National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer ID3811

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
Wording *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	Eisai	Lenvima, in combination with pembrolizumab, is indicated for the treatment [redacted] Therefore we suggest alternative wording as below: "To appraise the clinical and cost effectiveness of lenvatinib with pembrolizumab within its marketing authorisation [redacted]	Comment noted. The remit has been kept broad but notes that the technology will be appraised within its marketing authorisation.
	MSD	KEYTRUDA, in combination with lenvatinib, [redacted]	Comment noted. The remit has been kept broad but notes that the technology will be appraised within its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
	British Gynaecological Cancer Society (BGCS)	Yes	Comment noted. No action required.
Timing Issues *What is the relative urgency of this appraisal to the NHS?*	Eisai	The provisional scheduling for this topic is appropriate.	Comment noted. No action required.
	MSD	We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval. Information regarding anticipated regulatory timelines presented in UK PharmaScan accurately reflect current expectations.	Comment noted. No action required.
	BGCS	Disease progression following chemotherapy for advanced ovarian cancer is often not well controlled by further cytotoxic chemotherapy and other therapeutic strategies are urgently needed.	Comment noted. This appraisal has been scheduled into the work programme.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information *Consider the accuracy and completeness of this information.*	Eisai	Background information is accurate and complete.	Comment noted. No action required.
	MSD	No further comment	Comment noted. No action required.

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	BGCS	Yes	Comment noted. No action required.
The technology/ intervention *Is the description of the technology or technologies accurate?*	Eisai	The description of the technology is not accurate. Please use the following alternative wording: "Lenvatinib (Lenvima, Eisai) is a multi-kinase inhibitor. This selectively inhibits the kinase activities of all vascular endothelial growth factor receptors, in addition to other proangiogenic and oncogenic pathways, including fibroblast growth factor receptors, the platelet derived growth factor receptor alpha KIT and RET. It is administered orally."	The description of the technology section aims to provide a brief summary of the technology and is not designed to be exhaustive. The brand name of lenvatinib (Lenvima) was added.
	MSD	No further comment	Comment noted. No action required.
	BGCS	Yes	Comment noted. No action required.
Population *Is the population defined appropriately? Are there groups within this population that should be considered separately?*	Eisai	The population is not defined appropriately and needs to be in line with proposed indication wording as below: "[redacted]	The population description has been updated in line with the marketing authorisation.
	MSD	No further comment	Comment noted.
Comparators	Eisai	There is no clear standard of care in people with advanced endometrial cancer who have received prior systemic treatment.	Comments noted. Stakeholders' opinions recently gathered for

Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?		We suggest the comparators for the appraisal should be: • **Doxorubicin** BGCS guidelines[1] suggest doxorubicin can be used in the second line setting • **Carboplatin with paclitaxel** BGCS guidelines suggest carboplatin + paclitaxel can be considered in fit patients as a re-challenge if the treatment free-interval is more than six months. • **Cisplatin with paclitaxel** Clinical experts have suggested cisplatin with paclitaxel may be an option for when a platinum combination is considered. • **Weekly paclitaxel** We suggest the removal of weekly paclitaxel as the evidence is only supported by anecdotal evidence as stated by the BGCS and it's listing as an option is based upon ovarian cancer activity. • **Cyclophosphamide** We suggest the removal of cyclophosphamide as the BGCS guidelines state this is an option in the first line setting for fit patients with disseminated recurrent disease. The pivotal phase III study relates to previously treated patients. • **Hormone therapy** We suggest that hormone therapy is removed from the comparators, as per BGCS guidelines, this treatment is used for patients not fit for chemotherapy. One inclusion criteria for the pivotal phase III study is that patients have to have an ECOG performance status of 0 or 1. The guidelines also state "there is no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival".	this disease area noted that there are no universal standards for treatments of patients with advanced endometrial. However, currently some treatment options are available for patients. Therefore, the following comparators have been included in the updated scope: Chemotherapy, including: • carboplatin with paclitaxel; • paclitaxel monotherapy; • doxorubicin monotherapy; and • carboplatin monotherapy; Hormone therapy, and Best supportive care. The following comparators have been

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			excluded from the updated scope: cyclophosphamide and cisplatin.
	MSD	We suggest the comparators for the appraisal should be: • **Doxorubicin** BGCS guidelines suggest doxorubicin can be used in the second line setting • **Carboplatin with paclitaxel** BGCS guidelines suggest carboplatin + paclitaxel can be considered in fit patients as a re-challenge if the treatment free-interval is more than six months. • **Cisplatin with paclitaxel** Clinical experts have suggested cisplatin with paclitaxel may be an option for when a platinum combination is considered. Clinical experts have stated there is no clear standard of care for those who have had previous systemic treatment for advanced, recurrent or metastatic endometrial cancer. • **Weekly paclitaxel** We suggest the removal of weekly paclitaxel as the evidence is only supported by anecdotal evidence as stated by the BGCS and it's listing as an option is based upon ovarian cancer activity. • **Cyclophosphamide**	Comments noted. Stakeholders' opinions recently gathered for this disease area noted that there are no universal standards for treatments of patients with advanced endometrial cancer. However, currently some treatment options are available for patients. Therefore, the following comparators have been included in the updated scope: Chemotherapy, including: • carboplatin with paclitaxel;

[1] BGCS Uterine Cancer Guidelines: Recommendations for Practice, 2017

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		We suggest the removal of cyclophosphamide as the BGCS guidelines state this is an option in the first line setting for fit patients with disseminated recurrent disease. KEYNOTE-775 relates to previously treated patients. • **Hormone therapy** We suggest that hormone therapy is removed from the comparators, as per BGCS guidelines, this treatment is used for patients not fit for chemotherapy. One inclusion criteria for KEYNOTE-775 was patients had to have a ECOG performance status of 0 or 1. The guidelines also state "there is no evidence that hormonal treatment in patients with advanced or recurrent endometrial cancer improves overall survival	• paclitaxel monotherapy; • doxorubicin monotherapy; and • carboplatin monotherapy; Hormone therapy, and Best supportive care. The following comparators have been excluded from the updated scope: cyclophosphamide and cisplatin.
	BGCS	Yes	Comment noted. No action required.
Outcomes *Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	Eisai	The outcome measures listed are appropriate.	Comment noted. No action required.
	MSD	To include duration of response	Comment noted. Duration of response

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			has been added as an outcome measure.
Economic analysis *Comments on aspects such as the appropriate time horizon.*	Eisai	No comment	Comment noted. No action required.
	MSD	No further comment	Comment noted. No action required.
Equality and Diversity *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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* • *could exclude from full consideration any people*	Eisai	No comment	Comment noted. No action required.
	MSD	None identified, no further comment.	Comment noted. No action required.
	BGCS	I am not aware of any issues	Comment noted. No action required.

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protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed; • *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*			
Other considerations	Eisai	No comment	Comment noted. No action required.

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Suggestions for additional issues to be covered by the appraisal are welcome.	MSD	No further comment	Comment noted. No action required.
Innovation *Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you*	Eisai	Eisai do consider lenvatinib to be innovative as it is a multiple receptor tyrosine kinase (RTK) inhibitor with a novel, distinct binding mode that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2 and VEGFR3) and fibroblast growth factor (FGF) receptors (FGFR1, FGFR2, FGFR3 and FGFR4) in addition to other proangiogenic and oncogenic pathway-related RTKs (including the platelet-derived growth factor [PDGF] receptor PDGFRα; KIT; and RET) involved in tumour proliferation. Furthermore, when used in combination with pembrolizumab, the immunomodulatory effects of lenvatinib i.e. the suppression of monocytes and macrophages and proliferation of CD8+ T cell populations are thought to enhance the overall antitumor effect of the combination treatment. There is a high unmet need in patients with advanced endometrial cancer. No novel therapies have been licensed for use in endometrial cancer for nearly 50 years, despite a growing incidence of the disease. As highlighted above, there is no current clear standard of care for patients with advanced endometrial cancer who have received previous treatment and therefore Eisai considers lenvatinib and pembrolizumab to be a "step-change" in the management of the condition.	Comment noted. No action required.
	MSD	MSD considers lenvatinib + pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits.	Comment noted. No action required.

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understand to be available to enable the Appraisal Committee to take account of these benefits.		Lenvatinib + pembrolizumab has the potential to improve outcomes for patients who have received previous treatment in adults with advanced endometrial cancer.	
	BGCS	Yes. Data exist for benefit with immunotherapy in advanced endometrial cancer but a large proportion of patients do not respond or later develop resistance. By targeting abnormal tumour blood vessel formation VEGF inhibition may increase infiltration of immune effector cells and there may be synergistic effects of combined treatment in endometrial cancer which can improve outcomes.	Comment noted. No action required.
Questions for consultation *Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned timelines).*	Eisai	**Is the population in the scope defined appropriately?** No, please see comments above **Have all relevant comparators for lenvatinib with pembrolizumab been included in the scope?** Please see comments above **Which treatments are considered to be established clinical practice in the NHS for previously treated advanced, metastatic and recurrent endometrial cancer? How should best supportive care be defined?** Please see comments above **Are the outcomes listed appropriate?** Yes **Are there any subgroups of people in whom lenvatinib with pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?**	Comment noted.

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		At present there are no sub-groups that have been identified where lenvatinib with pembrolizumab will be more clinically and cost effective. **Where do you consider lenvatinib with pembrolizumab will fit into the existing NICE pathway for endometrial cancer, Urogenital conditions?** We anticipate that lenvatinib with pembrolizumab will be used in people with previously treated advanced endometrial cancer. **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 proposed remit and scope may need changing in order to meet these aims.** No anticipated impact **Do you consider lenvatinib with pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes, please see comments above. **Do you consider that the use of lenvatinib with pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** We do not currently consider that there will be substantial health-related benefits that are unlikely to be included in the QALY calculation.	

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		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? None anticipated	
	MSD	**Is the population in the scope defined appropriately?** Yes **Have all relevant comparators for lenvatinib with pembrolizumab been included in the scope?** See comments above **Which treatments are considered to be established clinical practice in the NHS for previously treated advanced, metastatic and recurrent endometrial cancer? How should best supportive care be defined?** See comments above **Are the outcomes listed appropriate?** Inclusion of duration of response is suggested **Are there any subgroups of people in whom lenvatinib with pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** At present there are no sub-groups that have been identified where lenvatinib with pembrolizumab will be more clinically and cost effective.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
		Where do you consider lenvatinib with pembrolizumab will fit into the existing NICE pathway for endometrial cancer, Urogenital conditions? We anticipate that lenvatinib with pembrolizumab will be used for people who have had previous systemic treatment for advanced, recurrent or metastatic endometrial cancer **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 proposed remit and scope may need changing in order to meet these aims.** No anticipated impact **Do you consider lenvatinib with pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes **Do you consider that the use of lenvatinib with pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** We do not consider that there will be substantial health-related benefits that are unlikely to be included in the QALY calculation. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice?**	

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		None anticipated	

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

Pfizer