National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab with axitinib for untreated locally advanced or metastatic renal cell carcinoma ID1426

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	Merck Sharp & Dohme Ltd	Please refer to the population comment.	Comment noted, no action required.
	Ipsen Ltd	No comment	No action required
	Kidney Cancer Support Network	No comment	No action required
	Royal College of Pathologists (UK)	First paragraph of the scope – would it be possible to use the phrase 'the most common subtypes, rather than 'the main ones'? How about; *RCC is the most common type of kidney cancer (more than 80% of the cases), but there are several subtypes of RCC. The main subtypes of RCC are clear cell (accounting for approximately 75% of cases), papillary and chromophobe.*	Comments noted. The wording has been updated to reflect this comment.

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		Paragraph 2 RCC is graded into stages I to IV It is confusing to use the terms 'grading' and 'staging' in the same sentence as these mean different things pathologically. Can you consider changing the phrase to; '*RCC is staged from stage I to stage IV*'.	Comments noted. The wording has been updated to reflect this comment.
		Paragraph 4 The paragraph begins; '*The aim of treatment is to stop the growth of new blood vessels within the tumour.'* However, it is not clear what this treatment is for as the prior paragraph discusses surgical options for localised disease. It may be helpful to specify that this sentence pertains to systemic treatment options for advanced disease.	Comments noted. The wording has been updated to reflect this comment.
		The Technology Section The wording of the detail regarding the clinical trial, paragraph 3; *'Pembrolizumab with axitinib is being studied in a clinical trial compared with sunitinib monotherapy in people with untreated advanced or metastatic RCC with clear cell component.'* I have concerns that there needs to be complete clarity regarding the classification/subtype of the tumour to be treated, for the purpose of this scope. Specifically, it is not clear whether the therapy is solely for patients with clear cell renal carcinoma.	Comment noted. The current wording is in line with NICE writing style. No action required.

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		Clear cell renal cell carcinoma is a well-defined subtype of renal cell carcinoma, morphologically, immunohistochemically, and genetically. Other subtypes of renal cell carcinoma can also show clear cell morphology (or a clear cell component) but this does not automatically confer their classification as clear cell renal cell carcinoma. Diagnostic histopathologists would need clarification on whether this therapy is approved for clear cell renal cell carcinoma or for any renal cell carcinoma as this may influence the way in which the tumour is reported (both primary tumour and metastatic tumour) and the ancillary investigations carried out on what may be limited biopsy material. This could have significant implications on pathology reporting practice. The oncologists would also need to be clear on whether a patient with a tumour other than clear cell RCC would be eligible for therapy. I have referred back to some of the original publications regarding the use of axitinib and pembrolizumab in patients with advanced renal cell carcinoma (Lancet Oncology 2018; 19(3):405-415) and can see that the patient group were those with advanced RCC which was said to be predominantly clear cell RCC. This could be interpreted differently to the statement for the scope above which refers to *RCC with clear cell component*. I am not sure whether the NICE guidance for the currently approved systemic therapies for RCC is specific for subtype of RCC, but at a glance it appears that the guidance for these other therapies is for advanced RCC but that subtype is *not specified*. The wording of the current scope would therefore seem to be a departure from the guidance for the other systemic therapies, although this may reflect the clinical trial data for these therapies. Does this	

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		specification in the current scope for tumours that have a clear cell component really reflect a different group of patients that may potentially benefit from this therapy excluding those with other subtypes of RCC? This is seemingly a more narrow specification than that for the other approved systemic therapies, including sunitinib.	
	NCRI-ACP-RCP-RCR	Yes	Comment noted, no action required.
Timing Issues	Merck Sharp & Dohme Ltd	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 PharmaScan accurately reflect current expectations.	Comment noted, no action required.
	Ipsen Ltd	No comment	No action required
	Kidney Cancer Support Network	No comment	No action required
	Royal College of Pathologists (UK)	As soon as possible	Comment noted. NICE has scheduled this topic into its work programme. See the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10331.
	NCRI-ACP-RCP-RCR	Relatively non-urgent	Comment noted. NICE has scheduled this topic

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			into its work programme. See the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10331.

Comment 2: the draft scope

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Background information	Merck Sharp & Dohme Ltd	For clarity, we would like to propose the following changes in the background section if possible: 1. We suggest that the sentence “However, around half of those who have surgery…” should be rephrased to “However, around half of those who have surgery develop advanced recurrence at a later date.”	Comments noted. The wording in the background section has been amended.
	Ipsen Ltd	The phrase 'The aim of treatment is to stop the growth of new blood vessels within the tumour' is correct for axitinib only. For pembrolizumab, the aim is to modulate the immune system to attack the tumour.	Comments noted. The wording in the background section has been amended.
	Kidney Cancer Support Network	The staging system most frequently used for staging RCC tumours is the TNM system, not the stage I to IV system. The last two sentences of the second paragraph about treatment needs to be re-worded for accuracy, as follows: Surgery, including nephron-sparing surgery, radical nephrectomy and ablative therapies, is the main treatment for localised and metastatic RCC. However,	Comments noted. The wording in the background section has been amended.

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		around half of those who have surgery for localised RCC develop metastatic disease later on. Paragraph 4 needs to be reworded as follows: After surgery, systemic therapies may be used to reduce the chance of the cancer recurring and to treat metastatic disease. The aim of systemic treatment with biological therapies is to stop the growth and spread of the cancer. This is accomplished through the use of medicines that stop the growth of new blood vessels within a tumour, interfere with the growth and survival of cancer cells, or enhance the immune system to fight the cancer. In untreated RCC……	
	Royal College of Pathologists (UK)	Please see comments above regarding the wording.	Comment noted, no action required.
	NCRI-ACP-RCP-RCR	The aim of treatment goes beyond stopping the growth of new blood vessels. This applies to VEGF TKI, but not immunotherapy, for example	Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal. No action required.
The technology/ intervention	Merck Sharp & Dohme Ltd	For clarity, we would like to propose the following changes in the intervention section if possible; 1. We suggest that the sentence “Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised…” should be rephrased to “Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, anti-programmed cell death 1 (PD-1) antibody involved in the	Comments noted. The scope has been updated to reflect this comment.

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		blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously."	
	Ipsen Ltd	Pembrolizumab does not currently have a marketing authorisation for RCC, but axitinib does. As a result, 'Pembrolizumab' in the fourth paragraph needs to be changed to 'Axitinib'.	Comment noted, paragraph has been updated to reflect this comment.
	Pfizer Ltd	A typo in the final paragraph before the table on page 2 states "Pembrolizumab has a marketing authorisation…" but should read "Axitinib has a marketing authorisation…"	Comment noted, paragraph has been updated to reflect this comment.
	Kidney Cancer Support Network	Yes, as far as we are aware.	Comment noted, no action required.
	Royal College of Pathologists (UK)	As soon as possible	Comment noted, no action required.
	NCRI-ACP-RCP-RCR	Note that NICE TA333 does NOT apply to pembrolizumab, but rather axitinib. Axitinib has approval for use in pre-treated RCC	Comment noted, paragraph has been updated to reflect this comment.
Population	Merck Sharp & Dohme Ltd	Please revise in line with proposed indication wording: [redacted]	Comment noted. The population has been amended to reflect the inclusion criteria of the

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			clinical trial. For further details see https://clinicaltrials.gov/ct2/show/NCT0285333
	Ipsen Ltd	No comment	No action required.
	Kidney Cancer Support Network	This definition should include patients who are PD-1 positive, since this will be the population for which the drug combination is most effective.	Comment noted. The current wording is in line with NICE writing style. No action required.
	Royal College of Pathologists (UK)	Please see above comments regarding the wording. There is a need for absolute clarification as to the subtype of renal cell carcinoma which is eligible for treatment as this is not clear in the draft scope. Specifically, is the therapy only for patients with clear cell renal cell carcinoma? This will have potential implications on pathology reporting.	Comment noted, population section has been updated to reflect this comment.
	NCRI-ACP-RCP-RCR	Yes	Comment noted, no action required.
Comparators	Merck Sharp & Dohme Ltd	No additional comments	No action required.
	Ipsen Ltd	The comparators listed are all appropriate.	Comment noted, no action required.
	Pfizer Ltd	If ID1335 is recommended by NICE, atezolizumab + bevacizumab would be a comparator.	Atezolizumab plus bevacizumab are not included as a

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			comparator in the scope because they are not expected to represent established NHS practice in England at the time of the company submission for this appraisal.
	Kidney Cancer Support Network	The comparators listed are considered the standard systemic treatments currently used in the NHS for untreated metastatic RCC	Comment noted, no action required.
	Royal College of Pathologists (UK)	I cannot comment in depth here, except to ask whether the currently approved systemic therapies are approved for all subtypes of RCC, in which case the subtype of RCC for the purpose of this scope needs to be very clear. If only clear cell RCC for this scope, then this is potentially different to currently available therapies? Please see comments above regarding wording.	Comment noted. The population in the trial reflects the population within the clinical trial. The committee will make its recommendations in line with the final marketing authorisation once known.
	NCRI-ACP-RCP-RCR	Yes	Comment noted, no action required.
Outcomes	Merck Sharp & Dohme Ltd	MSD agrees with the proposed outcome measures. However, it is known that the response to immunotherapies (immune-oncology drugs) may be delayed, but once triggered, is likely to be durable, bringing unquantifiable survival	Comment noted. The list of outcomes has

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		benefit for a subset of patients; therefore MSD suggests the inclusion of "Objective response rate" and "Disease control rate" as additional outcomes measures.	been amended to include response rate.
	Ipsen Ltd	No comment	No action required.
	Kidney Cancer Support Network	The outcome measures listed are appropriate for capturing the most important health-related benefits (and harms) of the treatment.	Comment noted, no action required.
	Royal College of Pathologists (UK)	I cannot comment here.	Comment noted, no action required.
	NCRI-ACP-RCP-RCR	Yes. Alongside landmark analysis.	Comment noted, no action required.
Economic analysis	Merck Sharp & Dohme Ltd	No additional comments.	No action required.
	Ipsen Ltd	No comment	No action required.
	Kidney Cancer Support Network	We consider the health economic assessment model used by NICE to be unsuitable for small patient groups (rare cancers): Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life-prolonging	Comments noted. The Appraisal Committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost

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		treatments during a desperately difficult time for both themselves and their families. "Costs will be considered from an NHS and Personal Social Services perspective." Which models will be used to determine the cost of Personal Social Services? How can NICE and the manufacturer estimate what social care will be needed for these patients?	effective or below which it would. For further information please see section 6.3 of the Guide to the methods of technology appraisal. Section 5 of the NICE reference case describes how personal and social services costs should be included.
	Royal College of Pathologists (UK)	No comment.	No action required.
Equality and Diversity	Merck Sharp & Dohme Ltd	No additional comments.	No action required.
	Ipsen Ltd	There are no equality issues to raise at this stage.	No action required
	Kidney Cancer Support Network	Administration of pembrolizumab requires hospital visits every 3 weeks and the use of a chemotherapy chair for the infusion. This will have financial implications for patients (travel to/from the hospital, accommodation costs for people in remote areas, time off work for hospital appointments etc.) and could exclude patients living in remote areas or patients from poor socioeconomic backgrounds from receiving treatment.	Comment noted. This does not relate to any groups protected by the legislation - committee's decision relates equally to all people in England.

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		The need for chemotherapy chair facilities and associated resources might restrict the use of this technology to specialised/high throughput regional centres.	Equality of access across England and socio-economic groups is not an equality issue to be addressed by committee.
	Royal College of Pathologists (UK)	Please see above comments regarding clarity over patient subgroups depending upon tumour classification/subtype. By specifying only clear cell RCC (if that is what is meant by RCC with clear cell component) this excludes other subtypes of RCC, which is seemingly different to the currently available systemic therapies. Need clarity that this in fact reflects the available clinical trial evidence.	Comment noted. The population in the scope reflects the population within the clinical trial. The committee will make its recommendations in line with the final marketing authorisation once known.
	NCRI-ACP-RCP-RCR	None noted	No action required.
Other considerations	Merck Sharp & Dohme Ltd	No additional comments.	No action required.
	Ipsen Ltd	No comment.	No action required.
	Kidney Cancer Support Network	None.	No action required.

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	Royal College of Pathologists (UK)	No comment.	No action required.
Innovation	Merck Sharp & Dohme Ltd	MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits in adult patients with locally advanced or metastatic renal cell carcinoma with clear cell component.	Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
	Ipsen Ltd	No comment.	No action required.
	Kidney Cancer Support Network	This technology will be one of the first immunotherapy plus targeted therapy combinations for use in the first-line treatment of metastatic RCC. We consider this to be a 'step-change' in the management of RCC patients, and are hopeful that the combination will provide significant health benefit for patients in terms of improved quality of life and overall survival.	Innovation will be considered by the appraisal committee when formulating its recommendations. No action required.

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	Royal College of Pathologists (UK)	No comment.	No action required.
	NCRI-ACP-RCP-RCR	First-line treatment options for patients with metastatic RCC have not altered in more than a decade. Whilst single agent TKIs are active, associated responses are not durable and OS has essentially plateaued. They are also toxic drugs. There is, therefore, a clear need for improved first-line treatment options for these patients. The combination of pembrolizumab with axitinib is one of a number of promising immunotherapy -TKI combinations currently being explored in phase III clinical trials. The data currently available for pembro-axi appears to be that from a single arm phase Ib trial involving a total of 52 patients. As such, the study was designed to principally establish safety and determine preliminary efficacy. Almost half of patients had good risk disease by IMDC criteria. The observed response rates and median duration of response are notable and certainly higher than observed with currently used single agent TKIs. However, it is unclear if the combination is superior to sequencing these agents. Data from a phase III trial of the combination versus sunitinib are awaited. Overall, the combination may well have the potential to represent a step-change in the management of patients with RCC. Currently, available data are limited though and a randomised phase III trial is on-going.	Innovation will be considered by the appraisal committee when formulating its recommendations. No action required.
Questions for consultation	Ipsen Ltd	1. Have all relevant comparators for pembrolizumab with axitinib been included in the scope? Yes.	Comments noted. No action required.

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		2. Which treatments are considered to be established clinical practice in the NHS for untreated metastatic renal cell carcinoma? Sunitinib, pazopanib and tivozanib are the treatments which are currently reimbursed for untreated RCC patients. However, sunitinib and pazopanib are considered to be currently established clinical practice in the NHS. 3. Are the outcomes listed appropriate? Yes. 4. Are there any subgroups of people in whom pembrolizumab with axitinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? No comment. 5. Where do you consider pembrolizumab with axitinib will fit into the existing NICE renal cancer pathway? It is expected that pembrolizumab with axitinib will be a treatment option for untreated advanced and metastatic RCC patients. 6. Do you consider pembrolizumab with axitinib 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)? No comment. 7. Do you consider that the use of pembrolizumab with axitinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No comment.	Comments noted. No action required. Comments noted. No action required. Comments noted. No action required. Comment noted. No action required. Comments noted. No action required.

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		8. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. No comment. 9. 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. No comment. 10. Would it be appropriate to use the cost comparison methodology for this topic? No. 11. Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? Unknown. 12. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes. 13. Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? No comment.	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comments noted. No action required. Comment noted. No action required. Comments noted. No action required.

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	Kidney Cancer Support Network	None	No action required.

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

Department of Health and Social Care

Renal Association