National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with cabozantinib for untreated advanced or metastatic renal cell carcinoma

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	Bristol Myers Squibb	This is an appropriate topic for NICE to consider	Comment noted. No action required.
	KCSN	The use of the word “untreated” is confusing for patients, since surgery is considered to be a treatment. “First-line treatment” is more appropriate.	“Untreated” has been used as a term to describe the population in previous technology appraisals in the same disease area. The population in the scope is kept broad at this stage to accommodate further changes to marketing authorisation wording. The company’s pivotal trial included patients who are not amenable to

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			surgery. No action required.
	Kidney Cancer UK	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Yes. Relevant wording	Comment noted. No action required.
Timing Issues	Bristol Myers Squibb	The appraisal should be prioritised by NICE as there is only one class of treatment (tyrosine kinase inhibitors) with a marketing authorisation and NICE approved for patients with untreated advanced or metastatic RCC. The addition of nivolumab in combination with cabozantinib would provide an additional treatment choice for patients. The prognosis of patients with RCC is linked to the stage of cancer at diagnosis, with the 5-year survival decreasing from 74% to 12% in patients diagnosed at stage 3 and 4, respectively. (Office for National Statistics, Cancer survival by stage at diagnosis for England, 2019. Available at https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed) Furthermore, priority scheduling of this appraisal will facilitate NICE's aim to publish guidance within 90 days of marketing authorisation.	Comment noted. No action required. NICE aims to ensure the timely production of guidance and has scheduled this topic into its work programme.
	KCSN	Moderately urgent, since there are already two immunotherapy/VEGF TKI combination treatments undergoing HTA at this time.	Comment noted. No action required. NICE aims to ensure the timely production of

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			guidance and has scheduled this topic into its work programme.
	NCRI-ACP-RCP-RCR	Fairly urgent. Important question. Suggest review within 3- 6 months	Comment noted. No action required. NICE aims to ensure the timely production of guidance and has scheduled this topic into its work programme.
	Kidney Cancer UK	From a patient organisation point of view this drug combination is important to be approved in a timely manner for patients of all risk (favourable, intermediate and poor) to get equal access to these medications.	Comment noted. No action required. NICE aims to ensure the timely production of guidance and has scheduled this topic into its work programme.
Additional comments on the draft remit	NCRI-ACP-RCP-RCR	No	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Bristol Myers Squibb	In the UK, IFN is not routinely used in clinical practice for the treatment of advanced or metastatic renal cell carcinoma	Thank you for your comments. The

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			management information in the background section has been updated in light of the comment.
	KCSN	Second paragraph: “RCC is graded into stages I to IV.” This should say “RCC is staged I to IV.” Or “RCC is categorised into stages I to IV.” Fourth paragraph – we are not aware of any clinicians currently using IFN-a. The sentences about IFN-a need to be updated to reflect current clinical practice. IL 2 is only available via clinical trial at one hospital in the UK and is not in routine use. Again, this sentence needs to be updated to reflect current clinical practice. Fifth paragraph – the use of the word “untreated” is confusing to patients. Does “untreated” include patients who have had a nephrectomy?	Thank you for your comments. The wording in the second paragraph has been updated. The reference to IFN-a and ILN-2 has been removed. With regards to the word “untreated” and nephrectomy, company’s pivotal trial included patients who are not amenable to surgery and “untreated” has been used to describe the population in the same disease area previously. No action required.
	NCRI-ACP-RCP-RCR	Accurate and complete	Comment noted. No action required.

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	Kidney Cancer UK	Interferon-alfa is not used anymore and could be taken out of the background.	Thank you for your comments. The reference to interferon-alfa has been removed.
The technology/ intervention *[Is the description of the technology or technologies accurate?]*	Bristol Myers Squibb	No comments	Comment noted. No action required.
	KCSN	Yes	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Yes, accurate	Comment noted. No action required.
	Kidney Cancer UK	yes	Comment noted. No action required
Population *[Is the population defined appropriately? Are there groups within this population that should be considered separately?]*	Bristol Myers Squibb	No comments	Comment noted. No action required.
	KCSN	The use of the word “untreated” is confusing for patients, since surgery is considered to be a treatment. Does “untreated” include patients who have had a nephrectomy?	Thank you for your comments. "Untreated” has been used as a term to describe the population in previous technology appraisals in the same disease area and the company’s pivotal trial included patients who are not

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			amenable to surgery. No action required.
	NCRI-ACP-RCP-RCR	Yes. Suggest consider favourable and intermediate/poor risk separately	Thank you for your comments. The population in the scope is kept broad at this stage to accommodate further changes to the marketing authorisation wording. Where evidence allows, subgroups may be considered. The intermediate/poor-risk subgroup has been added to the scope for this appraisal.
	Kidney Cancer UK	yes	Comment noted. No action required.
Comparators	Bristol Myers Squibb	All comparators included are considered relevant in the UK. It should be specified that both the marketing authorisation and NICE recommendation for cabozantinib is 'for disease that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria'	Thank you for your comments. This has been clarified in the scope.
	Pfizer	In line with the indication of cabozantinib monotherapy for untreated advanced or metastatic renal cell carcinoma, nivolumab+cabozantinib should	Thank you for your comments. This has

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		be compared to cabozantinib only for intermediate‑ or poor‑risk disease as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria. This is consistent with how cabozantinib has been included as a comparator in the two most recent technology appraisals in aRCC.	been clarified in the scope.
	KCSN	Combination treatments, such as ipilimumab/nivolumab, avelumab/axitinib and pembrolizumab/axitinib are not included as comparators. Although these combinations are currently not available as standard treatments on the NHS, by the time this appraisal is assessed they could well be. At the very least, ipilimumab/nivolumab should be considered as a comparator since it is currently available through the CDF.	Thank you for your comments. Technologies available through the Cancer Drugs Fund, and technologies that are currently being appraised by NICE are not in routine use and therefore are not considered as comparators. No action needed.
	NCRI-ACP-RCP-RCR	Standard of care should also include ipilimumab plus nivolumab, and axitinib plus pembrolizumab	Thank you for your comments. Technologies available through the Cancer Drugs Fund (ipilimumab plus nivolumab, TA581), and technologies that are currently being appraised by NICE

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			(axitinib plus pembrolizumab) are not in routine use and therefore are not considered as comparators. No action needed.
	Kidney Cancer UK	Currently the best standard of care would be sunitinib or pazopanib, except in poor risk where carbozantinib would be preferred.	Comment noted. No action required.
Outcomes *[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]*	Bristol Myers Squibb	No comments	Comment noted. No action required.
	KCSN	These are typical outcome measures for RCC clinical trials. We would like to see more emphasis put on HRQL/PRO data.	Thank you for your comments. Health-related quality of life is an outcome measure which is already in the scope. No action required.
	NCRI-ACP-RCP-RCR	yes	Comment noted. No action required.
	Kidney Cancer UK	yes	Comment noted. No action required.
Economic analysis	Bristol Myers Squibb	No comments	Comment noted. No action required.

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	KCSN	No comment.	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Analysis should include first 3-5 years of life	Thank you for your comment. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. No action required.
Equality and Diversity	Bristol Myers Squibb	No equality issues have been identified	Comment noted. No action required.
	KCSN	We would like to see people with rare subtypes of RCC included in the appraisal, since these people have the biggest unmet need for an effective treatment.	Thank you for your comment. NICE can only make recommendations for patient populations covered by the company's marketing authorisation. Where covered by the marketing authorisation

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			and if evidence allows, rare subtypes of RCC may be considered. No action required.
	NCRI-ACP-RCP-RCR	No issues with equality anticipated	Comment noted. No action required.
	Kidney Cancer UK	How this treatment could be given at home or closer for patients for patients unable to get to a hospital due to physical or mental disability. Equitable access to medication for all patients independent of geographical location. Consideration the impact of covid-19 has had on patient care and treatment. Evidence from NHS England tacking of cancer and covid-19 NCRI https://ukcoronaviruscancermonitoring.com/	Comment noted. Access to hospitals is an implementation issue; it is not an equality issue to be considered by the committee and cannot be addressed by NICE recommendations. No action required.
Other considerations	Bristol Myers Squibb	No comments	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	Nil	Comment noted. No action required.
Innovation	Bristol Myers Squibb	BMS consider nivolumab in combination with cabozantinib to be innovative in the treatment of advanced or metastatic RCC, as the combination is considered to have a complimentary mechanism of action through the use of an immunotherapy agent and tyrosine kinase inhibitor which constitutes a potential step change in management in this therapeutic area with the potential to make a significant impact on the current unmet need.	Comment noted. The extent to which the technology may be innovative will be considered in any appraisal of the

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		Nivolumab in combination with cabozantinib offers an additional treatment option supplementary to tyrosine kinase inhibitors (pazopanib, tivozanib, sunitinib and cabozantinib).	technology. No action required.
	KCSN	We do not consider nivolumab/cabozantinib to be innovative in its potential to make a significant impact on health-related benefits for advanced/metastatic RCC since there are other immunotherapy/VEGF TKI combinations available. A potential health-related benefit of the nivolumab/cabozantinib combination is the effectiveness of cabozantinib against bone metastases. Data for this benefit are anecdotal from patients on cabozantinib. Other health-related benefits include the well-tolerated side effect profile of nivolumab enabling the combination with cabozantinib. These data are well-documented from clinical trials with nivolumab.	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	We already have early data on combining a tyrosine kinase inhibitor with a PDL-1 inhibitor (axitinib plus pembrolizumab). Cabozantanib is arguably the most effective tyrosine kinase inhibitor compared to others. Combining this with a PDL-1 inhibitor could potentially be more efficacious. All benefits should be included in the QALY calculation	Comment noted. The extent to which the technology may be innovative will be considered in any appraisal of the technology. No action required.
	Kidney Cancer UK	Currently there are no other immunotherapy and VGFR combinations licenced. This combination is innovative due to it using two known medication to enhance each other. It has been shown that carbozananib creates a more immune permissive tumour environment and enhances response to the immune checkpoint inhibitor. This concept needs to understood by the panel as to why using these drugs in combination and not succession is important.	Comment noted. The extent to which the technology may be innovative will be considered in any appraisal of the

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		The combination has a favourable safety profile which will benefit the health of patients.	technology. No action required.
Questions for consultation	Bristol Myers Squibb	**Have all relevant comparators for nivolumab with cabozantinib been included in the scope?** All relevant comparators included are considered appropriate for the population defined within the scope. **Are the outcomes listed appropriate?** Outcomes listed in the scope are considered appropriate **Are there any subgroups of people in whom nivolumab with cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** In line with the trial population and anticipated license, we expect nivolumab in combination cabozantinib to be efficacious as a first line treatment option across all subgroups **Where do you consider nivolumab in combination with cabozantinib will fit into the existing NICE pathway, Renal cancer (2017)?** In the existing NICE treatment pathway for the treatment of Renal cancer, BMS expect nivolumab in combination with cabozantinib to be placed under "First-line treatment for advanced and metastatic renal cancer" **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.** BMS does not anticipate any barriers to adoption of nivolumab in combination with cabozantinib into routine practice.	Comment noted. No action required.

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		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. BMS considers the appraisal of nivolumab via the NICE STA process to be appropriate. **Would it be appropriate to use the cost comparison methodology for this topic?** **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** BMS anticipates that the clinical efficacy of nivolumab in combination with cabozantinib will be superior to the proposed comparators and is likely to offset any additional resource required for both the administration and management of the combination and treatment related side effects, respectively. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** The primary outcomes measure in Checkmate-9ER is progression free survival, with secondary outcomes measures which include overall survival and objective response rate which are considered relevant outcomes. **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?** BMS consider the key evidence to have been captured within the Checkmate-9ER trial and do not expect any relevant ongoing trials to read out in 2021.	
	KCSN	Need to consider ipilimumab/nivolumab as a comparator.	Thank you for your comments. Technologies

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		The use of the word 'untreated' is confusing for patients since surgery is considered a treatment. We consider nivolumab/cabozantinib to be a first- or second-line treatment for advanced/metastatic RCC. We would like to see people with rare subtypes of RCC included in the appraisal, since these people have the biggest unmet need for an effective treatment. We do not consider nivolumab/cabozantinib to be innovative in its potential to make a significant impact on health-related benefits for advanced/metastatic RCC since there are other immunotherapy/VEGF TKI combinations available. A potential barrier to adoption of this technology into NHS practice will be the availability of chemotherapy chairs for the infusion of nivolumab. Cost comparison methodology is appropriate if this technology is being assessed using the end of life criteria. The primary outcome of the trial (progression-free survival) needs to be enhanced with real-world evidence/patient-reported outcomes to improve its relevance to patients. Real world evidence for the nivolumab/ cabozantinib combination is reported in the following study: "Real-world outcomes of nivolumab and cabozantinib in metastatic renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium" Current Oncol. 2019 Apr; 26(2): e175–e179.	recommended in the Cancer Drugs Fund are not in routine practice and ipilimumab combined with nivolumab is not considered a comparator. NICE can only make recommendations for patient populations covered by the company's marketing authorisation. Where covered by the marketing authorisation and if evidence allows, subtypes of RCC may be considered. NICE expects that any relevant real-world evidence and patient-reported outcomes data will be considered during the appraisal. No action required.
	Kidney Cancer UK	Could this drug be considered for the cancer drugs fund?	Thank you for your comment. Where deemed appropriate,

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			the company may propose including the technology for the consideration of Cancer Drugs Fund in line with the NICE technical appraisal process, and input from the Cancer Drugs Fund team and NHS England will be sought. No action required.
Additional comments on the draft scope	Bristol Myers Squibb	None	Comment noted. No action required.
	NCRI-ACP-RCP-RCR	No	Comment noted. No action required.

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

Novartis