National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

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	MSD	The wording seems appropriate.	Comment noted. The remit has been amended.
	Kidney Cancer Support Network	Background There is no mention of the fact that a number of VEGF TKIs have failed as adjuvant treatment for RCC	Comment noted in background section.
	Kidney Cancer	Yes	Comment noted. No change to the scope
Timing Issues	MSD	We anticipate that the proposed appraisal should be scheduled to enable NICE to issue final guidance soon after regulatory approval.	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation

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			for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Kidney Cancer Support Network	High urgency	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.
	Kidney Cancer	An efficacious and tolerable adjuvant treatment for those who've had surgery for kidney cancer is a priority however there is no outcome data on this treatment in this setting yet	Comment noted. NICE aims to provide draft guidance to the NHS within 6 months from the date when marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit			Noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MSD	None.	Comment noted. No changes to the scope are needed.
	Kidney Cancer Support Network	Background There is no mention of the fact that a number of VEGF TKIs have failed as adjuvant treatment for RCC	Comment noted. The scope is a short summary of the disease current treatment. No changes to the scope are needed.
	Kidney Cancer	For accuracy, remove (nephrectomy) after ablation in '*…including radiofrequency ablation and cryoablation (nephrectomy).'*	Comment noted. The scope has been amended.
The technology/ intervention	MSD	None.	Comments noted.
	Kidney Cancer Support Network	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.	Comment noted. No changes to the scope are needed.

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	Kidney Cancer	yes	Comments noted.
Population	MSD	None.	Comment noted. No changes to the scope are needed.
	Kidney Cancer Support Network	The population is defined appropriately, although, we would like to see more non-clear cell RCC patients (including patients with hereditary RCC) included in clinical trials. These patients currently have an unmet need for an effective adjuvant treatment	The committee will appraise the technology within its marketing authorisation. No changes to the scope are needed.
	Kidney Cancer	- Be explicit whether those who've had a partial nephrectomy would be included i.e those with lower stage and grade renal masses. - Be explicit if available to those in all IMDC risk categories - Needs clarity if this treatment would be available for those who have been diagnosed with metastatic disease at the outset as in some cases they may have a nephrectomy prior to commencing treatment for the metastasis (in some cases under surveillance until more growth recorded) - Immunotherapy may not be tolerated by some due to pre existing health conditions or frailty. An alternative adjuvant treatment should be available to that group.	The committee will appraise the technology within its marketing authorisation. Only if it cannot make a recommendation across the full marketing authorisation will the committee consider if there are any clinically and biologically plausible subgroups for whom it may benefit and be cost effective. No changes to the scope are needed.

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Comparators	MSD	None.	Comment noted. No changes to the scope are needed.
	Kidney Cancer Support Network	None	Comments noted. No changes to the scope are needed.
	Kidney Cancer	Yes, standard care is surgery, ablation or active surveillance. No adjuvant treatment has been approved by NICE.	Comments noted. No changes to the scope are needed.
Outcomes	MSD	MSD would like to point out that *response rates* would not be an appropriate outcome measure to consider for adjuvant treatment post-nephrectomy (for the same reason, response rates are not an outcome assessed in the KEYNOTE-564 trial that will support this appraisal).	Comments noted. The outcomes have been amended.
	Kidney Cancer Support Network	Add identification of a prognostic/predictive biomarker Health-related quality of life data also need to be presented, especially for adjuvant treatment when a patient is taking treatment without any sign of active disease	Comment noted. A health relate quality of life outcome has been included. No changes to the scope are needed.
	Kidney Cancer	Yes	Comments noted. No changes to the scope are needed.

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Economic analysis	MSD	None.	Comment noted. No changes to the scope are needed.
	Kidney Cancer Support Network	None	Comment noted. No changes to the scope are needed.
	Kidney Cancer	No comment	Comment noted. No changes to the scope are needed.
Equality and Diversity	MSD	None.	Comment noted. No changes to the scope are needed.
	Kidney Cancer Support Network	Inclusion of non-clear cell RCC patients or patients with hereditary RCC in clinical trials. These patients currently have an unmet need for an effective adjuvant treatment Equality of access to the clinical trial/drug treatment on the NHS/CDF regardless of where the patient lives	The comments has been noted in the equality impact assessment form. No changes to the scope are needed.
	Kidney Cancer	This treatment may only be suitable for those who can travel to a hospital for infusion thus excluding those who are not mobile or otherwise unable to travel (social or economic reasons) . This may have particular impact on those in rural areas.	The comments has been noted in the equality impact assessment form. No changes to the scope are needed.

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Other considerations	MSD	None.	Comment noted. No changes to the scope are needed.
	Kidney Cancer Support Network	Improving outcomes in urological cancers (2002) Cancer service guideline CSG2. Review date TBC. This guideline is 18 years old and too out-of-date to be referred to here	Comment noted. I have passed your comment to the guidelines team. No changes to the scope are needed.
	Kidney Cancer	How would the implementation of this treatment affect the current sequencing and effectiveness of treatments of metastatic kidney cancer?	Comment noted. No changes to the scope are needed.
Innovation	MSD	MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits, by transforming the treatment pathway for these patients with the introduction of an effective adjuvant therapy. Pembrolizumab has the potential to improve outcomes for patients following nephrectomy for renal carcinoma.	Comments noted. No changes to the scope are needed.
	Kidney Cancer Support Network	This is the first immunotherapy to be tested as an adjuvant treatment for intermediate-risk RCC patients, so from that perspective it is innovative. Although, VEFG TKIs have been trialled as adjuvant treatments without success	Comments noted. No changes to the scope are needed.
	Kidney Cancer	This is a new and welcome addition to the treatment of people with localised kidney cancer. Standard care involves surveillance after surgery or ablation which can cause anxiety and distress in this population. We hear of people reporting 'scanziety' as they wait for CT scan results . Having the choice to	Comments noted. No changes to the scope are needed.

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		take active treatment may reassure this group and improve quality of life by reducing anxiety and stress. If the treatment is effective and reduces the risk of developing metastasis in this group this would have significant health related and quality of life benefits to this group. This type of treatment is not without side effects, so it should be considered that people may endure lower quality of life and decreased health (due to side effects) compared to current standard care. The data on side effects is from previously published trials on pembrolizumab monotherapy, however this is in advanced cancer population or in other tumour types in adjuvant setting	
Questions for consultation	MSD	**Question:** Would pembrolizumab be used as an adjuvant treatment for people who had partial nephrectomy? **Answer:** Yes, it would be used as an adjuvant treatment for people who had undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins. **Question:** Would pembrolizumab be used as an adjuvant treatment for people who had nephrectomy of their renal cell carcinoma but also had metastases? **Answer:** No, in alignment with the inclusion criteria of the KEYNOTE-564 trial, patients must be tumour-free and validated by either computed tomography or magnetic resonance imaging scan of the brain and chest, abdomen, and pelvis and a bone scan ≤28 days from randomisation. **Question:** Is nephrectomy ever carried out in people who are taking drug treatments for advanced renal cell carcinoma?	Comment noted. No changes to the scope are needed

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		Answer: Patients who had received prior anticancer therapy, monoclonal antibody, chemotherapy, or an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) before first dose of study treatment are excluded from the KEYNOTE-564 trial (which is the key trial supporting the use of pembrolizumab in this indication); consequently, such patients would not be eligible for treatment using pembrolizumab. **Question:** Have all relevant comparators for pembrolizumab been included in the scope? **Answer:** Yes. **Question:** What is established clinical management without pembrolizumab for people who have had nephrectomy? **Answer:** There is currently no NICE recommended therapy for the adjuvant treatment of patients who have had nephrectomy to treat renal cell carcinoma. Current established management for these patients is surveillance (via computer tomography, magnetic resonance imaging, ultrasound etc.). **Question:** Does this vary by stage of disease, and if so, how? **Answer:** There is currently no NICE recommended therapy for the adjuvant treatment of patients who have had nephrectomy to treat renal cell carcinoma, regardless of stage of disease prior to nephrectomy. **Question:** Are the outcomes listed appropriate? **Answer:** As noted previously, *response rates* would not be an appropriate outcome measure to consider for adjuvant treatment post-nephrectomy (for	

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		the same reason, response rates are not an outcome assessed in the KEYNOTE-564 trial). **Question:** Are there any subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? **Answer:** MSD does not currently anticipate there will be subgroups of people in whom pembrolizumab will be more clinically effective or cost effective. Further insights may be available once the data reads out from the KEYNOTE-564 study. **Question:** Where do you consider pembrolizumab will fit into the existing NICE pathway, Renal cancer? **Answer:** MSD considers that the NICE pathway on renal cell caner would require updating to allow pembrolizumab to fit into a newly created adjuvant treatment step, following the current nephrectomy step in the NICE pathway. **Question:** Could the proposed remit and scope exclude from full consideration any people protected by the equality legislation who fall within the patient population for which pembrolizumab will be licensed? **Answer:** MSD does not consider that the proposed remit and scope will exclude from full consideration any people protected by the equality legislation. **Question:** Could the proposed remit and scope 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?	

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		Answer: MSD does not consider that the proposed remit and scope will lead to recommendations that have a different impact on people protected by the equality legislation. **Question:** Could the proposed remit and scope have any adverse impact on people with a particular disability or disabilities? **Answer:** MSD does not consider that the proposed remit and scope will have any adverse impact on people with a particular disability or disabilities. **Question:** What evidence should be obtained to enable the Committee to identify and consider such impacts? **Answer:** Not applicable. **Question:** Do you consider 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)? **Answer:** Yes, as noted previously, MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits, by transforming the treatment pathway for these patients with the introduction of an effective adjuvant therapy. Pembrolizumab has the potential to improve outcomes for patients following nephrectomy for renal carcinoma. **Question:** Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?	

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		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. **Answer:** No, MSD does not consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation. **Question:** Do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. Answer: No, MSD does not consider that there will be any barriers to adoption of this technology into practice.	

	Kidney Cancer Support Network	**Population**
		• Would pembrolizumab be used as an adjuvant treatment for people:
		  • who had partial nephrectomy?
		  • who had nephrectomy of their renal cell carcinoma but also had metastases?
		
		I would expect pembrolizumab to be used as an adjuvant treatment for patients who have had partial nephrectomy and no sign of metastatic disease. I would not expect pembrolizumab to be used as an adjuvant treatment for patients with metastases – there are already a number of first-line treatments available for advanced RCC
		
		• Is nephrectomy ever carried out in people who are taking drug treatments for advanced renal cell carcinoma?
		
		As far as we know, it is rare for patients to have a nephrectomy while taking drug treatments for advanced RCC
		
		Comparators
			Comments noted. No changes to the scope are needed

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant comparators for pembrolizumab been included in the scope? We need to compare adjuvant immunotherapy with adjuvant VEGF TKIs What is established clinical management without pembrolizumab for people who have had nephrectomy? • Does this vary by stage of disease, and if so, how? People with favourable or intermediate disease will be follow-up every 3 months to assess metastatic spread and people with advanced disease will be started on either a TKI such as sunitinib or a combination of nivolumab plus ipilimumab Are the outcomes listed appropriate? We need to identify biomarkers for prognosis/predictive outcomes to differentiate between the first-line treatments for RCC Health-related quality of life data also need to be presented, especially for adjuvant treatment when a patient is taking treatment without any sign of active disease Are there any subgroups of people in whom pembrolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? Patients with non-clear cell or hereditary RCC have an unmet need for an effective first-line treatment Where do you consider pembrolizumab will fit into the existing NICE pathway, renal cancer?	

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		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? For example, the need for patients to travel frequently to hospital for infusions and the costs incurred either through travel and/or loss of work Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. See previous answer Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No, unless there is a dramatic improvement in PFS or OS in both clear cell and non-clear cell (or hereditary) RCC patients 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.	

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		Barriers to adoption will be efficacy, safety and/or cost. Patients may require clarification that having immunotherapy as an adjuvant treatment may compromise their eligibility for immunotherapy at some future point in time if/when their disease progresses	
	Kidney Cancer	Those with intermediate to poor IMDC may be more appropriate group for this treatment (trial is in this population)	
Additional comments on the draft scope	MSD	None	Noted.
	Kidney Cancer Support Network	None	Noted.
	Kidney Cancer	None	Noted.

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

None