National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Axitinib, everolimus, sorafenib and sunitinib for treated advanced or metastatic renal cell carcinoma

Response to consultee and commentator comments on the draft remit and draft scope

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
Appropriateness	Bayer	Sorafenib is a tyrosine kinases inhibitor licenced for the treatment of advanced renal cell carcinoma (RCC) patients unsuitable to or who failed prior cytokine therapy, in particular interferon-alpha or interleukin-2 based therapy. Since its last technology appraisal (TA 178), clinical practice in England and Wales has changed with cytokines usage rapidly decreasing because of their replacement with new first-line recommended agents such as sunitinib and pazopanib. Moreover, therapies like axitinib have already been recommended as a treatment option for adults with advanced renal cell carcinoma after failure of first-line tyrosine kinase inhibitor or cytokine. According to section 4.3.9 in TA 178 and section 4.5 in TA 333, the total number of patients affected by metastatic and/or advanced RCC in England and Wales is estimated at 4,000 and only 1% of them receive prior cytokine therapy. This implies the potential number of patients eligible for treatment with sorafenib to be below 40 cases. Other sources of data available to Bayer support these estimates. Given the size of the population considered, and the fact that there are other	Comment noted. Although the use of cytokines is decreasing and the population that has failed prior interferon-alpha or interleukin-2 based therapy, or is considered unsuitable for such therapy, may be small, there may still be some patients treated in this setting in whom sorafenib would be an option. Therefore, it was considered

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		therapies recommended in this place in the treatment pathway in England and Wales we would suggest that a review of TA178 at this time would not be an efficient use of NICE resources.	appropriate to include sorafenib in the remit. No action required.
	NCRI-RCP-ACP-RCR	Yes – agree.	Comment noted. No action required.
	Novartis	It is appropriate that the topic is referred.	Comment noted. No action required.
	Pfizer	No comments	No action required.
Wording	NCRI-RCP-ACP-RCR	Yes.	Comment noted. No action required.
	Novartis	Novartis has no suggested changes to the wording.	Comment noted. No action required.
	Pfizer	No comments	No action required.
Timing Issues	Bristol-Myers Squibb	Given the high unmet need in this patient population it is urgent for the Institute to ensure timely guidance for nivolumab. Please see additional comments on the draft scope for more detail.	Comment noted. Please see the response to the additional comments on the draft scope.
	NCRI-RCP-ACP-RCR	This is urgent for two reasons: 1. Access to drugs through the CDF is now more limited. **2.** Nivolumab represents a new technology with the potential for durable benefit. It would have been preferable for nivolumab to have been assessed through an STA to improve speed of decision making.	Comment noted. Nivolumab has been removed from this MTA, and will be appraised

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		Given the delay in CDF appraisal the drug is unavailable to the NHS currently. An rapid NICE decision (if positive) is an urgent requirement for RCC patients.	separately as an STA. No action required.
	Novartis	Due to the recent review and changes by the Cancer Drugs Fund (CDF), access to appropriate treatments for patients with renal cell carcinoma (RCC) who have received prior treatment, is far from ideal, and does not reflect international clinical practice and guidelines. This multiple technology appraisal (MTA) is needed urgently to provide appropriate access to these therapies, for RCC patients.	Comment noted. No action required.
	Pfizer	No comments	No action required.
Additional comments on the draft remit	Novartis	No comments at this stage.	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NCRI-RCP-ACP-RCR	Although the background information provides reference to other NICE guidelines for treatment in the metastatic setting, it might be useful to provide a short summary here of the evidence for the current approved treatment here? It would also be useful to include evidence for the suggested interventions in their suggested settings.	Comment noted. The background information does not normally include a summary of the evidence on the interventions or comparators.

Section	Consultee/ Commentator	Comments [sic]	Action
			No action required.
	Novartis	The information in this section is complete and accurate.	Comment noted. No action required.
	Pfizer	No comments	No action required.
The technology/ intervention	Bristol-Myers Squibb	Please see additional comments on the draft scope	Comment noted. Please see the response to the additional comments on the draft scope.
	NCRI-RCP-ACP-RCR	It should read: First line treatment for people who have not received VEGF targeted therapy received or who have had previous cytokine therapy (aldesleukin or interferon alfa). It is now extremely uncommon for patients to receive first line treatment with interferon – indeed this would be seen as sub optimal treatment therefore this group increasingly does not exist any more. The historical group of patients who received interferon in the past and are now progressing and requiring VEGF targeted therapy are vanishingly rare.	Comment noted. This MTA will only review second-line treatments. Although the use of interferon is decreasing and the population that has received prior interferon-based therapy may be small, there may still be some patients treated in this

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			setting. Therefore, it was considered appropriate to include treatment options for these patients separately in the scope. No action required.
	Novartis	The description of the technologies is accurate. Novartis considers, however, that sunitinib should not be included as an intervention for people who have received previous VEGF-targeted therapy. The existing NICE guidance TA178 has already reviewed sunitinib in second-line RCC, and has not recommended its use in this setting. In clinical practice and in the European society of medical oncology (ESMO) 2014, and European association of urology (EAU) 2014 guidelines, sunitinib is recommended in the first-line setting, and has no recommendation in the second-line setting after VEGF-targeted therapy. Furthermore, the two trials quoted in the UK summary of product characteristics (SPC) for the RCC indication of sunitinib, were only conducted in treatment-naïve patients in one study, and cytokine refractory patients in the other study.	Comment noted. Sunitinib has a marketing authorisation for the treatment of advanced/metastatic renal cell carcinoma in adults, and is an option in this setting, acknowledging that this may be in a small population. Therefore, it was considered appropriate to include it as an intervention in the scope. No action required.
	Pfizer	No comments	No action required.
Population	NCRI-RCP-	It should read : People with advanced or metastatic renal cell carcinoma.	Comment noted.

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	ACP-RCR		This MTA focuses on previously treated, advanced or metastatic renal cell carcinoma. No action required.
	Novartis	The population is defined appropriately.	Comment noted. No action required.
	Pfizer	No comments	No action required.
Comparators	NCRI-RCP-ACP-RCR	Yes.	Comment noted. No action required.
	Novartis	In the section of comparators, for people who have received previous VEGF-targeted therapy, the only comparator should be the relevant interventions listed, compared with each other. Best supportive care should be removed as a comparator. The ESMO 2014 and EAU 2014 guidelines, give no recommendation for best supportive care.	Comment noted. Best supportive care may be considered for patients who are unfit for systemic therapy. No action required.
	Pfizer	<u>Treatments currently used in the NHS</u> Pfizer believes this appraisal should focus on comparing medicines used routinely in NHS care for the population under review. Therefore, Pfizer suggests that NICE excludes: • Sunitinib as both an intervention and a comparator for *"people who have received prior cytokine therapy"* and *"people who have received previous VEGF-targeted therapy"* for the following reasons:	Comment noted. Sunitinib has a marketing authorisation for the treatment of advanced/metastatic renal cell carcinoma in adults, and is an option

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		i. Sunitinib is currently recommended by NICE as a possible first line treatment for people with advanced and/or metastatic RCC (TA169), and therefore is not routinely used as a second line treatment ii. There are very limited reliable data available for the use of sunitinib in people who have received prior systemic therapies; iii. Sunitinib was appraised and not recommended by NICE as a second line treatment for advance or metastatic RCC (TA178) in August 2009, which was moved to the *technology appraisal static list* in February 2012; and iv. Since February 2012, there has been no significant new evidence for the use of sunitinib as a second line treatment for people with RCC that would justify the decision to re-review the guidance published in TA178. • Pazopanib as a comparator for "people who have received prior cytokine therapy". Pazopanib is only indicated for the first line treatment of advanced RCC for patients who have received prior cytokine therapy for advanced disease (EMA-pazopanib), and was recommended by NICE as a first line treatment in February 2011 (TA215). Furthermore, Pfizer understands from clinical expert opinion that pazopanib is not routinely used as a second line treatment for RCC. References EMA-pazopanib. European Medicines Agency (EMA) – pazopanib EPAR. Link. Accessed: 19th Oct 2015 TA169. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. Link. Accessed: 19th Oct 2015 TA178. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. Link. Accessed: 19th Oct 2015	in this setting, acknowledging that this may be in a small population. Therefore, it was considered appropriate to include it as an intervention in the scope. Pazopanib has been excluded from the comparators for people who have received previous cytokine therapy.

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		TA215. Pazopanib for the first-line treatment of advanced renal cell carcinoma. Link. Accessed: 19th Oct 2015	
Outcomes	Bristol-Myers Squibb	Please see additional comments on the draft scope	Comment noted. Please see the response to the additional comments on the draft scope.
	NCRI-RCP-ACP-RCR	Not necessarily. The benefit of immunotherapies is often under-represented at the median OS or PFS point due to a minority group having durable benefit (NICE is aware of this – ref approval for ipilimumab in melanoma). Important additional outcome measures should include: 1. Hazard Ratio (reflective of benefit over the length of the curve) and 2. Landmark OS and PFS analyses at 1 year and 2 year	Comment noted. The suggested measures would be captured by overall survival and progression-free survival, which are included in the scope. No action required.
	Novartis	The outcome measures listed will capture the most important health related benefits and harms of the technologies. One improvement we suggest would be that consideration of response is not limited to objective response rate, but also includes clinical benefit rate / disease control rate. In a disease with the natural history of RCC, the achievement of stable disease with an intervention is also of clinical value.	Comment noted. The scope includes response rates as an outcome, and does not limit the consideration of response to objective response rate. No action required.
	Pfizer	Yes, these outcomes are sufficient to capture the health related benefits of	Comment noted. No

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		the technologies under review.	action required.
Economic analysis	Bristol-Myers Squibb	Please see additional comments on the draft scope	Comment noted. Please see the response to the additional comments on the draft scope.
	NCRI-RCP-ACP-RCR	This seems reasonable.	Comment noted. No action required.
	Novartis	As the economic case is still in development we do not have comments at this stage	No action required.
	Pfizer	No comments	No action required.
Equality and Diversity	NCRI-RCP-ACP-RCR	Currently the choice of first line treatment tends to be between pazopanib and sunitinib – based on the COMPARZ and PISCES data, patients often choose pazopanib, due to the perceived improved tolerability profile, which is very important when considering quality of life. However, it is very important that future treatment options are not limited based on the first line treatment choice. Limiting second line treatments according to first line treatment choice will result in inequality of access to 2nd line treatment and unnecessary toxicity exposure to first line patients.	Comment noted. The scope includes treatments for people who have received previous cytokine or VEGF-targeted therapy. No action required.
	Novartis	No comments at this stage.	No action required.
	Pfizer	No comments	No action required.

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Innovation	Bristol-Myers Squibb	Please see additional comments on the draft scope	Comment noted. Please see the response to the additional comments on the draft scope.
	NCRI-RCP-ACP-RCR	Nivolumab is innovative and is a 'step-change' in the management of this disease. Given the precedent set with other checkpoint inhibitor immunotherapies (ref ipilimumab in melanoma) it is likely that a subset of patents will have durable long term benefit that may be underestimated in the QALY calculation.	Comment noted. Professional groups are encouraged to describe the innovative nature of nivolumab in their evidence submissions. No action required.
	Novartis	Everolimus is an innovative anti-cancer therapy that has a significantly different mechanism of action to the other interventions under consideration in this MTA. Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. It reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours in vitro and in vivo.	Comment noted. The company is encouraged to describe the innovative nature of everolimus in its evidence submission. No action required.
	Pfizer	<u>Step-change in disease management</u> Axitinib is an oral small-molecule receptor tyrosine kinase inhibitor (TKI) that targets angiogenesis. It is a more potent inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3 in vitro compared with currently licensed TKI VEGFR inhibitors for mRCC. The mechanism for the superior efficacy of axitinib vs. sorafenib after failure of a tyrosine kinase inhibitor, while unclear may be due to axitinib's higher	Comment noted. The company is encouraged to describe the innovative nature of axitinib in its evidence submission.

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		selectivity and affinity for VEGFRs than sorafenib. We believe that axitinib compared to best supportive care, has demonstrated a positive impact in the treatment and survival of patients that have failed previous therapy. As there are no NICE approved drugs for this patient group, axitinib addresses this unmet need appropriately. <u>Not captured by the QALY</u> The societal impact of cancer is substantial (Hanly et al. 2015 and Luengo-Fernandez et al. 2013), in AXIS, axitinib was shown to provide PFS advantages which is maintained in the composite time to deterioration endpoint that included symptom deterioration and supports the notion that axitinib is associated with extended disease control and symptom control in this setting (Rini et al. 2011). However, potential alleviation of carer burden as a result of this benefit would not be captured in the QALY. References Hanly et al. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. Int J Cancer. 2015. 136(4):E136-45. Luengo-Fernandez et al. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. 2013 Nov;14(12):1165-74 Rini et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011. 378(9807):1931-9.	No action required.
Other considerations	Novartis	No suggestions at this stage	Comment noted. No action required.
	Pfizer	No comments	No action required.

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NICE Pathways	Novartis	Everolimus should fit into the NICE pathway in second-line and subsequent lines, where it is done so consistent with its marketing authorisation. This is supported by clinical practice and international guidelines (see ESMO 2014, and EAU 2014 guidelines)	Comment noted. No action required.
	Pfizer	All medicines included in this appraisal should be considered for use in the NICE renal cancer pathway in line with their marketing authorisations and NICE technology appraisal guidance.	Comment noted. No action required.
Questions for consultation	Bristol-Myers Squibb	Please see additional comments on the draft scope	Comment noted. Please see the response to the additional comments on the draft scope.
	Novartis	*Is it appropriate to appraise nivolumab through this process?* After reviewing the information on the Institute's technology appraisal process, we feel it is appropriate to appraise nivolumab through this process.	Comment noted. No action required.

	Pfizer	<u>Which treatments are considered to be established clinical practice in the NHS for advanced or metastatic RCC?</u>
		Feedback from clinical experts indicated that treatments considered established clinical practice for advanced or metastatic RCC include:
		• First line treatments
		  ○ best supportive care
		  ○ pazopanib
		  ○ sunitinib
		• Second line treatments
		  ○ axitinib
			Comment noted.
			Pazopanib has been excluded from the comparators for people who have received previous cytokine therapy.
			Nivolumab has been removed from this MTA, and will be appraised separately as an STA.

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		○ best supportive care ○ everolimus <u>Is pazopanib routinely used in clinical practice for people who have received previous cytokine therapy for advanced or metastatic RCC?</u> Pazopanib's is indicated for first line treatment of advanced RCC for patients who have received prior cytokine therapy for advanced disease (EMA-pazopanib). In routine current clinical practice, pazopanib is selected and used as a 1st line therapy option for the treatment of advanced or metastatic RCC. <u>How should best supportive care be defined?</u> BSC (defined as the provision of drug and non-drug therapy for the relief of symptoms and general patient management (TA333) <u>NICE intends to appraise axitinib, everolimus, nivolumab, sorafenib and sunitinib through its Multiple Technology Appraisal (MTA) Process. Is it appropriate to appraise nivolumab through this process?</u> Nivolumab should be considered within this appraisal if it is expected to gain a marketing authorisation in line with the appraisal timeline and the marketing authorisation aligns with the population outlined in the draft scope. <u>References</u> TA333. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. Link. Accessed: 19th Oct 2015	

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Additional comments on the draft scope	Bristol-Myers Squibb	BMS strongly disagree with including nivolumab in the draft scope for this MTA (for people who have received previous VEGF-targeted therapy), rather than scoping a separate STA for nivolumab. While the Institute has decided an MTA for the comparators in this indication is necessary, the inclusion of nivolumab risks avoidable delay for patients to the availability of an effective and innovative treatment. Most patients with pre-treated advanced renal cell carcinoma (RCC) will experience disease relapse within a year of receiving current second-line treatments; associated median survival times are less than 18 months (Motzer et al, 2010; 2013). There is a clear unmet need for a tolerable therapy in the second-line setting of RCC to provide greater improvement in overall survival (OS), compared to current available therapy, and to produce a long term durable response to treatment. The pivotal randomised trial for nivolumab, in previously treated patients with advanced or metastatic renal cell carcinoma (CHECKMATE 025; n=821) has demonstrated clinical superiority versus everolimus in OS (median 25.0 months versus 19.6 months; hazard ratio 0.73 [95% CI, 0.57 to 0.93]; p=0.002) and objective response rate (25% versus 5%; odds ratio 5.98 [95% Ci, 3.68 to 9.72]; p<0.001), and a preferable tolerability profile (Grade III or IV adverse event in 19% of nivolumab patients versus 37% of everolimus patients) (Motzer et al, 2015). The emergence of evidence for nivolumab in RCC has led a recent New England Journal of Medicine editorial to conclude nivolumab is "*the choice for patients who have disease progression while they are receiving VEGF-targeted therapy*" (Quinn et al, 2015). No other therapy to date, has demonstrated an OS (overall survival) benefit in a phase 3 clinical trial, in previously treated patients with metastatic RCC. Nivolumab is the first novel immunotherapy treatment in RCC. When used in the second-line setting, its unique mode of action (MOA), may circumvent the clinical resistance encountered on disease progression with the current first-line therapies, thus producing a superior clinical benefit. The same may not be achieved when the first-line treatment is followed by a drug that has a similar/overlapping MOA. The innovation of nivolumab is reflected in its receipt of a breakthrough therapy designation for the treatment of patients with advanced RCC in the US. Nivolumab promises a step change in the management of RCC by providing an overall survival benefit and therefore timely patient access following demonstration of cost-effectiveness is essential.	Comment noted. Nivolumab has been removed from this MTA, and will be appraised separately as an STA. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Novartis	None at this stage.	No action required.

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

The Royal College of Nursing