National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Bayer	-	-
	Eisai	-	-
	NCRI/RCP/RCR /ACP	This is an appropriate topic for NICE review. We have two licensed drugs in a condition with only best supportive care as an alternative/comparator. Only sorafenib is funded in England via Cancer Drugs Fund (CDF).	Comment noted.
Wording	Bayer	N/A	-
	Eisai	Yes, it reflects the current EMA approved label.	Comment noted.
	NCRI/RCP/RCR /ACP	Yes, although we would like the sequential use of these drugs to also be addressed.	The technologies will be appraised within their marketing authorisations and based on the evidence

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			available from the clinical trials. If the evidence allows, consideration will be given to subgroups based on previous treatment with tyrosine kinase inhibitors. Consultees will have the opportunity to discuss the decision problem in more detail at the stakeholder information meeting.
Timing Issues	Bayer	N/A	-
	Eisai	It is urgent as lenvatinib was approved by the EMA in May 2015 and is yet to be made available on the NHS in England and Wales. It is worth noting that to date Eisai is aware that a number of Individual Funding requests for lenvatinib in England and Wales have been submitted and rejected, meaning that no patients have received the treatment on the NHS in the 17 months since it has been approved.	Comment noted.
	NCRI/RCP/RCR /ACP	This is urgent. Many patients have now received one or other of these drugs either via the CDF or through clinical trial and are in need of a second line agent. There are two effective drugs licensed for this group of patients. Only sorafenib is funded via the CDF in England and SMC in Scotland. Our patients in Wales have no access to either drug. We feel strongly that both sorafenib and lenvatinib with their proven activity in	Comment noted.

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		this disease setting should also be available throughout the UK.	
Additional comments on the draft remit	Bayer	N/A	-
	Eisai	No	Comment noted.
	NCRI/RCP/RCR /ACP	-	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bayer	N/A	-
	Eisai	Most of the background information is accurate. We consider that is important to reflect that the British Thyroid Association's 'Guidelines for the management of thyroid cancer' were last updated in 2014 before the targeted therapies became available. More recently updated guidelines such as the National Comprehensive Cancer Network (NCCN) guidelines on Thyroid Carcinoma, updated in August 2016[1] and the American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, updated in January 2016[2] fully recommend the use of targeted	The background information section intends to reflect treatment options available in UK clinical practice. This section of the scope acknowledges that the use of external beam radiotherapy and

[1] National Comprehensive Cancer Network, NCCN. Thyroid Cancer. [Online]; 2016 [cited 2016 August 07. Available from: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

[2] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016; 26(1): 1-13326.

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		therapies (TKIs) as the first option in radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC), replacing chemotherapy. In addition, we consider that it is also important to include in the background information that sorafenib is currently available via the Cancer Drugs Fund in England only.	chemotherapy in palliative care has begun to be superseded in clinical practice by targeted therapies. The date the guideline was published has been added to the background section to make clear that this evidence may no longer be current This section includes information that sorafenib is currently available via the Cancer Drugs Fund.
	NCRI/RCP/RCR /ACP	Chemotherapy has no role in iodine refractory thyroid cancer. The response rates are less than 15%. Chemotherapy is not recommended by any national guidelines whereas sorafenib and lenvatinib are recommended as first line systemic therapies for iodine refractory disease. External beam radiotherapy has a role in symptom control only but has no survival advantage.	Comment noted. This section of the scope acknowledges that the use of external beam radiotherapy and chemotherapy in palliative care has begun to be superseded in clinical practice by targeted

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			therapies. This information will be taken into account into account when defining the appropriate comparators in the scope. No change required to the background section.
The technology/ intervention	Bayer	N/A	-
	Eisai	Yes, the description of the technology is accurate.	Comment noted.
	NCRI/RCP/RCR /ACP	This seems accurate. Both drugs have shown a PFS advantage over placebo.	Comment noted.
Population	Bayer	Based on median progression free survival (PFS) and a visual comparison of the placebo arms from the DECISION and SELECT trials (below) the populations do not look comparable. Sorafenib: DECISION trial: Placebo PFS: 5.8 months	The technologies will be appraised within their marketing authorisations. Sorafenib and lenvatinib have the same marketing authorisation and therefore the same target population. Uncertainties relating to the differences in the trial populations will be considered during the

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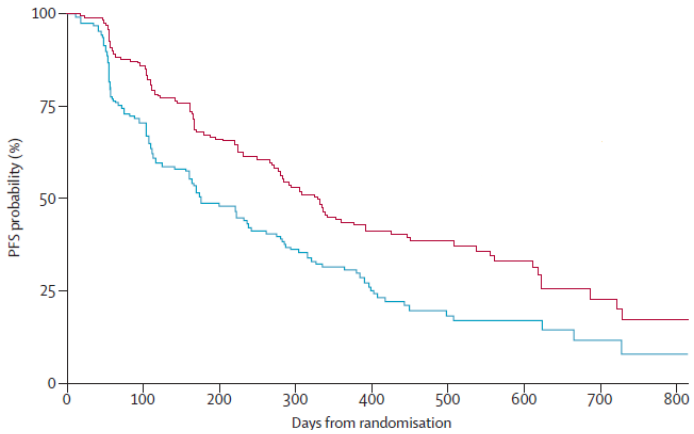
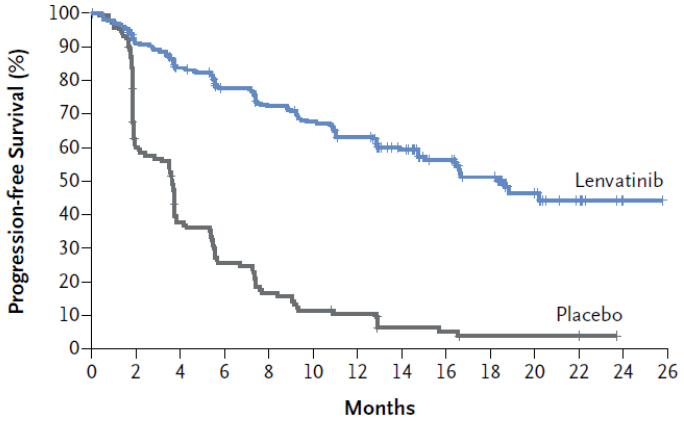
		 Lenvatinib: SELECT trial: Placebo PFS: 3.6 months 	appraisal. Consultees will have the opportunity to discuss the decision problem in more detail at the stakeholder information meeting.

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	Eisai	Yes, the population is defined appropriately. There are no groups within this population that should be considered separately. It is important to note that this is an orphan condition and the patient population is very small ie there are only approximately 260 patients with RAI-refractory DTC in England and Wales.	Comment noted.
	NCRI/RCP/RCR /ACP	About 10% of differentiated thyroid cancers will become iodine refractory and it in this population that these two drugs are indicated.	Comment noted.
Comparators	Bayer	Lenvatinib is not the current standard of care used in the NHS. • Chemotherapy: Doxorubicin does not provide any improvement in health outcomes, is associated with severe toxicity impact and is not used routinely in clinical practice • External beam radiotherapy: Is for only used for localised lesions only has a palliative effect.	Chemotherapy and external beam radiotherapy have been removed as specified best supportive care options. Consultees will have the opportunity to discuss what best supportive care options for people with this disease are used in clinical practice in more detail at the stakeholder information meeting
	Eisai	The list of comparators is correct.	Chemotherapy and external beam radiotherapy have been removed as specified best supportive care

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			options. Consultees will have the opportunity to discuss what best supportive care options for people with this disease are used in clinical practice in more detail at the stakeholder information meeting
	NCRI/RCP/RCR /ACP	Best supportive care. Chemotherapy would not be seen as a comparator.	Chemotherapy and external beam radiotherapy have been removed as specified best supportive care options. Consultees will have the opportunity to discuss what best supportive care options for people with this disease are used in clinical practice in more detail at the stakeholder information meeting
Outcomes	Bayer	N/A	-
	Eisai	Yes, the outcome measures listed are appropriate.	Comment noted.
	NCRI/RCP/RCR	Yes but we would also like ‘time to worsening symptoms’ included.	The outcome ‘time to

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	/ACP		worsening symptoms' is expected to be captured within other outcomes listed in the scope, for example the outcome 'quality of life'
Economic analysis	Bayer	N/A	-
	Eisai	No comments.	Comment noted.
	NCRI/RCP/RCR /ACP	No additional comments.	Comment noted.
Equality and Diversity	Bayer	N/A	-
	Eisai	No comments.	Comment noted.
	NCRI/RCP/RCR /ACP	We need equality in access of these drugs across England, Scotland and Wales. Currently a lot of distress is caused to patients due to the disparity in access according to geography.	Comment noted.
Innovation	Bayer	Sorafenib was the first systemic treatment for patients with differentiated thyroid cancer who are refractory to radioactive iodine therapy and when launched represented a step change in the management of the condition.	Comment noted.
	Eisai	Eisai do consider lenvatinib to be innovative as it is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel binding mode that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors	Comment noted.

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		VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs.[3] It exhibits rapid binding to the target molecule and potent inhibition of kinase activity, yielding a rapid and durable response in progressive RAI-refractory DTC. It is the only therapy that has reduced tumour size in the majority of patients (65% in the SELECT trial, including 4 complete responses) and the median time to objective response was 2 months (95% CI, 1.9-3.5).[4]	
	NCRI/RCP/RCR /ACP	Yes. In patients who respond to these drugs there is proven progression free survival.	Comment noted.
Other considerations	Bayer	N/A	-
	Eisai	No comments.	Comment noted.
	NCRI/RCP/RCR /ACP	We would strongly recommend the assessment of these drugs as both first and second line treatment for this population of patients who have no other treatment options other than best supportive care. As clinicians we would expect that all our patients falling into this category of radioiodine refractory disease would needs both drugs over the course of the natural history of their disease.	The technologies will be appraised within their marketing authorisations and based on the evidence available from the clinical trials. If the evidence allows, consideration will be

[3] Lenvima Summary of Product Characteristics, May 2015
[4] Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. N Engl J Med 2015; 372: 621-630

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			given to subgroups based on previous treatment with tyrosine kinase inhibitors. Consultees will have the opportunity to discuss the decision problem in more detail at the stakeholder information meeting.
Questions for consultation	Bayer	No further comments.	Comment noted.
	Eisai	Where do you consider lenvatinib and sorafenib will fit into the treatment pathway for differentiated thyroid cancer? As described above, the use of targeted therapies (TKIs) as the first option in radioactive iodine (RAI) refractory differentiated thyroid cancer (DTC), replacing chemotherapy, is now recommended by both the NCCN and ATA Guidelines. Lenvatinib is the only therapy that has reduced tumour size in the majority of patients (65% in the SELECT trial, including 4 complete responses) and it has also demonstrated a rapid median time to objective response of 2 months (95% CI, 1.9-3.5) in the same study.	Comment noted.
	NCRI/RCP/RCR /ACP	-	-
Additional comments on the	Bayer	Any additional comments on the draft scope	The technologies will be appraised within their

Section	Consultee/ Commentator	Comments [sic]	Action
draft scope		Based on median progression free survival (PFS) and a visual comparison of the placebo arms from the DECISION and SELECT trials the populations do not look comparable. • Sorafenib: DECISION trial: Placebo PFS: 5.8 months • Lenvatinib: SELECT trial: Placebo PFS: 3.6 months	marketing authorisations. Sorafenib and lenvatinib have the same marketing authorisation and therefore the same target population. Uncertainties relating to the differences in the trial populations will be considered during the appraisal. Consultees will have the opportunity to discuss the decision problem in more detail at the stakeholder information meeting.
	Eisai	-	-
	NCRI/RCP/RCR /ACP	-	-

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health