National Institute for Health and Care Excellence

Health Technology Evaluation

Treatments for renal cell carcinoma [ID6186]

Response to stakeholder organisation 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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Wording	Action Kidney Cancer	To appraise the clinical and cost effectiveness of treatments for renal cell carcinoma (RCC). To determine the standard treatment pathway for advanced RCC patients that can be personalised for individual needs.	The appraisal title is intentionally broad to capture clinical and cost effectiveness and pathway considerations. No change.
	NICE (medicines optimisation team)	Yes	No change.
	MSD	The wording of the remit is appropriate.	No change.

Section	Stakeholder	Comments [sic]	Action
	Ipsen	Ipsen agrees that cabozantinib (CABOMETYX®) with nivolumab should be appraised within its marketing authorisation for patients with untreated advanced or metastatic renal cell carcinoma (henceforth referred to as aRCC)	No change.
Additional comments on the draft remit	Action Kidney Cancer	None	No change.
	NICE (medicines optimisation team)	None	No change.
	MSD	None	No change.
	Ipsen	Ipsen would like it to be acknowledged that there is no overlap in either the evidence or the placement in the RCC treatment pathway between cabozantinib with nivolumab and belzutifan. There is, therefore, no overlap in the decision problems between the two appraisals. For this reason, Ipsen does not see the need to assess cabozantinib with nivolumab in a similar pathway as belzutifan other than to generate potential efficiencies within NICE processes (i.e., working with a similar EAG). Furthermore, Ipsen does not see the need for the EAG to develop a sequence model as sequencing is not appropriate to answering the decision problem for cabozantinib with nivolumab. NICE has assured Ipsen that the topic of sequencing will not impact the decision problem for cabozantinib with nivolumab in aRCC. Ipsen supports NICE in its ambition to identify efficiencies in its processes. For this reason and with the assurance that sequencing will not be a driver of commissioning decision-making, Ipsen supports NICE as a collaborative partner in piloting the pathways approach.	The decision point for each technology is based on available evidence at the time of scoping Decision problems may not overlap but may interact as NICE considers the whole pathway. No change.

Comment 2: the draft scope

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Background information	Action Kidney Cancer	Between 2016 and 2018 the average number of RCC cases was 13,322 and kidney cancer is the 7th most common cancer in the UK. The incidence of RCC is increasing, and cases are projected to rise by 26% in the UK between 2014 and 2035: https://www.cancerresearchuk.org/healthprofessional/cancer-statistics/statistics-by-cancertype/kidney-cancer/incidence#heading-Four. There are no screening tests for kidney cancer, and about half of all cases are detected incidentally when a person has a scan for a different condition. Since RCC is difficult to detect, about a third of people are diagnosed with late-stage disease after the cancer has spread. https://www.macmillan.org.uk/cancer-informationand-support/kidney-cancer/signs-and-symptomsof-kidney-cancer There are different staging systems for renal cell carcinoma, including the number system2. It looks at the number and size of kidney tumours. The number system has 4 stages: • Stage 1 and 2 (early stage where tumour is localised to the kidney) • Stage 3 (locally advanced stage with possible spread to regional lymph nodes) • Stage 4 (advanced, metastatic stage where tumour has spread beyond regional lymph nodes to other parts of the body) Usually, the TNM system is used for kidney cancer: https://www.cancerresearchuk.org/aboutcancer/kidney-cancer/stages-types-grades/tnm In 2017, 9,298 new kidney cancer cases were diagnosed in England3. Of those, 40.2% had stage 1 disease, 7.6% had stage 2 disease, 15.5% had stage 3	England-specific Office for National Statistics data used to describe the incidence of RCC. NICE could not identify more robust published data about 5-year survival but has removed these statistics to avoid misrepresenting the disease area. Added “In addition, immunotherapy combinations can be offered in the first line” to the advanced untreated paragraph. NICE have added clarification to the third line paragraph, noting TKIs could be given “as a third-line treatment if any of these treatments have not been previously used.” Fifth line treatment has not been included. The

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		disease and 20.5% had stage 4 disease4. The 5-year survival was 86.8%, 76.6%, 74.2% and 12.4% for stage 1,2,3, and stage 4 disease, respectively4. There must be more up to date information than this available? The CRUK site state 13,322 cases of kidney cancer are diagnosed each year and they have data on incidence by stage: https://www.cancerresearchuk.org/healthprofessional/cancer-statistics/statistics-by-cancertype/kidney-cancer/survival#heading-Three **1: Early stage to locally advanced stage, eligible for surgery** Early stage RCC (stages T1 and T2) is localised to the kidneys. Treatment options for localised tumours include laparoscopic or open surgery (nephrectomy), which can be partial (nephron sparing) or radical. Ablation, including stereotactic ablative radiotherapy (SABR), radiofrequency ablation (RFA), or cryoablation can also be used for small tumours. These are performed with curative intent. Nephrectomy is the only treatment option for locally advanced RCC (stage T3). After tumour resection, the cancer can be graded. Risk of recurrence is greater in higher-grade cancers. Pembrolizumab is recommended by NICE technology appraisal TA830 for adjuvant treatment after nephrectomy for people whose cancer is at increased risk of recurrence. **2: Advanced, metastatic first line** Current treatment options for untreated advanced/metastatic RCC include tyrosine kinase inhibitors (TKIs). TKIs offered for untreated RCC include sunitinib, pazopanib or tivozanib as recommended by NICE technology appraisal guidance (TA169, TA215 and TA512). In addition, immunotherapy combinations can be offered in the first line including avelumab with axitinib (a PD-1/PD-L1	treatment pathway will include treatments up to the fourth line of treatment only in line with feedback at the scoping workshop.

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		inhibitor with a TKI, TA645) for use within the Cancer Drugs Fund. For people with intermediate or poor-risk cancer as defined by the International Metastatic RCC Database Consortium (IMDC), TA542 recommends cabozantinib (a TKI), TA780 recommends nivolumab plus ipilimumab (a PD-1 inhibitor with a CTLA-4 inhibitor) and TAXXX recommends pembrolizumab plus lenvatinib (a PD-1/PD-L1 inhibitor plus a TKI). **4: Advanced, metastatic third line** If the disease progresses again, people may have axitinib (TA333), nivolumab (TA417), cabozantinib (TA463) or lenvatinib plus everolimus (TA498) as a third-line treatment if any of these treatments have not been previously used. **5: Advanced, metastatic fourth line** Everolimus is recommended by NICE (TA432) for disease that has progressed after VEGF therapy and is mainly used in clinical practice after 3 previous treatments, that is, as a fourth-line treatment. **6. Advanced, metastatic fifth line** Active surveillance and supportive care, including psychosocial support, is recommended when all lines of drug treatment have been exhausted.	
	NICE (medicines optimisation team)	Appears complete and easy to understand but topic experts will be able to clarify additional details. It may be helpful for users to include information on the International Metastatic RCC Database Consortium (IMDC) and Eastern Cooperative Oncology Group (ECOG) performance status score in the background information as this is part of treatment eligibility criteria in the cancer drugs fund (CDF), summary of product characteristics and some TAs. .	The scope has been have kept broad in relation to outcomes and prognostic statuses, making no specific mention of inclusion criterion or summary of product characteristics. Committee will consider all available

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			evidence and will appraise technologies within their marketing authorisations.
	MSD	The draft background information is broadly accurate and complete.	No change.
	Ipsen	Ipsen agrees the background information is accurate and complete.	No change.
The layout of the decision points	Action Kidney Cancer	Treatment of non-clear cell subtypes of RCC need to be considered as an unmet clinical need. There is no mention of the treatment pathway for these subtypes of RCC, although there is some evidence that cabozantinib (https://www.urotoday.com/conferencehighlights/asco-gu-2021/kidney-cancer/127958-asco-gu-2021-sunitinib-versus-cabozantinibcrizotinib-or-savolitinib-in-metastatic-papillaryrenal-cell-carcinoma-prcc-results-from-therandomized-phase-ii-swog-1500-study.html) and immunotherapy combinations are effective for papillary RCC (see link below).	NICE will appraise the technologies within their marketing authorisations and will consider all evidence within the evaluation.
	NICE (medicines optimisation team)	Topic experts will be able to advise if genetic factors are of significance in the treatment of renal cell carcinoma, along with associated health inequalities. Patient factors in relation to treatment options decisions are an important consideration in the clinical and cost-effectiveness assessment. For example, relevant factors for reducing health inequalities such as treatment burden minimised by fewer number of hospital visits for disadvantaged groups; or if risk of adverse drug reactions are more likely in specific subgroups. Would it be helpful to map the TA's on to the layout of the decision points? Potentially colour coded so that users can visualise where the new TA's will fit in the pathway?	The placement of the new technologies is detailed in Table 1.
	MSD	The decision points/indications relevant to belzutifan in the ID6154 appraisal are broadly correct. However, it would useful to explicit state the specific indication belzutifan is to be used in this case (as stated in the clinicaltrial.gov record for the supporting MK-6482-005 trial for this indication), i.e. in patients who have had disease progression on or after having received systemic treatment for	The placement of the new technologies is detailed in Table 1. The population has been left intentionally broad because the

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		locally advanced or metastatic RCC with both Programmed cell death 1 ligand 1 (PD-1/L1) checkpoint inhibitor and a vascular endothelial growth factor – tyrosine kinase inhibitor (VEGF-TKI) in sequence or in combination, and who have received no more than 3 prior systemic regimens for locally advanced or metastatic RCC. With regard to the layout of Figure 1, as there are two separate numbering systems being shown in the figure (tumour staging and NICE decision points), and three separate numbering systems are described in the paragraph immediately above the figure (decision points, tumour staging, and line of therapy) it may be worth making explicitly clear what each of the numbers are referring to (e.g. the in the current draft figure the decision point[?] numbers are not explicitly described to be such).	marketing authorisations are unknown at this time. NICE have updated the decision points to a letter system to avoid confusion with staging numbers.
	Ipsen	Cabozantinib with nivolumab is indicated for an all-risk population of 'patients with untreated advanced or metastatic renal cell carcinoma' and should be appraised in line with this indication (1). The phase 3 CheckMate 9ER trial of cabozantinib with nivolumab compared to sunitinib demonstrated consistent clinical benefits across all patients, irrespective of prognostic risk profile. Therefore, we would expect cabozantinib with nivolumab to evaluated in line with its licensed indication.	No change needed.
Population at each decision point	Action Kidney Cancer	Yes	No change.
	NICE (medicines optimisation team)	Agree with defined population Check with topic experts if it would be helpful to consider defining population at each decision point as per the IMDC system i.e., good/ intermediate/poor risk category as this is used in part to aid choice of treatment as per the CDF/ marketing authorisations and some NICE TAs	The scope has been left intentionally broad and avoided categorisation by specific systems. No change needed.

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	MSD	(See comment above)	See action above.
	Ipsen	Cabozantinib with nivolumab is indicated for an all-risk population of 'patients with untreated advanced or metastatic renal cell carcinoma' and should be appraised in line with this indication (1). The phase 3 CheckMate 9ER trial of cabozantinib with nivolumab compared to sunitinib demonstrated consistent clinical benefits across all patients, irrespective of prognostic risk profile. Therefore, we would expect cabozantinib with nivolumab to evaluated in line with its licensed indication.	No change.
Intervention at each decision point	Action Kidney Cancer	Yes	No change.
	NICE (medicines optimisation team)	Decision point 2 (advanced metastatic first line): Tivozanib TA512 (2018) is positioned first line for untreated advanced. TA512 states tivozanib is recommended if no previous treatment but NHSE commissioning policy (see CDF) allows for use after avelumab with axitinib (TA645, published after TA512 in 2020) Check with topic experts but current wording that TKIs are preferred first line for untreated metastatic advanced RCC may not reflect current practice. NHSE commissioning policy (see CDF) suggests that immunotherapies maybe first-line treatment options within patient specific criteria. For example; the CDF entry for nivolumab in with ipilimumab states: for the 1st line treatment of intermediate or poor risk advanced renal cell carcinoma where the following criteria are met… Decision point 3 (advanced metastatic 2nd line treatment): cabozonitib TA463 is positioned second line in advanced RCC. TA463 recommends use after VEGF but NHSE (CDF) allows after immunotherapy too, at decision point 2 (first line advanced TKIs that target VEGF) and immunotherapy are recommended, so NHSE have to allow for this. TA463 published in 2017, when only TKI would have been an option. Note that CDF also allows for use of pazopanib and tivozanib at this decision point too (both off-label use)	Comments on each decision point were discussed at workshop and no changes have been made to keep the treatment pathway and scope broad at this stage. Avelumab with axitinib is not a comparator as it is only available through the CDF. Placement of belzutifan and its comparators discussed at the workshop. In order to be eligible for belzutifan, people have to have had a

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		Decision point 3 (advanced metastatic 2nd line treatment): nivolumab TA417 is positioned second line in advanced. TA417 recommends nivolumab for previously treated advanced RCC but NHSE commissioning policy (see CDF) recommends after 1 / 2 lines previous angiogenic therapy (i.e. TKI or mTOR) Decision point 5 (advanced, metastatic 4th line): everolimus TA432 is positioned fourth line but TA allows for any use after VEGF, so could be 2nd, 3rd line too. This is based on expert consensus of current practice. Check with experts For the new TAs the pathway will be incorporating: Cabozonitib with nivolumab for untreated (i.e. first line treatment) lists all the first line options as comparators apart from avelumab with axitinib. Is this because it is a CDF-only recommended treatment rather than a standard TA (so not routine)? Belzutifan for after VEGF or immunotherapy lists comparators as all 2nd, 3rd, 4th line options apart from nivolumab – not sure why. Would it be helpful to consider patient factors at each decision point? It will be helpful to find out what specialists take into consideration when deciding on treatments when there are multiple options. For example, how are factors such as adverse drug reactions, personal experiences, oral vs I/V, patient preferences, dosing schedules, geographical location/ access to treatment, taken into account to inform shared decision making? Similarly, would it be helpful to users to consider including ECOG scores at the decision points as these are used in the CDF and in some TAs.	checkpoint inhibitor and a TKI. When people have had a checkpoint inhibitor, NHS prescribing rules prohibit a further checkpoint inhibitor. So, nivolumab is not listed as a comparator for belzutifan. The committee will consider any additional value not captured in the cost-effectiveness estimates, including patient factors. The presentation of the decision points will be explored.

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		Additional decision making factors maybe relevant information if the TAs are sequenced within the pathway on the basis of cost-effectiveness.	
	MSD	No, where belzutifan is to be placed in the pathway is not mentioned in either Figure 1 or the text around the numbered decision points immediately following Figure 1. While the place of belzutifan in the pathway may be roughly inferred from the (not sufficiently detailed/accurate [see comment above]) description in the "Population" row of Table 1, this does not adequately describe the place of belzutifan in the pathway to the appropriate level of accuracy/clarity.	The placement of the new technologies is detailed in Table 1. The population has been left intentionally broad because the marketing authorisation is unknown at this time.
	Ipsen	Cabozantinib with nivolumab is appropriately placed as a first line therapy in untreated advanced or metastatic renal cell carcinoma (aRCC).	No change.
Comparators at each decision point	Action Kidney Cancer	Pembrolizumab plus lenvatinib (a PD-1/PD-L1 inhibitor plus a TKI) has very recently been approved by NICE as a first-line treatment for people with intermediate-poor risk RCC. The FAD was published on 30 November 2022. Tivozinib is hardly ever used in England and Wales.	Pembrolizumab plus lenvatinib has now been included in the scope as a recommended treatment for previous untreated population, only for intermediate or poor risk disease as defined in the IMDC criteria (see NICE technology appraisal 858 for more information).
	NICE (medicines	See above, For cabozanitinib with nivolumab also avelumab with axitinib as per TA645 and CDF.	No change.

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	optimisation team)	Confirm with topic experts for any other omissions	
	MSD	The comparators listed for belzutifan in Table 1 are correct and complete.	No change.
	Ipsen	Ipsen agrees with the proposed comparators for the assessment of cabozantinib with nivolumab in the full all-risk aRCC population. Additionally, although currently in the Cancer Drugs Fund, avelumab plus axitinib is currently available to an all-risk aRCC NHS England population and hence should be a relevant comparator as it is an established first line treatment in in untreated advanced or metastatic renal cell carcinoma (aRCC) since being recommended by NICE in September 2020.	As avelumab plus axitinib is only available through the CDF, it not been included as a comparator for the cabozantinib with nivolumab decision problem.
Outcomes at each decision point	Action Kidney Cancer	Add identification of a prognostic/predictive biomarkers and duration of response. Add genetic analysis of the tumours of non-clear cell RCC patients. We are pleased to see overall survival at the top of the list. We are also pleased to see that quality of life is being considered.	Appropriate outcomes were discussed at the scoping workshop. NICE has added duration of response and time on treatment/time to next treatment to the final scope.
	NICE (medicines optimisation team)	Yes	No change.
	MSD	The outcomes listed are appropriate and will capture the relevant health related benefits of the technology. With regard to relevant disease specific or patients reported outcome measures, the MK-6482-005 trial of belzutifan that will support this appraisal collected information measured via the European Organization for Research and	No change.

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		Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-related Symptoms (FKSI-DRS), and European Quality of Life 5 Dimensions, 5-level Questionnaire (EuroQoL EQ-5D-5L) Health Utility Score instruments.	
	Ipsen	Ipsen agrees that the listed outcomes are appropriate.	No change.
Appropriateness of an evaluation and proposed evaluation route	Action Kidney Cancer	The evaluation is appropriate with the information and treatments available through NICE HTAs. However, we would like to know what happens to patients when they have exhausted all 4 lines of treatment. There needs to be a fifth line, which is currently active surveillance and supportive care. The impact on treatment decisions for patients is extremely significant. By restricting treatment options to 4 lines, patients may not necessarily be aware of the implications of their treatment decisions further down the line. For example, deciding to have ipilimumab plus nivolumab in the first line, could rule out having nivolumab as a third-line treatment, thereby reducing a patient's treatment options in the third line. Restricting access to 4 lines and complicating a patient's options could adversely affect patient outcomes. This is particularly important for those patients who are not well informed, from deprived backgrounds and no means to travel, and with no access to a kidney cancer expert.	Technologies will be evaluated within their marketing authorisations.
	NICE (medicines optimisation team)	This approach will be welcomed by the system as it will provide a recommended patient care pathway and improved coherence for future TAs published in this topic area. It may also provide an opportunity to identify any older NICE appraised treatments which have been superceded in current practice by newer therapies and if appropriate, retire the associated TAs	No change.

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	MSD	There is much about the proposed "proportional approach to technology appraisals sub process: pathways" that has yet to be published on the NICE website, which limits MSD's ability to provide a fully considered response to this question.	No change.
	Ipsen	Ipsen supports NICE as a collaborative partner in piloting the pathways approach. Ipsen has also received assurance from NICE that by taking part in this pilot, the timelines for decision-making will be upheld, avoiding further delays in access of NHS England aRCC patients to cabozantinib with nivolumab.	No change. Extra discussion had at scoping workshop and to be had throughout this pilot.
Equality	Action Kidney Cancer	Ensure there is good representation of people from BAME cultures and deprived areas of England and Wales. Equality of access to the clinical trials/drug treatments on the NHS/CDF regardless of where the patient lives.	NICE welcomes all evidence on health inequalities within the relevant population which will be considered by the committee at the time of the appraisal. Access to hospitals or treatment centres is an implementation issue, it is not an equality issue that can be addressed by NICE recommendations. Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal.

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			No changes made.
	NICE (medicines optimisation team)	Check with topic experts	No change.
	MSD	None	No change.
	Ipsen	Ipsen is not aware of any equality issues relating to the proposed remit and scope.	No change.
Other considerations	Action Kidney Cancer	We would like to know what happens to patients when they have exhausted all 4 lines of treatment. There needs to be a fifth line, which currently will be active surveillance and supportive care. Are there any treatments about to go through the NICE HTA process for fifth line treatment (apart from belzutifan, which is currently being appraised for VHL-associated RCC)?	Technologies will be evaluated within their marketing authorisations.
	NICE (medicines optimisation team)	Please consider the subpopulation of older people in examining the effects of treatment due to increased comorbidities and as a result different treatment tolerability and potential effectiveness	Issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. No changes made.
	MSD	None	No change.
	Ipsen	None	No change.
Questions for consultation	Action Kidney Cancer	**Third-, fourth- and fifth-line treatments** We understand that there is no clinical trial evidence base for the use of IO-IO and IO-TKI combinations as later lines of treatment. However, now that some of these combinations have been in use as standard treatments for several years,	Technologies will be evaluated within their marketing authorisations.

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		could real world evidence be used to confirm their use in the third line or later? Patients often come to the end of their treatment pathway and know that there are other treatments available that they have not had the chance to try. This is very distressing for patients when they run out of treatment options, and the only option available to them is to wait to die.	
	NICE (medicines optimisation team)	None	No change.
	MSD	**Question:** Have all relevant treatments for RCC been included in the scope? Which treatments are established clinical practice in the NHS at each point in the RCC pathway? **MSD response**: Yes, the treatment pathway as described in the scope is correct and describe the those used in established clinical practice. **Question:** Does the pathway described represent current NHS clinical care? Is the pathway split appropriately into clearly defined decision problems? **MSD response**: Yes, the treatment pathway is defined accurately and reflects current clinical practice. Note that nivolumab monotherapy in second line would not be a comparator for the patient population defined for ID6154 as the indication for belzutifan is for patients who have progressed after prior PD-1/L1 and VEGF-TKI-targeted therapies (in sequence or in combination), and a patient who has received a prior PD-1/L-1-targeted therapy would not receive nivolumab in a later line of therapy. **Question:** Is the staging system used to define patient populations and decision points the most relevant in NHS clinical practice? Are there other staging systems that have not been considered?	NICE agrees that nivolumab is not a comparator for belzutifan in previously treated patients. NICE has included 4 lines of advanced treatment based on clinical advice received during the scoping workshop. No other changes made.

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		MSD response: Yes, International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk stratification is the most commonly used tool/criteria in metastatic disease. **Question:** Are the positions for the proposed treatments in the pathway appropriate for NHS clinical practice? **MSD response**: Yes. **Question:** In the advanced metastatic setting, how many lines of treatment would an average person be expected to have in clinical practice? Does this vary? Are there any biological reasons for any variation? **MSD response**: Clinical expert advice received by MSD indicate that three lines maximum is likely and may vary based on patient tolerability. **Question:** How does what is had as first-line systemic treatment affect the second- and later-line systemic treatment? **MSD response**: The class of drug used in prior lines would typically not be used in subsequent lines, i.e. use of a PD-1/PD-L1 targeted immune-oncology treatment (e.g. nivolumab) as monotherapy or in combination (with e.g. a TKI) at first line would mean that a PD-1/PD-L1 targeted immune-oncology treatment as monotherapy or in combination would not be used in the second line. Belzutifan, being first in class, in its mechanism of action should not be impacted by this for the ID6154 indication, however belzutifan's indication is restricted to patients who have had disease progression on or after having received systemic treatment for locally advanced or metastatic RCC with both PD-1/L1 checkpoint inhibitor and a VEGF-TKI in sequence or in combination.	

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		Question: Are there rules about using an immunotherapy in the advanced setting if one has been used in the adjuvant setting (for example, pembrolizumab), or if not currently, what do you expect these rules to be in the future? **MSD response**: In the National Cancer Drugs Fund List (14-DEC-2022) criterion 5 on page 18 specifics that adjuvant therapy is required to have been completed more than 12 months prior to initiation of lenvatinib in combination with pembrolizumab for use in treatment-naïve patients with intermediate or poor risk advanced renal cell carcinoma. However, this wording does not exist for all advanced RCC entries in the Cancer Drugs Fund but is generally accepted by clinicians from insights gathered by MSD. In the case where disease recurrence occurs less than 12 months since completion of adjuvant therapy, and where a non-immunotherapy treatment is given as first-line treatment in the advanced setting, for the treatment decision for subsequent (second line) therapy, there does not appear to be consensus as to whether such a patient would be eligible for an immunotherapy in this setting. **Question:** Are there rules about using immunotherapies in sequence in the advanced setting? Or if not currently, what do you expect these rules to be in the future? **MSD response**: Current practice allows a patient to only receive one immuno-oncology agent in the advanced setting. There is currently a lack of data supporting rechallenging with immuno-oncology agents in the advanced setting. **Question:** What treatments are offered in the locally advanced setting? Are they different to those offered in the advanced metastatic setting? Are treatment sequencing rules in place if a tumour metastasises? **MSD response**: Locally advanced RCC managed through surgical intervention or ablative therapy. Beyond that the use of pembrolizumab monotherapy post-	

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		nephrectomy for those at increased risk of recurrence is the only treatment currently recommended by NICE. See response to the earlier question for CDF wording around treatment sequencing following use of subsequent immunotherapy for metastatic disease. **Question:** What are the key unanswered clinical questions about sequencing of treatments within RCC? Are you aware of any trials planned to address these? **MSD response**: **1**) The impact of adjuvant therapy on metastatic treatment options in the 1st and 2nd line setting and optimal sequencing strategy in metastatic RCC. **2**) Time to rechallenge with immunotherapies in advanced RCC. **3**) There are also questions around how the use of biomarkers and consequently precision medicine can contribute to the optimal sequencing of therapies in this patient population. **Question:** Are the outcomes listed appropriate? Have all core outcomes for RCC been considered? Have all relevant patient-reported outcomes been considered? Do outcomes differ across different points in the RCC pathway? **MSD response**: The outcomes listed in the draft scope are appropriate for the ID6154 appraisal for belzutifan. Patient-reported outcomes collected in the supporting MK-6482-005 trial are described earlier in this form. **Question:** Are there any groups of people in whom the proposed treatments are expected to be more clinically and cost effective? Are there other groups of people who should be examined separately? **MSD response**: We do not anticipate that there are any groups within the population that should be considered separately, or that there are subgroups in which the technology is expected to be more clinically or cost effective. MSD acknowledge that NICE have recommended exploring subgroups by tumour	

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		type and previous therapy. MSD will explore whether this is feasible, appropriate, and if patient numbers allow. **Question:** Is there any relevant real-world evidence or are there registries collecting data for people with RCC? **MSD response**: Yes. The SEER-Medicare database collects data on people in the US with RCC that have been used to within other NICE appraisals for RCC. **Question:** Would cabozantinib plus nivolumab or belzutifan be candidates for managed access? **MSD response**: [redacted] **Question:** Do you consider that the use of cabozantinib plus nivolumab or belzutifan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. **MSD response**: The use of belzutifan in the indication of relevance may result in potential substantial health-related quality of life benefits in patients' caregivers that are unlikely to be included in the QALY calculation. It has been demonstrated that for patients with RCC, their cancer and its associated treatment can be associated with significant health-related quality of life impact in their caregivers.	

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		As the indication to be appraised is in tumours where previous treatments have failed and where the disease may be progressing rapidly, the speed of progression of the cancer can make collection of nuanced quality of life and health-utility data in these patients challenging both practically and ethically. **Question:** To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adopting this technology into practice? If yes, please describe briefly. **MSD response**: No.	
	Ipsen	**Have all relevant treatments for RCC been included in the scope? Which treatments are established clinical practice in the NHS at each point in the RCC pathway?** Ipsen currently does not have a position to share in response to this question. **Does the pathway described represent current NHS clinical care? Is the pathway split appropriately into clearly defined decision problems?** Ipsen currently does not have a position to share in response to this question. **Is the staging system used to define patient populations and decision points the most relevant in NHS clinical practice? Are there other staging systems that have not been considered?** Ipsen understands that the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk score is used by clinicians to assess patients on presentation with aRCC. Ipsen currently does not have a position to share in response to the question regarding other staging systems.	NICE has included 4 lines of advanced treatment based on clinical advice received during the scoping workshop. The option of prior adjuvant treatments may affect the treatment options in the systemic treatment setting. The outcomes in the scope have been generalised across all decision points. Additional outcomes were discussed at the scoping workshop

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		Are the positions for the proposed treatments in the pathway appropriate for NHS clinical practice? Ipsen currently does not have a position to share in response to this question. **In the advanced metastatic setting, how many lines of treatment would an average person be expected to have in clinical practice? Does this vary? Are there any biological reasons for any variation?** A retrospective, observational, longitudinal study based on chart review of newly diagnosed adult mRCC patients (n=652) treated at two English hospitals from 2008 to 2015 prior to the introduction of combination therapies found that around 28% of patients receive second line therapy in the advanced metastatic setting (2). A more recent audit, from five UK sites for patients (n=515) treated between January 2018 and June 2021, suggests that, with more treatment options available, including combination/immunotherapy therapies, more patients are able to receive second and third-line therapies (69% and 34% respectively). Despite this, nearly one third of patients still only receive one line of treatment which highlights the need to deliver the most efficacious treatments first to optimise patient outcomes (3). Cabozantinib with nivolumab offers aRCC patients a first line treatment option associated with improved patient outcomes. **How does what is had as first-line systemic treatment affect the second- and later-line systemic treatment?** Ipsen currently does not have a position to share in response to this question. **Are there rules about using an immunotherapy in the advanced setting if one has been used in the adjuvant setting (for example, pembrolizumab), or if not currently, what do you expect these rules to be in the future?**	and have been added to the scope. No other changes made.

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		Variation exists in clinical treatment pathways for aRCC patients in the NHS, mostly as a result of prior treatment, risk stratification or clear cell histology (4). Ipsen is aware that NHS England are developing rules for the use of immunotherapies in sequence, which could be informed by and should broadly be consistent with the current clinical guidance on rechallenging in aRCC as published in ESMO and NCCN guidelines (4, 5). Ipsen does not consider adjuvant therapy relevant for decision making of cabozantinib with nivolumab in first line aRCC**.** **Are there rules about using immunotherapies in sequence in the advanced setting? Or if not currently, what do you expect these rules to be in the future?** Please see above response. **What treatments are offered in the locally advanced setting? Are they different to those offered in the advanced metastatic setting? Are treatment sequencing rules in place if a tumour metastasises?** Ipsen currently does not have a position to share in response to this question. **What are the key unanswered clinical questions about sequencing of treatments within RCC? Are you aware of any trials planned to address these?** Ipsen currently does not have a position to share in response to this question. **Are the outcomes listed appropriate? Have all core outcomes for RCC been considered? Have all relevant patient-reported outcomes been**	

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		considered? Do outcomes differ across different points in the RCC pathway? Ipsen would like clarification on what is intended by the latter part of this question as it is not clear, i.e., *do outcomes differ across different points in the RCC pathway*. **Are there any groups of people in whom the proposed treatments are expected to be more clinically and cost effective? Are there other groups of people who should be examined separately?** The phase 3 CheckMate 9ER trial of cabozantinib in combination with nivolumab compared to sunitinib demonstrated consistent clinical benefits across all patients, irrespective of prognostic risk profile. **Is there any relevant real-world evidence or are there registries collecting data for people with RCC?** Combination therapies are relatively new in this space but cabozantinib with nivolumab has been approved and is in use in clinical practice in other countries. A study is ongoing to gather RWE for cabozantinib with nivolumab called CaboCombo. It is possible that some real-world evidence will have been generated during this time which may become available during the appraisal process. **Would cabozantinib plus nivolumab or belzutifan be candidates for managed access?** Ipsen does not expect cabozantinib with nivolumab to be a candidate for managed access given the relative maturity of the data available from the CheckMate 9ER trial. The availability of median	

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		[redacted] data should be sufficient to inform decision making. **Do you consider that the use of cabozantinib plus nivolumab or belzutifan can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Cabozantinib with nivolumab is expected to provide additional indirect health benefits not fully captured in the QALY measure on account of cabozantinib's oral administration route when used as an alternative to one of the immuno-oncology (IO) components of an IO-IO combination. The additional health benefits are relevant within the initial immunotherapy loading period (i.e., initial 4 weeks) and again for patients treated with cabozantinib beyond the IO 2-year stopping rule (1).	
Additional comments on the draft scope	Action Kidney Cancer	Link about immunotherapy treatment for papillary RCC: https://www.urotoday.com/conferencehighlights/eikcs-2022/136700-eikcs-2022-papillary-renal-cellcarcinoma.html?utm_source=newsletter_10315&utm_medium=email&utm_campaign=challenges-in-thesurgical-management-of-locally-advanced-and-recurrent-disease-selecting-therapy-for-non-clear-cellrenal-cell-carcinoma-subtypes-and-more-from-the-3rd-day-of-the-2022-european-international-kidneycancer-symposium	No change.
	NICE (medicines optimisation team)	Both Karnofsky performance status and International Metastatic RCC Database Consortium (IMDC) system are used on CDF blueteq criteria and some TA. We need to consider how these are used in practice. (ask specialists) Would it be helpful to include a link to the CDF list in other documents?	No change.
	MSD	None	No change.

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	Ipsen	Under the heading of “Related NICE recommendations” and the subsection of “Technology appraisals in development:” there are some appraisals that need to be deleted/amended as they have been published. Please update to avoid confusion	Updated for final scope.

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

NHS Cheshire and Merseyside ICB

References

1. European Medicines Agency. SUMMARY OF PRODUCT CHARACTERISTICS CABOMETYX 20 mg Film-coated Tablets. Accessed December 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/cabometyx-epar-product-information_en.pdf.
2. Hawkins R, Fife K, Hurst M, Wang M, Naicker N, Nolasco S, et al. Treatment patterns and health outcomes in metastatic renal cell carcinoma patients treated with targeted systemic therapies in the UK. BMC Cancer. 2020;20(1):670.
3. McGrane J, Frazer R, Challapalli A, Ratnayake G, Lydon A, Parslow DS, et al. A multicenter real-world study reviewing systemic anticancer treatment choices and drop off rates between treatment lines for metastatic renal cell carcinoma in the United Kingdom: In the immunotherapy era. J Clin Oncol. 2022;40(6_suppl):358.
4. Powles T, Albiges L, Bex A, Grünwald V, Porta C, Procopio G, et al. ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma. Ann Oncol. 2021;32(12):1511-9.
5. Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al. Kidney Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(1):71-90.