National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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	Action
Wording	Eisai Ltd	Yes	Comment noted. No action required.
	Ipsen Ltd	Based on this draft scope it appears that there are two technologies being appraised (i.e. lenvatinib and everolimus or lenvatinib and pembrolizumab). Is that possible in a single technology appraisal?	Comment noted. The combination with everolimus is no longer included in this appraisal. However, this topic is proceeding as a multiple technology appraisal. The wording of the scope has been updated to reflect this process change.
	Kidney Cancer Support Network	The technology Lenvatinib (Kisplyx, Eisai) is a multiple receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors and other tyrosine kinase receptors that are involved in the growth of blood vessels to the tumour and tumour proliferation. It is administered orally.	Comments noted. The following changes have been made to the scope: - Lenvatinib: The wording has been updated as suggested. - Everolimus: The combination with everolimus is no longer included in

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		Everolimus (Afinitor, Novartis) is an oral active inhibitor of the mammalian target of rapamycin (mTOR) receptor, a central regulator of tumour cell division and blood vessel growth in cancer cells. It is administered orally. Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, programmed cell death 1 (PD-1) antibody called a checkpoint inhibitor that blocks the PD-1 protein receptor on cancer cells. Checkpoint inhibitors release the 'brakes' on the immune system enabling T cells to kill cancer cells more effectively. It is administered intravenously. Lenvatinib has a marketing authorisation in the UK in combination with everolimus for the treatment of adult patients with advanced RCC following prior VEGF-targeted therapy (NICE technology appraisal guidance 498).	this appraisal. Wording removed from scope. - Pembrolizumab: The current definition is in line with the summary of product characteristics for pembrolizumab. The mechanism of action has been updated to reflect this suggestion. The current description of the marketing authorisation is in line with NICE writing style. No action required.
	Kidney Cancer UK	Yes	Comment noted. No action required.
	Merck Sharp & Dohme Ltd	Yes, the remit is appropriate	Comment noted. No action required.
Timing Issues	Eisai Ltd	The provisional scheduling for this topic is appropriate.	NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has

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			scheduled this topic into its work programme. No action required.
	Kidney Cancer Support Network	Medium urgency	NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Kidney Cancer UK	It's important that this appraisal is carried out swiftly as the combination of lenvatanib and evorolimus offers an oral treatment option for those not suitable for immunotherapy that has better outcomes than the current oral monotherapy. The lenvatanib with pembrolizumab combination is much needed as an alternative to the current immunotherapy/ TKI combination as it provides clinicians with another option for this heterogenous disease.	NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Merck Sharp & Dohme Ltd	The provisional scheduling for this topic is appropriate.	NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.

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Additional comments on the draft remit	Merck Sharp & Dohme Ltd	MSD's responses only concern the combination of lenvatinib and pembrolizumab, with the exception of answers to the specific questions listed under "questions for consultation".	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Eisai Ltd	Background information is accurate and complete	Comment noted. No action required.
	Kidney Cancer Support	The background information is accurate and complete	Comment noted. No action required.
	Kidney Cancer UK	'However, around half of those who have surgery develop advanced disease later on' is not accurate. This is generally accepted to be 30 to 40%	Comment noted. The background information has been updated in line with the literature to: 'However, around 30% of those who have surgery develop advanced disease later on'.
	Merck Sharp & Dohme Ltd Network	Background information is accurate and complete.	Comment noted. No action required.
The technology/ intervention	Eisai Ltd	For consistency with previous scopes, we would like to propose the following change: "Lenvatinib (Kisplyx, 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	Comment noted. The current description of the technology is in line with NICE writing style. No action required

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		growth factor receptors, the platelet derived growth factor receptor alpha KIT and RET.”	
	Kidney Cancer Support Network	**The technology** Lenvatinib (Kisplyx, Eisai) is a multiple receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors and other tyrosine kinase receptors that are involved in the growth of blood vessels to the tumour and tumour proliferation. It is administered orally. Everolimus (Afinitor, Novartis) is an oral active inhibitor of the mammalian target of rapamycin (mTOR) receptor, a central regulator of tumour cell division and blood vessel growth in cancer cells. It is administered orally. Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, programmed cell death 1 (PD-1) antibody called a checkpoint inhibitor that blocks the PD-1 protein receptor on cancer cells. Checkpoint inhibitors release the ‘brakes’ on the immune system enabling T cells to kill cancer cells more effectively. It is administered intravenously. Lenvatinib has a marketing authorisation in the UK in combination with everolimus for the treatment of adult patients with advanced RCC following prior VEGF-targeted therapy (NICE technology appraisal guidance 498).	Comment noted. Please see previous response in wording section. No further action required.

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	Kidney Cancer UK	Accurate	Comment noted. No action required.
	Merck Sharp & Dohme Ltd	The description of the technology is accurate	Comment noted. No action required.
Population	Eisai Ltd	The population is defined appropriately.	Comment noted. No action required.
	Kidney Cancer Support Network	The population is defined appropriately, although, we would like to see more non-clear cell RCC patients included in clinical trials. These patients currently have an unmet need for an effective first-line treatment	Comment noted. No action required.
	Kidney Cancer UK	Population defined appropriately and no groups should be considered separately	Comment noted. No action required.
	Merck Sharp & Dohme Ltd	The population is defined appropriately.	Comment noted. No action required.
Comparators	Eisai Ltd	The list of comparators reflects the standard options for first line treatment in the NHS. Nivolumab + ipilimumab is currently included within the cancer drugs fund, due to be reviewed after the data collection period ends in August 2021. Under the current NICE process this would not be considered a comparator unless routinely commissioned prior to the start of this appraisal.	Comment noted. Nivolumab + ipilimumab is a comparator, subject to ongoing appraisal.
	Ipsen Ltd	Should axitinib and avelumab be included as a comparator? It is available via the CDF as is nivolumab and ipilimumab.	Comment noted. Avelumab with axitinib will not be available for routine commissioning therefore cannot be considered a comparator. Nivolumab + ipilimumab is a comparator, subject

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			to ongoing appraisal. No action required.
	Kidney Cancer Support Network	Add avelumab with axitinib – subject to ongoing CDF review	Comment noted. Avelumab with axitinib will not be available for routine commissioning therefore cannot be considered a comparator. Nivolumab + ipilimumab is a comparator, subject to ongoing appraisal. No action required
	Kidney Cancer UK	Avelumab and Axitinib for those with untreated advanced RCC at any IMDC risk category is missing . Others are used currently. The IO/TKI combination treatments could be considered best alternative care	Comment noted. Avelumab with axitinib will not be available for routine commissioning therefore cannot be considered a comparator. Nivolumab + ipilimumab is a comparator, subject to ongoing appraisal. No action required
	Merck Sharp & Dohme Ltd	We agree with the proposed comparators (pazopanib, sunitinib, tivozanib, cabozantinib [intermediate/poor-risk groups only]). We note the draft scope also mentions nivolumab + ipilimumab (subject to ongoing CDF review). Please note that based on the timelines for the CDF review following the end of the data collection period (as per the agreed data collection agreement), MSD does not consider that nivolumab +ipilimumab will be a comparator of relevance for ID3760, as it would not have entered routine commissioning prior to the start of this appraisal.	Comment noted. Nivolumab + ipilimumab is a comparator, subject to ongoing appraisal.

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Outcomes	Eisai Ltd	The outcome measures listed are appropriate.	Comment noted. No action required.
	Kidney Cancer Support Network	Add identification of a prognostic/predictive biomarker	Comment noted. The NICE guide to the methods of technology appraisal defines an outcome as 'The measure of the possible results of treatment with a preventive or therapeutic intervention'. The identification of prognostic/predictive biomarkers is not a direct measure of the results of treatment with lenvatinib with pembrolizumab. No action required.
	Kidney Cancer UK	Yes	Comment noted. No action required.
	Merck Sharp & Dohme Ltd	MSD considers that the outcome measures listed are appropriate. However, it is known that the response to immunotherapies (immuno-oncology drugs) may have a later onset but once triggered, is likely to be durable, bringing unquantifiable long-term survival benefit for a subset of patients. This benefit is not captured by the outcome measures listed; thus, MSD suggests the inclusion of "Duration of Response" as an additional outcome measure.	Comment noted. Duration of response is captured in the outcomes of response rate and progression-free-survival. No action required.
Economic analysis	Kidney Cancer Support Network	No comments	Comment noted. No action required.

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	Kidney Cancer UK	No comment	Comment noted. No action required.
	Merck Sharp & Dohme Ltd	No additional comments	Comment noted. No action required.
Equality and Diversity	Kidney Cancer Support Network	Inclusion of non-clear cell RCC patients in clinical trials. These patients currently have an unmet need for an effective first-line treatment Equality of access to the clinical trial/drug treatment on the NHS/CDF regardless of where the patient lives	Comments noted. People with non-clear cell RCC are included in the population. National variation in access to a technology is outside the remit of NICE technology appraisal guidance. No action required.
	Kidney Cancer UK	Equality demonstrated in draft scope	Comment noted. No action required.
	Merck Sharp & Dohme Ltd	No additional comments	Comment noted. No action required.
Other considerations	Kidney Cancer Support Network	Improving outcomes in urological cancers (2002) Cancer service guideline CSG2. Review date TBC. This guideline is too out-of-date to be referred to here	Comment noted. The scope has been updated to remove this guideline.
	Kidney Cancer UK	No suggestions	Comment noted. No action required.

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	Merck Sharp & Dohme Ltd	No additional comments	Comment noted. No action required.
Innovation	Eisai Ltd	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.	Comment noted. The appraisal committee will consider the innovative nature of lenvatinib with pembrolizumab during the appraisal.
	Kidney Cancer Support Network	Not particularly – we already have lenvatinib plus everolimus as a first-line treatment and there are 2 other VEGF-TKI/immunotherapy combinations available on the NHS in Scotland or the CDF in England/Wales	Comment noted. The appraisal committee will consider the innovative nature of lenvatinib with pembrolizumab during the appraisal.
	Kidney Cancer UK	• Yes, kidney cancer is heterogenous and treatment options need to reflect this. Lenvatanib and everolimus (evorolimus, an mTOR inhibitor acts on different disease modifying pathways than the existing first line options) add an oral combination for those with untreated advanced RCC with better outcomes. This means clinicians have another option for this patient group. The combination of pembrolizumab and lenvatanib adds to treatment options across the IMDC risk categories of which there is only one	Comment noted. The appraisal committee will consider the innovative nature of lenvatinib with pembrolizumab during the appraisal.

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		(Avelumab and Axitinib) at present. This combination works synergistically differently from the existing IO/TKI pathways. • Yes, both these treatments have benefits in progression free survival with similar side effects to the comparators. • Giving alternate options for patients can be invaluable especially in an era where personalised medicine may be introduced. It may be found that lenvatanib and evorolimus works for a set of patients where other treatments fail. A multitude of treatment options is always desirable. • More treatment options will improve the patient's disease outcomes and improve quality of life. The information about outcomes is from a press release from the company about the CLEAR /KEYNOTE-381 study which has completed but not published at this time	
	Merck Sharp & Dohme Ltd	MSD considers pembrolizumab in combination with lenvatinib to be innovative in its potential to make a significant and substantial impact on health-related benefits. Pembrolizumab in combination with lenvatinib has the potential to improve outcomes for patients with untreated advanced renal cell carcinoma and provide an alternative treatment option for patients with this condition.	Comment noted. The appraisal committee will consider the innovative nature of lenvatinib with pembrolizumab during the appraisal.
Questions for consultation	Eisai Ltd	**In NHS clinical practice, when would you expect lenvatinib to be used with pembrolizumab and when with everolimus?**	Comments noted. 'People with advanced RCC that is intermediate- or poor-risk as defined in IMDC criteria' has been

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		Lenvatinib with pembrolizumab or everolimus would be expected to be used in line with its expected marketing authorisation, i.e. [redacted] **Would the dose of lenvatinib used in clinical practice differ depending on whether it was given with everolimus or pembrolizumab**? The dosing of lenvatinib within the study depends on the treatment it is administered in combination with: • Lenvatinib 18 milligrams (mg) administered orally, once daily, with everolimus 5 mg administered orally, once daily • Lenvatinib 20 mg administered orally, once daily, plus pembrolizumab 200 mg administered intravenously (IV), every 3 weeks The dose is not expected to differ between study doses and those used in clinical practice. **Have all relevant comparators for lenvatinib with everolimus or lenvatinib with pembrolizumab been included in the scope?** Yes **Which treatments are considered to be established clinical practice in the NHS for untreated advanced renal cell carcinoma?**	added as a subgroup. No further action required.

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		The comparators listed in the scope are considered to be established clinical practice **Are the outcomes listed appropriate?** Yes **Are there any subgroups of people in whom lenvatinib with everolimus or lenvatinib with pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** The IMDC intermediate – poor risk subgroups may be examined separately from the favourable risk subgroup if the combination of lenvatinib with either pembrolizumab or everolimus appears more clinically effective in either of these **Where do you consider lenvatinib with everolimus or lenvatinib with pembrolizumab will fit into the existing NICE pathway, renal cancer?** It is expected that lenvatinib in combination with everolimus or pembrolizumab will fit into the NICE pathway, renal cancer as an option for first line treatment of advanced renal cancer	
	Ipsen Ltd	Based on this draft scope it appears that there are two technologies being appraised (i.e. lenvatinib and everolimus or lenvatinib and pembrolizumab). Is that possible in a single technology appraisal?	Comment noted. Please see response to previous comment in the wording section. No action required.

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	Kidney Cancer Support Network	**In NHS clinical practice, when would you expect lenvatinib to be used with pembrolizumab and when with everolimus?** When the there is an intolerance to mTOR inhibitors **Have all relevant comparators for lenvatinib with everolimus or lenvatinib with pembrolizumab been included in the scope?** We need to start comparing new combination treatments with existing combinations, such as ipilimumab plus nivolumab **Which treatments are considered to be established clinical practice in the NHS for untreated advanced renal cell carcinoma?** Sunitinib, pazopanib and ipilimumab plus nivolumab **Are the outcomes listed appropriate?** We need to identify biomarkers for prognosis/predictive outcomes to differentiate between the first-line treatments for RCC **Are there any subgroups of people in whom lenvatinib with everolimus or lenvatinib with pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately**? Patients with non-clear cell RCC have an unmet need for an effective first-line treatment.	Comments noted. Please see previous responses to comparator and outcomes comments. No action required.

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		Where do you consider lenvatinib with everolimus or lenvatinib with pembrolizumab will fit into the existing NICE pathway, renal cancer? Difficult to say without predictive/prognostic biomarkers **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:**] The scope does not need changing, but consideration needs to be taken into account regarding the location of patients – is there equality of access to the clinical trial/drug treatment on the NHS/CDF regardless of where the patient lives? **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts**. See previous answer **Do you consider lenvatinib with everolimus or 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)?**	

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		No, unless there is a dramatic improvement in PFS or OS in both clear cell and non-clear cell RCC patients **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** Data from the CLEAR phase III trial **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? If yes, please describe briefly.** Barriers to adoption will be efficacy, safety and/or cost.	
	Merck Sharp & Dohme Ltd	**Question: In NHS clinical practice, when would you expect lenvatinib to be used with pembrolizumab and when with everolimus**? Response: MSD expects that the combination of pembrolizumab with lenvatinib will be used in line with its expected marketing authorisation ([redacted]). MSD is unable to comment on when lenvatinib with everolimus would be used. **Question: Would the dose of lenvatinib used in clinical practice differ depending on whether it was given with everolimus or pembrolizumab?**	Comments noted. Please see previous responses to comparators and outcomes comments. No action required.

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		Response: Based on the methodology of the KEYNOTE-581 study, the dose of lenvatinib when used in combination with everolimus is 18 mg QD) and the dose of lenvatinib when used in combination with pembrolizumab is 20 mg QD. It is assumed that the dosing of any future licenced first-line indications for lenvatinib in combination with either everolimus or pembrolizumab will be 18 mg and 20 mg, respectively. **Question: Have all relevant comparators for lenvatinib with everolimus or lenvatinib with pembrolizumab been included in the scope**? Response: Yes, all relevant comparators have been included in the scope. **Question: Which treatments are considered to be established clinical practice in the NHS for untreated advanced renal cell carcinoma?** Response: The treatments considered to be established clinical practice in the NHS for untreated advanced renal cell carcinoma are tivozanib, pazopanib and sunitinib; cabozantinib is only recommended for patients classified as intermediate- or poor-risk (as defined by the IMDC criteria). **Question: Are the outcomes listed appropriate?** Response: We consider the listed outcomes to be appropriate if DoR is also included, see comment added in the relevant section above.	

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		Question: Are there any subgroups of people in whom lenvatinib with everolimus or lenvatinib with pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Response: As the results of the KEYNOTE-581 trial are not available yet, it is not possible to make assumptions about potential differences in clinical effectiveness between lenvatinib with everolimus or lenvatinib with pembrolizumab when considering any specific subgroups of patients. **Question: Where do you consider lenvatinib with everolimus or lenvatinib with pembrolizumab will fit into the existing NICE pathway, renal cancer?** Response: MSD considers pembrolizumab with lenvatinib will fit into the existing NICE pathway as a first-line treatment option for patients with advanced renal cell carcinoma (irrespective of IMDC risk group classification). **Additional comment:** MSD is in discussion with NICE about how best to accommodate this appraisal given that it is anticipated that both MSD and Eisai will be updating their labels with the indication above.	
Additional comments on the draft scope	Merck Sharp & Dohme Ltd	None	Comment noted. No action required.

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