National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Cabozantinib for untreated locally advanced or metastatic renal cell carcinoma

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	EUSA Pharma	Yes	Comment noted. No action required.
	Ipsen	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	The wording does reflect the relevant issues for consideration in this TA.	Comment noted. No action required.
	Pfizer	No comments	
Timing Issues	EUSA Pharma	Dependent on timelines for marketing authorisation	Comment noted. No action required.
	Ipsen	Cabozantinib extends progression-free survival in previously untreated patients with advanced RCC, compared with currently available treatments.	Comment noted. No action required.

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		This makes it an important new treatment option which should be appraised as a matter of priority.	
	NCRI-ACP-RCP-RCR	Moderate	Comment noted. No action required.
	Pfizer	No comments	No action required.
Additional comments on the draft remit	EUSA Pharma	None	No action required.
	NCRI-ACP-RCP-RCR	Of note, the current marketing authorisation for cabozantinib is for '*the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy*'. Not **'untreated locally advanced or metastatic renal cell carcinoma'** – the intended marketing authorisation.	Comment noted. NICE has published guidance on cabozantinib for previously treated advanced renal cell carcinoma (TA463). This appraisal relates to cabozantinib for untreated disease. To produce timely guidance, the NICE appraisal may start before the drug receives its marketing authorisation for the

Section	Consultee/ Commentator	Comments [sic]	Action
			indication under appraisal. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	EUSA Pharma	None	No action required.
	Ipsen	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Largely accurate and appropriate. Note the following:~ 1. P1. **Nephron sparing surgery may be curative in people with localised tumours.** That is accurate but incomplete. Localised radical approaches including nephron-sparing surgery, radical nephrectomy and ablative therapies may be curative in people with localised therapies. P1. **The aim of treatment is to stop the growth of new blood vessels….** That is not the aim of treatment. It is the mechanism of action of the most widely used treatments currently (the VEGF-directed therapies such as sunitinib, pazopanib and axitinib). However the aim of treatment is to prevent the growth and survival of cancer cells within the tumour such that the established tumours reduce in size and no further tumours develop with the aim of prolonging cancer control and survival.	Comment noted. The scope has been updated to reflect this comment.

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	Pfizer	No comments	No action required.
The technology/ intervention	EUSA Pharma	It may be helpful to add that cabozantinib has been studied in patients with poor or intermediate risk metastatic RCC [CABOSUN]. It should be noted that the key trials for the comparators (sunitinib, pazopanib and tivozanib) were in patients who were less sick than those in the CABOSUN study. For example, in COMPARZ, which compared sunitinib and pazopanib, patients had a Karnofsky performance score of 70-100% which means that they ranged from being able to care for themselves but were unable to carry out normal activities or work (70%) to being fully active (100%). In TIVO-1, the pivotal study for tivozanib, patients had an astern Cooperative Oncology Group (ECOG) score of 0-1 which equates to being restricted in physically strenuous activity but ambulatory and able to carry out light or sedentary work (1) to fully active, able to carry on all pre-disease performance without restriction (0). In contrast, patients in CABOSUN had an ECOG of 0-2 where 2 equates to ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours. Overall, 13% of patients enrolled in CABOSUN were ECOG 2. Risk score was also poorer in CABOSUN than in the trials for sunitinib, pazopanib and tivozanib. CABOSUN only included patients with poor or intermediate risk and excluded patients with favourable risk. In contrast, COMPARZ and TIVO-1 both included patients with favourable to poor risk. **References** Choueiri TK, Halabi S, Sanford BL et al. Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of	Comment noted. The scope has been updated to further define the patients included in the CABOSUN trial.

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		Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial. J Clin Oncol 2017;35(6):591-7. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013; 369(8): 722-31. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013; 31(30): 3791-9.	
	Ipsen	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
	Pfizer	CABOSUN trial (PI Toni Choueri) is comparing cabozantinib with sutent in **poor and intermediate** risk groups only, i.e. there are no favourable risk patients, therefore the statement “adults with untreated locally advanced or metastatic RCC” is deemed to be too broad.	Comment noted. The scope has been updated to further define the patients included in the CABOSUN trial.
Population	EUSA Pharma	See comment above	Comment noted. The scope tends to be broad when the technology does not have a marketing authorisation for the indication under

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			appraisal. However, NICE will only appraise a technology within its marketing authorisation. No action required.
	Ipsen	Yes. No obvious sub-groups have been identified	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Yes defined appropriately and there are no subgroups who should be considered separately.	Comment noted. No action required.
	Pfizer	See comment above, no evidence in favourable risk patients.	Comment noted. The scope tends to be broad when the technology does not have a marketing authorisation for the indication under appraisal. However, NICE will only appraise a technology within its marketing authorisation. No action required.

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Comparators	EUSA Pharma	Yes, pazopanib and sunitinib are currently approved by NICE for use in the NHS and are the standard of care. Tivozanib is currently under review by NICE and it is hoped that it will also be approved for use in the NHS. As noted below in **Related NICE recommendations and NICE pathways**, nivolumab is also under review by NICE as a potential option for first line treatment of RCC. [Nivolumab in combination with ipilimumab for untreated advanced or metastatic renal cell carcinoma'. Proposed NICE technology appraisal [ID1182]]. The publication date is yet to be confirmed and therefore it seems reasonable that it has not been included in the scope as a comparator. Should the publication date be within the period of the cabozantinib appraisal then we would expect it to be included within the scope.	Comment noted. Tivozanib is no longer a comparator in the scope because it is not expected to represent established NHS practice in England at the time of the company submission for this appraisal.
	Ipsen	The Draft Scope notes that tivozanib is not yet approved by NICE. If tivozanib is to be part of this appraisal, we would request early confirmation of same in order that we have sufficient time for it to be incorporated (see also the *'Economic analysis'* section, below.	Comment noted. Tivozanib is no longer a comparator in the scope because it is not expected to represent established NHS practice in England at the time of the company submission for this appraisal.
	NCRI-ACP-RCP-RCR	Yes. Sunitinib (the comparator in the relevant randomised trial CABOSUN) is the most widely used agent in this setting globally although we would not	Comment noted. Tivozanib is no longer a comparator in the scope

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		describe it as 'best' it is most appropriate. The other comparators are also relevant.	because it is not expected to represent established NHS practice in England at the time of the company submission for this appraisal.
	Pfizer	Yes, it is accurate	Comment noted. Tivozanib is no longer a comparator in the scope because it is not expected to represent established NHS practice in England at the time of the company submission for this appraisal.
Outcomes	EUSA Pharma	Yes Although it should be noted that the CABOSUN study did not collect quality of life data.	Comment noted. No action required.
	Ipsen	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.

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	Pfizer	Yes	Comment noted. No action required.
Economic analysis	EUSA Pharma	We note that there is a new section of copy which was not present in the tivozanib scope. *If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out.* We note that the use of a cost comparison has recently been introduced by NICE in instances where the new technology is similar in clinical efficacy and resource use.	Comment noted. This topic did not meet the criteria for cost comparison, and so will be appraised as a single technology appraisal (STA). For further details, see the Addendum to the Guide to the methods of technology appraisal. No action required.
	Ipsen	The comparison with tivozanib is likely to be highly uncertain given that the tivozanib trial is versus sorafenib rather than either sunitinib or pazopanib. The network required for making this comparison will, therefore, be weak. This is an exacerbation of the	Comment noted. Tivozanib is no longer a comparator in the scope because it is not expected to represent established NHS practice in England at the time of the company submission for this appraisal.

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	NCRI-ACP-RCP-RCR	Yes. The appropriate time horizon should consider median progressions free and overall survival from relevant other trials and sources of information (as 8-12 months for PFS, 22-30 months for OS).	Comment noted. No action required.
	Pfizer	No comments	No action required.
Equality and Diversity	EUSA Pharma	No	Comment noted. No action required.
	Ipsen	None	No action required.
	NCRI-ACP-RCP-RCR	No – the scope does not need changing to meet these criteria.	Comment noted. No action required.
	Pfizer	No comments	No action required.
Innovation	EUSA Pharma	No	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	*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)?* Yes. *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?* No.	Comment noted. No action required.

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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. The CABOSUN clinical trial. Choueiri et al J Clin Oncol 35.591-597.	
	Pfizer	No comments	No action required.
Other considerations	EUSA Pharma	None	No action required.
	Ipsen	None	No action required.
	NCRI-ACP-RCP-RCR	Note the recent data from the Checkmate 214 study which position the combination of nivolumab and ipilimumab as superior to suntinib for first line treatment of patients with intermediate and poor prognosis advanced renal cell carcinoma. These data were presented at the September 2017 European Society of Medical Oncology Annual Meeting. However these are new data, not yet published as a full manuscript.	Comment noted. NICE can only include technologies as comparators in the scope if they represent established NHS practice in England at the time of the company submission for the appraisal of the intervention. No action required.
	Pfizer	No other considerations	Comment noted. No action required.
	EUSA Pharma	No comment	No action required.

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Questions for consultation	NCRI-ACP-RCP-RCR	Q. Where do you consider cabozantinib will fit into the existing NICE renal cancer pathway? A. First line untreated advanced renal cell carcinoma. (although currently available in patients pre-treated with a VEGF-directed therapy). Q. Do you consider that there will be any barriers to adoption of this technology into practice? A. No. Q. Is the STA method appropriate? A. Yes. Q. Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? A. Yes similar in it resource use. Reason for consideration however is apparent superiority over current standard appropriate comparator of sunitinib. Q. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? A. Yes. The primary endpoint of the study was progression free survival with overall response rate, overall survival. And safety as relevant and important secondary endpoints. Q. Is there any substantial new evidence for the comparator technologies that has not been considered?	Comment noted. This topic did not meet the criteria for cost comparison, and so will be appraised as a single technology appraisal (STA). For further details, see the Addendum to the Guide to the methods of technology appraisal. No action required.

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		A. No. Q. Are there any important ongoing trials reporting in the next year? A. Yes. The Checkmate 214 study reported at the European Society of Medical Oncology annual meeting in September 2017. Numerous other trials of novel therapies are in progress in this setting of first line treatment of advanced renal carcinoma. These trials are predominantly investigating checkpoint inhibitor immunotherapy either as a single agent or in combination with other agents. These will report over the next 12-24 months and so the field is likely to change further however the only one of these that has reported at present is Checkmate 214. As described above this has reported that the combination of nivolumab and ipilimumab is superior to sunitinib for first line treatment of patients with intermediate and poor prognosis advanced renal cell carcinoma in terms of progression free and overall survival. However these are new data, not yet published as a full manuscript. In addition, although this trial reports superiority of the nivolumab+ipilimumab combination the precise groups in who this may be appropriate treatment is not yet clear, it is not yet licensed, approved or funded and it is toxic and not appropriate for all patients and therefore it is important that other advances in this setting that could be appropriate for a wide group of patients. We therefore strongly support consideration of cabozantinib by a Single Technology Appraisal at this time.	
	Pfizer	**Have all relevant comparators for cabozantinib been included in the scope?** Yes **Which treatments are considered to be established clinical practice in the NHS for untreated locally advanced or metastatic RCC?**	Comment noted. No action required.

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		Sunitinib & pazopanib **Are the outcomes listed appropriate?** Yes **Are there any subgroups of people in whom cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No comment **Where do you consider cabozantinib will fit into the existing NICE renal cancer pathway?** For untreated locally advanced or metastatic renal cell carcinoma. **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 • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** • No comment • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** No comment	

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		• **Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** • 2017 CHECKMATE 214 • 2018 ImMOTION 151	
Additional comments on the draft scope	EUSA Pharma	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