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
   - *Joint response from the* Royal College of Physicians

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

4. **Additional evidence** provided by the company, Eisai

5. **Assessment Group review of the additional evidence**, provided 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 2nd Appraisal Consultation Document (ACD2)

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	Bayer welcomes the committee's decision to recommend both lenvatinib and sorafenib as treatment options for patients with advanced RAI-R DTC. The decision to use lenvatinib or sorafenib is based on a patient's individual circumstances, such as pain and location of lesions, reflecting underlying differences in both mechanism of action and safety profile (1). Given there are no alternative treatment options, and the substantial clinical benefit achieved via active treatment, it is important patients have access to an option they can tolerate, and best meets the needs of their condition. The updated ACD included a restriction on the treatment of patients who have previously received a tyrosine kinase inhibitor (TKI). Given the small number of patients and high level of unmet need, sequential TKI treatment has the potential to offer significant benefit to patients, with modest budget implications.	Thank you for your comment. The committee considered all the evidence submitted for the group of patients who have previously received a tyrosine kinase inhibitor, including evidence from clinical trials, real-world studies and the lenvatinib compassionate use programme (see sections 3.6 to 3.8 of the FAD2). Because of the uncertainty about the clinical- and cost-effectiveness of the drugs when used sequentially, the committee concluded that its recommendation for sorafenib and lenvatinib is limited to people who have not had previous treatment with a tyrosine kinase inhibitor (section 3.23 of FAD2).
2	Company	Bayer	Bayer have no clinical evidence for sorafenib in patients previously treated with lenvatinib, as the phase III DECISION trial (2) was conducted prior to any other treatments being approved in this indication. Evidence for lenvatinib from the SELECT trial (3) shows comparable efficacy between a pre-defined TKI experienced sub-group who had previously received sorafenib, and a TKI naïve sub-group (for both PFS and ORR), with a shorter median treatment duration in the previously treated group (4). Should overall survival data be available for the TKI experienced sub-group, cost-effectiveness could be determined.	Thank you for your comment. The committee recognised that previous treatment with a tyrosine kinase inhibitor was not allowed in DECISION, therefore it considered that sorafenib can only be considered and recommended as a first tyrosine kinase inhibitor treatment for this indication (sections 3.6 and 3.23 of the FAD2). Eisai did not provide overall survival results or cost-effectiveness analysis for this subgroup, which resulted in the uncertainty about the clinical and cost-effectiveness of lenvatinib when used after a tyrosine kinase inhibitor.
3	Company	Eisai	Eisai do not believe that the summary of the clinical evidence is a reasonable interpretation of the evidence for the reasons below: Evidence from the compassionate use program in England has not been considered: Lenvatinib received its marketing authorisation in May 2015. At this time lenvatinib	Thank you for your comment. During the appraisal the committee considered the data from the compassionate use programme submitted at consultation and concluded that this data was not sufficient evidence for decision-making about the clinical effectiveness of lenvatinib when used after sorafenib (see section 3.7 of the FAD2).

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
			was not included in the CDF due to the planned CDF reforms. Pending NICE review, Eisai agreed to provide access to lenvatinib for eligible patients with differentiated thyroid cancer (DTC) who had received treatment with previous sorafenib and had progressed radiologically on/after sorafenib or were intolerant of sorafenib or contraindicated from using sorafenib. Between February 2017 and April 2018, Eisai has approved access for 52 patients via the scheme, all of whom had received prior treatment with sorafenib. Data on these patients currently available to Eisai is limited, but it is evident from the estimated time on treatment that there is a clear benefit of lenvatinib in second-line patients. Further details are provided and summarised in Appendix 1.	
4	Company	Eisai	Eisai do not believe that the summary of the clinical evidence is a reasonable interpretation of the evidence for the reasons below: Published real world evidence has not been considered: Recently published “real world” data from audits undertaken in France, Switzerland and Italy have demonstrated the benefit of lenvatinib in those patients who have been previously treated with at least one prior tyrosine kinase inhibitor (TKI). Further details are provided and summarised in Appendix 1.	Thank you for your comment. During the appraisal the committee considered the data from audits of lenvatinib use in France, Switzerland and Italy submitted at consultation and concluded that the audits did not provide convincing evidence of the clinical effectiveness of sequential treatment with lenvatinib after sorafenib (see section 3.8 of the FAD2).
5	Company	Eisai	Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS. In the SELECT study and as stated in section 3.6 of the ACD, the progression free survival (PFS) benefit associated with lenvatinib was maintained in all prespecified subgroups in the SELECT study. The median PFS with lenvatinib was 15.1 months among those who had received one prior treatment regimen with a TKI. It is important to note that the assessment group report concludes on page 154 that “… lenvatinib is more effective when compared with placebo/BSC for all patients and that prior VEGFR-targeted therapy (or even a treatment delay) does not influence the potential for a patient to benefit from treatment.” The company submission does state that the prior TKI sub group results should be interpreted with caution due to the smaller number of patients (25% and 20% of the lenvatinib and placebo groups respectively had one prior TKI). Therefore Eisai have provided some additional supportive “real-world” evidence which further demonstrates the clinical benefit in this patient group and that the NICE recommendations should, at the very least, take into account the patients who have been receiving lenvatinib as a second-line option in the compassionate use program.	Thank you for your comment. The committee considered all the evidence submitted for the group of patients who have previously received a tyrosine kinase inhibitor, including evidence from clinical trials, real-world studies and the lenvatinib compassionate use programme (see sections 3.6 to 3.8 of the FAD2). Because of the uncertainty about the clinical- and cost-effectiveness of the drugs when used sequentially, the committee concluded that its recommendation for sorafenib and lenvatinib is limited to people who have not had previous treatment with a tyrosine kinase inhibitor. . The remit for the technology appraisals programme is limited to England. Reimbursement decisions in other areas of the UK do not determine the appraisal committee’s decision.

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
			Both Eisai's and the assessment group's analysis of cost effectiveness were based on the ITT population from the SELECT study, which included both first and second line patients. Due to the inherent limitations and substantial uncertainty associated with assessing cost effectiveness in this small subgroup of patients, Eisai have not submitted any additional cost effectiveness evidence. Reimbursement for the unrestricted use of lenvatinib was approved by The Scottish Medicines Consortium (SMC) in October 2016 and by the All Wales Medicines Strategy Group (AWMSG) in October 2017. Eisai therefore urges NICE to reconsider the current restricted advice to address the inequality in access for UK patients.	
6	Consultee	NCRI-ACP-RCP-RCR	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.	Comment noted.
7	Consultee	NCRI-ACP-RCP-RCR	Whilst we accept the comment (section 3.21) that neither the companies nor the assessment group presented cost effectiveness analyses according to previous tyrosine kinase inhibitor (TKI) treatment, we do believe that there is evidence of significant clinical efficacy for Lenvatinib following previous TKI. Subgroup analysis within the SELECT trial demonstrated that the group of patients who had received a previous TKI derived almost the same improvement in progression free survival as previously untreated patients, as acknowledged in section 3.6. We would therefore like to propose that a separate cost-effectiveness analysis is undertaken for the subgroup of patients previously treated with a TKI to formally determine whether or not second line treatment can be considered cost-effective.	Thank you for your comment. The committee acknowledged that lenvatinib appears to delay disease progression in this group of people. Although the progression-free survival results and objective tumour response rates for the subgroup were similar to the results for the overall population in SELECT, the committee could not predict whether this would also apply to overall survival results. Eisai did not provide overall survival results or cost-effectiveness analysis for this subgroup, which resulted in the uncertainty about the clinical and cost-effectiveness of lenvatinib when used after a tyrosine kinase inhibitor (see sections 3.6 and 3.23 of the FAD2).
8	Web comment	Professional	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,	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.

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
			Wales, other countries in Europe and around the world. Patients in England will have best supportive care only with no disease modifying treatment options.	
9	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
10	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 haven’t made the neccessary arrangements for rare cancers to be included.	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
11	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. Yes, I have thyroid cancer and understand it's devastating effects for patients unable to have this medication.	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
12	Web	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	Thank you for your comment. The FAD2 recommends both lenvatinib and sorafenib as treatment options for

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
	comment		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.	progressive, locally advanced or metastatic, differentiated thyroid cancer (papillary, follicular or Hürthle cell) in adults whose disease does not respond to radioactive iodine and who have not received a prior tyrosine kinase inhibitor.
13	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
14	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor. The remit for the technology appraisals programme is limited to England. Reimbursement decisions in other areas of the UK do not determine the appraisal committee's decision.
15	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? 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?	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
16	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.

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
17	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 born in this country they will not be treated. Have the psychological effects of this been considered in the cost benefit analysis?	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
18	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. 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.	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
19	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. No, apart from having worked in the NHS all my life I am appalled at the way it is being dragged down and mishandled.	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
20	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.

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
21	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
22	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
23	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
24	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	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.

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
			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?	
25	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
26	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 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.	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
27	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
28	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
29	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	Thank you for your comment. The FAD2 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 and who have not received a prior

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
			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.	tyrosine kinase inhibitor.
30	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
31	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
32	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 FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
33	Web comment	Public	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.	Thank you for your comment. The FAD2 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 and who have not received a prior tyrosine kinase inhibitor.
34	Web comment	Public	To whom it may concern I am writing to add my voice to your consultation on "lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [ID 1059]". I am the Secretary/Director of the Thyroid Cancer Alliance (TCA) and a Trustee of The Thyroid Trust (TTT), and I was concerned to learn that the Final Appraisal	Thank you for your comment. The FAD2 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 and who have not received a prior

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
			Determination on lenvatinib and sorafenib was retracted due to a procedural error and particularly the implications it has for the use of lenvatinib. My understanding is that the retraction is a consequence of an additional section (section 3.6) inserted into the FAD, which led to the conclusion that both drugs were approved for first line use only. I believe this conclusion to be incorrect because the FAD initially recommended both drugs within their marketing authorisations. To then restrict their use to first line treatment only contradicts the initial advice and does not adequately allow for patients to be transferred from one drug to the other if they suffer side effects, since they may respond differently to the two drugs. It also does not appear to allow patients who were prescribed sorafenib when this was available through the UK Cancer Drugs Fund to transfer to lenvatinib. In addition, if the recommendation in section 3.6 is not amended, it will lead to inequality in access across the UK and Republic of Ireland and discriminate against patients in England. Lenvatinib was approved by both the FDA and the EMA in 2015 and was subsequently approved for unrestricted use by the Scottish Medicines Consortium in October 2016 and by the All Wales Medicines Strategy Group in October 2017, and has also been approved in the ROI, which means that patients in Scotland, Wales, and Ireland are already able to benefit from sorafenib and lenvatinib as both first and second line treatments. To quote your own press release, Mirella Marlow, acting director of the NICE centre for health technology evaluation, said: “Treatment options for these types of thyroid cancer are limited, so it is important that we are able to give patients much needed access to alternatives to best supportive care at this stage of their disease. These drugs will give patients extra time, as well as improving their quality of life.” I urge you to review the recommendation in favour of allowing both drugs to be used within their marketing authorisations and to give patients who qualify for treatment an unrestricted choice as is the case in the rest of the UK and in Ireland. Although the TCA and the TTT are not official stakeholders in this consultation I do hope that you will accept this submission from me as an interested member of the public with years of experience as a thyroid cancer patient advocate. I would appreciate it if you would acknowledge receipt. With kind regards	tyrosine kinase inhibitor.

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: 23rd April 2018

Response to the ACD

Bayer welcomes the committee's decision to recommend both lenvatinib and sorafenib as treatment options for patients with advanced RAI-R DTC. The decision to use lenvatinib or sorafenib is based on a patient's individual circumstances, such as pain and location of lesions, reflecting underlying differences in both mechanism of action and safety profile (1). Given there are no alternative treatment options, and the substantial clinical benefit achieved via active treatment, it is important patients have access to an option they can tolerate, and best meets the needs of their condition.

The updated ACD included a restriction on the treatment of patients who have previously received a tyrosine kinase inhibitor (TKI). Given the small number of patients and high level of unmet need, sequential TKI treatment has the potential to offer significant benefit to patients, with modest budget implications.

Bayer have no clinical evidence for sorafenib in patients previously treated with lenvatinib, as the phase III DECISION trial (2) was conducted prior to any other treatments being approved in this indication.

Evidence for lenvatinib from the SELECT trial (3) shows comparable efficacy between a pre-defined TKI experienced sub-group who had previously received sorafenib, and a TKI naïve sub-group (for both PFS and ORR), with a shorter median treatment duration in the previously treated group (4). Should overall survival data be available for the TKI experienced sub-group, cost-effectiveness could be determined.

References

1. National Institute Care and Health Excellence. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [ID1059]: Appraisal consultation: 2,. 2018.
2. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. The Lancet. 2014;384(9940):319-28.
3. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. New England Journal of Medicine. 2015;372(7):621-30.
4. Liverpool Reviews and Implementation Group (LRiG). Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [ID1059] Assessment Report. 2017.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document. Deadline for comments – 5pm on 23 April 2018. Submit your responses through NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Eisai Limited**]

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document. Deadline for comments – 5pm on 23 April 2018. Submit your responses through NICE Docs.

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 Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Eisai do not believe that the summary of the clinical evidence is a reasonable interpretation of the evidence for the reasons below:	
1	**Evidence from the compassionate use program in England has not been considered.** Lenvatinib received its marketing authorisation in May 2015. At this time lenvatinib was not included in the CDF due to the planned CDF reforms. Pending NICE review, Eisai agreed to provide access to lenvatinib for eligible patients with differentiated thyroid cancer (DTC) who had received treatment with previous sorafenib and had progressed radiologically on/after sorafenib or were intolerant of sorafenib or contraindicated from using sorafenib. Between February 2017 and April 2018, Eisai has approved access for 52 patients via the scheme, all of whom had received prior treatment with sorafenib. Data on these patients currently available to Eisai is limited, but it is evident from the estimated time on treatment that there is a clear benefit of lenvatinib in second-line patients. Further details are provided and summarised in Appendix 1.
2	**Published real world evidence has not been considered.** Recently published “real world” data from audits undertaken in France, Switzerland and Italy have demonstrated the benefit of lenvatinib in those patients who have been previously treated with at least one prior tyrosine kinase inhibitor (TKI).

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document. Deadline for comments – 5pm on 23 April 2018. Submit your responses through NICE Docs.

	Further details are provided and summarised in Appendix 1.

Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS.

In the SELECT study and as stated in section 3.6 of the ACD, the progression free survival (PFS) benefit associated with lenvatinib was maintained in all prespecified subgroups in the SELECT study. The median PFS with lenvatinib was 15.1 months among those who had received one prior treatment regimen with a TKI. It is important to note that the assessment group report concludes on page 154 that "… lenvatinib is more effective when compared with placebo/BSC for all patients and that prior VEGFR-targeted therapy (or even a treatment delay) does not influence the potential for a patient to benefit from treatment."

The company submission does state that the prior TKI sub group results should be interpreted with caution due to the smaller number of patients (25% and 20% of the lenvatinib and placebo groups respectively had one prior TKI). Therefore Eisai have provided some additional supportive "real-world" evidence which further demonstrates the clinical benefit in this patient group and that the NICE recommendations should, at the very least, take into account the patients who have been receiving lenvatinib as a second-line option in the compassionate use program.

Both Eisai's and the assessment group's analysis of cost effectiveness were based on the ITT population from the SELECT study, which included both first and second line patients. Due to the inherent limitations and substantial uncertainty associated with assessing cost effectiveness in this small subgroup of patients, Eisai have not submitted any additional cost effectiveness evidence.

Reimbursement for the **unrestricted** use of lenvatinib was approved by The Scottish Medicines Consortium (SMC) in October 2016 and by the All Wales Medicines Strategy Group (AWMSG) in October 2017. Eisai therefore urges NICE to reconsider the current restricted advice to address the inequality in access for UK patients.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.

Please return through NICE Docs

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document. Deadline for comments – 5pm on 23 April 2018. Submit your responses through NICE Docs.

- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document. Deadline for comments – 5pm on 23 April 2018. Submit your responses through NICE Docs.

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

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document. Deadline for comments – 5pm on 23 April 2018. Submit your responses through NICE Docs.

Name of commentator person completing form:	[redacted]
Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	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.
General	Whilst we accept the comment (section 3.21) that neither the companies nor the assessment group presented cost effectiveness analyses according to previous tyrosine kinase inhibitor (TKI) treatment, we do believe that there is evidence of significant clinical efficacy for Lenvatinib following previous TKI. Subgroup analysis within the SELECT trial demonstrated that the group of patients who had received a previous TKI derived almost the same improvement in progression free survival as previously untreated patients, as acknowledged in section 3.6. We would therefore like to propose that a separate cost-effectiveness analysis is undertaken for the subgroup of patients previously treated with a TKI to formally determine whether or not second line treatment can be considered cost-effective.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or

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

Consultation on the appraisal consultation document. Deadline for comments – 5pm on 23 April 2018. Submit your responses through NICE Docs.

the person could be identified.

- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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

Name	[redacted]
Role	Carer
Comments:	

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
Comments:	

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
Comments:	

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.

Yes, I have thyroid cancer and understand it's devastating effects for patients unable to have this medication.

Name	[redacted]
Role	Patient
Comments:	
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
Comments:	
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
Comments:	
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
Comments:	

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?

Furthermore, if Thyroid cancer is rare. Why would it not be available?

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
Comments:	
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
Comments:	
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 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
Comments:	

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.

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
Comments:	
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. 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
Comments:	
"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
Comments:	
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
Comments:	
If something will help prolong the lives of young people then it should be made available to them.	

Name	[redacted]
Role	Public
Comments:	
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
Comments:	
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
Comments:	
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
Comments:	
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
Comments:	
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. Nothing relevant other than having loved ones affected by your disgraceful decision	

Name	[redacted]
Role	Public
Comments:	
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
Comments:	
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
Comments:	

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
Comments:	
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
Comments:	
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
Comments:	
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]
Comments:	
To whom it may concern I am writing to add my voice to your consultation on "lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [ID 1059]". I am the Secretary/Director of the Thyroid Cancer Alliance (TCA) and a Trustee of The Thyroid Trust (TTT), and I was concerned to learn that the Final Appraisal Determination on lenvatinib and sorafenib was retracted due to a procedural error and particularly the implications it has for the use of lenvatinib. My understanding is that the retraction is a consequence of an additional section (section 3.6) inserted into the FAD, which led to the conclusion that both drugs were approved for first line use only. I believe this conclusion to be incorrect because the FAD initially recommended both drugs within their marketing authorisations. To then restrict their use to first line treatment only contradicts the initial advice and does not adequately allow for	

patients to be transferred from one drug to the other if they suffer side effects, since they may respond differently to the two drugs. It also does not appear to allow patients who were prescribed sorafenib when this was available through the UK Cancer Drugs Fund to transfer to lenvatinib.

In addition, if the recommendation in section 3.6 is not amended, it will lead to inequality in access across the UK and Republic of Ireland and discriminate against patients in England. Lenvatinib was approved by both the FDA and the EMA in 2015 and was subsequently approved for unrestricted use by the Scottish Medicines Consortium in October 2016 and by the All Wales Medicines Strategy Group in October 2017, and has also been approved in the ROI, which means that patients in Scotland, Wales, and Ireland are already able to benefit from sorafenib and lenvatinib as both first and second line treatments.
To quote your own press release, Mirella Marlow, acting director of the NICE centre for health technology evaluation, said: “Treatment options for these types of thyroid cancer are limited, so it is important that we are able to give patients much needed access to alternatives to best supportive care at this stage of their disease. These drugs will give patients extra time, as well as improving their quality of life.”

I urge you to review the recommendation in favour of allowing both drugs to be used within their marketing authorisations and to give patients who qualify for treatment an unrestricted choice as is the case in the rest of the UK and in Ireland.
Although the TCA and the TTT are not official stakeholders in this consultation I do hope that you will accept this submission from me as an interested member of the public with years of experience as a thyroid cancer patient advocate.
I would appreciate it if you would acknowledge receipt.

With kind regards

Name	[redacted]
Role	NHS Professional
Organisation	Thyroid Cancer sub group of NCRI Head and Neck clinical studies group

Comments:

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.

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

1. Data from the compassionate use program in England

Lenvatinib received its marketing authorisation in May 2015. At this time lenvatinib was not included in the CDF due to the planned CDF reforms. Pending NICE review, Eisai agreed to provide access to lenvatinib for eligible patients with differentiated thyroid cancer (DTC) who had received treatment with previous sorafenib and has progressed radiologically on/after sorafenib or is intolerant of sorafenib or contraindicated from using sorafenib. Between February 2017 and April 2018, Eisai has approved access for 52 patients via the scheme, all of whom had received prior treatment with sorafenib.

Data on these patients currently available to Eisai is limited, but it is evident from the estimated time on treatment that there is a clear benefit of lenvatinib in second-line patients. The current estimated average duration of treatment for those patients who have stopped treatment on the scheme is 6.56 months, which is consistent with published "real-world" evidence.

Of the 52 approved patients, 34 patients remain on the scheme the details of which are summarised below. Once Eisai approves a patient on the scheme (see approval date below), lenvatinib is shipped to the relevant hospital within 2 days of a confirmed order. The estimated time on treatment is calculated based on the confirmed order date until Eisai receive confirmation of a patient stopping treatment. The estimated current dose is based on the dose of lenvatinib ordered for each patient.

Patient	Approval date	Starting dose/mg	Estimated Current Dose/mg	Estimated Time on Treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient	Approval date	Starting dose/mg	Estimated Current Dose/mg	Estimated Time on Treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient	Approval date	Starting dose/mg	Estimated Current Dose/mg	Estimated Time on Treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

18 patients have stopped treatment on the compassionate use scheme and their details are summarised below.

Patient	Approval date	Starting dose/mg	Estimated end of treatment dose/mg	Estimated Time on Treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient	Approval date	Starting dose/mg	Estimated end of treatment dose/mg	Estimated Time on Treatment
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2. Additional "real-world" evidence in second-line patients

Recently published "real world" data from audits undertaken in France (1), Switzerland (2) and Italy (3) have demonstrated the benefit of lenvatinib in those patients who have been previously treated with at least one prior tyrosine kinase inhibitor (TKI).

Table 1 below summarises relevant patient characteristics and efficacy results from the SELECT study and these audits.

Unlike the SELECT study, all three audits included a large proportion of patients who had received at least one prior TKI and show a clear benefit of lenvatinib in the real world setting.

Table 1 Summary of real world evidence

	SELECT	FRENCH AUDIT[1]	SWISS AUDIT[2]	ITALIAN AUDIT[3]
Patient Characteristics				
No. of patients on lenvatinib	261	75	13	12
No of patients who had received no prior therapies	195 (74.7%)	24 (32%)	4 (23%)	4 (33.3%)
No. of patients who previously received ≥1 prior TKI	66 (25.3%)	32 (42.7%)[‡]	7 (53.8%)[b]	8 (66.7%)
Efficacy results*				
Median PFS (months) ITT population**	19.4	10	7.2	NR[d]
Median OS (months) ITT population[#]	11.0	Not reached	22.7	NR[d]
Complete Response + Partial Response	169 (64.8%)	23 (31%)[a]	4 (30.8%)	5 (41.7%)
Stable Disease	60 (23.0%)	38 (51%)[a]	4 (30.8%)	2 (16.7%)
Duration of treatment				
Median (in months)	16.0	6	5	NR
Dosing information				
Average dose	15.5mg (median) 16,3mg (mean)	20mg (median) NR	NR[c] NR	NR 18.2mg (mean)

Abbreviations: ITT, Intent to treat; NR, not reported; OS, overall survival; PFS, progression free survival; TKI, tyrosine kinase inhibitor;
* All efficacy results from SELECT are as per data cutoff date of 31 August 2015
** Investigator assessed
[#] Adjusted with RPSFT model
[‡] 50 patients received at least one prior TKI and 18 received more than one prior TKI
[a] In 51 patients who received at least one prior therapy, PR and SD were observed in 13 (25%) and 26 (51%), respectively
[b] 1 patient received sorafenib, pazopanib and vandetanib and a second received two prior TKIs
[c] 6 patients had dose reduction to 14mg and 1 to 10mg
[d] 6- and 12-month PFS rates were 63.6% and 54.6%, respectively; OS at 6 and 12 months were 83.3% and 75.0%

References:

1. Berdelou, A et al. Lenvatinib for the treatment of radio-iodine refractory thyroid cancer in real-life practice. Thyroid 2018; 28(1):1-21
2. Balmelli C, et al. Lenvatinib in Advanced Radioiodine-Refractory Thyroid Cancer – A Retrospective Analysis of the Swiss Lenvatinib Named Patient Program. Journal of Cancer 2018; 9(2): 250-255
3. Nervo A, et al. Lenvatinib in Advanced Radioiodine-refractory Thyroid Cancer: A Snapshot of Real-life Clinical Practice. Anticancer Research 2018; 38: 1643-1649

AG response to comments and new evidence following ACD2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

Assessment Group (AG) response to company comments and new evidence following the second Appraisal Consultation Document (ACD2)

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

3 May 2018

Contains commercial in confidence data

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP
A MEMBER OF THE RUSSELL GROUP

1 Introduction

Following the second NICE Appraisal Consultation Document (ACD2) for lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine,[1] responses were received by Eisai and Bayer, the companies who manufacture lenvatinib and sorafenib, respectively. Eisai also presented new evidence. This document presents the Assessment group (AG) response to the company responses and new evidence presented.

2 Provisional recommendation from ACD2 for which new evidence has been presented

Lenvatinib and sorafenib are recommended as options for treating progressive, locally advanced or metastatic differentiated thyroid cancer (papillary, follicular or Hürthle cell) [hereafter referred to as RR-DTC] in adults whose disease does not respond to radioactive iodine, only if they have not had a tyrosine kinase inhibitor (TKI) [e.g. lenvatinib or sorafenib] before.

3 Eisai comment on ACD2

Overall Eisai does not believe that the provisional recommendations in ACD2 provide sound and suitable guidance to the NHS. Eisai do not believe that the summary of the clinical evidence is a reasonable interpretation of the evidence because:

1. Evidence from the compassionate use program in England has not been considered.

2. Published 'real world' evidence has not been considered.

Eisai also highlight:

- As stated in section 3.6 of ACD2, the progression-free survival (PFS) benefit associated with lenvatinib was maintained in all prespecified subgroups in the SELECT trial[2] including those who had received one prior treatment regimen with a TKI.

- The original company submission from Eisai states that the prior TKI subgroup results should be interpreted with caution due to the smaller number of patients (25% and 20% of the lenvatinib and placebo arms respectively had one prior TKI). Thus, additional supportive 'real world' evidence has been presented which demonstrates the clinical benefit in this patient group. Therefore, the NICE recommendations should, at the very least, take into account the patients who have been receiving lenvatinib as a second-line option in the compassionate use program.

- Both Eisai's and the AG's analysis of cost effectiveness were based on the intention-to-treat (ITT) population from the SELECT trial, which included both first and second line patients. Due to the inherent limitations and substantial uncertainty associated with assessing cost effectiveness in this small subgroup of patients, Eisai has not submitted any additional cost effectiveness evidence.

- Reimbursement for the unrestricted use of lenvatinib was approved by The Scottish Medicines Consortium (SMC) in October 2016 and by the All Wales Medicines Strategy Group (AWMSG) in October 2017. Eisai therefore urges NICE to reconsider the current restricted advice to address the inequality in access for UK patients.

4 New evidence presented by Eisai

4.1 Compassionate use program in England

Since lenvatinib received its marketing authorisation in May 2015, Eisai has agreed to provide access to lenvatinib for patients with RR-DTC via a compassionate use program. To be eligible, patients must have previously received treatment with sorafenib and progressed radiologically on/after sorafenib or be intolerant of sorafenib or contraindicated from using sorafenib. Between February 2017 and April 2018, access has been approved for 52 patients via the scheme, all of whom had received prior treatment with sorafenib.

Eisai highlight that currently available data from the compassionate use program are limited. Nonetheless, it is argued that the estimated time on treatment shows that there is a clear benefit of lenvatinib in second-line patients. Eisai also state that the current estimated average duration of treatment for those patients who have stopped treatment on the scheme (n=18) is 6.56 months, which is consistent with published 'real world' evidence (5 months in the Swiss audit and 6 months in the French audit).

4.2 Published 'real world' evidence

In addition to data from the compassionate use program, Eisai argue that recently published 'real world' data from audits undertaken in France,[3] Switzerland[4] and Italy[5] have demonstrated the benefit of lenvatinib in those patients who have been previously treated with at least one prior TKI.

5 Bayer comment on ACD2

Bayer highlight that the DECISION trial,[6] which is the only randomised controlled trial (RCT) evidence for sorafenib versus placebo, was conducted prior to any other treatments being approved in this indication (i.e. RR-DTC). Therefore, Bayer has no evidence for the effectiveness of sorafenib following previous treatment with lenvatinib.

Bayer also highlight that RCT evidence for lenvatinib from the SELECT trial shows comparable efficacy between a pre-defined TKI experienced subgroup who had previously received sorafenib and a TKI naïve subgroup (for both PFS and objective tumour response rate [ORR]), with a shorter median treatment duration in the previously treated group.[7]

Finally, Bayer state that should overall survival (OS) data be available for the TKI experienced subgroup, cost-effectiveness for this subgroup could be determined.

6 Assessment Group response to company comments and new evidence

6.1 AG comment on ACD2 responses from the companies

The AG concurs with Bayer that there is only RCT evidence for lenvatinib following sorafenib, not sorafenib following lenvatinib. As highlighted in the original AG report, most patients who had previously received a TKI had received sorafenib (77.4%). The median duration of any prior TKI therapy was approximately 11 months in both arms.

The AG concurs with both companies that the PFS benefit is maintained whether patients previously received treatment with a TKI or not (Table 1). The AG concurs with Bayer that this is also true of ORR (Table 2). The AG also concurs with Eisai that these subgroup results should be interpreted with caution due to the small number of patients previously treated with a TKI (n=93), particularly in the placebo arm (n=27).

Given the above, even if OS data were available for the subgroup of patients previously treated with a TKI, the AG considers that any additional cost effectiveness analyses would be subject to many limitations and much uncertainty. The AG therefore considers that the cost effectiveness analyses it has already presented are the most appropriate for considering the cost effectiveness of lenvatinib.

Table 1 Progression-free survival findings in patients previously and not previously treated with a TKI in the SELECT trial, first data-cut (November 2013)*

Outcome	Prior TKI treatment		No prior TKI treatment	
	Lenvatinib (n=66)	Placebo (n=27)	Lenvatinib (n=195)	Placebo (n=104)
Median progression-free survival in months	15.1	3.6	18.7	3.6
Hazard ratio (95% confidence interval)	0.22 (0.12 to 0.41)		0.20 (0.14 to 0.27)	

TKI=tyrosine kinase inhibitor
*Progression-free survival assessed by blinded independent review
Source: Liverpool Reviews and Implementation Group (LRiG),[7] Table 10 (data taken from Figure S1 of the supplementary appendix to the published paper of the SELECT trial[2])

Table 2 Tumour objective response findings in patients previously and not previously treated with a TKI in the SELECT trial, first data-cut (November 2013)

Outcome	Prior TKI treatment		No prior TKI treatment	
	Lenvatinib (n=66)	Placebo (n=27)	Lenvatinib (n=195)	Placebo (n=104)
Objective tumour response rate, % (95% confidence interval)	62.1 (50.4 to 73.8)	3.7 (0.0 to 10.8)	65.6 (59.0 to 72.3)	1.0 (0.0 to 2.8)
Hazard ratio (95% confidence interval)	15.57 (4.06 to 59.72)		58.88 (18.95 to 182.91)	

TKI=tyrosine kinase inhibitor
Source: Liverpool Reviews and Implementation Group (LRiG),[7] Table 48 (data taken from Table S4 of the supplementary appendix to the published paper of the SELECT trial[2])

6.2 Overall survival by subgroup in the SELECT trial

As highlighted above, subgroup data for OS are lacking. Given that the PFS and ORR subgroup results are similar to the ITT results, it may be expected that OS data would also be similar to the OS results for the ITT population. However, OS data by subgroup were not presented by Eisai.

In the ITT population, median OS was 41.6 months in the lenvatinib arm and 34.5 months in the placebo arm. The results were not found to be statistically significantly different (unadjusted hazard ratio [HR]=0.84, 95% confidence intervals (CIs): 0.62 to 1.13; nominal p=0.25). OS results adjusted for crossover (since 81.4% of patients crossed over from placebo to lenvatinib on disease progression) using the rank preserving structural failure time model were found to be statistically significantly different, in favour of lenvatinib (HR=0.54, bootstrapping CIs: 0.36 to 0.80; nominal p<0.01). However, the AG concluded that the assumption of proportional hazards does not hold for either of the OS analyses. Thus, HRs are not an appropriate summary of treatment effect for OS for the SELECT trial. It is not possible to know whether the reported HRs would overestimate or underestimate the effect of lenvatinib in comparison to placebo. Consequently, the AG considers that statements about the statistical significance of results in the ITT population should be interpreted with caution. Thus, even if OS data were available for the subgroups, these same limitations may apply to the data.

6.3 AG comment on evidence from all data sources

In Table 1 of its appendix to its response to ACD2, Eisai summarise the audit data alongside data from the SELECT trial. The AG summarises the data from this table alongside additional baseline and safety data it has extracted from these studies alongside data from the compassionate use program in Table 3. The AG notes that some of the data it has extracted differ to that reported by Eisai. Where discrepancies occur, these are highlighted in the text in Section 6.4.

The AG also notes that the company presents data showing median OS of 11 months for patients in the SELECT trial in its ACD2 response appendix. This ERG is confused by this estimate for two reasons:

1. The estimate is reported to be adjusted for crossover. Only the estimate for patients who were randomised to the placebo arm should be adjusted for crossover. However, the other data for the SELECT trial presented by the company appear to relate to patients randomised to the lenvatinib arm.

2. The AG also questions whether the estimate has been wrongly reported since the unadjusted median OS in both arms of the trial exceed 34 months. Furthermore, the estimate of median OS of 11 months is lower than the estimate for PFS in the lenvatinib arm of the same trial.

Table 3 Summary of evidence presented by Eisai (supplemented with extra AG data extraction)

Characteristics and results	SELECT trial	Com-passionate use program[†]	French audit	Swiss audit	Italian audit
Patient characteristics					
Received lenvatinib, n	261	52	75	13	12
≥1 prior TKI, n (%)	66 (25.3)	52 (100.0)	50 (66.7)[‡]	8 (62.0)[b]	8 (66.7)
Age, median (IQR) years	64 (27 to 89)	--	65 (35 to 88)	72 (±16.8)	61 (52 to 68)
Male, n (%)	125 (47.9)	--	42 (56.0)	--	3 (25.0)
Median time from metastatic or RR-DTC diagnosis, months	39.3	--	32	48	37.2
Lung metastases, n (%)	226 (86.6)	--	66 (88.0)	12 (92.3)	9 (75.0)
Bone metastases, n (%)	104 (39.8)	--	44 (58.7)	9 (69.2)	5 (41.7)
Lymph node, n (%)	138 (52.9)	--	52 (69.3)	4 (30.8)	11 (91.7)
Treatment duration/dosing					
Median, months	16.0	[redacted]	6	9.98	--
Average dose (median) Average dose (mean)	15.5mg 16.3mg	[redacted]	20mg --	14mg[c] 18.3mg[c]	-- 18.2mg
Median follow-up, months					
OS analysis	37.8	--	7	--	13.3
PFS analysis, blinded review	17.1	--	--	--	--
PFS analysis, investigator	37.8	--	7	--	13.3
ORR analysis	17.1	--	7	--	13.3
Efficacy results*					
Median OS (months) All patients All patients, OS adjusted[#]	 41.6 11.0	 -- --	 Not reached --	 22.7 --	 Not reached --
Median PFS, months All patients, investigator All patients, blinded review ≥1 prior TKI, investigator	 19.4 18.3 15.1	 -- -- --	 10 -- --	 7.2 -- --	 Not reached -- --
ORR, n (%)	169 (64.8)	--	23 (31)[a]	4 (30.8)	5 (41.7)
Safety results (all patients)					
Dose interruptions, n (%)	215 (82.4)	--	44 (58.7)	--	10 (83.3)
Dose reductions, n (%)	177 (67.8)	--	23 (30.7)	7 (53.8)	9 (75.0)
Discontinued treatment, n (%)[§]	43 (16.5)	--	12 (16.0)	3 (23.1)	2 (16.7)

'--'=not reported or not applicable; CI=confidence interval; IQR=inter-quartile range; ITT=intention-to-treat; ORR=objective tumour response rate (Complete Response + Partial Response); OS=overall survival; PFS=progression free survival; TKI=tyrosine kinase inhibitor

* All efficacy results from SELECT are reported using ITT analysis

[#] Reported by Eisai to be adjusted for treatment crossover with the rank preserving structural failure time model

[†] Data reported for 34 patients who remain on the treatment on the compassionate use scheme and 18 patients who have stopped treatment on the compassionate use scheme

[§] Discontinuations are reported for patients who withdrew due to toxicity/adverse events only

[‡] 50 patients in the French audit received at least one prior TKI and 18 received more than one prior TKI

[a] In 51 patients who received at least one form of prior therapy in the French audit, PR was observed in 13 (25%) patients

[b] In the Swiss audit, 1 patient received sorafenib, pazopanib and vandetanib and a second received sorafenib and pazopanib; Eisai reported 7 (53.8%) patients had received a prior TKI

[c] 6 patients had dose reduction to 14mg and 1 to 10mg, median and mean dose calculated by the AG using this information

Source: Appendix to Eisai response to ACD2, AG report[7] and published papers[3-5]

6.4 AG interpretation of the evidence from all data sources

The largest obstacle in attempting to interpret the data presented is that the patient characteristics are not similar across studies. Most obviously, there are differences in the proportions of patients who previously received a TKI but as the authors of the French audit discuss, only 17 (23%) patients of its included patients would have also been eligible for inclusion in the SELECT trial. The authors of the French audit note that the ORR was 47% in these 17 patients compared to 31% in the study as a whole. The AG notes that this compares to 64.8% reported for all patients treated with lenvatinib in the SELECT trial (and 62.1% for patients treated with lenvatinib who had received one prior TKI).

There are however other important differences in patient characteristics between the studies (age, sex, time from diagnosis, site of metastases), as summarised in Table 3. The authors of the audits have also highlighted differences with the SELECT trial, with all stating that the 'real world' studies were likely to include patients with a worse prognosis than patients in the SELECT trial. Reasons cited by the study authors (in addition to the higher proportions of patients who had previously received a TKI) included:

- French audit: patients were "sicker and more heavily pre-treated"
- Swiss audit: patients had "more advanced disease … 69% of patients had bone metastases, a known negative prognostic factor" (compared to 39.8% in the SELECT trial)
- Italian audit: "the male/female ratio and the distribution of histological subtypes were quite different…. therefore, it could be argued that our patients might have a worse prognosis than those of the SELECT trial".

Interpreting efficacy findings from the studies is also problematic due to differences in the duration of treatment. For example, the AG calculated the duration of treatment in all 52 patients in the compassionate use program to be [redacted] months, Eisai reported this to be 6.56 months in the 18 patients who had completed treatment to be between 5 and 6 months in the Swiss and French audits, respectively. These treatment durations compare to 16 months reported for patients in the SELECT trial in its ACD2 response appendix (or 13.8 months that Eisai reported in its original submission).

Differences in the duration of treatment are reflected in differences in the length of follow-up. The length of follow-up for the primary data-cut in the SELECT trial was 17.1 months and at the third and most recent data-cut, was 37.8 months, much longer than the length of time that

patients in 'real world' studies have been reported to have been followed up for (the apparent discrepancy in treatment duration for the SELECT trial between Eisai's original submission and its appendix to its ACD2 response may reflect the different length of follow-up at these different data-cuts). In the audits, the longest median treatment duration is reported to be 9.98 months in the Swiss audit (contrary to the 5 months cited by Eisai in its ACD2 response appendix).

In turn, differences in treatment duration and length of follow-up will influence the estimates of median OS and PFS reported in the studies. Thus, for example, as can be seen from Table 3, in contrast to the SELECT trial and Swiss audit which report estimates of median OS, the French and Italian audits report the median OS is not reached; the length of follow-up in these studies is notably much shorter than in the SELECT trial.

Median PFS could only be estimated for patients treated with lenvatinib in two of the audits (the French and Swiss audits). In both audits, median PFS was lower than reported in the SELECT trial, including median PFS reported in the subgroup of patients who had received one prior TKI in the SELECT trial. However, given these audits include a relatively small number of patients (particularly the Swiss audit) but proportionately more patients with a worse prognosis than in the SELECT trial, this is not surprising. It is nonetheless noticeable that median PFS in these audits (7.2 months to 10 months) exceeds median PFS reported for patients who did not receive lenvatinib in the SELECT trial (3.7 months by investigator assessment or 3.6 months by blinded review; 3.6 months by blinded review for patients who previously did not receive a TKI). The estimates also exceed median PFS reported for patients in the placebo arm of the DECISION trial (5.4 months by investigator assessment or 5.8 months by blinded review). This may suggest that even in patients previously treated with a TKI, median PFS exceeds that of patients who are untreated (receive best supportive care). However, as the two RCTs and the two audits differ in terms of setting and patient populations, it would be inappropriate to draw firm conclusions from such a naïve comparison.

Safety results in relation to dose interruptions, reductions and discontinuation may be a useful comparative measure across studies. This is because, as noted in the AG report, and by the authors of the Italian audit, most adverse events (AEs) for patients treated with lenvatinib typically occur early in the treatment process. Therefore, the length of follow-up is less likely to be important for comparative purposes. The frequency of dose interruptions, reductions and discontinuations reported in the 'real world' studies were generally in line with the frequencies reported in the SELECT trial.

Overall, considering the additional evidence presented as a whole, it is not possible to conclusively determine the absolute or relative effects of treatment with lenvatinib. This is because, aside from other issues of heterogeneity, the efficacy results for patients in the audits are only presented for *all* patients, regardless of whether they had previously received a TKI. Unfortunately, no efficacy results are available for patients in the compassionate use program in England, all of whom had received a previous TKI. Therefore, the SELECT trial is the only trial from which it is possible to estimate relative effectiveness since this is the only study with a comparator arm.

6.5 AG conclusions

The AG does not consider the data presented by Eisai present any more conclusive evidence than the subgroup findings it previously reported for the SELECT trial. The lack of any efficacy data from the compassionate use program is particularly disappointing, if understandable given the length of this program to date. If available, OS findings from the SELECT trial by subgroup may be more informative with regard to evidence for clinical effectiveness. However, this would not compensate for the small numbers of patients and violations of the proportional hazards assumption as previously highlighted by the AG. Therefore, the AG consider that if additional subgroup data were made available this would not be sufficient to allow a robust estimate of cost effectiveness to be calculated.

7 References

1. National Institute Care and Health Excellence. Appraisal Consultation Document. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Issue date: 29 March 2018. 2018; Available from: https://www.nice.org.uk/guidance/gid-ta10101/documents/html-content-3. Accessed 30 April 2018.
2. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R*, et al.* Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med. 2015; 372:621-30.
3. Berdelou A, Borget I, Godbert Y, Nguyen T, Garcia ME, Chougnet CN*, et al.* Lenvatinib for the Treatment of Radioiodine-Refractory Thyroid Cancer in Real-Life Practice. Thyroid. 2017.
4. Balmelli C, Railic N, Siano M, Feuerlein K, Cathomas R, Cristina V*, et al.* Lenvatinib in Advanced Radioiodine-Refractory Thyroid Cancer - A Retrospective Analysis of the Swiss Lenvatinib Named Patient Program. J Cancer. 2018; 9:250-5.
5. Nervo A, Gallo M, Sama MT, Felicetti F, Alfano M, Migliore E*, et al.* Lenvatinib in Advanced Radioiodine-refractory Thyroid Cancer: A Snapshot of Real-life Clinical Practice. Anticancer Res. 2018; 38:1643-9.
6. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L*, et al.* Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014; 384:319-28.
7. Liverpool Reviews and Implementation Group (LRiG). Assessment Report. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine: a systematic review and economic evaluation. 2017; Available from:

https://www.nice.org.uk/guidance/gid-ta10101/documents/assessment-report. Accessed 30 April 2018.