6: Overall survival in the DECISION trial, with fitted unconstrained 2-phase exponential trends (transition from K-M data to exponential extrapolation at data points indicated)

2.2 Bayer alternative analyses of overall survival data

Bayer has proposed the same three alternative approaches to re-analysis of DECISION trial OS data, as for PFS.

Figures 7 and 8 allow direct comparison of the company's three modified extrapolation models with the AG 2-phase exponential method. All three Bayer models show clear long-term trends which result in increasing bias towards over-estimating OS in the sorafenib arm when compared to both the trial data and the AG model. Similarly, two of the three proposed models for the placebo arm also show long-term over-estimation.

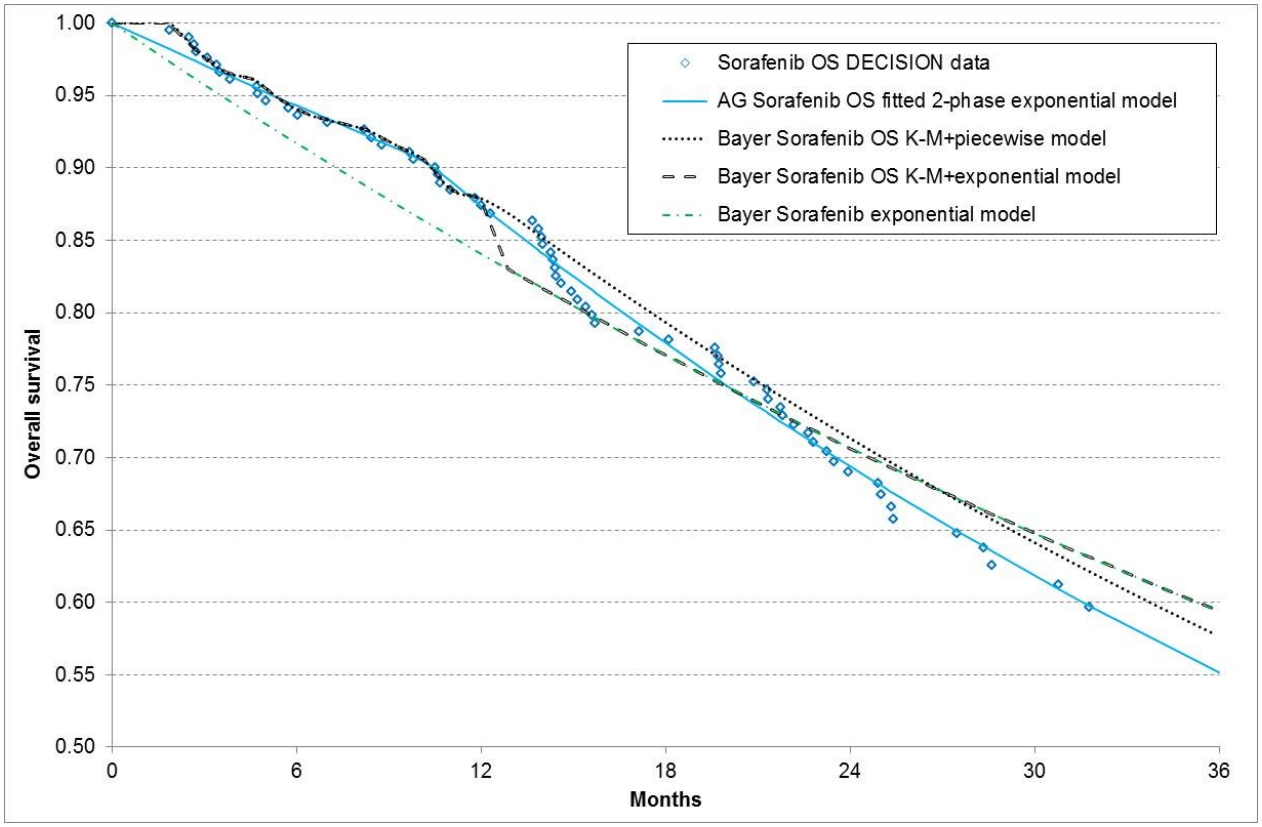

Figure 7: Overall survival in the sorafenib arm of the DECISION trial, showing the three models proposed by Bayer, compared to the AG 2-phase exponential model

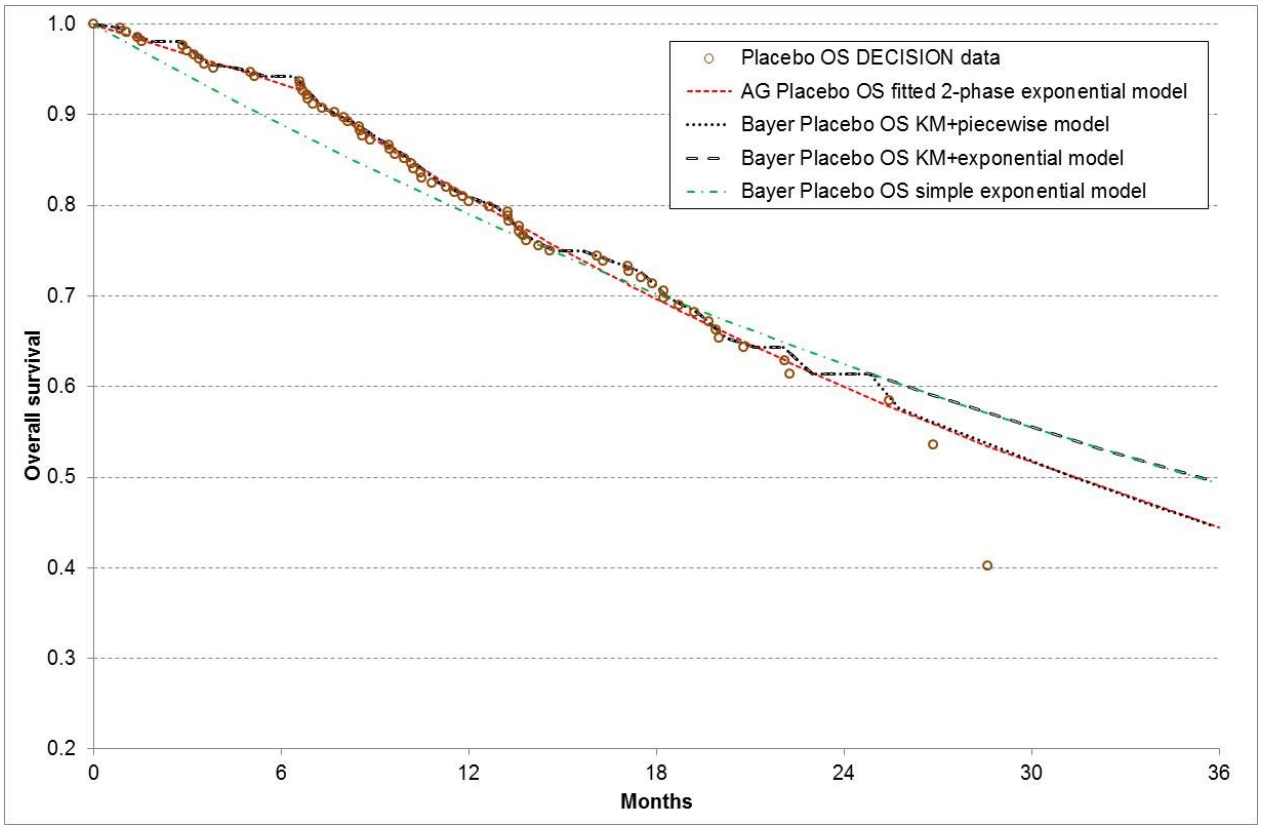

Figure 8: Overall survival in the placebo arm of the DECISION trial, showing the three models proposed by Bayer, compared to the AG 2-phase exponential model

3 CONCLUSION

Comparison of the performance of the AG method of extrapolating both PFS and OS trial data from the DECISION trial with the three alternative methods proposed by Bayer demonstrates that the former provides more accurate and reliable estimates of time to event variables than do the alternatives. After careful reconsideration of the analyses presented by Bayer we remain of the view that the AG modelling is robust and more appropriate as a basis for assessing the cost-effectiveness of sorafenib.