NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for treated or metastatic renal cell carcinoma [ID853]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Company response to the Appraisal Consultation Document** from: Bristol-Myers Squibb:
   - ACD response
   - Patient Access Scheme submission template

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Kidney Cancer UK
   - Kidney Cancer Support Network

   The Department of Health, Novartis and Pfizer indicated that they had no comments

4. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Paul Nathan – clinical expert, nominated by the NCRI Bladder & Renal Cancer CSG-RCP-ACP-RCR Squibb
   - Jon Birchall - patient expert, nominated by the Kidney Cancer Support Network
   - Alison Fielding – patient expert, nominated by the Kidney Cancer Support Network

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Evidence Review Group critique of the additional information**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Nivolumab for previously treated advanced renal cell carcinoma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

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.

Comments received from consultees

Consultee	Comment [sic]	Response
Bristol-Myers Squibb	*Has all of the relevant evidence been taken into account?* The committee has not seen results from its preferred analysis (as stated in Section 4.21 of the ACD), which we address in this response. In addition, the economic results used to inform recommendations in the ACD do not take into account the expected plateau in long-run survival for nivolumab patients noted in Sections 4.5, 4.15 and 4.29 of the ACD. We present in this response further analyses and evidence of the expected immunotherapeutic survival plateau that allow expectations of survival benefit to be explicitly considered in cost-effectiveness results. Thirdly, Bristol-Myers Squibb (BMS) wish to propose a Patient Access Scheme (PAS) in the form of a simple confidential discount to the acquisition cost of nivolumab, which could not be considered in the first Appraisal Committee Meeting (ACM). This PAS increases the estimated cost-effectiveness of nivolumab in RCC substantially. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* While we feel the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence base, we note some misrepresentations and factual inaccuracies, which we document in this response. *Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?* No. *Are the recommendations sound and a suitable basis for guidance to the NHS?* Given the implications of the proposed PAS and additional key evidence and analyses presented in this response, the ACD recommendations are not a sound and suitable basis for guidance to the NHS. From the clarity provided in this response, we hope that a positive recommendation for nivolumab in advanced previously treated RCC can be reached in the second ACM on the 4th of August 2016. The remainder of this response comprises three parts. Part **Error! Reference source not found.** presents: analyses aligning with the committee's preferred base case; further evidence on the expected plateua in overall survival for nivolumab patients; and demonstrates the economic impact of the proposed PAS. Part 2 discusses perceived misrepresentations and factual inaccuracies in the ACD. Part **Error! Reference source not found.** contains references.	Thank you for your response. The committee considered the company's comments and additional evidence carefully.

Bristol-Myers Squibb	**The committee's preferred analysis** Section 4.21 of the ACD describes the committee's preferred analysis as differing from the company's base case by the incorporation of the following assumptions: • assume axitinib is as effective as everolimus for progression-free survival and overall survival • use a log-normal distribution to model time-to-stopping treatment • assume utility values for axitinib and everolimus are equal Section 4.22 of the ACD gives further insight into the committee's preferred approach to capture treatment costs. Where the ERG argued for the inclusion of the cost of all delayed and missed doses in the economic appraisal, we appreciate the committee's recognition that that the ERG's preferred base case overestimated the ICERs because it included the costs of all missed and delayed doses. Though it is a valid argument that the cost of briefly delayed doses may fall upon the NHS in practice, our base case approach of excluding one treatment cycle cost for each delayed dose accounted for this. As stated in Section 5.5.2 of the company submission (CS), the mean dose delay in CheckMate 025 was 14 days. While some short delays may not lead to an NHS cost saving, long delays may lead to two or more doses being missed. Figure 1 shows the distrubition of nivolumab dose delays in Checkmate 025. Figure 1: Histogram of dose delays, CheckMate 025 nivolumab patients *[Figure provided but not reproduced here.]* Nevertheless, in order to adopt a cautious approach, we propose excluding the cost of delayed doses if the delay is at least 7 days. In CheckMate 025, 4.002% of planned doses were delayed by at least 7 days. Combined with the proportion of doses missed (2.5%), a total of 93.498% of planned nivolumab doses are estimated to be paid for by the NHS in practice. Table 1 shows results from a revised base case, that incorporates this more conservative approach to cost the proportion of nivolumab doses received, and aligns to the committee's stated base case preferences, as listed above. Without any discount to acquisition costs, nivolumab is estimated to offer a health gain of 0.61 QALYs versus axitinib, at an incremental cost-effectiveness ratio of £63,907 per QALY gained. Please note this ICER is not relevant to decision making because of the PAS proposed, and is discussed in section 1.3. Table 1: Results from interpretation of committee's preferred analysis, all list prices *[Table provided but not reproduced here.]*	Thank you for your comments. Please see section 4.17 of the final appraisal determination (FAD).
Bristol-Myers	**Incorporating evidence on long-term survival benefits of immunotherapy**	Thank you for your comments.

Squibb	As noted in Section 4.5 of the ACD, the committee's clinical experts advised that an overall-survival curve with a 'long tail' may be shown for RCC patients who are treated with nivolumab; an expectation based on sound biological rationale encompassing the immunogenic nature of RCC and the immunomodulatory mechanisms of nivolumab. While the CheckMate 025 data are too immature to demonstrate a survival plateau, the follow-up data from CheckMate 003 and CheckMate 010 support this hypothesis. The long run survival data from CheckMate 003 and CheckMate 010 are summarised in Table 2 alongside data for CheckMate 025 and base case model survival estimates. Table 2 demonstrates how from 2 years after randomisation, where CheckMate 003, 010 and 025 OS estimates are broadly similar, the economic model underpredicts long-term RCC data from CheckMate 003 from 3 years onwards. Table 2: Summary of evidence on overall survival from nivolumab in RCC clinical trial programme in comparison to the base case economic submission *[Table provided but not reproduced here.]* As described in the CS, the tendency towards an overall survival plateau indicated in CheckMate 003 and 010 RCC patients is consistent with: • the immunogenic nature of advanced RCC (first demonstrated in trials of IL-2 cytokine immunotherapy where a proportion of patients achieved long-term response)5-8 • the immunotherapeutic mechanism of action of nivolumab7 • overall survival evidence for nivolumab in previously treated melanoma (35% at latest follow-up of 5 years, CheckMate 003)9 • overall survival evidence for ipilimumab in melanoma (plateau from 21% at 3 years with follow-up data for up to 10 years where OS remains above 17%, pooled analysis of 10 studies including two Phase III studies)10 The clinical community's confidence in an immunotherapeutic survival plateau for previously treated RCC patients who are treated with nivolumab is clearly well grounded in evidence. It was therefore disappointing to read the following text in Section 4.15 of the ACD: "The committee noted that it had not seen any evidence to support the assumption in the company's scenario analysis [in which base case nivolumab mortality risk was assumed to be that of the age-matched general population after 5 years], and it was not clear how this scenario compared with the long term data from CheckMate 003 and CheckMate 010. The committee concluded that the company's scenario assuming better long-term survival with nivolumab was not based on evidence" We understand that the committee has not seen a 'long-term survival' scenario analysis with its preferred assumptions (which we aim to address here), but had hoped that the sceanrio we presented was both clearly	Please see sections 4.5 and 4.15 of the final appraisal determination (FAD).

driven by evidence and even conservative in its assumptions, once a long-term survival benefit is assumed. Table 2 illustrates how this scenario substantially underestimates the overall survival estimates from CheckMate 003 RCC patients from the end of CheckMate 025 follow-up to 5 years. Data beyond 5 years are not available for nivolumab in RCC or other indications, however the long-term melanoma data 10 and the rationale behind an immunotherapeutic survival plateau based on the MOA, both support the use of age-matched general population mortality data from this point onwards.

To generate further evidence and rationale to inform economic analysis which incorporates the clinical evidence, clinical expectation and biological rationale for a long-term survival plateau, BMS conducted telephone interviews with two of the Consultant NHS Oncologists who helped inform and validate clinical assumptions in the CS. The interviews comprised of a brief pre-read and five pre-defined questions. Following our approach for reporting Medical Oncologist expert advice in the CS 11, these interview materials are provided as part of this response in the interest of transparency 12, including the five pre-defined questions and the Medical Oncologists' separate responses, which are also shown in Table 3.

Table 3: NHS Clinical Experts' responses to five questions on long-term survival for patients similar to those in CheckMate 025

Pre-defined Interview Question	NHS Clinician UK Professor of Medical Oncology who wishes to remain ananymous	Professor John Wagstaff Professor of Medical Oncology, The College of Medicine, Swansea University
1. Do you expect an immunotherapeutic survival plateau effect for RCC nivolumab patients who achieve long-term survival, and if so, why?	Yes, I expect a survival plateau for nivolumab treated patients with mRCC. RCC is classified as an immunogenic disease, which is similar to melanoma. There is no reason to suppose that the outcomes observed will be any different in one or the other.	Yes, I would expect there to be a survival plateau, similar to the effect seen with immunotherapies in melanoma. This however would be a lower plateau, given the relative response rates observed.
2. Do you feel that the survival curve in Figure 1 under-predicts long-run survival for CheckMate 025 patients who survive beyond	Yes, that's correct. The curve presented in Figure 1 does not have an inflection point where you would expect one to be (between years 1 and 5), therefore it does	Yes I agree. This model does under-predict what we will see in reality. The expectation is that sustained remissions will be seen with nivolumab treated mRCC patients and so there will be a plateau to

	data collection? [Figure 1 is Figure 28 of the Company Submission – base case survival curve fits to CheckMate 025 Kaplan-Meier data]	not demonstrate a typical tail as that which has been observed in similar melanoma patients. This survival curve is likely to underestimate the true benefit of nivolumab.	the survival curve – I do not expect this line to reach 0.		
	3. Do you expect the immunotherapeutic survival plateau to allow patients who reach this stage to have survival rates similar to the general population?	Yes, patients that reach this phase in the curve would have a similar survival rate to those in the general population.	Yes, this makes sense, however it should be noted that this model depicted above, does not represent what a true plateau should look like anyway. In my experience, given that 70% of patients are likely to experience a remission, it would lead to the estimation of around 20% of patients comprising the plateau phase of the curve. This pattern would be similar to the long-term survival curve seen in melanoma patients treated with nivolumab and ipilimumab.		
	4. How long after treatment initiation would you expect the immunotherapeutic survival plateau to become visible if CheckMate 025 patients could be observed indefinitely?	As there is a paucity of mature data in these patients with this treatment in RCC, it would be difficult to give a certain numerical answer, however given the mechanism of action of this immunotherapy drug, as well as similar acting agents, the expectation would be that a plateau would be observed approximately 2-3 years after initiation of treatment.	We expect a similar impact to those patients with melanoma treated with nivolumab. Thus a plateau potentially would be seen around 3 years, from this point it would be expected that the patients would have a similar death rate to those in the general population (as mentioned earlier).		
	5. What in your opinion is the likelihood, or probability, that the immunotherapeutic survival plateau you expect	Yes that is correct, it is likely that there would be a survival plateau observed.	Yes, as stated previously, this is very likely		

for CheckMate 025 would be seen, if it were possible to observe CheckMate 025 patients indefinitely?			
Key: mRCC, metastatic renal cell carcinoma; NHS, National Health Service; RCC, renal cell carcinoma; UK, United Kingdom			

It is hoped that these responses, alongside other evidence, highlight that the committee's preferred analysis (as interpreted in Part 1.1, Table 1) does not take into consideration the best informed expectations of long-term overall survival prospects for nivolumab's licensed RCC indication, if access to nivolumab is available.
Recognising the uncertainty around the expected survival plateau for this patient group given the unavailability of gold-standard data, the data in Table 3 alongside the other evidence collated here may be most useful for decision making as part of an economic analysis that explicitly incorporates this uncertainty.
Bojke et al described model averaging in their review and application of methods to charactise structural uncertainty in decision analytic models.13 This approach involves weighting multiple plausible models with different structural assumptions by some measure of their credibility. Here, it may be most informative to weight the most plausible approach that assumes no immunotherapy survival plateau (the committee's preferred analysis, Table 1) with a plausible and conservative approach that incorporates a survival plateau, weighted by a conservative estimate of the likelihood that such a plateau would present in patients similar to those in the nivolumab arm of CheckMate 025.
Table 4 shows model averaging results, assuming a 50% probability that the risk of mortality is that of the general population from five years onwards. This scenario is consistent with the data in Table 4 and evidence from ipilimumab melanoma patients 10 in its use of general population mortality risk from the point of plateau, and conservative both in weighting the models 50:50 (from NHS Onclologists' responses to Question 5 in Table 4) and in assuming the survival plateau begins at five years, given the evidence in Table 4, data from ipilimumab melanoma patients 10 and survival estimates from CheckMate 003 (between three and five years).
Nevertheless, at list prices, the results in Table 4 suggest nivolumab is a highly cost-effective end-of-life treatment option for previously treated RCC patients.
Table 5 shows results in which assumptions differ from the Table 4 analysis only in that the survival plateau is assumed to begin at 3 years, to align with the conservative end of the two NHS Onclologists' best estimates of this parameter. These results may be the most informative for decision-making, and suggest an ICER well below the cost-effectiveness threshold for an end-of-life medicine, using list prices.

	Table 4: Results from model averaging; 50% probability of immunotherapeutic tail at 5 years. The committee's preferred analysis, list prices**.** *[Table provided but not reproduced here.]* Table 5: Results from model averaging; 50% probability of immunotherapeutic tail at 5 years. The committee's preferred analysis, list prices *[Table provided but not reproduced here.]*	
Bristol-Myers Squibb	**The proposed patient access scheme** BMS wish to propose a Patient Access Scheme (PAS) in the form of a simple [redacted] confidential discount to the acquisition cost of nivolumab. This PAS increases the estimated cost-effectiveness of nivolumab in RCC substantially. Table 6 shows results from the interpretation of the committee's preferred analysis, where the PAS discount is applied to nivolumab and list prices are assumed for axitinib and everolimus. [Table *provided but not reproduced here.]* Table **7** shows the sensitivity of the key ICER versus axitinib to assumptions about the confidential discount to axitinib. The PAS ICER remains below the end-of-life threshold of £50,000 per QALY gained even assuming a discount as high as [redacted] for the acquisition cost of axitinib. Importantly, the results in Table 6 and [Table *provided but not reproduced here.]* Table **7** are highly conservative in light of Part **Error! Reference source not found.** of this response in that they are blind to the immunotherpeutic survival plateau expected for nivolumab patients. [Table *provided but not reproduced here.]* Table **8** and Table 9 show these results from the model averaging approach incorporating uncertainty around the long-term survival prospects of nivolumab patients, where a 50% probability of an immunotherapeutic survival plateau at 5 years is assumed. Table 10 and Table 11 show these results where instead a 50% probability of an immunotherapeutic survival plateau at 3 years is assumed. As described in Part **Error! Reference source not found.**, both of these approaches can be considered conservative given expectations for long-term survival. Taking the more conservative approach to incorporate uncertainty around the long-run immunotherapeutic survival benefits of nivolumab, Table 9 suggests that nivolumab is the cost-effective alternative to axitinib even if an acquisition cost discount of [redacted] is assumed for axitinib. The results in Table 11 suggest that if evidence around the likelihood and timing of a long-term survival plateau is incorporated, the PAS ICER for nivolumab vs axitinib may be below [redacted], even when a [redacted] acquisition cost discount is assumed for axitinib. It is hoped that these results illustrate the clear benefit and cost-effectiveness offered by nivolumab for previously treated RCC patients who are currently treated with axitinib in the NHS, when: the proposed PAS for nivolumab	Thank you for your comments. Please see sections 4.22 and 4.23 of the final appraisal determination (FAD).

	is incorporated; the committee's stated preferences for the economic base case are used; and particularly when conservative estimates of the immunotherapeutic survival benefit of nivolumab are explicitly considered. Table 6: Results from interpretation of committee's preferred analysis, including PAS for nivolumab *[Table provided but not reproduced here.]* Table 7: Sensitivity of nivolumab vs axitinib ICER to axitinib price discounts, interpretation of committee's preferred analysis, including PAS for nivolumab *[Table provided but not reproduced here.]* Table 8: Results from model averaging; 50% probability of immunotherapeutic tail at 5 years. The committee's preferred analysis, including PAS for nivolumab *[Table provided but not reproduced here.]* Table 9: Sensitivity of nivolumab vs axitinib ICER to axitinib price discounts, model averaging; 50% probability of immunotherapeutic tail at 5 years, including PAS for nivolumab *[Table provided but not reproduced here.]* Table 10: Results from model averaging; 50% probability of immunotherapeutic tail at 3 years. The committee's preferred analysis, including PAS for nivolumab *[Table provided but not reproduced here.]* Table 11: Sensitivity of nivolumab vs axitinib ICER to axitinib price discounts, model averaging; 50% probability of immunotherapeutic tail at 3 years, including PAS for nivolumab *[Table provided but not reproduced here.]*	
Bristol-Myers Squibb	**<u>Perceived misrepresentations and factual inaccuracies</u>** **Health-related quality of life (HRQL) evidence** We do not challenge that the observed differences between EQ-5D data for CheckMate 025 everolimus patients and AXIS axitinib patients may be partially driven by patient- and study-level differences, and present results with the committee's preferred assumptions regarding HRQL in Parts **Error! Reference source not found.**, **Error! Reference source not found.** and 0 of this response. However, we highlight that while we presented justifications for assuming higher utility for everolimus patients versus axitinib patients both in the CS and in response to the Evidence Review Group's 21st March 2016 Clarification Questions, the assumption of equal	Thank you for your comments. Please see sections 4.5, 4.20 and 4.21 of the final appraisal determination (FAD).

	utility across everolimus and axitinib is based solely on expert opinion. Section 4.19 of the ACD: *"The utility values were lower for axitinib than for everolimus, but the committee heard from the clinical experts that in their experience, health-related quality of life was similar for people whose condition was being treated with these drugs. The committee concluded that the company's utility values were not appropriate."* We suggest that if expert opinion is solely relied on as the basis for utility assumptions in decision making, it is with the same rationale that the data on immunotherapeutic survival effect and approach to explicitly capture these data in cost-effectiveness estimates documented in Part **Error! Reference source not found.** should also be used. In Section 4.19 of the ACD, the post-treatment, post-RECIST progression HRQL benefit of nivolumab vs everolimus and axitinib is questioned. The text recognises the benefit of not having to recover from treatment-related adverse events associated with axitinib or everolimus, but does not account for the expected prolonged HRQL benefit of having received a programmed death ligand-1 [PD-L1] checkpoint inhibitor, as opposed to a Tyrosine kinase inhibitor (TKI) or mammalian target of rapamycin (mTOR) inhibitor. As documented in Part **Error! Reference source not found.** of this response, the CS and in response to the Evidence Review Group's (ERG's) 21st March 2016 Clarification Questions, the immune-response mechanism of nivolumab implies benefit both beyond RECIST-defined progression and beyond treatment discontinuation. As well as extending life, this post-treatment, post-progression benefit is reasoned to improve HRQL. By reducing the burden of disease symptoms, immune-response disease suppression is highly likely to improve patient HRQL for post-progressive patients. In addition, as described in Section 5.4 of the CS, patient quality of life is affected by thoughts of the future and ongoing treatment effectiveness.[11] [14] For post-progressive patients, the evidence and clinical expectation of the post-progression, post-treatment immune-response benefit of nivolumab may afford hope. We therefore hope Section 4.19 can be revised, in the light that as well as being the gold standard evidence for HRQL, the mixed model analysis estimates of patient-level CheckMate 025 EQ-5D data informing the economic analysis may well underestimate the relative utility benefit of nivolumab versus axitinib and everolimus in the post-treatment, post-progression model health state. We would also like to raise two further minor points. First, Section 4.19 of the ACD notes that CheckMate 025 was open-label, "*which may mean that patients overestimate the utility benefit of novel treatments such as nivolumab"*. While CheckMate 025 was open-label out of clear necessity, it seems highly unlikely that this implies overestimation of utility benefit. Patients being aware that they are receiving nivolumab instead of everolimus will reflect clinical practice, and the evidence summarised in Part **Error! Reference source not found.** of this response suggets that any optimism for the relative benefit of nivolumab is based on clinical rationale and evidence, and not novelty. Differences in toxicity and response rates are sufficient to explain the differences in utility across treatment arms of CheckMate 025, as observed in the patient-reported EQ-5D data. Differences in	

	utility between nivolumab and everolimus patients may in fact be expected to widen with further evidence of a plateau survival effect. We kindly request the ACD text is revised to balance these possibilities. Second, Section 4.20 of the ACD refers to an analysis performed by the ERG in which utility for everolimus patients is assumed to be equal to the TA333 utility value reported for axitinib patients in the AXIS trial, and nivolumab patient utility assumed equal to this value plus the difference in utility across nivolumab and everolimus patients in CheckMate 025. Such a scenario, which eschews gold-standard utility data reported directly by the key effectiveness trial patients in favour of unjustified assumptions, is not fitting with Section 5.3 of NICE's Guide to the methods of technology appraisal guidance.[15] The ACD text does not implicitly state that this scenario should be used for decision making, but does imply results from the scenario have some merit, and in fact more merit than the CS utility assumptions. We kindly request that the text referring to this scenario is removed, on the basis that it is uninformative.	
	Comparative effectiveness evidence While we do not challenge a conclusion that the results of the network meta-analysis (NMA) are uncertain, and present results with the committee's preferred assumptions regarding relative effectiveness in Parts **Error! Reference source not found.**, **Error! Reference source not found.** and 0 of this response, we note from Section 4.12 of the ACD that the committee's preferred assumption of exactly equal overall survival across everolimus and axitinib is based solely on expert opinion. In line with Part 0 of this response, we suggest that if such expert opinion is used as the basis for comparative effectiveness estimates in decision making, the data on immunotherapeutic survival effect and approach to explicitly capture these data in cost-effectiveness estimates documented in Part **Error! Reference source not found.** should also be used to inform decision making. The current wording around bias suggests the NMA results are biased in favour of nivolumab and we do not believe any strong conclusions around the direction of bias can be made. We would like to respond to some of the specific statements on differences between trials to support this belief: **Number of previous treatments**: to clarify, the VEG105192 and TIVO-1 trials recruited patients who had 0-1 previous treatments with subgroup data provided for pre-treated patients, CheckMate 025 recruited patients who had 1 or 2 previous treatments, the GOLD trial recruited patients who had 2 previous treatments, and other trials recruited patients who had 1 previous treatment (though exact treatment history for patients enrolled in Yang 2003 is unclear). As discussed at the committee meeting, pre-planned subgroup analysis based on number of prior anti-angiogenic regimens in the advanced / metastatic setting in CheckMate 025 showed a significant survival benefit for nivolumab regardless of treatment history (that is, treatment history is not predictive for treatment effect) when using CRF data (see Section 0 of this response for further detail on why this is the preferred data source for subgroup analysis).	Thank you for your comments. Please see sections 4.5, 4.10, 4.11, 4.12, 4.14, of the final appraisal determination (FAD).

	Choice of previous treatments: we believe the clinical experts were considering therapeutic class here and it should be clarified that previous cytokine therapy versus previous targeted therapy is thought to affect the condition's response to subsequent treatment. This can be clearly observed in subgroup analysis of the AXIS trial where absolute outcomes markedly differ based on treatment history but relative treatment effect remains constant.[16] Selection of the prior sunitinib subgroup from the AXIS trial aimed to select results from the patient group most reflective of English clinical practice. Of the trials contributing to the decision problem network (CheckMate 025, RECORD-1, TARGET, AXIS), data for patients who had previously received anti-angiogenic therapy were available for all but the TARGET trial; this trial compared sorafenib with placebo as second-line therapy in patients who had received cytokine therapy first-line. Considering the potential impact of therapeutic class, there may be some positive bias for sorafenib in this trial: patients had their first exposure to VEGF-targeted therapy and thus did not have previous resistance to this class of agents; and patients receiving cytokines first-line tend to have a shorter lead-time to receiving second-line treatment.[16] **Prognosis of patients at baseline**: apologies for the confusion regarding adjustments to account for differences in baseline risk. To clarify, no statistical adjustments were made; however, the meta-analysis conducted intentionally used a relative measure of treatment efficacy (the log hazard ratio) to avoid the requirement for patients recruited to different trials within the network to have the same prognosis. **The methods used to adjust for treatment crossover**: the comments here suggest crossover and subsequent therapy are synonymous which is not true when considering their potential impact on the meta-analysis results. Crossover is part of the study design involving patients switching from the control arm to the experimental arm (most often) at the time of progression (prior to un-blinding). Crossover causes a direct imbalance in treatment arms and thus directly impacts relative measures of treatment efficacy. Subsequent therapy is administered after study treatment discontinuation and patient unblinding; subsequent therapy applies to all patients and reflects real world practice. Subsequent therapy does not cause a direct imbalance in treatment arms, an indirect imbalance may be observed if subsequent therapy use is imbalanced across treatment arms but this is not the case in trials included in the network for meta-analysis including the CheckMate 025 or the AXIS trial where patients received subsequent therapy in equal, balanced measure irrespective of randomised treatment: CheckMate 025, nivolumab arm = 55%, everolimus arm = 63%[17]; AXIS, axitinib arm = 54%; sorafenib arm = 57%.[16] We would also like to note that comments on prognosis of patients in AXIS *'poorer prognosis of patients in AXIS'* (section 4.11) contradict the committee conclusions that there *'was no way to assess whether the prognosis of the trial patients was similar'* (section 4.10). While this may reflect the ERG comments, committee conclusions should also be referred to here. As discussed at the committee meeting, the apparent difference is as likely to be an artefact of inconsistent assessment of performance status scales across trials and clinical experts agreed that the prognosis of patients in AXIS and CheckMate 025 were similar and reflected standard clinical practice.	

	Furthermore, as noted above, the meta-analysis methodology adopted does not require an assumption of comparable prognosis across included trials. In addition, comments on not adjusting for subsequent treatments in AXIS are not considered relevant in accordance with reasoning provided previously and discussed at the committee meeting. It is expected that subsequent therapy, whether it is used after randomised study drug discontinuation or after discontinuation of the crossover drug (in trials that include crossover as part of protocol), will influence OS results of both control and experimental study arms. However, this is same for all studies, thus subsequent therapy is not a study protocol intervention and does not need adjusting for. In consideration of the above, the conclusion that the meta-analysis was likely to be biased in favour of nivolumab is thought to be unjustifiably strong. The meta-analysis approach was designed with a view to providing the required estimate of comparative efficacy from all available evidence (in the absence of direct data) in the most appropriate manner, with steps taken to minimise bias where possible. There is no doubt that there are limitations with the meta-analysis provided (as discussed within the submission) and thus uncertainty associated with the results of the meta-analysis (as reflected in the wide confidence intervals observed), but we do not believe that there is a clear direction of bias. For example, contrary to assumptions of bias in favour of nivolumab, it could be argued that given the anticipated immunotherapy related plateau in longer-term OS data (as documented in Part **Error! Reference source not found.** of this response, commented by the ERG in their critique of the submission and agreed by clinical experts at the committee meeting), the assumption of proportional hazards across treatments mean the meta-analysis results favour non-immunotherapies within the network, that is, the potential long-term survival benefit of nivolumab is not captured. In addition, please consider more detail around the statement *'the committee noted that the company's network meta-analysis showed axitinib was less effective than everolimus'* (section 4.12). To clarify, the meta-analysis provided showed a slight trend favouring everolimus over axitinib in estimates of OS using crossover adjusted/crossover free data where available, and estimates of PFS (based on the point estimate, small numerical difference). Results of the meta-analysis of OS using ITT data showed no difference between these agents which was more in line with the expectations of the clinical community. Following NICE DSU TD16, results from the crossover adjusted meta-analysis were considered the most appropriate for cost-effectiveness analysis and were thus utilised in the base case presented for nivolumab with a sensitivity analysis utilising results from the ITT meta-analysis also presented. These analyses utilise the clinical evidence available and thus provide evidence-based estimates that we believe should be preferred to an opinion based assumption of a hazard ratio (HR) of 1 which does not represent the uncertainty around estimates of comparative efficacy derived from an absence of direct evidence. While, for the reasons stated above, we disagree that an assumed HR of 1 with no account for uncertainty is the best available estimate for the relative effectiveness of everolimus and axitinib, for ease of exposition we have adopted the committees preferred approach for further economic modelling.	

	In Section 4.14 of the ACD, the company's approach to survival analysis of CheckMate 025 data is criticised. We refer you to the kind words of the ERG in Section 5.5.5 of their STA Report: *"The ERG appreciates that the company implemented in the electronic model an extremely broad set of survival models tested in the analyses. The company included both independent and dependent fits for 6 parametric models and 6 spline-based models for all outcomes, for a total of 24 models for each of the 3 time-to-event endpoints, i.e. OS, PFS and TTD. This resulted in an extremely transparent and flexible model, which allowed the ERG to conduct a broad range of sensitivity analyses around the modelling assumptions"* The approach to survival model selection was conducted in line with NICE Decision Support Unit Technical Support Document 14 [18] and was driven by both statistical fit, visual tests of assumptions and clinical validation,[11] crucial for overall survival given data immaturity, as clearly reported in Section 5.3 of the CS and as recognised in the ERG's STA Report. The ERG conducted further tests and analyses to their satisfaction, and did not change survival model selection assumptions from the CS base case for overall or progression-free survival. The ERG's preferences for time to treatment discontinuation model selection inform the committee's stated preferences for analysis (Part **Error! Reference source not found.** of this response). We hope that this information reassures the committee in its preferences for analysis, and kindly request that the factual inaccuracies highlighted are removed from Section 4.14 of the ACD. Lastly, Section 4.5 of the ACD reports: "*CheckMate 025 data showed that only about 15% of patients were still having nivolumab after 2 years. The committee considered that when median survival with nivolumab was just over 2 years (25 months; see section 4.5), it was implausible to assume that more than a few people would live to 5 years."* Given the evidence on immunotherpeutic survival effects in Parts **Error! Reference source not found.** and 0 of this response, in the CS and heard at committee on 8th June 2016, we suggest the committee may wish to revise this wording.	
	Subgroup analysis We would like to clarify the outcomes in subgroup analysis of patients with 1 or 2 previous treatments as invited. The hazard (HR) for overall survival (OS) benefit in 1 and 2 prior anti-angiogenic therapy subgroups quoted at the time of the committee meeting (HR 0.79[95% CI 0.63-0.99] for 1 prior anti-angiogenic & HR 0.65 [95%CI 0.43-0.99] for 2 prior anti-angiogenics) was derived from the case report form (CRF) data source contained within the clinical study report (CSR). The HRs for OS quoted in the CheckMate 025 publication[3] for the 2 subgroups, was derived from the interactive voice response system (IVRS) data source available at that time. The information provided during the committee meeting, using the CRF data from the CheckMate 025 CSR is considered a more robust data source than the IVRS data. The IVRS data contains only 3 stratification factors including number of prior anti-angiogenic therapies that are recorded at study entry, are not verified, and are	Thank you for your comments. Please see section 4.7 of the final appraisal determination (FAD).

	generally not changed once entered. The data within the CRF are collected at site alongside a comprehensive list of baseline, efficacy and safety factors that are crosschecked, corrected for errors and verified by the independent study monitor. The CRF data source is thus more robust and reliable. The CRF data was used to calculate the HR for the 2 patient subgroups (1 versus 2 prior anti-angiogenics) and published in the CSR (please refer to page 117 of CheckMate 025 CSR). It is these data (CSR data using CRF data source) that were used to file for regulatory approval for nivolumab in this indication with the US food and drug administration (FDA) and the European Medicines Agency (EMA). As the CRF data source is subjected to a second objective verification, we ask that the committee disregard subgroup results that appear in the CheckMate 025 publication[3], and use the subgroup outcomes data on Figure 7.2.1-1: page 117 of the CSR (and provided in the manufacturer submission; Figure 14, page 80).	
Bristol-Myers Squibb	**Factual inaccuracies** Aside from the issues described previously, BMS identified one factual inaccuracy and some misquotations in the ACD, described in Table 12. Table 12: Factual inaccuracy *[Table provided but not reproduced here.]*	Thank you for your comments. Please see section 4.5 of the final appraisal determination (FAD).

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Kidney Cancer Support Network	I am obviously disappointed at the draft recommendation of the Committee. The decision has caused much upset in both the patient and clinical communities. Advanced Renal Cell Carcinoma patients are typically fatigued and find it difficult to respond to consultations such as these which are by their nature very technical and economically driven. Some have responded to the decision directly to you and others have added their names to the Kidney Cancer UK petition. The latter may not be the right channel but it is all many people can manage. I hope that you can consider the strength of the patient view even at this stage.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).

	I believe that there would be a complete loss of faith in the NICE process in evaluating break through treatments if this decision stands. Numerous clinicians had been talking about it to patients as a next option and the withdrawal of this hope is difficult to cope with. Many patients nowadays have access to world wide data on treatments and have followed the ASCO reports and recent papers on overall survival of a third at 5 years. (Copy of presentation also attached.) TKIs like Sutent, Pazopanib and Axitinib are hard going for patients. In the absence of better treatments they are welcome as they extend the length of lives. Immunotherapy drugs offer an opportunity to extend the length and the breadth of life. I accept that there were not direct trials comparing Axitinib and Nivolumab and but still feel that the right course of action is to commission Nivolumab - if not as standard commissioning, it should be available as an option to clinicians via the Cancer Drugs Fund and outcomes monitored appropriately. In terms of the the ICER values, I hope that an agreement can be reached with BMS to bring the cost within range. I may not be able to work out an ICER but I do know that 60% of £1 is worth more than 0% of £10.	
RCP/ACP/CSG	We believe the committee have inadequately taken into consideration the mode of action and resulting durable benefit of immunotherapy in advanced RCC. 1. The committee state that (4.5) “the committee was aware that trials which stop early because they show a benefit tend to overestimate the size of the treatment effect”. This statement is inaccurate for immunotherapy agents where, in fact, the converse is true. Because a group of patients experience durable benefit, early analyses do not capture this benefit. 2. The committee state (4.5) “it was not clear whether the patients in these trials were like those in the NHS”. The committee did not ask clinical experts whether patients in the 003 and 010 studies were representative of UK patients at a similar point in their disease. For the committee’s information they will be representative of the UK population. 3. The committee state (4.5) “when median survival with nivolumab was just over 2 years (25 months; see section 4.5), it was implausible to assume that more than a few people would live to 5 years”. In our view this statement reflects the fact that the committee have not adequately appreciated the fact that there are many examples of immuno-oncology agents in which the median survival bears	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1, 4.5 and 4.10 of the FAD.

	little relationship to the fact that a significant proportion of patients (many more than a few) would be expected to have durable benefit. Indeed, if the plateau of patients experiencing long term survival is anything under 50%, the median will not reflect their benefit. We refer the committee to the ipilimumab meta-analysis data in melanoma – the data set for which there is longest follow-up data available (attached). You will note that the median OS is 11.4 months (ref attached), but because of the shape of the survival curve the vast majority of patients alive at 3 years are also alive at 5,7 and 10 years. The 003 and 010 studies have less mature follow up data but demonstrate a similar shaped curve. The precedent for immunotherapy induced long term durable remissions in Renal Cancer was established with high dose Interleukin-2 (IL-2). IL-2 never became a standard of care due to a combination of toxicity and low response rates. Many of the minority of patients who had responses however experienced durable responses lasting more than 10 years (Klapper et al). There is therefore a) precedent in RCC that immunotherapy can induce durable long term benefit b) evidence from other cancers that immune checkpoint inhibitors can induce long term benefit c) evidence for clinical activity with nivolumab in RCC from the 025, 010 and 003 studies in which there is emerging evidence that the survival curve is that which is expected with immunotherapy – that a significant group of patients will experience long term benefit. The committee's view that "it was implausible to assume that more than a few people would live to 5 years" is, in fact, implausible. 4. The committee state (4.10) that "Number of previous treatments: CheckMate 025 recruited patients who had had 1 or 2 previous treatments, while the other trials recruited patients who had only had 1 previous treatment". This is inaccurate. The RECORD-1 study included patients who had more than 1 prior treatment. 5. The committee and the ERG have overstated the importance of subsequent treatments on outcomes for patients participating in the TARGET, AXIS, RECORD-1 and 025 studies. The reality is that those third and fourth line treatments available at the time of conduct of the studies will have had a negligible impact upon survival. The ERGs view that the benefit of axitinib is underestimated is inaccurate.	

	6. The committee's approach that "The committee concluded that the company's scenario assuming better long-term survival with nivolumab was not based on evidence, so it preferred to use trial data to estimate survival as had been done in the company's base case and the ERG's base case" resulted in the selection of models that a) do not represent the shape of survival curves seen with active immunotherapies (see 3 above) and b) therefore result in the selection of curves that are highly unlikely to represent reality. The committee's approach means that it is highly likely that their assessment will be based on assumptions that do not reflect reality.	
Kidney Cancer UK	Kidney Cancer UK and the former charity The James Whale Fund for Kidney Cancer have supported patients with kidney cancer for over 10 years and have seen first-hand how the current first and second line treatments often fall short for people with metastatic renal cell carcinoma. Commonly, people become resistant or intolerant to tyrosine kinase inhibitors and are then left without options. The clinical trials for axitinib and everolimus (the alternative 2nd/3rd line treatments) did not show significant improval in overall survival in the pivotal randomized trials that tested them 1 2. There is a huge unmet need to offer another, very different option to people with metastatic renal cell carcinoma. Nivolumab offers hope to patients in this situation because it acts via a very different mechanism. After 1st line treatment failure doctors currently can only offer another tyrosine kinase inhibitor (TKI) which might give more of the same side effects and/or probably won't work as well because they will have already had a drug which works by a similar mechanism. Kidney Cancer UK strongly feel that nivolumab will offer hope and another very different option for these patients. Nivolumab acts on different receptors and pathways to TKI's and it works by enhancing the body's own immune system rather than inhibiting angiogenesis or tumour growth itself. It is a completely different way of attacking a tumour, which might work extremely well for some people. We don't understand why the chance to try this mechanism of attacking tumours would not be available for people with very little other options. When nivolumab works for patients the results have shown that they are long lasting. Earlier phase nivolumab trials (phase 1 and 2) have shown that a third of patients are still alive 4-5 years later. 3 As with many medicines, there may be	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.5 of the final appraisal determination (FAD).

	groups of patients that respond to certain drugs and not others, it seems unfair to deny the group that might respond well that chance. Nivolumab has been recommended for use in patients with metastatic melanoma for both 1st and 2nd line use. The two-year survival of patients with melanoma treated with nivolumab is around 50% 4 which is very similar to the two-year survival seen in the 025 trial for renal cancer patients. It therefore very likely that the survival curve for the 025 trial will mirror that seen with nivolumab in melanoma with a plateau in survival appearing at around 35%. This has been shown in the earlier phase trials in advanced renal cancer as described above. 3 We have heard positive things from patients who have received nivolumab as part of a clinical trial. Dr Fran King took nivolumab as a third line treatment as part of a clinical trial. He has shared his experience as a recorded interview on our website blog. The medicine gave him great hope, his tumours have shrunk and nivolumab is currently working well for him. To view this interview please follow this link: http://www.kcuk.org.uk/patient-consultant-experience/. Kate Fife, Dr Fran Kings oncologist at Addenbrookes Hospital, Cambridge also describes how well nivolumab is tolerated by patients. Kidney Cancer UK feel strongly that there is a need for an alternative 2nd or 3rd line treatment which acts via very different mechanisms to TKI's. The NICE approval of nivolumab would mean that patients would have access to three lines of therapy, which would improve survival rates. After we heard that nivolumab might not be recommended following the first committee meeting, Kidney Cancer UK launched a petition in support of nivolumab being recommended, almost 1000 people signed it in the first 2 days. Many of our supporters have been waiting for good news about the NICE recommendation of nivolumab and we hope that they will not be disappointed.	
Kidney Cancer Support Network	The NICE technology appraisal committee have not recommended nivolumab for use within its marketing authorisation for the treatment of advanced renal cell carcinoma (RCC) patients after failure of prior systemic therapy. This is despite nivolumab's proven effectiveness at prolonging the life of kidney cancer patients by 5.4 months compared to everolimus in the CheckMate-025 trial, and the survival data from the earlier phase I and II clinical trials (CheckMate-003 and 010) where about one third of patients are still alive after 4+ years. The Kidney Cancer Support Network's response to the nivolumab ACD has been	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1, 4.1, 4.5 and 4.22 of the final appraisal determination (FAD).

	informed by the views of advanced kidney cancer patients who are taking nivolumab as part of a clinical trial or through the Early Access to Medicines Scheme (EAMS) in the UK. 1. Innovative, breakthrough therapy Nivolumab has been proven to be a clinically effective and well-tolerated drug, and designated a breakthrough therapy by the FDA for the treatment of advanced or metastatic RCC. As a breakthrough therapy, nivolumab has been fast tracked for approval in a number of countries, and was previously approved for use under the Medicines and Healthcare products Regulatory Agency (MHRA) Early Access to Medicines Scheme (EAMS) in the UK. Nivolumab is the first in a new class of immunotherapy drugs, and is already available in North America and Europe for advanced RCC. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that immunotherapy drugs are made available to patients in order that they have the best possible care. If immunotherapy drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. A contributory factor to poor survival rates in the UK is possibly due to the restrictions in clinical choice brought about by UK regulatory authorities. The committee's decision to not recommend nivolumab for advanced RCC patients after failure of prior systemic therapy, denies terminally ill kidney cancer patients access to innovative and effective treatment through NHS England, despite the drug being available for melanoma patients living in England, and kidney cancer patients living in other European countries. This is confusing for the patient community because the committee has acknowledged the fact that nivolumab meets the end-of-life criteria, but recommends the drug as not a good use of NHS England resources. The committee does not attempt to explain how they reconcile these two positions to those affected by their decision. 2. Prolonged survival The phase I and II clinical trials (CheckMate-003 and 010), which were conducted in North America, Finland and Italy, provide compelling evidence for the long-term	

	survival of advanced RCC patients after treatment with nivolumab in the second-line or later setting. The five-year survival rate is 34% after treatment with nivolumab in CheckMate-003, and 29% of patients treated with nivolumab in CheckMate-010 are still alive at 4 years. Although the committee acknowledge these findings, the ACD states the committee agreed 'it was implausible to assume that more than a few people would live to 5 years' since only 15% of patients were receiving nivolumab after 2 years in CheckMate-025. This is merely the opinion of the committee and is not evidence-based, and the Kidney Cancer Support Network, together with the patient community, are disappointed that the long-term survival data from the earlier clinical trials is dismissed out-of-hand in the ACD. In this instance, the Kidney Cancer Support Network consider the committee did not take all available evidence into account when arriving at their preliminary decision not to approve nivolumab. The phase I and II clinical trials in RCC point to a significant minority (about a third) of long-term survivors, as already seen from the melanoma data. These trials provide the longest follow-up reported to date with any PD-1/PD-L1 agent in advanced RCC. They also provide evidence to show that long-term survival is achievable regardless of risk group, performance status, or best overall response. NICE have already approved nivolumab for the treatment of advanced melanoma patients in both the first- and second-line setting. Clinical trials with melanoma patients show a two-year survival rate of around 50%, which is very similar to the two-year survival seen in CheckMate-025 with advanced RCC patients. It is, therefore, very likely that the survival curve for CheckMate-025 will be similar to that seen with nivolumab in melanoma, and will plateau with survival at around one third of patients, as already seen in the phase I and II clinical trials, albeit in small patient populations. Bearing this in mind, if the committee is minded not to approve nivolumab, the Kidney Cancer Support Network urge NICE to reconsider nivolumab for the new Cancer Drugs Fund (CDF) while further survival data are collected from the CheckMate-025 trial to provide evidence for this prolonged survival effect in advanced RCC patients. With less than 4,000 patients diagnosed with advanced RCC per year, this disease is designated a rare cancer. This should be considered when setting time limits for the collection of survival data, and the 24-month period for collection of addition evidence specified in the ACD (and the	

	CDF SOP) to be extended for this small patient population. The phase I and II clinical trials in RCC did not take place in the UK; however, the following is a statement from one of the original North American patients who took part in the early clinical trials with nivolumab, and has survived 4+ years with limited toxicity and no disease progression. "When I began treatment I was in a state of helplessness. The abdominal tumour was located in such a position that it was growing so fast and caused so much pain I was unable to function. I was taking very high doses of Opiate pain medication with the result that I had no appetite and combined with side effects of Sutent my weight dropped to 139 pounds from 210 pounds. I lost large amounts of muscle. As a result I was eventually confined to a wheelchair. I was unable to carry out even basic tasks and from being a very physically strong man who was very active and worked on my small ranch, I could do nothing for myself. I was very ill; I was told I had about 12 months to live. Tumours were growing aggressively. Response to Nivolumab: complete response. All tumours completely disappeared very rapidly after the first four infusions [of nivolumab]. [I had no side effects] for the first 74 infusions. After several years and following infusion number 75 the following side effects commenced. Inflammation in most joints causing pain, inflammation in lungs causing symptoms of asthma, shortness of breath, fatigue. Lung inflammation is well controlled with Prednisone. Joint pain is well controlled with Gabapentin. In about two months of commencing treatment, the pain began to subside and very shortly ceased completely. This was the first indication Nivolumab was working. The improvement in my quality of life was immediate and profound. I could walk again, I could eat again, I had energy again, all of which have continued to the present day even with the recent appearance of side effects, the effects of which are minimal on my quality and enjoyment of life. Obviously the change in my health has impacted the life of my wife. I can now care for myself in every way and be a help to her. I am no longer dependent on any one. I can put in a full day of hard physical work on the ranch on all but the day following treatment." Nowadays, kidney cancer patients do not exist in silos. They communicate widely; international discussion forums exist where patients talk to one another daily. An	

	international coalition of patient organisations (www.ikcc.org) currently has 22 member countries. IKCC has published and maintains a very informative website, which brings together information about immunotherapies to patients around the world (www.10forio.info). Patients and clinicians are right to expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so they have the same choices as patients in other countries. 3. Clinical effectiveness The Kidney Cancer Support Network and our members are confused as to why nivolumab can be approved for use on the NHS for advanced melanoma, but not for advanced RCC. Nivolumab was approved for melanoma based on progression-free survival (PFS) data, which does not carry as much weight as overall survival (OS) for cancer patients. PFS is often used as an alternative to OS, which is seen as the most reliable endpoint in clinical trials. Nivolumab has shown convincing OS improvement in advanced RCC patients in all three clinical trials to date (CheckMate-025, 003 and 010). Furthermore, the hazard ratios for the RCC data are higher than those for melanoma, which are very low. However, the comparative arm in the melanoma trials is chemotherapy, which is a fairly ineffective treatment. The comparative arm in the RCC trials was everolimus, which has been proven to be relatively effective in the second-line setting. Therefore, the hazard ratios for the melanoma data are bound to look good when compared to the RCC data. In the opinion of the Kidney Cancer Support Network, the data for the RCC patients are not substantially different to those for the melanoma patients, and do not warrant a negative recommendation while the melanoma data results in a positive recommendation. We would like to know why these two tumour types are being treated differently, and kidney cancer patients are being disadvantaged. This could be seen as demonstrating inequality in the use and interpretation of the STA process against kidney cancer patients. The Kidney Cancer Support Network considers the committee failed to assess the potential disadvantage to kidney cancer patients when arriving at their preliminary decision not to approve nivolumab. 4. Safety, tolerability and quality of life CheckMate-025 shows that nivolumab is better tolerated than everolimus, where	

	only 19% of nivolumab patients reported grade 3-4 adverse events compared to 37% in the everolimus group. Furthermore, most treatment-related adverse events occurred within the first 6 months of treatment, whereas everolimus toxicity continued throughout treatment. Treatment-related adverse events leading to discontinuation of therapy occurred in 8% of nivolumab patients and 13% of everolimus patients. We do not believe the ACD places sufficient value on the importance of the patient experience and quality of life issues when comparing nivolumab with everolimus or axitinib. We are also aware anecdotally that nivolumab appears to improve quality of life and is better tolerated than tyrosine kinase inhibitors, such as axitinib. The following patient statements are proof of this fact: *[Patient statements provided but not reproduced here.]* From the evidence we have gathered from the Kidney Cancer Support Network group of advanced RCC patients currently taking nivolumab through EAMS, it appears that this drug allows patients to lead a relatively 'normal' life and, in a lot of cases, patients can return to work, resume family life, and contribute socially and economically to their communities. *[Patient statements provided but not reproduced here.]* 5. Choice of treatment and unmet need at third line In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available, and without nivolumab, the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the second- and third-line, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life. Current second-line treatment options are not effective for everyone, and can be difficult to access. Undue restrictions in accessing nivolumab would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the second-line and a potential choice in the third-line setting would	

	enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient. Nivolumab will also address the massive unmet need for treatment options in the third-line. 6. Cost effectiveness We are disappointed that yet again another drug for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare cancer): Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life-prolonging treatments during a desperately difficult time for both themselves and their families. We understand that nivolumab is expensive, and we appreciate the budgetary implications, but nonetheless NICE and the manufacturers must negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as failure of professional competence. NICE and the manufacturer need to think outside the box to agree an alternative funding scheme, and work collaboratively to negotiate an acceptable patient access scheme to ensure kidney cancer patients who need it can have access to this latest clinically effective drug. 7. Effect of NICE's decision on UK clinical research As we mentioned in our original statement for this STA, we are concerned that NICE's decision not to recommend nivolumab may negatively impact the clinical research environment in the UK. Patients who participated in UK clinical trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of nivolumab on the NHS in England, we must question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from	

	new, innovative and clinically effective drugs if NICE fail to allow these drugs to get to the patients who need them. A rejection of nivolumab will mean that a substantial number of late stage kidney cancer patients will be denied the opportunity to benefit from the new era of clinically effective immunotherapy drugs. Thank you for allowing the Kidney Cancer Support Network and our nominated patient experts to take part in this single technology appraisal. We welcome the opportunity to put forward the views of our Kidney Cancer Support Network patient community for this important health technology appraisal of nivolumab in advanced or metastatic renal cell carcinoma, in particular the large group of patients currently benefitting from nivolumab who are witnessing at first hand the very real and positive impact of this drug in the treatment of their disease. *[Additional member statements provided but not reproduced here.]*	

Comments received from commentators

Commentator	Comment [sic]	Response
Novartis	We do not have any comment on the ACD.	Thank you.

Comments received from members of the public

Role*	Comment [sic]	Response
NHS Professional	Dear Committee, I am writing this comment in support for the Nivolumab application to highlight the following, based on the published results of the CHECKMATE 025 trial: 1. Patients on Nivolumab achieved a response rate of 25% following failure of antiangiogenic agents. 2. In the subgroup analysis for overall survival patients with poor and intermediate MSKCC risk score and those with 1 previous line of antiangiogenic agents benefited from Nivolumab. 3. PD-L1 expression is not a useful predictive biomarker 4. Nivolumab was well tolerated with few G3/G4 toxicities, mainly fatigue and nausea.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).

	My conclusion would be to offer Nivolumab in patients with intermediate and poor MSKCC risk who progressed on 1st line antiangiogenic treatment. I would ask the company to contribute to a prospective research project of using genomic profiling to identify a mutational signature that will predict response. Until the point of defining a reliable predictive biomarker the company should reimburse the NHS the cost of the drug for non-responders.	
Patient	I am really worried about the initial decision by NICE. As a kidney cancer patient aged 44 and with two young children to support, I feel that Nivolumab would give me, and many others, a chance to extend our lives and for me personally to support my children growing up. Renal cancer is incredibly difficult to detect until it has metastised and so a lot of people like myself have to face up to a very difficult battle. I urge you to reconsider.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Public	Whilst not an expert surely the option of this treatment can benefit those who effectively need it - any benefit has to be worthwhile	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Relative	I'm concerned the NHS spends money on cosmetic surgery and tummy tucks, yet a potentially life saving drug for a very difficult to detect cancer is declined. I struggle to comprehend why beauty is more important than the beauty of life.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Relative	My relative is 44 year old and has two small kids. He should not be denied the chance to spend more precious time n with them. It's to think that someone played God with their chance of living and declined declined this new treatment. The problem is not just a person dying, but the suffering caused to hundreds of people around that person.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Carer	Please reconsider your decision to not make this drug available on the nhs. If it could extend the life of my children's father by a few years then it would make such a difference to us. We have two boys aged 8 and 11 who are too young to lose their dad at only 44 to advanced kidney cancer.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Public	I feel that there is an unmet need for patients with advanced kidney cancer and	Thank you for your comments.

	that these patients need more drug options especially for drugs that work in a different ways and offer hope if people become resistant to current medication. this drug provides that choice/hope.	Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Patient	Why nivolumab would be recommended by NICE recently for use in skin cancer but not for advanced kidney cancer, and as such, what are the reasons behind this initial recommendation to be published. The drug has shown great promise in both diseases, it is our understanding that the price of the drug is the same in both cases and the number of people who would benefit from this drug is similar.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Carer	There is finally some hope for life to be saved, yet -for some reason, someone had the power to decide the fate of others and deny new treatment to those who are desperately hanging on to hope to see their children grow, to enjoy a few more years with the loved ones. This treatment must go ahead- for the love of live! As evidence suggests in the links below, other countries value the life of their citizens: http://www.agenziafarmaco.gov.it/it/content/attivazione-del-registro-opdivo-05072016 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002478.jsp&mid=WC0b01ac058004d5c1 Does it mean that UK citizens are treated as second hand patients?	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
NHS Professional	Disease progression after 2 lines of treatment in patient with RCC is an unmet need. Majority of patients are unfit for even second line TKI due to poor performane status and significant toxicities from 1st line TKI which preclude going on with 2nd line of same class of drugs. But there is a small group of patients who sadly have progressed through both the lines of TKI and still very fit and these group of patients will substantially benefit from having access to Nivolumab. The appraisal has rightly highlighted the improvement in overall survival at the cost of minimal side effects. The argument that "substantial uncertainty about the extent of the survival benefit when measured over the long term" is not very correct given the short period of follow up to accumulate this data. Previous trials with immunotherapy drugs in other cancers have shown long term survival benefits which could be extrapolated to patients with RCC and probably in time this will become apparent on futher follow up data from CHEKMATE025.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.5 of the final appraisal determination (FAD).

	I have treated patients with Nivolumab under early access medicines scheme and have seen significant improvement in patients QoL and survival which they wouldn't have benefited without this drug. I would request the appraisal committee to further review its decision. And if Nivolumab could not go onto routine commissioning then it has to be at least considered under CDF. Such patients as those who could benefit from this are a small cohort.	
Carer	I appreciate that kidney cancer has 2 lines of treatment already, but these treatments are older and the Nivoluamb is a new type of therapy which a lot of cancer patients in the uk are being denied. We have to give these drugs a chance to see the real effectiveness of them. Clinical trial only portion a certain amount of people and cancer takes no prisoners in who it chooses to attack. My husband has already received a form of immunotherapy that's been around since the 80's and for some this treatment has cured them of kidney cancer. For my husband it gained us a year of progression free survival which whilst giving birth to our first son I was eternally grateful for. Please think about the bigger picture, each cancer patient is different in every way, how thier bodies react and how well they cope, a side effect to one wouldn't be to another and people's perception of pain is very different. Cancer is a new normal that you learn to live with, and live with for a long as possible and drugs such a Nivoluamb can help people do that. Please let it be thier choice to live and spend precious time with loved ones.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Carer	What I feel you have failed to address is the many people who were depending on this as a last resort. My husband is on his last chemotherapy that he can now have. Then he has nothing. You have taken away his last chance of life. Taking away memories that he could have had with his family. What cost can you put on life. What cost can you put on your loved one. How would you feel if your loved one had been denied access to this drug. I am now the one that has to explain to my family why there is no further treatment avaliable for their dad because the 'men in suits say no'	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Carer	You heard incontrovertible evidence from the checkmate trial that Nivolumab extends life by 6 months relative to other second line treatments. The cost is broadly comparable with TKI and other treatments and there is room for further negotiation with the drug company. Further evidence of usage around the world	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.1 of the final appraisal

	of improved outcomes is widely available. As well as improved outcomes there is clear evidence of better quality of life on. Nivolumab which one could argue is even more important when you are talking about extending the life of someone with an advanced cancer diagnosis and a poor prognosis relative to the general population. For all these reasons I completely disagree with your decision to not recommend Nivolumab for approval on the NHS. It is an important development in the treatment of RCC which is still underfunded and under researched relative to other cancers. To deny a terminally ill person the opportunity of 6 more months of life at a tolerable quality level is an un acceptable decision and I cannot see your grounds for making this decision, having read through the entirety of your report. There are a range of variants of RCC that are not fully understood yet but Nicolumab has been proven to work well on a range of sub variants such as sarcomatoid RCC which responds poorly to TKI's. I urge you t reconsider your opinion and listen to the clinicians who advised you that this treatment provides an alternative treatment, the likes of which are not currently available to them to prescribe and which has PROVEN benefits in terms of 6 months of extra life and likely fewer sever side effects. My husband was accepted under the EAMS scheme because there were no other treatment options. Nivolumab was his only hope of extending his life. At 43 and with a 1 year old daughter, every single month that his life could be extended was priceless and precious to us.	determination (FAD).
Patient	Nivolumab is a innovative therapy which many patients are achieving excellent results, recent reports from American Society of Clinical Oncology show that a third of patients were alive 5 years after treatment. Not being able to access new drugs in UK lag for cancer care, having a terminal illness causes depression not just for patients but for family members. Having access to Nivolumab would help patients know that all reasonable steps are being taken for a good quality of life. Yes this is a newer drug but the impact of survival is far greater. Let's face it how would YOU feel, knowing theirs a drug that can help your survival.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.5 of the final appraisal determination (FAD).
Patient	I just want to supplement the patient views with my comments. As a kidney patient I feel very strongly that all patients should have equal access to the best possible treatment no matter where we live, especially as NICE themselves accept Nivolumab as clinically effective. The drug is available in other	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1, 4.1 and 4.5 of the final appraisal

	countries and if we want to see survival rates in the UK improve (as they are poorer than other parts of Europe), then we need the best drugs. I also feel strongly that us patients in the UK should not be disadvantaged. Nivolumab is an innovative therapy with which I am aware that many patients worldwide are achieving excellent results. I am also aware of the recent updated reports to the American Society of Clinical Oncology, which showed that a third of patients were alive 5 years after treatment initiation on Nivolumab and believe that this data should be assessed when making comparisons to other drugs. Why should we be penalised? Not being able to access new drugs is making the UK lag in cancer care for renal cell carcinoma. We are all aware that having a terminal illness causes depression to patients and our families, but having access to Nivolumab would help us to know that all reasonable steps had been taken for our survival. Alternative drugs are similar in their action and immunotherapy offers hope for a response in patients who haven't had success on other drugs. Please understand that the quality of life on Nivolumab seems to be much better in terms of the side effect profile. I am aware that many patients have been able to return to work and exercise after starting Nivolumab. I do however accept that this is still a newer drug and that data is still being collected on its overall impact on survival, but I feel it is important that NHS patients can benefit from the treatment immediately and that data is collected to reinforce its efficacy.	determination (FAD).
Patient	I would like to refer to the nivolumab data available from the USA (American society clinical oncology) showing that 1 third of patients are still alive after 5 years from starting treatment and other countries show are showing similar excellent results, I believe this data should be assessed when making comparisons to other drugs. Immunotherapy by its nature offers potential gains to patients for whom other treatments have fail or are no longer effective. I would also refer you to the lesser side effects which are observed with nivolumab allowing patients to return to a normal life includung returning to work a major, quality of life issue. I would not like to see the NHS fall behind other devoloped countries in the treatment of RCC and whilst I appreciate that this is a new drug with few trails in the country so far I believe that the evidence could be gathered	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1, 4.1 and 4.5 of the final appraisal determination (FAD).

	whilst the drug is in use to prove its value and effectiveness.	
Patient	Currently receiving HD - IL2 . Nivolumab has all the signs of a far less arduous treatment with non inpatient costs. It's been approved for other cancer types. It's been approved in Europe. It's appears to be the way forward not to approve makes nhs treatment fall behind other European countries. Immunotherapy should be promoted not held back. Let's return renal cell cancer victims back to being useful members of society my business has been on hold but now I am planning expansion. Kind regards	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Carer	My dad was diagnosed in nov 2014. He is doing well but possibly facing the fact the cancer may have returned after having kindney removed due to rcc . Nivolumab is an innovative therapy that many patients worldwide are achieving excellent results. recent reports to the American Society of Clinical Oncology showed that a third of patients were alive 5 years after treatment initiation on Nivolumab and believe that this data should be assessed when making comparisons to other drugs. The stress and upset that disease brings to the lives of both patients and family members is immense !!! Knowing that there is a drug that works , (albeit small data samples at the moment)! Is the only hope some families have ! If this drug us proven to work on small samples then surely it will continue to be just as effective on larger samples !! Please approve this	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.5 of the final appraisal determination (FAD).
Patient	Having been diagnosed 2 years ago and so far lucky enough not to require treatment I have been following certain trials from across the water in the USA with much interest - in particular nivolumab and it's amazing success stories. As a type 1 diabetic I know that if and when I need treatment it will be a difficult thing to find a drug that won't give me side effects detriments to me and that is why I strongly believe this new drug to be a major leap forward as the side effects are minimal with some amazing results. This would certainly benefit me and many other diabetics not to mention anyone else. The lack of side effects will I believe save money in the long term and will encourage greater research in the power of immunotherapy. I sincerely hope that NICE rethink the decision and give this incredible drug the go ahead to the NHS.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.5 of the final appraisal determination (FAD).
Carer	My husband, [redacted],was diagnosed with RCC on 3/4/13 and had his right kidney removed on 21/5/13 .He had not had any symptoms of disease and the cancer was found by accident after he had injured himself at work. My husband was then transferred to the care of Professor John Wagstaff at South	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.1 of the final appraisal

	West Wales Cancer Centre in August 2013 to treat spread of disease. He was firstly treated with Pazopanib which caused several side effects such as hypertension,nausea and loss of appetite. In September 2015 my husband started on Axitinib .We had hoped this drug would work well but the treatment was stopped in February 2016 when my husband developed severe sepsis.We were extremely fortunate that this happened when Nivolumab became available under EAMS. My argument for NICE recommendation for Nivolumab is the quality of life with this treatment and lack of side effects. Axitinib caused severe side effects for my husband and at times he was unable to eat or walk.Axitinib caused diarrohea ,severe blistering to feet and mouth and we had to seek help from a chiropodist to try and enable him to walk but even she couldn,t help him. In all my husband lost 5 stone in weight during his time on TKIs Since his starting on Nivolumab ,my husband's health has improved dramatically ,he eats well and has started to put on weight again.Even though he is 66 years of age he works 5 days a week and now can enjoy his pastime of fishing on Saturday and Sunday. My husband has a very strong character but even he struggled with the side effects of Axitinib. Even though Nivolumab is a very expensive drug hopefully there will be a reduction in costs of prescribing medication for side effects. I do not want any Kidney Cancer patient to die because of cost when we have a potentially life changing drug on the horizon.	determination (FAD).
Public	As the father of a daughter (wiho has2 very young children and a husband) I would urge NICE to approve nivolumab at their August review meeting. The trials indicate that this drug has an improved rate of success and is being used for the treatment of melanoma and both of which were trial led at or around the same time. Please respect and accept the expert opinion in you possession that exhorts you to approve this treatment	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Patient	41 year old health male no symptoms I was diagnosed with RCC August 2013 week before i got married had my kidney removed in the September 2013, confirmed metastasis to lung in the November 2013. Started HDIL2 in february 2014 5 rounds suffered all the horrendous side effects	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination

	associated with this for 12 months unfortunately new lung tumor which was removed in august 2015 however more metastasis to lungs started Paz which i currently take. Have all the side effects diarrhea nausea no taste weakness but i manage to work 5 days a week running two companies which i wish to continue doing to provide for my 2 year old son and baby due to be born this week. The chance offered by this drug to keep me alive to work and provide for my family and keep employed the people who work for me is worth the cost it would require.	(FAD).
Patient	I have stage 4 renal cell carcinoma and am currently taking Pazopanib. I have been taking this for three years and four months with good results so have already beaten the odds on how it supposedly works "statistically ". However I'm under no illusions that my time on it must be nearing its end. When I heard that Nivolumab was going to be approved it filled me with a lot of hope. I've read about its good success rate and how some people have even had their tumours completely disappear and how people are so happy with how little side effects there are compared with the TKI's. If we have a drug that can work this well even if it isn't for everyone, please give us the chance to try it.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Patient	As a cancer patient who has been told I have a higher chance of my cancer returning in the future, I wish to make my thoughts on the removal of Nivolumab heard. Having a terminal illness causes depression to the patient and their family, having access to Nivolumab would help them to know that all reasonable steps had been taken for their survival. The quality of life on Nivolumab seems to be much better in terms of the side effect profile. I am aware that many patients have been able to return to work and exercise after starting Nivolumab. This is a newer drug and that data is still being collected on its overall impact on survival. It is important that NHS patients can benefit from the treatment immediately and that data is collected to reinforce its efficacy. Not allow patients access to new drugs is making the UK lag in cancer care for renal cell carcinoma.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Patient	In October 2014 I was diagnosed with Kidney Cancer, the tumour when it was discovered was the size of a honeydew melon. I had a radical nephrectomy and am, touch wood, clear. My consultant has said that he has never seen anyone with a tumour my size where the cancer hasnâ€™t come back and reading my histology, it seems as if it is inevitable that at some stage it will come back.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.5 of the final appraisal determination (FAD).

	When I found all of that out I obviously did a lot of research and frankly the drugs on offer, whilst some have had good results, the side effects can be grim. I, like others, have followed NICE and was hopeful that Nivolumab would be considered suitable but I understand cost is a major factor. I do not feel enough studies have been done to warrant that decision when you consider that the recent updated reports to the American Society of Clinical Oncology showed that a third of patients were alive 5 years after treatment initiation on Nivolumab. Can you advise if this was taken into account when making your decision? Could you look at RCC at a whole and actually look at all the drugs on offer, look at Axitinib , Sunitinib, Everolimus and now Nivolumab and see between the them which is actually the best for kidney cancer patients? Obviously it wont be a case of one drug fits all but Nivolumab seems to be that for other cancers as well. I feel that the UK is becoming a third world country when it comes to cancer as a whole. We are years behind other countries and whilst I fully appreciate that they do not have the NHS, there should be an element of looking at what works and what is in the patients best interests. I have an 11 year old son who I want to see grow up and I am truly scared that when/if the cancer comes back, the drugs offered will make me too ill to be a proper mother and then of course sometimes the cancer can be so aggressive that neither of the two drugs work. The few people who have trialled Nivolumab are saying they were lost causes and after a few months on it, are almost back to how they used to be prior to cancer with no side effects. Please help us.	
Carer	This drug should approve. As my husband was on the drug trail which this was one of the drugs he was given. His cancer shrunk by 80% and on our last visit it has now gone. If it had not have been for this drug he would not be here now. It is short sightedness as in the long run it will not on save live by money as. Please approve this drug and prolong people lives	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Patient	I have advanced renal cel carcinoma and take sunitinib. I have extreme difficulties with side effects and cannot take the full dose. The metastases in my bone and organs are growing. I have had to retire from work because of the side effects and my quality of life is very poor. I am devastated to learn that this alternative treatment may not be available.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
NHS	Dear NICE,	Thank you for your comments.

Professional	Currently there are two drugs licensed for second line use following failure of first line vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors in patients with metastatic renal cell carcinoma. These are axitinib and everolimus. Neither of these agents produced a significant improval in overall survival in the pivotal randomized trials that tested them1,2. NICE have only sanctioned the use of one of these namely axitinib. Even then the guidance states â€œBecause the remit referred to NICE by the Department of Health for this technology appraisal only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory fundingâ€ . The other VEGFR tyrosine kinase inhibitor licensed and approved by NICE for first line use is pazopanib. This agent is equally effective to sunitinib3 and is preferred by both the patients and their treating physicians4. Because of the way the NICE guidance for axitinib is written oncologists are being forced to use the less preferred option of sunitinib as first line treatment in order to ensure that their patients get access to second line axitinib. In the dose escalation trial of nivolumab there is longer survival data than in the 025 phase5 trial (see figure below)6. The median survival was 22.4 months but there is a plateau in survival at around 40%. This survival curve is very similar to that seen in melanoma where NICE have approved nivolumab for use in the NHS. These data suggest that a significant cohort of these patients will get sustained long term survival. With this in mind it is therefore very disappointing that NICE have not approved nivolumab for second line use. This drug did produce a significant improvement in overall survival in both patients who had received prior sunitinib and pazopanib5. Approving nivolumab as a second line treatment would have allowed the first line use of the preferred pazopanib as well as sunitinib. In patients with metastatic melanoma NICE have approved nivolumab for both first and second line use. The two-year survival of patients with melanoma treated with nivolumab is around 50%7 which is very similar to the two-year survival seen in the 025 trial for renal cancer patients. It therefore very likely that the survival curve for the 025 trial will mirror that seen with nivolumab in melanoma with a plateau in survival appearing at around 35%. Furthermore, NICE have approved the combination of ipilimumab plus nivolumab for the first line treatment of	Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.5 of the final appraisal determination (FAD).

	metastatic melanoma patients based only on response rates and progression free survival. No survival data are available for this combination. It is therefore difficult to understand why NICE have not approved nivolumab in renal cancer patients where improved response rates, progression-free survival AND overall survival are superior to a standard of care control (everolimus). Further-more in the pivotal 025 trial patients were entered who had received two VEGFR receptor tyrosine kinase inhibitors (sunitinib/pazopanib & axitinib). As third line use it also improved overall survival. The NICE approval of nivolumab would mean that patients would have access three lines of therapy. We have previously shown the importance of second and third line treatment in optimizing the overall survival of patients with metastatic renal cancer in the real world8. Median survival was 20.9 months for those patients receiving only one line of therapy compared with 33.0 months for those who received two or three lines of treatment. It is our belief that approving the use of nivolumab would undoubtedly improve on these overall survival figures bearing in mind that third line everolimus did not impact on overall survival in the RECORD 1 trial2. With all of the above in mind we would urge you to reconsider your decision not to approve nivolumab.	
Patient	I have advanced renal cell carcinoma and take sunitinib. I have extreme difficulties with side effects and cannot take the full dose. The metastases in my bone and organs are growing. I have had to retire from work because of the side effects and my quality of life is very poor. I am devastated to learn that this alternative treatment may not be available. I have registered and made a comment on the above consultation, but because the comment section did not allow for a fuller description I am also sending this email. I am a Consultant Clinical Psychologist with the Cambridgeshire and Peterborough NHS Foundation Trust, but am writing as a patient of Dr Kate Fife at Addenbrookes. I was diagnosed with advanced renal cell carcinoma in November and had my left kidney removed in December. I have been taking sunitinib since February this year. I have extreme difficulties with the side effects of sunitinib, and after two weeks of taking 50mg the dose had to be reduced to 37.5. I have also changed the schedule by which I take the sunitinib. Regardless of this, I continue to get very	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).

	marked side effects, particularly of fatigue and mouth ulcers. At this dose the metastases are not properly controlled and particularly the cells in the bone of my left arm continue to grow. I have had to retire from work and return on very reduced hours because of the fatigue and because my job involves talking both to patients and staff for a large part of the day, which I can no longer do. The quality of my life is badly affected and so, I assume, is my life expectancy. Dr Fife and I had started to think about the possibility of changing to nivolumab, and I was therefore extremely upset to learn from her that NICE are not including this in their recommended treatments for renal cell carcinoma. As I understand it, this means that there is no longer a real alternative to TKIs, and that my only alternatives are to continue with debilitating side effects or to step down to supportive care only.	
Public	This is an appeal letter on behalf of Nivolumab. I can only speak from personal experience of a friend who was taken onto the Early Access to Medicine Scheme (EAMs) and received this drug. [redacted] and his wife [redacted] have worked tirelessly raising money for the Kidney Cancer research fund and for Facing up to Kidney Cancer charity to help other sufferers and support early diagnosis of this terrible disease. He was given the chance of the EAMs and took it willingly. Since he started treatment in April scan results after only 6 doses of Nivolumab, over 3 months show 'stable disease'. This is fantastic news in such a short time as the last scan in March showed an increase in the two biggest lung mets by 65%. The results are proof of this treatment bringing results. Nivolumab is an innovative therapy with which you are aware that many patients worldwide are achieving excellent results. Recent evidence and reports to the American Society of Clinical Oncology shows that a third of patients were alive 5 years after treatment initiation on Nivolumab and believe that this data should be assessed when making comparisons to other drugs. The UK cancer care for renal cell carcinoma is lagging behind if new treatment and drugs cannot be accessed. That the quality of life on Nivolumab seems to be much better in terms of the side effect profile. You are aware that many patients have been able to return to work and exercise after starting Nivolumab. [redacted] is an example of this and the day after his treatment is back at work, working away from home in a busy environment as	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1, 4.1 and 4.5 of the final appraisal determination (FAD).

	a consultant agronomist and farm business advisor. I accept that this is still a newer drug and that data is still being collected on its overall impact on survival but I feel it is important that NHS patients can benefit from the treatment immediately and that data is collected to reinforce its efficacy. I hope that you will take my letter of support seriously and consider my appeal for the use of this treatment.	
Patient	Eighteen months ago I was told that my situation was hopeless and my life expectancy was likely to be 2 to 3 years. After 3 months on Nivolumab I have stable disease and am still in full time work as the side effects are so minor. This drug is of imense value to we kidney cancer patients , for whom hope is a rare comodity. There is no other comparable drug with such a low toxicity profile which has the potential to hold this terrible disease at bay. It is imperative that we find a way to make the drug available and to find out which patients it can help.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Carer	My name is [redacted], I attended your original committee meeting as a member of the public/carer while my husband [redacted]gave evidence as an expert patient witness as he has been receiving fortnightly infusions of Nivolumab since the end of April. This new immunotherapy PD-1 type drug Nivolumab is so important to all renal cell carcinoma (RCC) patients everywhere. Today 25th July 2016 we got the news we had been so hoping for – after only six infusions of Opdivo – [redacted]'s latest CT report shows 'stable disease'. His previous CT report in March showed the two largest lung nodules had grown 65% since December. It is hard to put on paper exactly what this means to all of us all but it is truly wonderful, and this is why it is so very important that other RCC patients get this same chance to try to extend their lives too. We do know Opdivo needs to be urgently prescribed to patients. The facts are simple - it works for many people and the drug is so well tolerated and improves the quality of life so much that it is absolutely vital for approval to be granted and for all those on the NICE appraisal committee to please seriously reconsider their initial decision. There are so many aspects of [redacted]'s life, and the lives of our family and friends, which are touched by his incurable diagnosis of kidney cancer. Although Jon was lucky to be able to access Nivolumab, three months ago, under the Early Access to Medicine Scheme (EAMs). We know there are many other RCC patients in	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1, 4.1, 4.5 and 4.22 of the final appraisal determination (FAD).

	England desperately waiting for it to be approved, and their options are fast running out. Many of them we know personally and count them as our friends and they too have families and jobs and they cling to this glimmer of hope that this new immunotherapy drug bring as tightly as a limpet sticks to a rock on a fast running tide. Nivolumab is an innovative therapy with many patients worldwide achieving excellent results. There are recent updated reports to the American Society of Clinical Oncology, which showed that a third of patients were still alive five years after treatment initiation on Nivolumab and we believe that this data should be included and investigated by NICE when making comparisons to other drugs. Sadly it is not a cure, but it can significantly extend the lives of Stage 4 cancer patients, and a few RCC patients in the USA have reached the longed for no evidence of disease (NED). Stage 4 means that the cancer has spread from the initial tumour and it is now a terminal illness. Not being able to access new drugs means the UK lags behind the rest of the world for renal cell carcinoma cancer care. Having a terminal illness frequently causes serious bouts of depression to the patient and their family, often with huge costs to the NHS and the nation's productivity, and access to Nivolumab would help them to cope better by knowing that all reasonable steps had been taken either for their own or their family member's survival. Knowing that everything, which can be done, has been done is truly a small crumb of comfort when dealing with grave illness. We have lived with this cancer journey since 2013, starting with two misdiagnoses, a failed treatment, and disease progression. All these things are very, very stressful and debilitating for everyone involved. The current available crop of drugs for kidney cancer (i.e.: Sutent, Axinitib and Pazoponib) are similar to each other in their mode of action and their copious unpleasant and debilitating side effects, and this new immunotherapy offers real hope for a response in patients who haven't had success on other drugs. Jon's quality of life on Nivolumab seems to be much better in terms of the side effect profile of many of the other drugs currently prescribed for kidney cancer. Conventional chemotherapy does not work for RCC and it is a notoriously difficult disease to treat. [redacted] has not yet had any of the TKI type drugs but despite travelling the long way to London for treatment by infusion every two weeks, and suffering a few minor side effects such a fatigue, itchy skin and headaches, he	

	remains able to work full time which not only contributes to the Treasury but also to his feeling of identity, and self efficacy. These are two huge plus points, and add so much to a Stage 4 cancer patient's life, and that of their family. [redacted]'s only other treatment for his Stage 4 RCC was High Dose Interleukin 2, and this is administered in a specialised hospital setting for a week at a time, and it is very dangerous. [redacted] became seriously ill with jaundice and ascites and took almost a year to recover from that treatment, and although it hadn't worked at the time we knew he'd tried everything he could and this gave both of us a little peace of mind as we wrestled with the terminal diagnosis. We accept that Nivolumab is still a new drug and we know further data is still being collected on its overall impact on survival, which is partly why EAMs was made available. We believe that approx. 200 patients are on the EAMs scheme in the UK and we feel it is vital that NHS kidney cancer patients in England will be able to benefit from this Immunotherapy treatment immediately and that more data is collected to reinforce its efficacy. Surely it is possible to negotiate a reasonable price at which it can be prescribed, to satisfy both the budgets of the NHS and Bristol Squibb Myers (BMS), as a drug they can't sell because of its price is not good for the company, the health service, or the patients. My family and I will always be eternally grateful to BMS for accepting [redacted] on the early access scheme, and it is only right that others get this chance too. We know not everyone with RCC will respond to immunotherapy treatments but knowing that there is a drug, which extends the lives of so many patients I believe it is unspeakably cruel not to prescribe it. [redacted] was patient witness at your original committee meeting and he told the NICE panel: "Let's get Nivolumab out there are see what it can do", and this will only happen with NICE approval, so please approve it and give everyone with kidney cancer a chance of hope and longer lives. Yours faithfully [redacted]	
Public	I am writing to ask that the drug Nivolumab for kidney cancer is able to prescribed as there have been such good results both here on the early access routes and abroad. It would be wonderful if those that need it can have access to this drug in the UK given its positive results and the hope it has given to a number of families in	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).

	helping their loved ones maintain stability with their illness. Thank you for considering this appeal.	
Patient	I am a 65 yr old female with metastatic KC. My cancer is inoperable and incurable but currently being treated with Axitinib (a second line medication after Pazopanib stopped working) I was diagnosed in 2012 ànd am now nearly 3 1/2 years into this journey. It means a lot to believe Nivolumab could become available and help me. Before I became ill with cancer I was a person who proactively looked after my health in order to be strong and healthy. I offered care and support to my grandchildren and indeed helped others in an educational and voluntary capacity. With the coming of Cancer I had to withdraw from these activities but also sadly from being able to live as fully and actively as I would wish. As a cancer sufferer I ultimately hope for a cure and try as far as possible to remain optimistic The approval of Nivolumab, with its lesser side effects and longer longevity, according to the latest evidence, would give hope to me and others and give me more time to spend with my family and grandchildren.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).
Patient	Medical History Survivor of renal cell carcinoma for 7 years. Stage 4 for 4 years. Sutent on the Star trial - 3 months Side Effects uncontrollable vomiting, diarrhoea, rapid weight loss and muscle wasting ending in three weeks of hospital and a long recuperation. Pazopanib for 20 months with no activity in spinal mets and the disappearance of the psoas met. Liver met under control with shrinkage. Side effects. Nausea, exhaustion, high blood pressure, hypothyroidism and diarrhoea. Managed with regular medication breaks and varying the dose. Axitinib from April 2014. Following aggressive liver met growth, now stable with some shrinkage. No other visible disease. Side Effects. Intermittent nausea, diarrhoea, muscle pain and severe fatigue. High blood pressure, Hypothyroidism. Managed with medication, regular medication breaks and variable doses of Axitinib Functional Status Registered disabled. Unable to drive. Unable to work. Limited mobility.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1, 4.1 and 4.5 of the final appraisal determination (FAD).

	Next step No further treatment available unless Nivolumab is agreed. Summary As an active member of international patient support groups. I have watched with fascination and growing hope, the development of the innovative immunotherapy drug Nivolumab from the initial trial to fast track approval by the FDA in the USA, based on the rapid and superior effectiveness of the treatment to all others. I have three friends from the original trial group patients who started when they were near end stage. The following is a summary of their experience. Nivolumab from 2011, 2011 and 2012. All three became free of their tumours within months. All were stage 4 on commencement with no other options and prognoses of less than 1 year. Side effect profile - minimal. Functional Status They have resumed work and are physically active. They continue on the treatment and are still tumour free. Latest research results show superior longevity as well as a healthier life. The recently published reports from the American Society of Clinical Oncology showed that one third of patients are alive four to five years after the start of treatment. Please take this new research into consideration. Nivolumab is now available across Europe and in the USA. Nivolumab can give us the potential for a markedly longer survival and a better quality of life than any other currently available. Potential for Further Research. We are still a long way from fully understanding Nivolumab, who it will work for and just how much greater potential it may prove to have. In order to ascertain this, you and our clinicians need further data which can only come from giving us full access and studying the results over the longer term. Please let us provide that data by allowing us to access it. An Equal Opportunity for Life. The UK has a wonderful record in medical care but we are holding ourselves back in comparison with so many other countries because we do not have rapid access to new drugs. I know that this is being worked on but time is critical when you are dying a little more every day while you watch others survive and flourish because they do not live here. We must re-establish that excellence in care. A Superior and Highly Effective Drug – Nivolumab. Can you imagine what it is like	

	to have a terminal illness or worse, be the loved ones caring for that person, to face the torture of knowing that this drug is available in so many other countries while it is denied here. It is hard to comprehend why the conclusions that it is a superior and highly effective drug with fewer side effects are valid all over the world but not accepted here. Another option for those who do not respond to TKIs. In this infinitely variable disease, the great trickster of the cancers, many have little or no response to current drugs. The TKIs, in spite of their variation, offer a broadly similar mode of action and those who do not respond to them need to have the hope that there is something out there for them. A better option. • I would reiterate that the quality of life is generally vastly superior on Nivolumab than even on Axitinib, for me the gentler of the TKIs. The TKIs have seen me hospitalized for dehydration, sepsis and rapid fluctuations in my blood pressure causing falls and injury. I am happy to endure all of this to stay with my family but it makes life more difficult, causes the health service extra work and in terms of my ability to contribute to society, severely limits my effectiveness. Pills to control the nausea, to lower my blood pressure and control the diarrhea, all have their own side effects. When I look at the lives my US friends are now able to live, I feel envious. The accumulated costs of looking after the infinite variation of side effects related emergencies and spells in hospital must be considerable, over and above the suffering of those who endure them and the impact on those they love. Based on the latest evidence, we know this is a good option and we ask that you make it available to us now. I write this feeling like a starving child from a Victorian melodrama nose pressed to the window of a home where an affluent family are feasting. Please let us join the rest of the advanced nations. The evidence is there.	
Relative	I am writing to you today as a plea to reconsider taking on Nivolumab on the NHS for the treatment of renal cell carcinoma. We speak from personal experience as my husband is currently participating on a clinical trial of the drug. I am writing to you with regards to the licensing of Nivolumab for the treatment of Renal cancer.	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).

	In August 2015 we were shocked and devastated when my husband, age 46, was diagnosed with stage 4 kidney cancer. He had shown no symptoms,and we had led a very busy life with our two young children age 8 and 10 and his two older children, this was until he began passing large amounts of blood and clots in his urine on a Sunday afternoon three days before we were due to fly to Spain. He was eventually hospitalised as the catheter he had put in repeatedly became blocked with clots, whilst they did tests to discover the cause and this was when we found out the truly awful reason. The prognosis of terminal cancer ripped our lives apart. He has T4-V1-N0-M1-G4. We have tried to remain as positive as we can and retain as much normality for our children as possible, but as you can appreciate, it has been, and continues to be an emotional rollercoaster. [redacted] had surgery in September of a radical nephrectomy, splenectomy and retroperitoneal lymph node dissection. Sadly, at the scan post operatively we found that the pre- existing pulmonary nodules had increased 20-30%. Rob was placed on Sunitinib in October and initially showed a good response, but the second scan showed that there was a much more mixed response. We were advised again that we should get our affairs in order. We were devastated. But we were offered a lifeline. At this time a clinical trial had opened at Addenbrookes for Nivolumab which he was offered. [redacted] began on Nivolumab in March and has felt really well on it. He has had no side affects, except some tiredness. This Friday, [redacted] had his second set of scans and we found out that ALL of his tumours have reduced in size! Almost a miracle, something we hadn't dared hope for. He has been brought precious time and is feeling really well. Well enough to work full time, play with the children, cycle, run, play on the beach, go on holiday and enjoy precious family time. If we hadn't been offered this clinical trial, I can't bear to think where we would be. The prospect of this life line drug not being available when his year on the trial finishes is awful. [redacted] is my soulmate, my best friend, a wonderful Dad, much loved son and brother. Nivolumab means he is still here with us. It needs to be made available to people who have this awful illness to give them a chance. We would be happy to answer any further questions from a patient and his family perspective, though would not wish to go public due to our young boys. Please consider how Nivolumab has really helped people like Rob, live a relatively	

	normal life when we thought this would never be the case again, when making your decision whether to licence this drug for NHS use. We know money is a huge problem within the NHS, but it really does make a difference.	
Carer	My husband is stage IV kidney cancer patient with secondaries to lungs, lymph nodes, pancreas and maxilla area. He had a radical nephrectomy and after a trial on BIBF1120 (Nintedanib) he then had a maxillectomy. Stability was achieved in the secondaries at the time except in the maxilla area. After the surgery he started Pazopanib and this resulted in near stability except in the maxilla area and so had further surgery to de-bulk the tumour in that area. During the time on the drugs he managed to work part-time and financially support his family. Fatigue was an issue and everything had to be planned around knowing where he could rest and had access to toilet facilities. Other prescription drugs were needed to deal with the side effects caused by the kidney cancer drug. The stress of wondering if a drug was working or not cannot be underestimated but the knowledge that there are other options available was very important and reassuring. My husband has now started Axitinib due to Pazopanib not controlling the facial tumour. The fatigue is considerably worse and he is now unable to work. His whole body seems to ache and bones hurt. The side effects of Axitinib appear for him to be much tougher than on Pazopanib. The stress on the whole family seeing him so unwell and knowing there are no more drugs available to him if this treatment fails is immense. There seems to be no consideration given to rarer cancer patients with secondaries in unusual places or in bones. No research seems to look at patients where the secondaries are in places the TKIs do not appear to work, where patients do not tolerate these drugs or for those patients for whom the drugs for kidney cancer simply do not work. Why should my husband not have access to a drug which may work for his unusual circumstances instead of a type of drug which is not achieving the desired outcome for all his metastases? An immunotherapy drug such as Nivolumab with a different mode of action could allow him to participate actively in family life and to enable him to return to work and surely this has to be taken into account – to us it is so important. Quality of life is vitally important. Independence from daily drug routines so that we don't have to make sure we get home in time	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see sections 1.1 and 4.1 of the final appraisal determination (FAD).

	or take pills with us so we can change plans. Every day our lives revolve around drug regime and his fatigue. Financial independence and ability to work is important for his self-esteem and confidence and plays a vital part in his battle and that every cancer patient has to fight. Having kidney cancer is difficult and trying to support my husband and our family is upsetting enough without the added stress of financial worries and not knowing whether he can access the latest clinically effective treatments. Please reconsider your preliminary decision and allow patients with rarer cancers to access Nivolumab, a drug which has already been approved for melanoma patients.	
Relative	Yes, we understand the NHS is a finite resource , it is patronising to tell us so, we are not ignorant, we were brought up by parents born in the 20s & 30s who taught us respect and values. To do our part when we can ,both of us pay for private services for treatment relating to side effects from the cancer drugs. [redacted]'s feet need a lot of tlc due to the axitinib, we pay privately for this. He was referred for heart investigations, again due to axitinib use, we paid privately. I was on watch & wait for my lymphoma last year but the hospital weren't listening to my concerns .....so I paid £1200 for MRI scan at private hospital and guess what, the pain in my leg (I had moaned of for a year) was that a large tumour had eaten away my femur. The NHS then went into a spin and fitted a titanium rod in my leg , a cost that would never have been had they listened to begin with. No apology, no refund of my £1200 .....money that yes we can afford because we saved for our old age.....but we may as well spend it now as there won't be old age, the cancer will finish us before the govt pension age. A good "medicine " for cancer is "hope". [redacted] was given that last year when told of nivolumab. Exact words of the consultant were "hold on until next year".... ie, survive, cope with the awful side effects of axitinib , then a committee decides to take away the hope and the improved new treatment. Oh, and finally, when you tell us the NHS is a finite resource , try telling that to all those who access our free at the point of service facilities the moment they arrive here either illegally or from countries the NHS could invoice but don't. Then there's the appalling waste of equipment , mobility aids, given for free (oh	Thank you for your comments. Nivolumab is now recommended as a treatment option. Please see section 1.1 of the final appraisal determination (FAD).

	very nice) but when you bother to return them a jobsworth refuses to take them .... No smoking signs outside hospital seem to be there simply for patients to stand by leaning on their drip, tubes in, pjs on and having a fag.....do staff move them on , no, they wander back in, bringing germs on their often bare feet or socks, and have some more treatment before putting up a proverbial 2 fingers as they go out for another fag. I could tell you about one of the hospital wards [redacted] was on & the night there was a "do " to go to but all staff could not attend due to being on shift. Just the same as [redacted]'s 32 years of Police shifts, you put your shifts in the diary , go to work , then do your activities on time off. Oh no, not in the NHS, ward sister drafted in agency and every single member of staff could attend the "do". Not only a "cost" on the finite resource but leaving patients vulnerable too. My case rests at this point, but there is plenty more, I have bitten my tongue for 3 years and it's starting to hurt.	

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health

Bristol-Myers Squibb Response to:

National Institute for Health and Care Excellence

Appraisal Consultation Document – Nivolumab for previously treated advanced renal cell carcinoma [ID853]

July 2016

Dear Amanda,

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for nivolumab for previously treated advanced renal cell carcinoma (RCC) [ID853].

Has all of the relevant evidence been taken into account?

The committee has not seen results from its preferred analysis (as stated in Section 4.21 of the ACD), which we address in this response.

In addition, the economic results used to inform recommendations in the ACD do not take into account the expected plateau in long-run survival for nivolumab patients noted in Sections 4.5, 4.15 and 4.29 of the ACD. We present in this response further analyses and evidence of the expected immunotherapeutic survival plateau that allow expectations of survival benefit to be explicitly considered with increased certainty in cost-effectiveness results.

Thirdly, Bristol-Myers Squibb (BMS) wish to propose a Patient Access Scheme (PAS) in the form of a simple confidential discount to the acquisition cost of nivolumab, which could not be considered in the first Appraisal Committee Meeting (ACM). This PAS increases the estimated cost-effectiveness of nivolumab in RCC substantially.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

While we feel the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence base, we note some misrepresentations and factual inaccuracies, which we document in this response.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Given the implications of the proposed PAS and additional key evidence and analyses presented in this response, the ACD recommendations are not a sound and suitable basis for guidance to the NHS. From the clarity provided in this response, we hope that a positive recommendation for nivolumab in advanced previously treated RCC can be reached in the second ACM on the 4th of August 2016.

The remainder of this response comprises three parts. Part 1 presents: analyses aligning with the committee's preferred base case; further evidence on the expected plateua in overall survival for nivolumab patients; and demonstrates the economic impact of the proposed PAS. Part 2 discusses perceived misrepresentations and factual inaccuracies in the ACD. Part 3 contains references.

Yours sincerely,

Emir Cevro

Sr. Health Economist, Health Economics and Outcomes Research,

Bristol-Myers Squibb

1 Additional analyses, evidence and core comments

1.1 The committee's preferred analysis

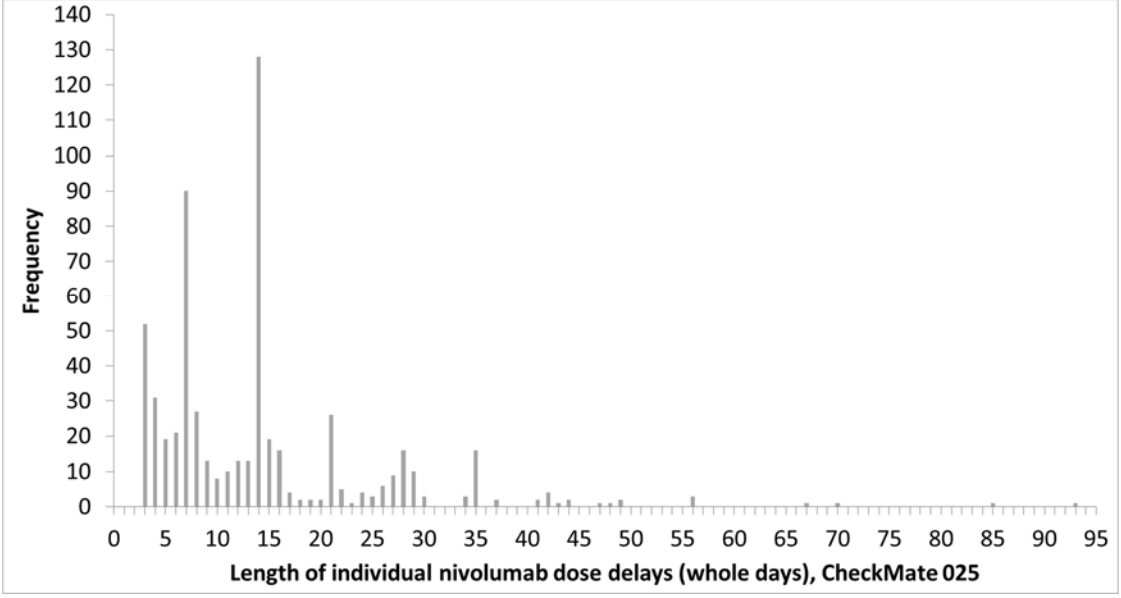
Section 4.21 of the ACD describes the committee's preferred analysis as differing from the company's base case by the incorporation of the following assumptions:

- assume axitinib is as effective as everolimus for progression-free survival and overall survival
- use a log-normal distribution to model time-to-stopping treatment
- assume utility values for axitinib and everolimus are equal

Section 4.22 of the ACD gives further insight into the committee's preferred approach to capture treatment costs. Where the ERG argued for the inclusion of the cost of all delayed and missed doses in the economic appraisal, we appreciate the committee's recognition that that the ERG's preferred base case overestimated the ICERs because it included the costs of all missed and delayed doses.

Though it is a valid argument that the cost of briefly delayed doses may fall upon the NHS in practice, our base case approach of excluding one treatment cycle cost for each delayed dose accounted for this. As stated in Section 5.5.2 of the company submission (CS), the mean dose delay in CheckMate 025 was 14 days. While some short delays may not lead to an NHS cost saving, long delays may lead to two or more doses being missed. Figure 1 shows the distrubition of nivolumab dose delays in Checkmate 025.

Figure 1: Histogram of dose delays, CheckMate 025 nivolumab patients



Nevertheless, in order to adopt a cautious approach, we propose excluding the cost of delayed doses if the delay is at least 7 days. In CheckMate 025, 4.002% of planned doses were delayed by at least 7 days. Combined with the proportion of doses missed (2.5%), a total of 93.498% of planned nivolumab doses are estimated to be paid for by the NHS in practice.

Table 1 shows results from a revised base case, that incorporates this more conservative approach to cost the proportion of nivolumab doses received, and aligns to the committee's stated base case preferences, as listed above.[1] Without any discount to acquisition costs, nivolumab is estimated to offer a health gain of 0.61 QALYs versus axitinib, at an incremental cost-effectiveness ratio of £63,907 per QALY gained. Please note this ICER is not relevant to decision making because of the PAS proposed, and is discussed in section 1.3.

[1] The proportion of planned everolimus and axitinib doses assumed to be received remain consistent with the CS.

Table 1: Results from interpretation of committee's preferred analysis, all list prices

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£91,555.24	2.30	3.39				
Axitinib	£52,682.58	1.69	2.55	£38,872.67	0.61	0.84	£63,907.83
Everolimus	£40,658.59	1.69	2.55	£50,896.65	0.61	0.84	£83,675.62
BSC	£10,525.24	1.00	1.47	£81,030.00	1.30	1.92	£62,555.71
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

1.2 Incorporating evidence on long-term survival benefits of immunotherapy

As noted in Section 4.5 of the ACD, the committee's clinical experts advised that an overall-survival curve with a 'long tail' may be shown for RCC patients who are treated with nivolumab; an expectation based on sound biological rationale encompassing the immunogenic nature of RCC and the immunomodulatory mechanisms of nivolumab. While the CheckMate 025 data are too immature to demonstrate a survival plateau, the follow-up data from CheckMate 003 and CheckMate 010 support this hypothesis.

The long run survival data from CheckMate 003 and CheckMate 010 are summarised in Table 2 alongside data for CheckMate 025 and base case model survival estimates. Table 2 demonstrates how from 2 years after randomisation, where CheckMate 003, 010 and 025 OS estimates are broadly similar, the economic model underpredicts long-term RCC data from CheckMate 003 from 3 years onwards.

Table 2: Summary of evidence on overall survival from nivolumab in RCC clinical trial programme in comparison to the base case economic submission

Study	Phase	Outcome	Value	Reference
CheckMate 003	Ib	2-year OS	48%	McDermott *et al.* 2015 [1]
CheckMate 010	II		48% (42-52% depending on dose)	Plimack *et al.* 2015 [2]
CheckMate 025	III		52%	Motzer *et al.* 2015 [3]
Base case model			53%	Figure 28, CS
CheckMate 003	Ib	3-year OS	44%	McDermott *et al.* 2015 [1]
CheckMate 010	II		35% (33-40% depending on dose)	Plimack *et al.* 2015 [2]
Base case model			38%	Figure 28, CS
CheckMate 003	Ib	4-year OS	38%	McDermott *et al.* 2015 [1]
CheckMate 010	II		29%	McDermott et *al.* 2016[4]
Base case model			28%	Figure 28, CS
CheckMate 003	Ib	5-year OS	34%	McDermott et *al.* 2016[4]
Base case model			21%	Figure 28, CS

Key: ASCO, American Society of Clinical Oncology; CS, company submission; OS, overall survival; RCC, renal cell carcinoma.

As described in the CS, the tendency towards an overall survival plateau indicated in CheckMate 003 and 010 RCC patients is consistent with:

- the immunogenic nature of advanced RCC (first demonstrated in trials of IL-2 cytokine immunotherapy where a proportion of patients achieved long-term response)[5-8]
- the immunotherapeutic mechanism of action of nivolumab[7]
- overall survival evidence for nivolumab in previously treated melanoma (35% at latest follow-up of 5 years, CheckMate 003)[9]
- overall survival evidence for ipilimumab in melanoma (plateau from 21% at 3 years with follow-up data for up to 10 years where OS remains above 17%, pooled analysis of 10 studies including two Phase III studies)[10]

The clinical community's confidence in an immunotherapeutic survival plateau for previously treated RCC patients who are treated with nivolumab is clearly well grounded in evidence. It was therefore disappointing to read the following text in Section 4.15 of the ACD:

"The committee noted that it had not seen any evidence to support the assumption in the company's scenario analysis [in which base case nivolumab mortality risk was assumed to be that of the age-matched general population after 5 years], *and it was not clear how this scenario compared with the long term data from CheckMate 003 and CheckMate 010. The committee concluded that the company's scenario assuming better long-term survival with nivolumab was not based on evidence"*

We understand that the committee has not seen a 'long-term survival' scenario analysis with its preferred assumptions (which we aim to address here), but had hoped that the sceanrio we presented was both clearly driven by evidence and furthermore was conservative in its assumptions, once a long-term survival benefit is assumed.

Table 2 illustrates how this scenario substantially underestimates the overall survival estimates from CheckMate 003 RCC patients from the end of CheckMate 025 follow-up to 5 years. Data beyond 5 years are not available for nivolumab in RCC or other indications, however the long-term melanoma data [10] and the rationale behind an immunotherapeutic survival plateau based on the MOA, both support the use of age-matched general population mortality data from this point onwards.

To generate further evidence and rationale to inform economic analysis which incorporates the clinical evidence, clinical expectation and biological rationale for a long-term survival plateau, BMS conducted telephone interviews with two of the Consultant NHS Oncologists who helped inform and validate clinical assumptions in the CS. The interviews comprised of a brief pre-read and five pre-defined questions. Following our approach for reporting Medical Oncologist expert advice in the CS [11], these interview materials are provided as part of this response in the interest of transparency [12], including the five

pre-defined questions and the Medical Oncologists' separate responses, which are also shown in Table 3.

Table 3: NHS Clinical Experts' responses to five questions on long-term survival for patients similar to those in CheckMate 025

Pre-defined Interview Question	**NHS Clinician** **UK Professor of Medical Oncology who wishes to remain ananymous**	**Professor John Wagstaff** **Professor of Medical Oncology, The College of Medicine, Swansea University**
1. Do you expect an immunotherapeutic survival plateau effect for RCC nivolumab patients who achieve long-term survival, and if so, why?	Yes, I expect a survival plateau for nivolumab treated patients with mRCC. RCC is classified as an immunogenic disease, which is similar to melanoma. There is no reason to suppose that the outcomes observed will be any different in one or the other.	Yes, I would expect there to be a survival plateau, similar to the effect seen with immunotherapies in melanoma. This however would be a lower plateau, given the relative response rates observed.
2. Do you feel that the survival curve in Figure 1 under-predicts long-run survival for CheckMate 025 patients who survive beyond data collection? [Figure 1 is Figure 28 of the Company Submission – base case survival curve fits to CheckMate 025 Kaplan-Meier data]	Yes, that's correct. The curve presented in Figure 1 does not have an inflection point where you would expect one to be (between years 1 and 5), therefore it does not demonstrate a typical tail as that which has been observed in similar melanoma patients. This survival curve is likely to underestimate the true benefit of nivolumab.	Yes I agree. This model does under-predict what we will see in reality. The expectation is that sustained remissions will be seen with nivolumab treated mRCC patients and so there will be a plateau to the survival curve – I do not expect this line to reach 0.

Pre-defined Interview Question	NHS Clinician UK Professor of Medical Oncology who wishes to remain ananymous	Professor John Wagstaff Professor of Medical Oncology, The College of Medicine, Swansea University
3. Do you expect the immunotherapeutic survival plateau to allow patients who reach this stage to have survival rates similar to the general population?	Yes, patients that reach this phase in the curve would have a similar survival rate to those in the general population.	Yes, this makes sense, however it should be noted that this model depicted above, does not represent what a true plateau should look like anyway. In my experience, given that 70% of patients are likely to experience a remission, it would lead to the estimation of around 20% of patients comprising the plateau phase of the curve. This pattern would be similar to the long-term survival curve seen in melanoma patients treated with nivolumab and ipilimumab.
4. How long after treatment initiation would you expect the immunotherapeutic survival plateau to become visible if CheckMate 025 patients could be observed indefinitely?	As there is a paucity of mature data in these patients with this treatment in RCC, it would be difficult to give a certain numerical answer, however given the mechanism of action of this immunotherapy drug, as well as similar acting agents, the expectation would be that a plateau would be observed approximately 2-3 years after initiation of treatment.	We expect a similar impact to those patients with melanoma treated with nivolumab. Thus a plateau potentially would be seen around 3 years, from this point it would be expected that the patients would have a similar death rate to those in the general population (as mentioned earlier).

Pre-defined Interview Question	NHS Clinician UK Professor of Medical Oncology who wishes to remain ananymous	Professor John Wagstaff Professor of Medical Oncology, The College of Medicine, Swansea University
5. What in your opinion is the likelihood, or probability, that the immunotherapeutic survival plateau you expect for CheckMate 025 would be seen, if it were possible to observe CheckMate 025 patients indefinitely?	Yes that is correct, it is likely that there would be a survival plateau observed.	Yes, as stated previously, this is very likely
Key: mRCC, metastatic renal cell carcinoma; NHS, National Health Service; RCC, renal cell carcinoma; UK, United Kingdom		

It is hoped that these responses, alongside other evidence, highlight that the committee's preferred analysis (as interpreted in Part 1.1, Table 1) does not take into consideration the best informed expectations of long-term overall survival prospects for nivolumab's licensed RCC indication, if access to nivolumab is available.

Recognising the uncertainty around the expected survival plateau for this patient group given the unavailability of gold-standard data, the data in Table 3 alongside the other evidence collated here may be most useful for decision making as part of an economic analysis that explicitly incorporates this uncertainty.

Bojke et al described *model averaging* in their review and application of methods to charactise structural uncertainty in decision analytic models.[13] This approach involves weighting multiple plausible models with different structural assumptions by some measure of their credibility. Here, it may be most informative to weight the most plausible approach that assumes no immunotherapy survival plateau (the committee's preferred analysis, Table 1) with a plausible and conservative approach that incorporates a survival plateau, weighted by a conservative estimate of the likelihood that such a plateau would present in patients similar to those in the nivolumab arm of CheckMate 025.

Table 4 shows model averaging results, assuming a 50% probability that the risk of mortality is that of the general population from five years onwards. This scenario is consistent with the data in Table 4 and evidence from ipilimumab melanoma patients [10] in its use of general population mortality risk from the point of plateau, and conservative both in weighting the models 50:50 (from NHS Onclologists' responses to Question 5 in Table 4) and in assuming the survival plateau begins at five years, given the evidence in Table 4, data from ipilimumab melanoma patients [10] and survival estimates from CheckMate 003 (between three and five years). Nevertheless, at list prices, the results in Table 4 suggest nivolumab is a highly cost-effective end-of-life treatment option for previously treated RCC patients.

Table 5 shows results in which assumptions differ from the Table 4 analysis only in that the survival plateau is assumed to begin at 3 years, to align with the conservative end of the two NHS Onclologists' best estimates of this parameter. These results may be the most informative for decision-making, and suggest an ICER well below the cost-effectiveness threshold for an end-of-life medicine, using list prices.

Table 4: Results from model averaging; 50% probability of immunotherapeutic tail at 5 years. The committee's preferred analysis, list prices

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£94,307.71	2.88	4.75				
Axitinib	£52,682.58	1.69	2.55	£41,625.13	1.19	2.20	£34,998.32
Everolimus	£40,658.59	1.69	2.55	£53,649.12	1.19	2.20	£45,108.06
BSC	£10,525.24	1.00	1.47	£83,782.47	1.88	3.28	£44,650.39
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

Table 5: Results from model averaging; 50% probability of immunotherapeutic tail at 3 years. The committee's preferred analysis, list prices

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£97,636.05	3.56	6.22				
Axitinib	£52,682.58	1.69	2.55	£44,953.48	1.88	3.67	£23,973.47
Everolimus	£40,658.59	1.69	2.55	£56,977.46	1.88	3.67	£30,385.80
BSC	£10,525.24	1.00	1.47	£87,110.81	2.56	4.76	£33,998.47
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.							

1.3 The proposed patient access scheme

BMS wish to propose a Patient Access Scheme (PAS) in the form of a simple [redacted] confidential discount to the acquisition cost of nivolumab. This PAS increases the estimated cost-effectiveness of nivolumab in RCC substantially.

Table 6 shows results from the interpretation of the committee's preferred analysis, where the PAS discount is applied to nivolumab and list prices are assumed for axitinib and everolimus. Table 7 shows the sensitivity of the key ICER versus axitinib to assumptions about the confidential discount to axitinib. The PAS ICER remains below the end-of-life threshold of £50,000 per QALY gained even assuming a discount as high as [redacted] for the acquisition cost of axitinib.

Importantly, the results in Table 6 and Table 7 are highly conservative in light of Part 1.2 of this response in that they are blind to the immunotherpeutic survival plateau expected for nivolumab patients. Table 8 and Table 9 show these results from the model averaging approach incorporating uncertainty around the long-term survival prospects of nivolumab patients, where a 50% probability of an immunotherapeutic survival plateau at 5 years is assumed. Table 10 and Table 11 show these results where instead a 50% probability of an immunotherapeutic survival plateau at 3 years is assumed. As described in Part 1.2, both of these approaches can be considered conservative given expectations for long-term survival.

Taking the more conservative approach to incorporate uncertainty around the long-run immunotherapeutic survival benefits of nivolumab, Table 9 suggests that nivolumab is the cost-effective alternative to axitinib even if an acquisition cost discount of [redacted] is assumed for axitinib. The results in Table 11 suggest that if evidence around the likelihood and timing of a long-term survival plateau is incorporated, the PAS ICER for nivolumab vs axitinib may be below [redacted], even when a [redacted] acquisition cost discount is assumed for axitinib.

It is hoped that these results illustrate the clear benefit and cost-effectiveness offered by nivolumab for previously treated RCC patients who are currently treated with axitinib in the NHS, when: the proposed PAS for nivolumab is incorporated; the committee's stated preferences for the economic base case

are used; and particularly when conservative estimates of the immunotherapeutic survival benefit of nivolumab are explicitly considered.

Table 6: Results from interpretation of committee's preferred analysis, including PAS for nivolumab

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	[redacted]	2.30	3.39				
Axitinib	£52,682.58	1.69	2.55	[redacted]	0.61	0.84	[redacted]
Everolimus	£40,658.59	1.69	2.55	[redacted]	0.61	0.84	[redacted]
BSC	£10,525.24	1.00	1.47	[redacted]	1.30	1.92	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 7: Sensitivity of nivolumab vs axitinib ICER to axitinib price discounts, interpretation of committee's preferred analysis, including PAS for nivolumab

Axitinib price discount	ICER, nivolumab versus axitinib
0%	[redacted]
5%	[redacted]
10%	[redacted]
15%	[redacted]
20%	[redacted]
25%	[redacted]
30%	[redacted]
35%	[redacted]
40%	[redacted]
45%	[redacted]
50%	[redacted]
55%	[redacted]
60%	[redacted]
65%	[redacted]
70%	[redacted]
75%	[redacted]
80%	[redacted]
85%	[redacted]
90%	[redacted]

Axitinib price discount	ICER, nivolumab versus axitinib
95%	[redacted]
100%	[redacted]
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme	

Table 8: Results from model averaging; 50% probability of immunotherapeutic tail at 5 years. The committee's preferred analysis, including PAS for nivolumab

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	[redacted]	2.88	4.75				
Axitinib	£52,682.58	1.69	2.55	[redacted]	1.19	2.20	[redacted]
Everolimus	£40,658.59	1.69	2.55	[redacted]	1.19	2.20	[redacted]
BSC	£10,525.24	1.00	1.47	[redacted]	1.88	3.28	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 9: Sensitivity of nivolumab vs axitinib ICER to axitinib price discounts, model averaging; 50% probability of immunotherapeutic tail at 5 years, including PAS for nivolumab

Axitinib price discount	ICER, nivolumab versus axitinib
0%	[redacted]
5%	[redacted]
10%	[redacted]
15%	[redacted]
20%	[redacted]
25%	[redacted]
30%	[redacted]
35%	[redacted]
40%	[redacted]
45%	[redacted]
50%	[redacted]
55%	[redacted]
60%	[redacted]
65%	[redacted]
70%	[redacted]
75%	[redacted]
80%	[redacted]
85%	[redacted]
90%	[redacted]

Axitinib price discount	ICER, nivolumab versus axitinib
95%	[redacted]
100%	[redacted]
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme	

Table 10: Results from model averaging; 50% probability of immunotherapeutic tail at 3 years. The committee's preferred analysis, including PAS for nivolumab

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	[redacted]	3.56	6.22				
Axitinib	£52,682.58	1.69	2.55	[redacted]	1.88	3.67	[redacted]
Everolimus	£40,658.59	1.69	2.55	[redacted]	1.88	3.67	[redacted]
BSC	£10,525.24	1.00	1.47	[redacted]	2.56	4.76	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 11: Sensitivity of nivolumab vs axitinib ICER to axitinib price discounts, model averaging; 50% probability of immunotherapeutic tail at 3 years, including PAS for nivolumab

Axitinib price discount	ICER, nivolumab versus axitinib
0%	[redacted]
5%	[redacted]
10%	[redacted]
15%	[redacted]
20%	[redacted]
25%	[redacted]
30%	[redacted]
35%	[redacted]
40%	[redacted]
45%	[redacted]
50%	[redacted]
55%	[redacted]
60%	[redacted]
65%	[redacted]
70%	[redacted]
75%	[redacted]
80%	[redacted]
85%	[redacted]
90%	[redacted]

Axitinib price discount	ICER, nivolumab versus axitinib
95%	[redacted]
100%	[redacted]
Key: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme	

2 Perceived misrepresentations and factual inaccuracies

2.1 Health-related quality of life (HRQL) evidence

We do not challenge that the observed differences between EQ-5D data for CheckMate 025 everolimus patients and AXIS axitinib patients may be partially driven by patient- and study-level differences, and present results with the committee's preferred assumptions regarding HRQL in Parts 1.1, 1.2 and 1.3 of this response. However, we highlight that while we presented justifications for assuming higher utility for everolimus patients versus axitinib patients both in the CS and in response to the Evidence Review Group's 21st March 2016 Clarification Questions, the assumption of equal utility across everolimus and axitinib is based solely on expert opinion. Section 4.19 of the ACD:

"The utility values were lower for axitinib than for everolimus, but the committee heard from the clinical experts that in their experience, health-related quality of life was similar for people whose condition was being treated with these drugs. The committee concluded that the company's utility values were not appropriate."

We suggest that if expert opinion is solely relied on as the basis for utility assumptions in decision making, it is with the same rationale that the data on immunotherapeutic survival effect and approach to explicitly capture these data in cost-effectiveness estimates documented in Part 1.2 should also be used.

In Section 4.19 of the ACD, the post-treatment, post-RECIST progression HRQL benefit of nivolumab vs everolimus and axitinib is questioned. The text recognises the benefit of not having to recover from treatment-related adverse events associated with axitinib or everolimus, but does not account for the expected prolonged HRQL benefit of having received a programmed death

ligand-1 [PD-L1] checkpoint inhibitor, as opposed to a Tyrosine kinase inhibitor (TKI) or mammalian target of rapamycin (mTOR) inhibitor.

As documented in Part 1.2 of this response, the CS and in response to the Evidence Review Group's (ERG's) 21st March 2016 Clarification Questions, the immune-response mechanism of nivolumab implies benefit both beyond RECIST-defined progression and beyond treatment discontinuation.

As well as extending life, this post-treatment, post-progression benefit is reasoned to improve HRQL. By reducing the burden of disease symptoms, immune-response disease suppression is highly likely to improve patient HRQL for post-progressive patients. In addition, as described in Section 5.4 of the CS, patient quality of life is affected by thoughts of the future and ongoing treatment effectiveness.[11 14] For post-progressive patients, the evidence and clinical expectation of the post-progression, post-treatment immune-response benefit of nivolumab may afford hope.

We therefore hope Section 4.19 can be revised, in the light that as well as being the gold standard evidence for HRQL, the mixed model analysis estimates of patient-level CheckMate 025 EQ-5D data informing the economic analysis may well underestimate the relative utility benefit of nivolumab versus axitinib and everolimus in the post-treatment, post-progression model health state.

We would also like to raise two further minor points. First, Section 4.19 of the ACD notes that CheckMate 025 was open-label, "*which may mean that patients overestimate the utility benefit of novel treatments such as nivolumab"*. While CheckMate 025 was open-label out of clear necessity, it seems highly unlikely that this implies overestimation of utility benefit. Patients being aware that they are receiving nivolumab instead of everolimus will reflect clinical practice, and the evidence summarised in Part 1.2 of this response suggets that any optimism for the relative benefit of nivolumab is based on clinical rationale and evidence, and not novelty. Differences in toxicity and response rates are sufficient to explain the differences in utility across treatment arms of CheckMate 025, as observed in the patient-reported

EQ-5D data. Differences in utility between nivolumab and everolimus patients may in fact be expected to widen with further evidence of a plateau survival effect. We kindly request the ACD text is revised to balance these possibilities.

Second, Section 4.20 of the ACD refers to an analysis performed by the ERG in which utility for everolimus patients is assumed to be equal to the TA333 utility value reported for axitinib patients in the AXIS trial, and nivolumab patient utility assumed equal to this value plus the difference in utility across nivolumab and everolimus patients in CheckMate 025.

Such a scenario, which eschews gold-standard utility data reported directly by the key effectiveness trial patients in favour of unjustified assumptions, is not fitting with Section 5.3 of NICE's Guide to the methods of technology appraisal guidance.[15] The ACD text does not implicitly state that this scenario should be used for decision making, but does imply results from the scenario have some merit, and in fact more merit than the CS utility assumptions. We kindly request that the text referring to this scenario is removed, on the basis that it is uninformative.

2.2 Comparative effectiveness evidence

While we do not challenge a conclusion that the results of the network meta-analysis (NMA) are uncertain, and present results with the committee's preferred assumptions regarding relative effectiveness in Parts 1.1, 1.2 and 1.3 of this response, we note from Section 4.12 of the ACD that the committee's preferred assumption of exactly equal overall survival across everolimus and axitinib is based solely on expert opinion. In line with Part 2.1 of this response, we suggest that if such expert opinion is used as the basis for comparative effectiveness estimates in decision making, the data on immunotherapeutic survival effect and approach to explicitly capture these data in cost-effectiveness estimates documented in Part 1.2 should also be used to inform decision making.

The current wording around bias suggests the NMA results are biased in favour of nivolumab and we do not believe any strong conclusions around the direction of bias can be made. We would like to respond to some of the specific statements on differences between trials to support this belief:

- **Number of previous treatments**: to clarify, the VEG105192 and TIVO-1 trials recruited patients who had 0-1 previous treatments with subgroup data provided for pre-treated patients, CheckMate 025 recruited patients who had 1 or 2 previous treatments, the GOLD trial recruited patients who had 2 previous treatments, and other trials recruited patients who had 1 previous treatment (though exact treatment history for patients enrolled in Yang 2003 is unclear). As discussed at the committee meeting, pre-planned subgroup analysis based on number of prior anti-angiogenic regimens in the advanced / metastatic setting in CheckMate 025 showed a significant survival benefit for nivolumab regardless of treatment history (that is, treatment history is not predictive for treatment effect) when using CRF data (see Section 2.3 of this response for further detail on why this is the preferred data source for subgroup analysis).
- **Choice of previous treatments**: we believe the clinical experts were considering therapeutic class here and it should be clarified that previous cytokine therapy versus previous targeted therapy is thought to affect the condition's response to subsequent treatment. This can be clearly observed in subgroup analysis of the AXIS trial where absolute outcomes markedly differ based on treatment history but relative treatment effect remains constant.[16] Selection of the prior sunitinib subgroup from the AXIS trial aimed to select results from the patient group most reflective of English clinical practice. Of the trials contributing to the decision problem network (CheckMate 025, RECORD-1, TARGET, AXIS), data for patients who had previously received anti-angiogenic therapy were available for all but the TARGET trial; this trial compared sorafenib with placebo as second-line therapy in patients who had received cytokine therapy first-line. Considering the potential impact of therapeutic class, there may be some positive bias

for sorafenib in this trial: patients had their first exposure to VEGF-targeted therapy and thus did not have previous resistance to this class of agents; and patients receiving cytokines first-line tend to have a shorter lead-time to receiving second-line treatment.[16]

- **Prognosis of patients at baseline**: apologies for the confusion regarding adjustments to account for differences in baseline risk. To clarify, no statistical adjustments were made; however, the meta-analysis conducted intentionally used a relative measure of treatment efficacy (the log hazard ratio) to avoid the requirement for patients recruited to different trials within the network to have the same prognosis.
- **The methods used to adjust for treatment crossover**: the comments here suggest crossover and subsequent therapy are synonymous which is not true when considering their potential impact on the meta-analysis results. Crossover is part of the study design involving patients switching from the control arm to the experimental arm (most often) at the time of progression (prior to un-blinding). Crossover causes a direct imbalance in treatment arms and thus directly impacts relative measures of treatment efficacy. Subsequent therapy is administered after study treatment discontinuation and patient unblinding; subsequent therapy applies to all patients and reflects real world practice. Subsequent therapy does not cause a direct imbalance in treatment arms, an indirect imbalance may be observed if subsequent therapy use is imbalanced across treatment arms but this is not the case in trials included in the network for meta-analysis including the CheckMate 025 or the AXIS trial where patients received subsequent therapy in equal, balanced measure irrespective of randomised treatment: CheckMate 025, nivolumab arm = 55%, everolimus arm = 63%[17]; AXIS, axitinib arm = 54%; sorafenib arm = 57%.[16]

We would also like to note that comments on prognosis of patients in AXIS *'poorer prognosis of patients in AXIS'* (section 4.11) contradict the committee conclusions that there *'was no way to assess whether the prognosis of the trial patients was similar'* (section 4.10). While this may reflect the ERG comments, committee conclusions should also be referred to here. As discussed at the committee meeting, the apparent difference is as likely to be an artefact of inconsistent assessment of performance status scales across trials and clinical experts agreed that the prognosis of patients in AXIS and CheckMate 025 were similar and reflected standard clinical practice. Furthermore, as noted above, the meta-analysis methodology adopted does not require an assumption of comparable prognosis across included trials. In addition, comments on not adjusting for subsequent treatments in AXIS are not considered relevant in accordance with reasoning provided previously and discussed at the committee meeting. It is expected that subsequent therapy, whether it is used after randomised study drug discontinuation or after discontinuation of the crossover drug (in trials that include crossover as part of protocol), will influence OS results of both control and experimental study arms. However, this is same for all studies, thus subsequent therapy is not a study protocol intervention and does not need adjusting for.

In consideration of the above, the conclusion that the meta-analysis was likely to be biased in favour of nivolumab is thought to be unjustifiably strong. The meta-analysis approach was designed with a view to providing the required estimate of comparative efficacy from all available evidence (in the absence of direct data) in the most appropriate manner, with steps taken to minimise bias where possible. There is no doubt that there are limitations with the meta-analysis provided (as discussed within the submission) and thus uncertainty associated with the results of the meta-analysis (as reflected in the wide confidence intervals observed), but we do not believe that there is a clear direction of bias. For example, contrary to assumptions of bias in favour of nivolumab, it could be argued that given the anticipated immunotherapy related plateau in longer-term OS data (as documented in Part 1.2 of this response, commented by the ERG in their critique of the submission and agreed by clinical experts at the committee meeting), the assumption of

proportional hazards across treatments mean the meta-analysis results favour non-immunotherapies within the network, that is, the potential long-term survival benefit of nivolumab is not captured.

In addition, please consider more detail around the statement *'the committee noted that the company's network meta-analysis showed axitinib was less effective than everolimus'* (section 4.12). To clarify, the meta-analysis provided showed a slight trend favouring everolimus over axitinib in estimates of OS using crossover adjusted/crossover free data where available, and estimates of PFS (based on the point estimate, small numerical difference). Results of the meta-analysis of OS using ITT data showed no difference between these agents which was more in line with the expectations of the clinical community. Following NICE DSU TD16, results from the crossover adjusted meta-analysis were considered the most appropriate for cost-effectiveness analysis and were thus utilised in the base case presented for nivolumab with a sensitivity analysis utilising results from the ITT meta-analysis also presented. These analyses utilise the clinical evidence available and thus provide evidence-based estimates that we believe should be preferred to an opinion based assumption of a hazard ratio (HR) of 1 which does not represent the uncertainty around estimates of comparative efficacy derived from an absence of direct evidence. While, for the reasons stated above, we disagree that an assumed HR of 1 with no account for uncertainty is the best available estimate for the relative effectiveness of everolimus and axitinib, for ease of exposition we have adopted the committees preferred approach for further economic modelling.

In Section 4.14 of the ACD, the company's approach to survival analysis of CheckMate 025 data is criticised. We refer you to the kind words of the ERG in Section 5.5.5 of their STA Report:

"The ERG appreciates that the company implemented in the electronic model an extremely broad set of survival models tested in the analyses. The company included both independent and dependent fits for 6 parametric models and 6 spline-based models for all outcomes, for a total of 24 models

for each of the 3 time-to-event endpoints, i.e. OS, PFS and TTD. This resulted in an extremely transparent and flexible model, which allowed the ERG to conduct a broad range of sensitivity analyses around the modelling assumptions"

The approach to survival model selection was conducted in line with NICE Decision Support Unit Technical Support Document 14 [18] and was driven by both statistical fit, visual tests of assumptions and clinical validation,[11] crucial for overall survival given data immaturity, as clearly reported in Section 5.3 of the CS and as recognised in the ERG's STA Report. The ERG conducted further tests and analyses to their satisfaction, and did not change survival model selection assumptions from the CS base case for overall or progression-free survival. The ERG's preferences for time to treatment discontinuation model selection inform the committee's stated preferences for analysis (Part 1.1 of this response). We hope that this information reassures the committee in its preferences for analysis, and kindly request that the factual inaccuracies highlighted are removed from Section 4.14 of the ACD.

Lastly, Section 4.5 of the ACD reports:

"*CheckMate 025 data showed that only about 15% of patients were still having nivolumab after 2 years. The committee considered that when median survival with nivolumab was just over 2 years (25 months; see section 4.5), it was implausible to assume that more than a few people would live to 5 years."*

Given the evidence on immunotherpeutic survival effects in Parts 1.2 and 1.3 of this response, in the CS and heard at committee on 8th June 2016, we suggest the committee may wish to revise this wording.

2.3 Subgroup analysis

We would like to clarify the outcomes in subgroup analysis of patients with 1 or 2 previous treatments as invited. The hazard (HR) for overall survival (OS) benefit in 1 and 2 prior anti-angiogenic therapy subgroups quoted at the time of the committee meeting (HR 0.79[95% CI 0.63-0.99] for 1 prior anti-angiogenic & HR 0.65 [95%CI 0.43-0.99] for 2 prior anti-angiogenics) was

derived from the case report form (CRF) data source contained within the clinical study report (CSR). The HRs for OS quoted in the CheckMate 025 publication[3] for the 2 subgroups, was derived from the interactive voice response system (IVRS) data source available at that time.

The information provided during the committee meeting, using the CRF data from the CheckMate 025 CSR is considered a more robust data source than the IVRS data. The IVRS data contains only 3 stratification factors including number of prior anti-angiogenic therapies that are recorded at study entry, are not verified, and are generally not changed once entered. The data within the CRF are collected at site alongside a comprehensive list of baseline, efficacy and safety factors that are crosschecked, corrected for errors and verified by the independent study monitor. The CRF data source is thus more robust and reliable. The CRF data was used to calculate the HR for the 2 patient subgroups (1 versus 2 prior anti-angiogenics) and published in the CSR (please refer to page 117 of CheckMate 025 CSR). It is these data (CSR data using CRF data source) that were used to file for regulatory approval for nivolumab in this indication with the US food and drug administration (FDA) and the European Medicines Agency (EMA).

As the CRF data source is subjected to a second objective verification, we ask that the committee disregard subgroup results that appear in the CheckMate 025 publication[3], and use the subgroup outcomes data on Figure 7.2.1-1: page 117 of the CSR (and provided in the manufacturer submission; Figure 14, page 80).

2.4 Factual inaccuracies

Aside from the issues described previously, BMS identified one factual inaccuracy and some misquotations in the ACD, described in Table 12.

Table 12: Factual inaccuracy

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.5; Page 7: Stated that "CheckMate 010 showed that 44% were alive after 3 years."	In CheckMate 010, 3-year OS rates were 33-40% depending on nivolumab dose.	Factual inaccuracy
Section 4.5; Page 7: Stated that "the company's submission stated that, when nivolumab is used to treat melanoma, survival curves show 'long tails' for overall survival meaning that most patients die early but some patients survive for a long time."	Rephrase sentence to remove suggestion that patients die early with nivolumab in melanoma; survival gain is greater in a proportion of patients but currently reads as if nivolumab is responsible for early death. Suggested change to correctly represent CS: "the company's submission stated that, when nivolumab is used to treat melanoma, survival curves show 'long tails' for overall survival meaning that a proportion of patients survive for a long time."	Misquotation
Section 4.5; Page 7: Stated that "The committee noted that the company chose not to use these data to inform its economic model (instead using CheckMate 025)"	Longer-term data from early Phase trials were used to inform the immunotherapeutic survival plateau scenario presented in the CS. Suggested change to correctly represent this: "The committee noted that the company chose not to use these data to inform its economic model (instead using CheckMate 025) in the presented base case"	Misquotation

3 References

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

October 2009

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

Generic Name: Nivolumab

Brand Name: Opdivo®

Disease area: Kidney Cancer

Indication: OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults.

3.2 Please outline the rationale for developing the patient access scheme.

When the NICE Appraisal Committee's preferred modelling assumptions are used, along with the current list price of nivolumab, the incremental cost-effectiveness ratio (ICER) is higher than NICE's anticipated willingness to pay threshold. BMS is therefore proposing a simple discount scheme to meet NICE cost-effectiveness criteria for England and Wales.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The proposed patient access scheme is a simple discount scheme.

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?

- How are the criteria measured and why have the measures been chosen?

The proposed Opdivo® patient access scheme (PAS) will apply to all patients covered by NICE guidance for Opdivo® as monotherapy for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

As noted above, BMS is proposing a simple discount PAS, allowing the drug to meet NICE cost-effectiveness criteria for England and Wales. This would apply to all patients as per final NICE guidance.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

Population	**Proportion of patients**	**Number of patients**	**Reference**
Kidney Cancer	N/A	10,130	(54)
Patients with RCC	80%	8,104	(15, 16)
Patients with advanced RCC	30%	2,431	(18, 56-59)
Patients who receive 1st line therapy	75%	1,823	(45, 60)
Patients who receive 2nd line therapy	50%	**912**	(12, 60)

References as provided in the original company submission to NICE.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

As part of the scheme, we would offer a fixed price across all indications which is equivalent to a [redacted]% discount (based on current list price). The proposed discount will be reflected on the original invoice for direct supply of Opdivo® and no rebates need to be calculated and paid.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

A fixed price (which will not vary with any change to the UK list price) is proposed, if list price is reduced to below the fixed PAS price then this would

become the new price point for the PAS. The proposed discount will be reflected on the original invoice for direct supply of Opdivo® to NHS Trusts.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

Not applicable.

3.10 Please provide details of the duration of the scheme.

The proposed scheme will be in place from the date of guidance publication and until NICE next reviews the guidance for OPDIVO as monotherapy for the treatment of advanced renal cell carcinoma (RCC) after prior therapy in adults and a final decision has been published on the NICE website. In the event of negative NICE advice (i.e. for NICE appraisal ID853), the PAS will not apply.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

Not applicable.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

As noted above, the proposed discount will be reflected on the original invoice for direct supply of Opdivo®.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

Cost effectiveness

3.14 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Adjustments to dose intensity assumptions to meet interpretations of the Appraisal Committee (AC) preferences are described in Bristol-Myers Squibb's (BMS's) response to the AC Document (ACD), delivered on 26th July 2016.

3.15 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

We have updated the base case model to meet interpretations of the AC's preferences are described in BMS's response to the ACD, and shared this model version with a description of changes. The only other changes were minor changes to analyse results for different long-term survival assumptions, and these have been documented and shared with the NICE project team. Please note that the results presented in Sections 4.7 to 4.11 represent an underestimation of long-term survival for nivolumab patients based on the best available evidence documented in the Company Submission (CS), the ACD and BMS's ACD response.

3.16 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also

provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The functionality to include a simple price discount for the intervention or comparator drugs was included in the CS model, so no change to incorporate the submitted PAS was necessary.

3.17 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

Please refer to Section 4 of the CS.

3.18 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'**Error! Hyperlink reference not valid.**.

No such costs are applicable.

3.19 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

No such costs are applicable.

Summary results

Base-case analysis

3.20 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

Table 1 shows results from the revised base case, that incorporates a more conservative approach than the CS to cost the proportion of nivolumab doses received and aligns to the committee's stated base case preferences, and is analogous to Table 1 of BMS's ACD Response document. Table 2 shows results from this base case when the nivolumab PAS discount is included, and is analogous to Table 6 of BMS's ACD Response document.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 1: Base case results from ACD response interpretation of committee's preferred analysis, without PAS

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	£91,555.24	2.30	3.39				
Axitinib	£52,682.58	1.69	2.55	£38,872.67	0.61	0.84	£63,907.83
Everolimus	£40,658.59	1.69	2.55	£50,896.65	0.61	0.84	£83,675.62
BSC	£10,525.24	1.00	1.47	£81,030.00	1.30	1.92	£62,555.71

Key: ACD, Appraisal Committee Document; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

Table 2: Base case results from ACD response interpretation of committee's preferred analysis, without PAS

	Total costs	Total QALYs	Total life years	Incremental, nivolumab versus comparator			ICER (nivolumab vs.)
				Costs	QALYs	Life years	
Nivolumab	[redacted]	2.30	3.39				
Axitinib	£52,682.58	1.69	2.55	[redacted]	0.61	0.84	[redacted]
Everolimus	£40,658.59	1.69	2.55	[redacted]	0.61	0.84	[redacted]
BSC	£10,525.24	1.00	1.47	[redacted]	1.30	1.92	[redacted]

Key: ACD, Appraisal Committee Document; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year.

3.21 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

Please see incremental pairwise results, presented in Section 4.7.

Sensitivity analyses

3.22 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Figure 1 and Figure 2 show tornado diagrams depicting the ten parameters with the greatest influence upon the estimate of incremental net benefit in the one-way sensitivity analysis (OWSA) with and without the PAS for nivolumab, and the influence they had upon results when varied to upper and lower 95% CI values, for the key comparison to axitinib. The analyses assume a willingness-to-pay threshold of £50,000 per QALY gained.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Figure 1: Tornado diagram showing OWSA results, nivolumab versus axitinib, interpretation of committee's preferred analysis, without PAS

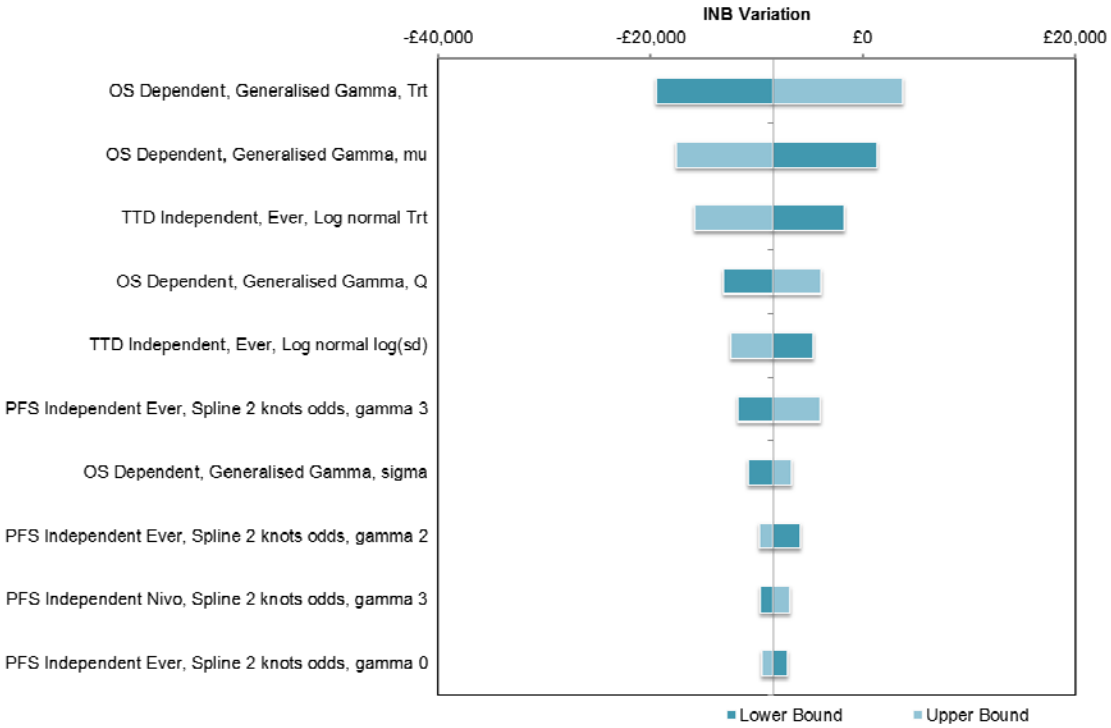

Figure 2: Tornado diagram showing OWSA results, nivolumab versus axitinib, interpretation of committee's preferred analysis, with PAS

Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; INB, incremental net benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to treatment discontinuation.

3.23 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 3 and Figure 4 show PSA scatterplot for the key comparison of nivolumab versus axitinib, with and without the nivolumab PAS. Ten thousand PSA iterations were run; as described in the CS, a sufficient number for the point estimate of the HR for OS, everolimus versus axitinib, to stabilise. Table 3 shows mean probabilistic base case results.

Figure 3: PSA scatterplot, nivolumab versus axitinib, interpretation of committee's preferred analysis, without PAS

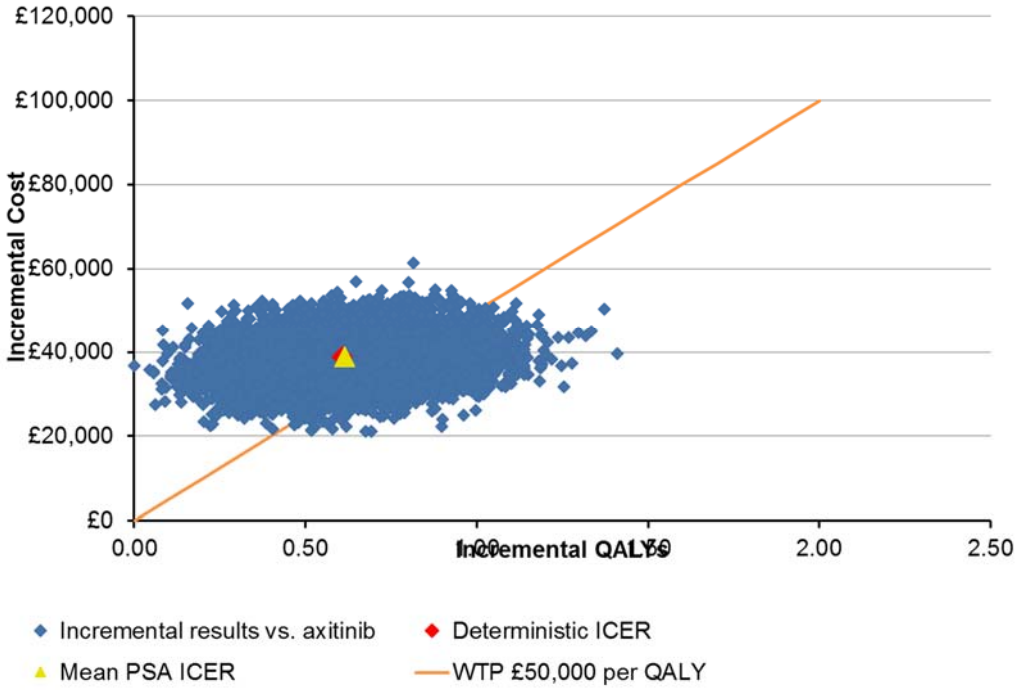

Figure 4: PSA scatterplot, nivolumab versus axitinib, interpretation of committee's preferred analysis, with PAS

[redacted]

Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay

Table 3: Mean probabilistic base case results, pairwise comparisons, interpretation of committee's preferred analysis, without PAS

	Total costs	QALYs	Life Years	Incremental, Nivolumab versus comparator			ICER
				Costs	QALYs	Life Years	
Nivolumab	£91,836	2.33	3.47				
Axitinib	£53,148	1.72	2.62	£38,689	0.61	0.85	£62,932
Everolimus	£40,818	1.72	2.62	£51,018	0.61	0.85	£82,988
BSC	£11,273	1.16	1.76	£80,563	1.18	1.71	£68,475
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year.							

Table 3: Mean probabilistic base case results, pairwise comparisons, interpretation of committee's preferred analysis, with PAS

	Total costs	QALYs	Life Years	Incremental, Nivolumab versus comparator			ICER
				Costs	QALYs	Life Years	
Nivolumab	[redacted]	2.33	3.47				
Axitinib	£53,148	1.72	2.62	[redacted]	0.61	0.85	[redacted]
Everolimus	£40,818	1.72	2.62	[redacted]	0.61	0.85	[redacted]
BSC	£11,273	1.16	1.76	[redacted]	1.18	1.71	[redacted]
Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, Patient Access Scheme; QALY, quality-adjusted life year.							

3.24 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

Table 4 shows results from scenario analyses varying key assumptions in the base case key comparison to axitinib, with and without the PAS for nivolumab, and is analogous to Table 73 of the CS.

Table 4: Scenario analysis results, interpretation of committee's preferred analysis, with and without PAS

Parameter	Base case	Scenario analysis	Nivolumab vs Axitinib ICER, without PAS	Nivolumab vs Axitinib ICER, with PAS
BASE CASE			£63,908	[redacted]
Discount rate (costs and utilities)	3.5%	6%	£69,140	[redacted]
Discount rate (costs and utilities)	3.5%	0%	£56,026	[redacted]
Time horizon	30 years	20 years	£65,009	[redacted]
Time horizon	30 years	25 years	£64,223	[redacted]
Time horizon	30 years	35 years	£63,783	[redacted]
OS NMA analysis choice	Crossover-adjusted	ITT	£63,908	[redacted]
OS curve choice	Generalised Gamma	Exponential	£68,857	[redacted]
Vial sharing	No	Yes	£59,567	[redacted]
Nivolumab survival benefit	No immuno-response effect	Include immuno-response effect	£25,066	[redacted]
Health state resource use	TA 333 assumptions	Clinician estimates	£62,001	[redacted]
Subsequent treatment costs for nivolumab	As per CHECKMATE-025	Equal to everolimus	£65,889	[redacted]
Axitinib utility source	AXIS patients	TA 333 historical estimates	£61,295	[redacted]
Axitinib utility source	AXIS patients	025 Trial everolimus patients	£63,908	[redacted]
AE utility decrements	Exclude	Include	£63,886	[redacted]
Average patient weight	025 Western European patients	IPSOS UK estimate	£52,893	[redacted]

Key: AE, adverse event; BSC, best supportive care; ITT, intention to treat; NMA, network meta-analysis; OS, overall survival, PAS, Patient Access Scheme; TA, Technology Appraisal

3.25 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

3.26 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

We believe this has been covered in our responses to Sections 4.7 to 4.11.

4 Appendices

4.1 Appendix A: Additional documents

4.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Response

4.2 Appendix B: Details of outcome-based schemes

4.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Response

4.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Response

4.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Response

4.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Response

4.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Response

4.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Response

4.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the

additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Response

4.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

4.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Response to the Nivolumab ACD.

Dear NICE,

Kidney Cancer UK and the former charity The James Whale Fund for Kidney Cancer have supported patients with kidney cancer for over 10 years and have seen first-hand how the current first and second line treatments often fall short for people with metastatic renal cell carcinoma. Commonly, people become resistant or intolerant to tyrosine kinase inhibitors and are then left without options. The clinical trials for axitinib and everolimus (the alternative 2nd/3rd line treatments) did not show significant improval in overall survival in the pivotal randomized trials that tested them [1] [2]. There is a huge unmet need to offer another, very different option to people with metastatic renal cell carcinoma.

Nivolumab offers hope to patients in this situation because it acts via a very different mechanism. After 1st line treatment failure doctors currently can only offer another tyrosine kinase inhibitor (TKI) which might give more of the same side effects and/or probably won't work as well because they will have already had a drug which works by a similar mechanism. Kidney Cancer UK strongly feel that nivolumab will offer hope and another very different option for these patients. Nivolumab acts on different receptors and pathways to TKI's and it works by enhancing the body's own immune system rather than inhibiting angiogenesis or tumour growth itself. It is a completely different way of attacking a tumour, which might work extremely well for some people. We don't understand why the chance to try this mechanism of attacking tumours would not be available for people with very little other options.

When nivolumab works for patients the results have shown that they are long lasting. Earlier phase nivolumab trials (phase 1 and 2) have shown that a third of patients are still alive 4-5 years later. [3] As with many medicines, there may be groups of patients that respond to certain drugs and not others, it seems unfair to deny the group that might respond well that chance.

Nivolumab has been recommended for use in patients with metastatic melanoma for both 1st and 2nd line use. The two-year survival of patients with melanoma treated with nivolumab is around 50% [4] which is very similar to the two-year survival seen in the 025 trial for renal cancer patients. It therefore very likely that the survival curve for the 025 trial will mirror that seen with nivolumab in melanoma with a plateau in survival appearing at around 35%. This has been shown in the earlier phase trials in advanced renal cancer as described above. [3]

We have heard positive things from patients who have received nivolumab as part of a clinical trial. Dr Fran King took nivolumab as a third line treatment as part of a clinical trial. He has shared his experience as a recorded interview on our website blog. The medicine gave him great hope, his tumours have shrunk and nivolumab is currently working well for him. To view this interview please follow this link: http://www.kcuk.org.uk/patient-consultant-experience/. Kate Fife, Dr Fran Kings oncologist at Addenbrookes Hospital, Cambridge also describes how well nivolumab is tolerated by patients.

Kidney Cancer UK feel strongly that there is a need for an alternative 2nd or 3rd line treatment which acts via very different mechanisms to TKI's. The NICE approval of nivolumab would mean that patients would have access to three lines of therapy, which would improve survival rates.

After we heard that nivolumab might not be recommended following the first committee meeting, Kidney Cancer UK launched a petition in support of nivolumab being recommended, almost 1000 people signed it in the first 2 days. Many of our supporters have been waiting for good news about the NICE recommendation of nivolumab and we hope that they will not be disappointed.

Yours sincerely,

[redacted]

References:

1. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Motzer RJ et al. Lancet Oncology 2013; 14: 552–62.
2. Phase 3 Trial of Everolimus for Metastatic Renal Cell Carcinoma: final results and analysis of prognostice factors. Motzer RJ et al. Cancer 2010; 116:4256–65.
3. McDermmott et al, 2015. Survival, durable response and long term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. Journal of clinical oncology. ASCO. 33: 1-8
4. Durable, long-term survival in previously treated patients with advanced melanoma (MEL) who received nivolumab (NIVO) monotherapy in a phase I trial
   Hodi FS et al: AACR Annual Meeting April 2016 abs. CT001

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Response to the Appraisal Consultation Document: Nivolumab for previously treated advanced or metastatic renal cell carcinoma [ID853]

Kidney Cancer Support Network Statement

The NICE technology appraisal committee have not recommended nivolumab for use within its marketing authorisation for the treatment of advanced renal cell carcinoma (RCC) patients after failure of prior systemic therapy. This is despite nivolumab's proven effectiveness at prolonging the life of kidney cancer patients by 5.4 months compared to everolimus in the CheckMate-025 trial, and the survival data from the earlier phase I and II clinical trials (CheckMate-003 and 010) where about one third of patients are still alive after 4+ years.

The Kidney Cancer Support Network's response to the nivolumab ACD has been informed by the views of advanced kidney cancer patients who are taking nivolumab as part of a clinical trial or through the Early Access to Medicines Scheme (EAMS) in the UK.

1. Innovative, breakthrough therapy

Nivolumab has been proven to be a clinically effective and well-tolerated drug, and **designated a breakthrough therapy by the FDA for the treatment of advanced or metastatic RCC**. As a breakthrough therapy, nivolumab has been fast tracked for approval in a number of countries, and was previously approved for use under the Medicines and Healthcare products Regulatory Agency (MHRA) Early Access to Medicines Scheme (EAMS) in the UK.

Nivolumab is the first in a new class of immunotherapy drugs, and is already available in North America and Europe for advanced RCC. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that immunotherapy drugs are made available to patients in order that they have the best possible care. If immunotherapy drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. A contributory factor to poor survival rates in the UK is possibly due to the restrictions in clinical choice brought about by UK regulatory authorities.

The committee's decision to not recommend nivolumab for advanced RCC patients after failure of prior systemic therapy, denies terminally ill kidney cancer patients access to innovative and effective treatment through NHS England, despite the drug being available for melanoma patients living in England, and kidney cancer patients living in other European countries. This is confusing for the patient community because the committee has acknowledged the fact that nivolumab meets the end-of-life criteria, but recommends the drug as not a good use of NHS England resources. The committee does not attempt to explain how they reconcile these two positions to those affected by their decision.

2. Prolonged survival

The phase I and II clinical trials (CheckMate-003 and 010), which were conducted in North America, Finland and Italy, provide compelling evidence for the long-term survival of advanced RCC patients after treatment with

nivolumab in the second-line or later setting. The five-year survival rate is 34% after treatment with nivolumab in CheckMate-003, and 29% of patients treated with nivolumab in CheckMate-010 are still alive at 4 years. Although the committee acknowledge these findings, the ACD states the committee agreed 'it was implausible to assume that more than a few people would live to 5 years' since only 15% of patients were receiving nivolumab after 2 years in CheckMate-025. This is merely the opinion of the committee and is not evidence-based, and the Kidney Cancer Support Network, together with the patient community, are disappointed that the long-term survival data from the earlier clinical trials is dismissed out-of-hand in the ACD. In this instance, the Kidney Cancer Support Network consider the committee did not take all available evidence into account when arriving at their preliminary decision not to approve nivolumab.

The phase I and II clinical trials in RCC point to a significant minority (about a third) of long-term survivors, as already seen from the melanoma data. These trials provide the longest follow-up reported to date with any PD-1/PD-L1 agent in advanced RCC. They also provide evidence to show that long-term survival is achievable regardless of risk group, performance status, or best overall response.

NICE have already approved nivolumab for the treatment of advanced melanoma patients in both the first- and second-line setting. Clinical trials with melanoma patients show a two-year survival rate of around 50%, which is very similar to the two-year survival seen in CheckMate-025 with advanced RCC patients. It is, therefore, very likely that the survival curve for CheckMate-025 will be similar to that seen with nivolumab in melanoma, and will plateau with survival at around one third of patients, as already seen in the phase I and II clinical trials, albeit in small patient populations.

Bearing this in mind, if the committee is minded not to approve nivolumab, the **Kidney Cancer Support Network urge NICE to reconsider nivolumab for the new Cancer Drugs Fund (CDF) while further survival data are collected from the CheckMate-025 trial** to provide evidence for this prolonged survival effect in advanced RCC patients. With less than 4,000 patients diagnosed with advanced RCC per year, this disease is designated a rare cancer. This should be considered when setting time limits for the collection of survival data, and the 24-month period for collection of addition evidence specified in the ACD (and the CDF SOP) to be extended for this small patient population.

The phase I and II clinical trials in RCC did not take place in the UK; however, the following is a statement from one of the original North American patients who took part in the early clinical trials with nivolumab, and has survived 4+ years with limited toxicity and no disease progression.

> *"When I began treatment I was in a state of helplessness. The abdominal tumour was located in such a position that it was growing so fast and caused so much pain I was unable to function. I was taking very high doses of Opiate pain medication with the result that I had no appetite and combined with side effects of Sutent my weight dropped to 139 pounds from 210 pounds. I lost large amounts of muscle. As a result I was eventually confined to a wheelchair. I was unable to carry out even basic tasks and from being a very physically strong man who was very active and worked on my small ranch, I could do nothing for myself. I was very ill; I was told I had about 12 months to live. Tumours were growing aggressively.*
>
> *Response to Nivolumab: complete response. All tumours completely disappeared very rapidly after the first four infusions [of nivolumab]. [I had no side effects] for the first 74 infusions. After several years and following infusion number 75 the following side effects commenced. Inflammation in most joints causing pain, inflammation in lungs causing symptoms of asthma, shortness of breath, fatigue. Lung inflammation is well controlled with Prednisone. Joint pain is well controlled with Gabapentin.*
>
> *In about two months of commencing treatment, the pain began to subside and very shortly ceased completely. This was the first indication Nivolumab was working. The improvement in my quality of life was immediate and profound. I could walk again, I could eat again, I had energy again, all of which have continued to the present day even with the recent appearance of side effects, the effects of which are minimal on my quality and enjoyment of life. Obviously the change in my health has impacted the life of my wife. I can now care for myself in every way and be a help to her. I am no longer dependent on any one. I can put in a full day of hard physical work on the ranch on all but the day following treatment."*

Nowadays, kidney cancer patients do not exist in silos. They communicate widely; international discussion forums exist where patients talk to one another daily. An international coalition of patient organisations (www.ikcc.org) currently has 22 member countries. IKCC has published and maintains a very informative website, which brings

together information about immunotherapies to patients around the world (www.10forio.info). Patients and clinicians are right to expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so they have the same choices as patients in other countries.

3. Clinical effectiveness

The Kidney Cancer Support Network and our members are confused as to why nivolumab can be approved for use on the NHS for advanced melanoma, but not for advanced RCC. Nivolumab was approved for melanoma based on progression-free survival (PFS) data, which does not carry as much weight as overall survival (OS) for cancer patients. PFS is often used as an alternative to OS, which is seen as the most reliable endpoint in clinical trials. Nivolumab has shown convincing OS improvement in advanced RCC patients in all three clinical trials to date (CheckMate-025, 003 and 010).

Furthermore, the hazard ratios for the RCC data are higher than those for melanoma, which are very low. However, the comparative arm in the melanoma trials is chemotherapy, which is a fairly ineffective treatment. The comparative arm in the RCC trials was everolimus, which has been proven to be relatively effective in the second-line setting. Therefore, the hazard ratios for the melanoma data are bound to look good when compared to the RCC data.

In the opinion of the Kidney Cancer Support Network, **the data for the RCC patients are not substantially different to those for the melanoma patients, and do not warrant a negative recommendation while the melanoma data results in a positive recommendation**. We would like to know why these two tumour types are being treated differently, and kidney cancer patients are being disadvantaged. This could be seen as demonstrating inequality in the use and interpretation of the STA process against kidney cancer patients. The Kidney Cancer Support Network considers the committee failed to assess the potential disadvantage to kidney cancer patients when arriving at their preliminary decision not to approve nivolumab.

4. Safety, tolerability and quality of life

CheckMate-025 shows that nivolumab is better tolerated than everolimus, where only 19% of nivolumab patients reported grade 3-4 adverse events compared to 37% in the everolimus group. Furthermore, most treatment-related adverse events occurred within the first 6 months of treatment, whereas everolimus toxicity continued throughout treatment. Treatment-related adverse events leading to discontinuation of therapy occurred in 8% of nivolumab patients and 13% of everolimus patients. **We do not believe the ACD places sufficient value on the importance of the patient experience and quality of life issues** when comparing nivolumab with everolimus or axitinib.

We are also aware anecdotally that nivolumab appears to improve quality of life and is better tolerated than tyrosine kinase inhibitors, such as axitinib. The following patient statements are proof of this fact:

> *"Whereas the side effects from sunitinib were bearable I found that for axitinib these were definitely not. Although I was on a minimum dosage over a 12-month period from April 15 I lost 25 kg as I couldn't eat or drink. I also suffered from severe tiredness and upset stomach ....basically the drug was much too toxic and was killing me. Within 2 weeks of stopping axitinib I was back to normal with eating and drinking and living a more normal life style. I have yet to show any side effects from Nivolump [sic] although I still need to go to bed earlier than I used to do! I have only had 8 iva sessions so side effects maybe lurking around the corner! Long may they lurk!"*
>
> *"I've had 4 infusions so far and the difference in the treatment is incredible. I've had no side effects and feel like my quality of life has improved immensely. My father passed away last year of the same cancer, so to have this drug available now for people like me has given me, my family and friends so much positivity and excitement about the future of cancer treatment."*
>
> *"….. my husband started on Axitinib. We had hoped this drug would work well but the treatment was stopped …. when my husband developed severe sepsis. We were extremely fortunate that this happened when Nivolumab became available under EAMS. Axitinib caused severe side effects for my husband and at times he was unable to eat or walk. Axitinib caused diarrohea, severe blistering to feet and mouth and we had to seek help from a chiropodist to try and enable him to walk but even she couldn't help him. In all my husband lost 5 stone in weight during his time on TKIs. Since his starting on Nivolumab, my*

husband's health has improved dramatically, he eats well and has started to put on weight again. Even though he is 66 years of age he works 5 days a week and now can enjoy his pastime of fishing on Saturday and Sunday. My husband has a very strong character but even he struggled with the side effects of Axitinib. Even though Nivolumab is a very expensive drug hopefully there will be a reduction in costs of prescribing medication for side effects. I do not want any Kidney Cancer patient to die because of cost when we have a potentially life changing drug on the horizon."

The following statement is from a patient currently on nivolumab in the third-line, but who also has experience with both pazopanib and everolimus. This statement provides anecdotal evidence of the improved tolerability of nivolumab compared to everolimus:

"I was on pazopanib …… when my oncologist determined that it was starting to fail. At that point I was advised that everolimus was to be made available to me …….. Initially side effects were minimal, however about a month [sic] I started to get very bad mouth ulcers, which took a few weeks to clear up, fatigue and tiredness. Also experienced anaemia and had 2 blood transfusions. I suffered from nosebleeds, mainly when blowing my nose! Lung condition didn't help and was experiencing dry cough and breathlessness as well. Experienced lots of indigestion also had mild doses of feeling shaky and shivery. Ct scan showed that everolimus was struggling and the decision to try for Nivolumab taken in Feb/March 2016……This new drug has enabled me to lead as normal a life as possible; side effects have been minimal although I have lost some weight (around 6lbs). I do have some itchiness on lower legs and arms but this is dealt with by taking standard over the counter antihistamines. I am finding Nivolumab kinder on my system than Everolimus previously."

From the evidence we have gathered from the Kidney Cancer Support Network group of advanced RCC patients currently taking nivolumab through EAMS, it appears that this drug allows patients to lead a relatively 'normal' life and, in a lot of cases, patients can return to work, resume family life, and contribute socially and economically to their communities.

"The hope this has given me, and my family, is one of the greatest medicines in its own right, to enhance the quality of my life. The reduced overall side effects enable me to continue working full time, and to have a good quality of life…… the biggest side effect of metastasised renal cell carcinoma is death, from where I am sitting there is nothing to lose and much to gain. We understand that cost is one of the biggest barriers to the general use of Nivolumab, and other immunotherapy drugs. Here I must point out the glaringly obvious, barring a miracle, it is extremely unlikely that I will ever draw my state pension. I see no economic or ethical reason why those funds to which I have contributed to for the whole of my working life, cannot to be used to enhance and extend the remaining few year so [sic] my life. The extra years, which the drugs give me, enable me to carry on working, using the accumulated knowledge and experience, gathered through my working life, for the benefit of the various farming enterprises which I manage……..I'm making a hugely positive contribution to society, and the wider economy, and I wish to be able to carry on with this and more importantly to ensure that others, whatever their circumstances, will have the same opportunities."

"Back home yesterday and took my GSXR1000 out for a 3 hour ride. Life's just amazing right now and if nothing else, following years of TKI's, Opdivo nivolumab has given me my life back……. My personal opinion is that Opdivo Nivolumab should be immediately available for all cancer patients where experience shows that this is of benefit …… my experience is that Nivolumab far exceeds the two prior systemic therapies and certainly in terms of energy and moral. Further, I know for a fact I would not have been able to undertake any work whilst on TKI's but definitely under Nivolumab. As a cancer patient…….. I am pleased to confirm that Opdivo Nivolumab has brought me back from the brink of death, able to regain my life."

5. Choice of treatment and unmet need at third line

In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatments for individual patients from those available, and **without nivolumab, the clinician's choice of treatment is seriously compromised**. Without treatment alternatives in the second- and

third-line, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.

Current second-line treatment options are not effective for everyone, and can be difficult to access. Undue restrictions in accessing nivolumab would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the second-line and a potential choice in the third-line setting would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient. Nivolumab will also address the massive unmet need for treatment options in the third-line.

6. Cost effectiveness

We are disappointed that **yet again another drug for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare cancer):** Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life-prolonging treatments during a desperately difficult time for both themselves and their families.

We understand that nivolumab is expensive, and we appreciate the budgetary implications, but nonetheless NICE and the manufacturers must negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as failure of professional competence. NICE and the manufacturer need to think outside the box to agree an alternative funding scheme, and work collaboratively to negotiate an acceptable patient access scheme to ensure kidney cancer patients who need it can have access to this latest clinically effective drug.

7. Effect of NICE's decision on UK clinical research

As we mentioned in our original statement for this STA, we are concerned that NICE's decision not to recommend nivolumab may negatively impact the clinical research environment in the UK. Patients who participated in UK clinical trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of nivolumab on the NHS in England, we must question whether patients will continue to support future research by taking part in clinical trials.

Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if NICE fail to allow these drugs to get to the patients who need them. A rejection of nivolumab will mean that a substantial number of late stage kidney cancer patients will be denied the opportunity to benefit from the new era of clinically effective immunotherapy drugs.

Thank you for allowing the Kidney Cancer Support Network and our nominated patient experts to take part in this single technology appraisal. We welcome the opportunity to put forward the views of our Kidney Cancer Support Network patient community for this important health technology appraisal of nivolumab in advanced or metastatic renal cell carcinoma, in particular the large group of patients currently benefitting from nivolumab who are witnessing at first hand the very real and positive impact of this drug in the treatment of their disease.

Best regards

[redacted]
Kidney Cancer Support Network
Web: www.kidneycancersupportnetwork.co.uk
Email: [redacted]

Consultees & Commentators: Renal cell carcinoma (metastatic, treated) - nivolumab [ID853]

Additional comments from KCSN members

1) Statement from mRCC patient [redacted].

Hi [redacted],

I'm going to attempt to write something that I hope you are ok to send for me as technical difficulties here on holiday in Portugal .

"I'm not clever with words but here goes. Hope is at the core of every cancer patients life. Hope there will be a tomorrow, hope there will be time to watch children grow and hope that your life doesn't have a limit to its worth. Nivolumab has been my hope and I was absolutely distraught when I heard the decision that in the case of kidney cancer, it was felt it wasn't cost effective although it was clinically effective. A price on all that I am has been set. I feel I along with others, deserve the very best available care and a chance to live. It means everything and right now my heart is broken. Surely the ongoing care and the tki's offered now would cost a considerable amount over several years. Nivolumab could cure in some cases. I am so sorry to write this way but it is definitely issuing a death sentence for some of us. We deserve better. If there were, for instance, several of us kidney cancer lined up and you said shoot 2, there would be an outcry. This is no different. Please reconsider and approve nivolumab. It means everything.

[redacted]

2) Statement from mRCC patient [redacted] (currently on holiday but wishes to comment)

We are away at the moment but would like to ask you to pass the following comments to N I C E in support of nivolumab. We don't feel that N I CE has taken full account of the tremendous difference in the quality of life issues – and that matters hugely to patients like me who want to carry on working and providing for their families. Sutent has worked well for me with minimal side effects which is fantastic for the short term but the distress this issue about nivolumab and the preliminary refusal not to provide funding for NHS patients like me, has caused both me and my wife huge stress. Coupled with the point made about depression and not being able to have future responsibility for my family's financial security if I cannot continue to work, has caused my wife and I unprecedented on-going clinical depression Add to this the severe anxiety about our future as a family and you can see how cancer and potential lack of effective treatment invades every part of our life. To have the certainty of clinically effective drugs being made available to me when this TKI fails is priceless to me and my family and must be taken into account.

I am still working full time although some days this is difficult; I am paying my dues earning money so I do not have to rely on the state. I do not expect the state to pay for me when I can provide for myself, but I do expect to be treated fairly, it is beyond belief that this organisation has the power to condemn me to a premature death by not providing the best possible care while providing the same drug to other cancer patients. This is not only my life but my loved ones lives and their futures on the line and I don't see this has had any value placed on it in the N I C E papers they have released and it needs to be taken into account. Carers and families seem unvalued by this cancer drugs process.

[redacted].

3) Statement from mRCC patient [redacted]

I just want to supplement the patient views with my own comments.

As a kidney patient I feel very strongly that all patients should have equal access to the best possible treatment no matter where we live, especially as NICE themselves accept Nivolumab as clinically effective. The drug is available in other countries and if we want to see survival rates in the UK improve (as they are poorer than other parts of Europe), then we need the best drugs. I also feel strongly that patients in the UK should not be disadvantaged.

Nivolumab is an innovative therapy with which I am aware that many patients worldwide are achieving excellent results. I am also aware of the recent updated reports to the American Society of Clinical Oncology, which showed that a third of patients were alive 5 years after treatment initiation on Nivolumab and believe that this data should be assessed when making comparisons to other drugs. Why should we be penalised?

Not being able to access new drugs is making the UK lag in cancer care for renal cell carcinoma.

We are all aware that having a terminal illness causes depression to patients and our families, but having access to Nivolumab would help us to know that all reasonable steps had been taken for our survival.

Alternative drugs are similar in their action and immunotherapy offers hope for a response in patients who haven't had success on other drugs.

Please understand that the quality of life on Nivolumab seems to be much better in terms of the side effect profile. I am aware that many patients have been able to return to work and exercise after starting Nivolumab.

I do however accept that this is still a newer drug and that data is still being collected on its overall impact on survival, but I feel it is important that NHS patients can benefit from the treatment immediately and that data is collected to reinforce its efficacy.

[redacted]

Ends.

East and North Hertfordshire NHS
NHS Trust

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18/7/16

To: NICE Appraisal Committee

Re: RCP/ACP/CSG Comments on NICE ACD – Nivolumab for Previously Treated Advanced Renal Cell Carcinoma

We believe the committee have inadequately taken into consideration the mode of action and resulting durable benefit of immunotherapy in advanced RCC.

1. The committee state that (4.5) "the committee was aware that trials which stop early because they show a benefit tend to overestimate the size of the treatment effect". This statement is inaccurate for immunotherapy agents where, in fact, the converse is true. Because a group of patients experience durable benefit, early analyses do not capture this benefit.

2. The committee state (4.5) "it was not clear whether the patients in these trials were like those in the NHS". The committee did not ask clinical experts whether patients in the 003 and 010 studies were representative of UK patients at a similar point in their disease. For the committee's information they will be representative of the UK population.

3. The committee state (4.5) "when median survival with nivolumab was just over 2 years (25 months; see section 4.5), it was implausible to assume that more than a few people would live to 5 years". In our view this statement reflects the fact that the committee have not adequately appreciated the fact that there are many examples of immuno-oncology agents in which the median survival bears little relationship to the fact that a significant proportion of patients (many more than a few) would be expected to have durable benefit. Indeed, if the plateau of patients experiencing long term survival is anything under 50%, the median will not reflect their benefit.

   We refer the committee to the ipilimumab meta-analysis data in melanoma – the data set for which there is longest follow-up data available (attached). You will note that the median OS is 11.4 months (ref attached), but because of the shape of the survival curve

the vast majority of patients alive at 3 years are also alive at 5,7 and 10 years. The 003 and 010 studies have less mature follow up data but demonstrate a similar shaped curve.

The precedent for immunotherapy induced long term durable remissions in Renal Cancer was established with high dose Interleukin-2 (IL-2). IL-2 never became a standard of care due to a combination of toxicity and low response rates. Many of the minority of patients who had responses however experienced durable responses lasting more than 10 years (Klapper et al).

There is therefore a) precedent in RCC that immunotherapy can induce durable long term benefit b) evidence from other cancers that immune checkpoint inhibitors can induce long term benefit c) evidence for clinical activity with nivolumab in RCC from the 025, 010 and 003 studies in which there is emerging evidence that the survival curve is that which is expected with immunotherapy – that a significant group of patients will experience long term benefit.

The committee's view that "it was implausible to assume that more than a few people would live to 5 years" is, in fact, implausible.

4. The committee state (4.10) that "Number of previous treatments: CheckMate 025 recruited patients who had had 1 or 2 previous treatments, while the other trials recruited patients who had only had 1 previous treatment". This is inaccurate. The RECORD-1 study included patients who had more than 1 prior treatment.

5. The committee and the ERG have overstated the importance of subsequent treatments on outcomes for patients participating in the TARGET, AXIS, RECORD-1 and 025 studies. The reality is that those third and fourth line treatments available at the time of conduct of the studies will have had a negligible impact upon survival. The ERGs view that the benefit of axitinib is underestimated is inaccurate.

6. The committee's approach that "The committee concluded that the company's scenario assuming better long-term survival with nivolumab was not based on evidence, so it preferred to use trial data to estimate survival as had been done in the company's base case and the ERG's base case" resulted in the selection of models that a) do not represent the shape of survival curves seen with active immunotherapies (see 3 above) and b) therefore result in the selection of curves that are highly unlikely to represent reality. The committee's approach means that it is highly likely that their assessment will be based on assumptions that do not reflect reality.

Dr. Paul Nathan MBBS, PhD, FRCP
Bladder & Renal Cancer NCRI CSG co-chair
Consultant Medical Oncologist

Ref:

Schadendorf et al, Pooled analysis of long term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. JCO 2015, **33** (17) 1889

Klapper et al, High-dose Interleukin-2 for the treatment of metastatic renal cell carcinoma. Cancer 2001 **113** (2) 293

Name	Jon Birchall
Role	Patient
Location	England
Conflict	
Comments on the ACD:	
Eighteen months ago I was told that my situation was hopeless and my life expectancy was likely to be 2 to 3 years. After 3 months on Nivolumab I have stable disease and am still in full time work as the side effects are so minor. This drug is of imense value to we kidney cancer patients , for whom hope is a rare comodity. There is no other comparable drug with such a low toxicity profile which has the potential to hold this terrible disease at bay. It is imperative that we find a way to make the drug available and to find out which patients it can help.	

Response of Alison Fielding (patient expert) to NICE recommendation on Renal cell carcinoma (metastatic, treated) - nivolumab [ID853]

I am obviously disappointed at the draft recommendation of the Committee. The decision has caused much upset in both the patient and clinical communities. Advanced Renal Cell Carcinoma patients are typically fatigued and find it difficult to respond to consultations such as these which are by their nature very technical and economically driven. Some have responded to the decision directly to you and others have added their names to the Kidney Cancer UK petition. The latter may not be the right channel but it is all many people can manage. I hope that you can consider the strength of the patient view even at this stage.

I believe that there would be a complete loss of faith in the NICE process in evaluating break through treatments if this decision stands. Numerous clinicians had been talking about it to patients as a next option and the withdrawal of this hope is difficult to cope with. Many patients nowadays have access to world wide data on treatments and have followed the ASCO reports and recent papers on overall survival of a third at 5 years. (Copy of presentation also attached.)
TKIs like Sutent, Pazopanib and Axitinib are hard going for patients. In the absence of better treatments they are welcome as they extend the length of lives. Immunotherapy drugs offer an opportunity to extend the length and the breadth of life.

I accept that there were not direct trials comparing Axitinib and Nivolumab and but still feel that the right course of action is to commission Nivolumab - if not as standard commissioning, it should be available as an option to clinicians via the Cancer Drugs Fund and outcomes monitored appropriately.

In terms of the the ICER values, I hope that an agreement can be reached with BMS to bring the cost within range. I may not be able to work out an ICER but I do know that 60% of £1 is worth more than 0% of £10.

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Organisation	University Hospitals Birmingham
Location	England
Conflict	N/A
Comments on the ACD:	
Dear Committee, I am writing this comment in support for the Nivolumab application to highlight the following, based on the published results of the CHECKMATE 025 trial: 1. Patients on Nivolumab achieved a response rate of 25% following failure of antiangiogenic agents. 2. In the subgroup analysis for overall survival patients with poor and intermediate MSKCC risk score and those with 1 previous line of antiangiogenic agents benefited from Nivolumab. 3. PD-L1 expression is not a useful predictive biomarker 4. Nivolumab was well tolerated with few G3/G4 toxicities, mainly fatigue and nausea. My conclusion would be to offer Nivolumab in patients with intermediate and poor MSKCC risk who progressed on 1st line antiangiogenic treatment. I would ask the company to contribute to a prospective research project of using genomic profiling to identify a mutational signature that will predict response. Until the point of defining a reliable predictive biomarker the company should reimburse the NHS the cost of the drug for non-responders.	

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	
I am really worried about the initial decision by NICE. As a kidney cancer patient aged 44 and with two young children to support, I feel that Nivolumab would give me, and many others, a chance to extend our lives and for me personally to support my children growing up. Renal cancer is incredibly difficult to detect until it has metastised and so a lot of people like myself have to face up to a very difficult battle. I urge you to reconsider.	

Name	[redacted]
Role	Public
Location	England
Conflict	No
Comments on the ACD:	
Whilst not an expert surely the option of this treatment can benefit those who effectively need it -	

any benefit has to be worthwhile

Name	[redacted]
Role	Relative
Location	Europe
Conflict	N/A
Comments on the ACD:	
I'm concerned the NHS spends money on cosmetic surgery and tummy tucks, yet a potentially life saving drug for a very difficult to detect cancer is declined. I struggle to comprehend why beauty is more important than the beauty of life. My relative is 44 year old and has two small kids. He should not be denied the chance to spend more precious time n with them. It's to think that someone played God with their chance of living and declined declined this new treatment. The problem is not just a person dying, but the suffering caused to hundreds of people around that person. M	

Name	[redacted]
Role	Carer
Location	England
Conflict	N/A
Comments on the ACD:	
Please reconsider your decision to not make this drug available on the nhs. If it could extend the life of my children's father by a few years then it would make such a difference to us. We have two boys aged 8 and 11 who are too young to lose their dad at only 44 to advanced kidney cancer.	

Name	[redacted]
Role	Public
Location	England
Conflict	No
Comments on the ACD:	
I feel that there is an unmet need for patients with advanced kidney cancer and that these patients need more drug options especially for drugs that work in a different ways and offer hope if people become resistant to current medication. this drug provides that choice/hope.	

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	
Why nivolumab would be recommended by NICE recently for use in skin cancer but not for advanced kidney cancer, and as such, what are the reasons behind this initial recommendation to be published. The drug has shown great promise in both diseases, it is our understanding that the price of the drug is the same in both cases and the number of people who would benefit from this drug is similar.	

Name	[redacted]

Role	Carer
Location	Europe
Conflict	No
Comments on the ACD:	
There is finally some hope for life to be saved, yet -for some reason, someone had the power to decide the fate of others and deny new treatment to those who are desperately hanging on to hope to see their children grow, to enjoy a few more years with the loved ones. This treatment must go ahead- for the love of live! As evidence suggests in the links below, other countries value the life of their citizens: http://www.agenziafarmaco.gov.it/it/content/attivazione-del-registro-opdivo-05072016 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/02/news_detail_002478.jsp&mid=WC0b01ac058004d5c1 Does it mean that UK citizens are treated as second hand patients?	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Location	England
Conflict	No
Comments on the ACD:	
Disease progression after 2 lines of treatment in patient with RCC is an unmet need. Majority of patients are unfit for even second line TKI due to poor performane status and significant toxicities from 1st line TKI which preclude going on with 2nd line of same class of drugs. But there is a small group of patients who sadly have progressed through both the lines of TKI and still very fit and these group of patients will substantially benefit from having access to Nivolumab. The appraisal has rightly highlighted the improvement in overall survival at the cost of minimal side effects. The argument that "substantial uncertainty about the extent of the survival benefit when measured over the long term" is not very correct given the short period of follow up to accumulate this data. Previous trials with immunotherapy drugs in other cancers have shown long term survival benefits which could be extrapolated to patients with RCC and probably in time this will become apparent on futher follow up data from CHEKMATE025. I have treated patients with Nivolumab under early access medicines scheme and have seen significant improvement in patients QoL and survival which they wouldn't have benefited without this drug. I would request the appraisal committee to further review its decision. And if Nivolumab could not go onto routine commissioning then it has to be at least considered under CDF. Such patients as those who could benefit from this are a small cohort.	

Name	[redacted]
Role	Carer
Location	England
Conflict	No
Comments on the ACD:	
I appreciate that kidney cancer has 2 lines of treatment already, but these treatments are older and the Nivoluamb is a new type of therapy which a lot of cancer patients in the uk are being denied. We have to give these drugs a chance to see the real effectiveness of them. Clinical trial only	

portion a certain amount of people and cancer takes no prisoners in who it chooses to attack.

My husband has already received a form of immunotherapy that's been around since the 80's and for some this treatment has cured them of kidney cancer. For my husband it gained us a year of progression free survival which whilst giving birth to our first son I was eternally grateful for. Please think about the bigger picture, each cancer patient is different in every way, how thier bodies react and how well they cope, a side effect to one wouldn't be to another and people's perception of pain is very different. Cancer is a new normal that you learn to live with, and live with for a long as possible and drugs such a Nivoluamb can help people do that. Please let it be thier choice to live and spend precious time with loved ones.

Name	[redacted]
Role	Carer
Location	England
Conflict	No
Comments on the ACD:	

What I feel you have failed to address is the many people who were depending on this as a last resort. My husband is on his last chemotherapy that he can now have. Then he has nothing. You have taken away his last chance of life. Taking away memories that he could have had with his family. What cost can you put on life. What cost can you put on your loved one. How would you feel if your loved one had been denied access to this drug. I am now the one that has to explain to my family why there is no further treatment avaliable for their dad because the 'men in suits say no'

Name	[redacted]
Role	Carer
Location	England
Conflict	No
Comments on the ACD:	

My husband was accepted under the EAMS scheme because there were no other treatment options. Nivolumab was his only hope of extending his life. At 43 and with a 1 year old daughter, every single month that his life could be extended was priceless and precious to us.

You heard incontrovertible evidence from the checkmate trial that Nivolumab extends life by 6 months relative to other second line treatments. The cost is broadly comparable with TKI and other treatments and there is room for further negotiation with the drug company. Further evidence of usage around the world of improved outcomes is widely available. As well as improved outcomes there is clear evidence of better quality of life on. Nivolumab which one could argue is even more important when you are talking about extending the life of someone with an advanced cancer diagnosis and a poor prognosis relative to the general population.

For all these reasons I completely disagree with your decision to not recommend Nivolumab for approval on the NHS. It is an important development in the treatment of RCC which is still underfunded and under researched relative to other cancers. To deny a terminally ill person the opportunity of 6 more months of life at a tolerable quality level is an un acceptable decision and I cannot see your grounds for making this decision, having read through the entirety of your report. There are a range of variants of RCC that are not fully understood yet but Nicolumab has been proven to work well on a range of sub variants such as sarcomatoid RCC which responds poorly to TKI's. I urge you t reconsider your opinion and listen to the clinicians who advised you that this treatment provides an alternative treatment, the likes of which are not currently available to them to prescribe and which has PROVEN benefits in terms of 6 months of extra life and likely fewer sever side effects.

Name	[redacted]
Role	Patient
Location	Wales
Conflict	N/A
Comments on the ACD:	
Nivolumab is a innovative therapy which many patients are achieving excellent results, recent reports from American Society of Clinical Oncology show that a third of patients were alive 5 years after treatment. Not being able to access new drugs in UK lag for cancer care, having a terminal illness causes depression not just for patients but for family members. Having access to Nivolumab would help patients know that all reasonable steps are being taken for a good quality of life. Yes this is a newer drug but the impact of survival is far greater. Let's face it how would YOU feel, knowing theirs a drug that can help your survival.	

Name	[redacted]
Role	Patient
Location	N. Ireland
Conflict	No
Comments on the ACD:	

just want to supplement the patient views with my comments.

As a kidney patient I feel very strongly that all patients should have equal access to the best possible treatment no matter where we live, especially as NICE themselves accept Nivolumab as clinically effective. The drug is available in other countries and if we want to see survival rates in the UK improve (as they are poorer than other parts of Europe), then we need the best drugs. I also feel strongly that us patients in the UK should not be disadvantaged.

Nivolumab is an innovative therapy with which I am aware that many patients worldwide are achieving excellent results. I am also aware of the recent updated reports to the American Society of Clinical Oncology, which showed that a third of patients were alive 5 years after treatment initiation on Nivolumab and believe that this data should be assessed when making comparisons to other drugs. Why should we be penalised?

Not being able to access new drugs is making the UK lag in cancer care for renal cell carcinoma.

We are all aware that having a terminal illness causes depression to patients and our families, but having access to Nivolumab would help us to know that all reasonable steps had been taken for our survival.

Alternative drugs are similar in their action and immunotherapy offers hope for a response in patients who haven't had success on other drugs.

Please understand that the quality of life on Nivolumab seems to be much better in terms of the side effect profile. I am aware that many patients have been able to return to work and exercise after starting Nivolumab.

I do however accept that this is still a newer drug and that data is still being collected on its overall impact on survival, but I feel it is important that NHS patients can benefit from the treatment immediately and that data is collected to reinforce its efficacy.

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	
I would like to refer to the nivolumab data available from the USA (American society clinical oncology) showing that 1 third of patients are still alive after 5 years from starting treatment and other countries show are showing similar excellent results, I believe this data should be assessed when making comparisons to other drugs. Immunotherapy by its nature offers potential gains to patients for whom other treatments have fail or are no longer effective. I would also refer you to the lesser side effects which are observed with nivolumab allowing patients to return to a normal life includung returning to work a major, quality of life issue. I would not like to see the NHS fall behind other devoloped countries in the treatment of RCC and whilst I appreciate that this is a new drug with few trails in the country so far I believe that the evidence could be gathered whilst the drug is in use to prove its value and effectiveness.	

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	
Currently receiving HD - IL2 . Nivolumab has all the signs of a far less arduous treatment with non inpatient costs. It's been approved for other cancer types. It's been approved in Europe. It's appears to be the way forward not to approve makes nhs treatment fall behind other European countries. Immunotherapy should be promoted not held back. Let's return renal cell cancer victims back to being useful members of society my business has been on hold but now I am planning expansion. Kind regards	

Name	[redacted]
Role	Carer
Location	England
Conflict	No
Comments on the ACD:	
My dad was diagnosed in nov 2014. He is doing well but possibly facing the fact the cancer may have returned after having kindney removed due to rcc . Nivolumab is an innovative therapy that many patients worldwide are achieving excellent results. recent reports to the American Society of Clinical Oncology showed that a third of patients were alive 5 years after treatment initiation on Nivolumab and believe that this data should be assessed when making comparisons to other drugs. The stress and upset that disease brings to the lives of both patients and family members is immense !!! Knowing that there is a drug that works , (albeit small data samples at the moment)! Is the only hope some families have ! If this drug us proven to work on small samples then surely it will continue to be just as effective on larger samples !! Please approve this	

Name	[redacted]
Role	Patient
Location	Other
Conflict	No
Comments on the ACD:	

Having been diagnosed 2 years ago and so far lucky enough not to require treatment I have been following certain trials from across the water in the USA with much interest - in particular nivolumab and it's amazing success stories. As a type 1 diabetic I know that if and when I need treatment it will be a difficult thing to find a drug that won't give me side effects detriments to me and that is why I strongly believe this new drug to be a major leap forward as the side effects are minimal with some amazing results. This would certainly benefit me and many other diabetics not to mention anyone else. The lack of side effects will I believe save money in the long term and will encourage greater research in the power of immunotherapy. I sincerely hope that NICE rethink the decision and give this incredible drug the go ahead to the NHS.

Name	[redacted]
Role	Carer
Location	Wales
Conflict	No
Comments on the ACD:	

My husband, [redacted] ,was diagnosed with RCC on 3/4/13 and had his right kidney removed on 21/5/13 .He had not had any symptoms of disease and the cancer was found by accident after he had injured himself at work.

My husband was then transferred to the care of Professor [redacted] at South West Wales Cancer Centre in August 2013 to treat spread of disease.

He was firstly treated with Pazopanib which caused several side effects such as hypertension,nausea and loss of appetite.

In September 2015 my husband started on Axitinib .We had hoped this drug would work well but the treatment was stopped in February 2016 when my husband developed severe sepsis.We were extremely fortunate that this happened when Nivolumab became available under EAMS.

My argument for NICE recommendation for Nivolumab is the quality of life with this treatment and lack of side effects.

Axitinib caused severe side effects for my husband and at times he was unable to eat or walk.Axitinib caused diarrohea ,severe blistering to feet and mouth and we had to seek help from a chiropodist to try and enable him to walk but even she couldn,t help him.

In all my husband lost 5 stone in weight during his time on TKIs

Since his starting on Nivolumab ,my husband's health has improved dramatically ,he eats well and has started to put on weight again.Even though he is 66 years of age he works 5 days a week and now can enjoy his pastime of fishing on Saturday and Sunday.

My husband has a very strong character but even he struggled with the side effects of Axitinib.

Even though Nivolumab is a very expensive drug hopefully there will be a reduction in costs of prescribing medication for side effects.

I do not want any Kidney Cancer patient to die because of cost when we have a potentially life changing drug on the horizon.

Name	[redacted]
Role	Public
Location	
Conflict	N/A

Comments on the ACD:
As the father of a daughter (wiho has2 very young children and a husband) I would urge NICE to approve nivolumab at their August review meeting. The trials indicate that this drug has an improved rate of success and is being used for the treatment of melanoma and both of which were trial led at or around the same time. Please respect and accept the expert opinion in you possession that exhorts you to approve this treatment

Name	[redacted]
Role	Patient
Location	Wales
Conflict	N/A
Comments on the ACD:	
I have stage 4 renal cell carcinoma and am currently taking Pazopanib. I have been taking this for three years and four months with good results so have already beaten the odds on how it supposedly works "statistically ". However I'm under no illusions that my time on it must be nearing its end. When I heard that Nivolumab was going to be approved it filled me with a lot of hope. I've read about its good success rate and how some people have even had their tumours completely disappear and how people are so happy with how little side effects there are compared with the TKI's. If we have a drug that can work this well even if it isn't for everyone, please give us the chance to try it.	

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	
As a cancer patient who has been told I have a higher chance of my cancer returning in the future, I wish to make my thoughts on the removal of Nivolumab heard. Having a terminal illness causes depression to the patient and their family, having access to Nivolumab would help them to know that all reasonable steps had been taken for their survival. The quality of life on Nivolumab seems to be much better in terms of the side effect profile. I am aware that many patients have been able to return to work and exercise after starting Nivolumab. This is a newer drug and that data is still being collected on its overall impact on survival. It is important that NHS patients can benefit from the treatment immediately and that data is collected to reinforce its efficacy. Not allow patients access to new drugs is making the UK lag in cancer care for renal cell carcinoma.	

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	
In October 2014 I was diagnosed with Kidney Cancer, the tumour when it was discovered was the size of a honeydew melon. I had a radical nephrectomy and am, touch wood, clear. My consultant has said that he has never seen anyone with a tumour my size where the cancer hasn™t come back and reading my histology, it seems as if it is inevitable that at some stage it will come back. When I found all of that out I obviously did a lot of research and frankly the drugs on offer, whilst some have had good results, the side effects can be grim. I, like others, have followed NICE and was hopeful that Nivolumab would be considered suitable but I understand cost is a major factor. I do not feel enough studies have been done to warrant that decision when you consider that the	

recent updated reports to the American Society of Clinical Oncology showed that a third of patients were alive 5 years after treatment initiation on Nivolumab. Can you advise if this was taken into account when making your decision?

Could you look at RCC at a whole and actually look at all the drugs on offer, look at Axitinib , Sunitinib, Everolimus and now Nivolumab and see between the them which is actually the best for kidney cancer patients? Obviously it wont be a case of one drug fits all but Nivolumab seems to be that for other cancers as well.

I feel that the UK is becoming a third world country when it comes to cancer as a whole. We are years behind other countries and whilst I fully appreciate that they do not have the NHS, there should be an element of looking at what works and what is in the patients best interests. I have an 11 year old son who I want to see grow up and I am truly scared that when/if the cancer comes back, the drugs offered will make me too ill to be a proper mother and then of course sometimes the cancer can be so aggressive that neither of the two drugs work. The few people who have trialled Nivolumab are saying they were lost causes and after a few months on it, are almost back to how they used to be prior to cancer with no side effects.

Please help us.

Name	[redacted]
Role	Carer
Location	England
Conflict	No
Comments on the ACD:	
This drug should approve. As my husband was on the drug trail which this was one of the drugs he was given. His cancer shrunk by 80% and on our last visit it has now gone. If it had not have been for this drug he would not be here now. It is short sightedness as in the long run it will not on save live by money as. Please approve this drug and prolong people lives	

Name	[redacted]
Role	Patient
Location	England
Conflict	No
Comments on the ACD:	
I have advanced renal cel carcinoma and take sunitinib. I have extreme difficulties with side effects and cannot take the full dose. The metastases in my bone and organs are growing. I have had to retire from work because of the side effects and my quality of life is very poor. I am devastated to learn that this alternative treatment may not be available.	

Name	[redacted]
Role	NHS Professional
Other role	Professor of Medical Oncology & Honorary NHS Consultant
Location	Wales
Conflict	No
Comments on the ACD:	
Dear NICE, Currently there are two drugs licensed for second line use following failure of first line vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors in patients with metastatic renal cell carcinoma. These are axitinib and everolimus. Neither of these agents produced a	

significant improval in overall survival in the pivotal randomized trials that tested them1,2. NICE have only sanctioned the use of one of these namely axitinib. Even then the guidance states Because the remit referred to NICE by the Department of Health for this technology appraisal only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory funding . The other VEGFR tyrosine kinase inhibitor licensed and approved by NICE for first line use is pazopanib. This agent is equally effective to sunitinib3 and is preferred by both the patients and their treating physicians4. Because of the way the NICE guidance for axitinib is written oncologists are being forced to use the less preferred option of sunitinib as first line treatment in order to ensure that their patients get access to second line axitinib.

In the dose escalation trial of nivolumab there is longer survival data than in the 025 phase5 trial (see figure below)6. The median survival was 22.4 months but there is a plateau in survival at around 40%. This survival curve is very similar to that seen in melanoma where NICE have approved nivolumab for use in the NHS. These data suggest that a significant cohort of these patients will get sustained long term survival.

With this in mind it is therefore very disappointing that NICE have not approved nivolumab for second line use. This drug did produce a significant improvement in overall survival in both patients who had received prior sunitinib and pazopanib5. Approving nivolumab as a second line treatment would have allowed the first line use of the preferred pazopanib as well as sunitinib.

In patients with metastatic melanoma NICE have approved nivolumab for both first and second line use. The two-year survival of patients with melanoma treated with nivolumab is around 50%7 which is very similar to the two-year survival seen in the 025 trial for renal cancer patients. It therefore very likely that the survival curve for the 025 trial will mirror that seen with nivolumab in melanoma with a plateau in survival appearing at around 35%. Furthermore, NICE have approved the combination of ipilimumab plus nivolumab for the first line treatment of metastatic melanoma patients based only on response rates and progression free survival. No survival data are available for this combination. It is therefore difficult to understand why NICE have not approved nivolumab in renal cancer patients where improved response rates, progression-free survival AND overall survival are superior to a standard of care control (everolimus).

Further-more in the pivotal 025 trial patients were entered who had received two VEGFR receptor tyrosine kinase inhibitors (sunitinib/pazopanib & axitinib). As third line use it also improved overall survival. The NICE approval of nivolumab would mean that patients would have access three lines of therapy. We have previously shown the importance of second and third line treatment in optimizing the overall survival of patients with metastatic renal cancer in the real world8. Median survival was 20.9 months for those patients receiving only one line of therapy compared with 33.0 months for those who received two or three lines of treatment. It is our belief that approving the use of nivolumab would undoubtedly improve on these overall survival figures bearing in mind that third line everolimus did not impact on overall survival in the RECORD 1 trial2.

With all of the above in mind we would urge you to reconsider your decision not to approve nivolumab.

Yours sincerely,

Professor [redacted]

Consultant Medical Oncologist, South West Wales Cancer Institute, Swansea, UK

Name	[redacted]
Role	Patient
Location	England
Conflict	No

Comments on the ACD:

I have advanced renal cel carcinoma and take sunitinib. I have extreme difficulties with side effects and cannot take the full dose. The metastases in my bone and organs are growing. I have had to retire from work because of the side effects and my quality of life is very poor. I am devastated to learn that this alternative treatment may not be available.

I have registered and made a comment on the above consultation, but because the comment section did not allow for a fuller description I am also sending this email.

I am a Consultant Clinical Psychologist with the [redacted], but am writing as a patient of Dr [redacted] at [redacted]. I was diagnosed with advanced renal cell carcinoma in November and had my left kidney removed in December. I have been taking sunitinib since February this year.

I have extreme difficulties with the side effects of sunitinib, and after two weeks of taking 50mg the dose had to be reduced to 37.5. I have also changed the schedule by which I take the sunitinib. Regardless of this, I continue to get very marked side effects, particularly of fatigue and mouth ulcers. At this dose the metastases are not properly controlled and particularly the cells in the bone of my left arm continue to grow.

I have had to retire from work and return on very reduced hours because of the fatigue and because my job involves talking both to patients and staff for a large part of the day, which I can no longer do. The quality of my life is badly affected and so, I assume, is my life expectancy.

Dr [redacted] and I had started to think about the possibility of changing to nivolumab, and I was therefore extremely upset to learn from her that NICE are not including this in their recommended treatments for renal cell carcinoma. As I understand it, this means that there is no longer a real alternative to TKIs, and that my only alternatives are to continue with debilitating side effects or to step down to supportive care only.

Name	[redacted]

Comments on the ACD:

This is an appeal letter on behalf of Nivolumab. I can only speak from personal experience of a friend who was taken onto the Early Access to Medicine Scheme (EAMs) and received this drug. Jon Birchall and his wife Sarah have worked tirelessly raising money for the Kidney Cancer research fund and for Facing up to Kidney Cancer charity to help other sufferers and support early diagnosis of this terrible disease. He was given the chance of the EAMs and took it willingly. Since he started treatment in April scan results after only 6 doses of Nivolumab, over 3 months show 'stable disease'. This is fantastic news in such a short time as the last scan in March showed an increase in the two biggest lung mets by 65%. The results are proof of this treatment bringing results. Nivolumab is an innovative therapy with which you are aware that many patients worldwide are achieving excellent results. Recent evidence and reports to the American Society of Clinical Oncology shows that a third of patients were alive 5 years after treatment initiation on Nivolumab and believe that this data should be assessed when making comparisons to other drugs.

The UK cancer care for renal cell carcinoma is lagging behind if new treatment and drugs cannot be accessed.

That the quality of life on Nivolumab seems to be much better in terms of the side effect profile. You are aware that many patients have been able to return to work and exercise after starting

Nivolumab. Jon is an example of this and the day after his treatment is back at work, working away from home in a busy environment as a consultant agronomist and farm business advisor.

I accept that this is still a newer drug and that data is still being collected on its overall impact on survival but I feel it is important that NHS patients can benefit from the treatment immediately and that data is collected to reinforce its efficacy.

I hope that you will take my letter of support seriously and consider my appeal for the use of this treatment.

Name	Sarah Birchall
Role	Carer
Location	England
Conflict	No

Comments on the ACD:

My name is Sarah Birchall, I attended your original committee meeting as a member of the public/carer while my husband Jon Birchall gave evidence as an expert patient witness as he has been receiving fortnightly infusions of Nivolumab since the end of April. This new immunotherapy PD-1 type drug Nivolumab is so important to all renal cell carcinoma (RCC) patients everywhere.

Today 25th July 2016 we got the news we had been so hoping for – after only six infusions of Opdivo – Jon's latest CT report shows 'stable disease'. His previous CT report in March showed the two largest lung nodules had grown 65% since December. It is hard to put on paper exactly what this means to all of us all but it is truly wonderful, and this is why it is so very important that other RCC patients get this same chance to try to extend their lives too. We do know Opdivo needs to be urgently prescribed to patients. The facts are simple - it works for many people and the drug is so well tolerated and improves the quality of life so much that it is absolutely vital for approval to be granted and for all those on the NICE appraisal committee to please seriously reconsider their initial decision.

There are so many aspects of Jon's life, and the lives of our family and friends, which are touched by his incurable diagnosis of kidney cancer. Although Jon was lucky to be able to access Nivolumab, three months ago, under the Early Access to Medicine Scheme (EAMs). We know there are many other RCC patients in England desperately waiting for it to be approved, and their options are fast running out. Many of them we know personally and count them as our friends and they too have families and jobs and they cling to this glimmer of hope that this new immunotherapy drug bring as tightly as a limpet sticks to a rock on a fast running tide.

Nivolumab is an innovative therapy with many patients worldwide achieving excellent results. There are recent updated reports to the American Society of Clinical Oncology, which showed that a third of patients were still alive five years after treatment initiation on Nivolumab and we believe that this data should be included and investigated by NICE when making comparisons to other drugs. Sadly it is not a cure, but it can significantly extend the lives of Stage 4 cancer patients, and a few RCC patients in the USA have reached the longed for no evidence of disease (NED). Stage 4 means that the cancer has spread from the initial tumour and it is now a terminal illness.

Not being able to access new drugs means the UK lags behind the rest of the world for renal cell carcinoma cancer care. Having a terminal illness frequently causes serious bouts of depression to the patient and their family, often with huge costs to the NHS and the nation's productivity, and access to Nivolumab would help them to cope better by knowing that all reasonable steps had been taken either for their own or their family member's survival. Knowing that everything, which can be done, has been done is truly a small crumb of comfort when dealing with grave illness. We have lived with this cancer journey since 2013, starting with two misdiagnoses, a failed treatment, and disease progression. All these things are very, very stressful and debilitating for everyone involved.

The current available crop of drugs for kidney cancer (i.e.: Sutent, Axinitib and Pazoponib) are similar to each other in their mode of action and their copious unpleasant and debilitating side effects, and this new immunotherapy offers real hope for a response in patients who haven't had success on other drugs.

Jon's quality of life on Nivolumab seems to be much better in terms of the side effect profile of many of the other drugs currently prescribed for kidney cancer. Conventional chemotherapy does not work for RCC and it is a notoriously difficult disease to treat. Jon has not yet had any of the TKI type drugs but despite travelling the long way to London for treatment by infusion every two weeks, and suffering a few minor side effects such a fatigue, itchy skin and headaches, he remains able to work full time which not only contributes to the Treasury but also to his feeling of identity, and self efficacy. These are two huge plus points, and add so much to a Stage 4 cancer patient's life, and that of their family.

Jon's only other treatment for his Stage 4 RCC was High Dose Interleukin 2, and this is administered in a specialised hospital setting for a week at a time, and it is very dangerous. Jon became seriously ill with jaundice and ascites and took almost a year to recover from that treatment, and although it hadn't worked at the time we knew he'd tried everything he could and this gave both of us a little peace of mind as we wrestled with the terminal diagnosis.

We accept that Nivolumab is still a new drug and we know further data is still being collected on its overall impact on survival, which is partly why EAMs was made available. We believe that approx. 200 patients are on the EAMs scheme in the UK and we feel it is vital that NHS kidney cancer patients in England will be able to benefit from this Immunotherapy treatment immediately and that more data is collected to reinforce its efficacy. Surely it is possible to negotiate a reasonable price at which it can be prescribed, to satisfy both the budgets of the NHS and Bristol Squibb Myers (BMS), as a drug they can't sell because of its price is not good for the company, the health service, or the patients.

My family and I will always be eternally grateful to BMS for accepting Jon on the early access scheme, and it is only right that others get this chance too. We know not everyone with RCC will respond to immunotherapy treatments but knowing that there is a drug, which extends the lives of so many patients I believe it is unspeakably cruel not to prescribe it.

Jon was patient witness at your original committee meeting and he told the NICE panel: "Let's get Nivolumab out there are see what it can do", and this will only happen with NICE approval, so please approve it and give everyone with kidney cancer a chance of hope and longer lives.

Yours faithfully

Mrs Sarah Lucy Birchall

Name	[redacted]
Location	England
Conflict	No
Comments on the ACD:	

I am writing to ask that the drug Nivolumab for kidney cancer is able to prescribed as there have been such good results both here on the early access routes and abroad.

It would be wonderful if those that need it can have access to this drug in the UK given its positive results and the hope it has given to a number of families in helping their loved ones maintain stability with their illness.

Thank you for considering this appeal.

Name	[redacted]
Role	Patient
Comments on the ACD:	
I am a 65 yr old female with metastatic KC. My cancer is inoperable and incurable but currently being treated with Axitinib (a second line medication after Pazopanib stopped working) I was diagnosed in 2012 ànd am now nearly 3 1/2 years into this journey. It means a lot to believe Nivolumab could become available and help me. Before I became ill with cancer I was a person who proactively looked after my health in order to be strong and healthy. I offered care and support to my grandchildren and indeed helped others in an educational and voluntary capacity. With the coming of Cancer I had to withdraw from these activities but also sadly from being able to live as fully and actively as I would wish. As a cancer sufferer I ultimately hope for a cure and try as far as possible to remain optimistic The approval of Nivolumab, with its lesser side effects and longer longevity, according to the latest evidence, would give hope to me and others and give me more time to spend with my family and grandchildren.	

Name	[redacted]
Conflict	
Comments on the ACD:	

Medical History

Survivor of renal cell carcinoma for 7 years. Stage 4 for 4 years.

Sutent on the Star trial - 3 months

Side Effects uncontrollable vomiting, diarrhoea, rapid weight loss and muscle wasting ending in three weeks of hospital and a long recuperation.

Pazopanib for 20 months with no activity in spinal mets and the disappearance of the psoas met. Liver met under control with shrinkage.

Side effects. Nausea, exhaustion, high blood pressure, hypothyroidism and diarrhoea.

Managed with regular medication breaks and varying the dose.

Axitinib from April 2014. Following aggressive liver met growth, now stable with some shrinkage. No other visible disease.

Side Effects. Intermittent nausea, diarrhoea, muscle pain and severe fatigue. High blood pressure, Hypothyroidism.

Managed with medication, regular medication breaks and variable doses of Axitinib

Functional Status Registered disabled. Unable to drive. Unable to work. Limited mobility.

Next step

No further treatment available unless Nivolumab is agreed.

Summary

As an active member of international patient support groups. I have watched with fascination and growing hope, the development of the innovative immunotherapy drug Nivolumab from the initial trial to fast track approval by the FDA in the USA, based on the rapid and superior effectiveness of the treatment to all others.

I have three friends from the original trial group patients who started when they were near end stage. The following is a summary of their experience.

Nivolumab from 2011, 2011 and 2012.

All three became free of their tumours within months. All were stage 4 on commencement with no other options and prognoses of less than 1 year.

Side effect profile - minimal.

Functional Status They have resumed work and are physically active. They continue on the treatment and are still tumour free.

Latest research results show superior longevity as well as a healthier life. The recently published reports from the American Society of Clinical Oncology showed that one third of patients are alive four to five years after the start of treatment. Please take this new research into consideration. Nivolumab is now available across Europe and in the USA. Nivolumab can give us the potential for a markedly longer survival and a better quality of life than any other currently available.

Potential for Further Research. We are still a long way from fully understanding Nivolumab, who it will work for and just how much greater potential it may prove to have. In order to ascertain this, you and our clinicians need further data which can only come from giving us full access and studying the results over the longer term. Please let us provide that data by allowing us to access it.

An Equal Opportunity for Life. The UK has a wonderful record in medical care but we are holding ourselves back in comparison with so many other countries because we do not have rapid access to new drugs. I know that this is being worked on but time is critical when you are dying a little more every day while you watch others survive and flourish because they do not live here. We must re-establish that excellence in care.

A Superior and Highly Effective Drug – Nivolumab. Can you imagine what it is like to have a terminal illness or worse, be the loved ones caring for that person, to face the torture of knowing that this drug is available in so many other countries while it is denied here. It is hard to comprehend why the conclusions that it is a superior and highly effective drug with fewer side effects are valid all over the world but not accepted here.

Another option for those who do not respond to TKIs.
In this infinitely variable disease, the great trickster of the cancers, many have little or no response to current drugs. The TKIs, in spite of their variation, offer a broadly similar mode of action and those who do not respond to them need to have the hope that there is something out there for them.

A better option.

- I would reiterate that the quality of life is generally vastly superior on Nivolumab than even on Axitinib, for me the gentler of the TKIs. The TKIs have seen me hospitalized for dehydration, sepsis and rapid fluctuations in my blood pressure causing falls and injury. I am happy to endure all of this to stay with my family but it makes life more difficult, causes the health service extra work and in terms of my ability to contribute to society, severely limits my effectiveness. Pills to control the nausea, to lower my blood pressure and control the diarrhea, all have their own side effects. When I look at the lives my US friends are now able to live, I feel envious. The accumulated costs of looking after the infinite variation of side effects related emergencies and spells in hospital must be considerable, over and above the suffering of those who endure them and the impact on those they love.

Based on the latest evidence, we know this is a good option and we ask that you make it

available to us now. I write this feeling like a starving child from a Victorian melodrama nose pressed to the window of a home where an affluent family are feasting. Please let us join the rest of the advanced nations. The evidence is there.

Name	[redacted]
Role	Relative
Comments on the ACD:	

I am writing to you today as a plea to reconsider taking on Nivolumab on the NHS for the treatment of renal cell carcinoma.
We speak from personal experience as my husband is currently participating on a clinical trial of the drug.

I am writing to you with regards to the licensing of Nivolumab for the treatment of Renal cancer.

In August 2015 we were shocked and devastated when my husband, age 46, was diagnosed with stage 4 kidney cancer. He had shown no symptoms,and we had led a very busy life with our two young children age 8 and 10 and his two older children, this was until he began passing large amounts of blood and clots in his urine on a Sunday afternoon three days before we were due to fly to Spain. He was eventually hospitalised as the catheter he had put in repeatedly became blocked with clots, whilst they did tests to discover the cause and this was when we found out the truly awful reason. The prognosis of terminal cancer ripped our lives apart. He has T4-V1-N0-M1-G4.

We have tried to remain as positive as we can and retain as much normality for our children as possible, but as you can appreciate, it has been, and continues to be an emotional rollercoaster.

[redacted] had surgery in September of a radical nephrectomy, splenectomy and retroperitoneal lymph node dissection. Sadly, at the scan post operatively we found that the pre- existing pulmonary nodules had increased 20-30%. [redacted] was placed on Sunitinib in October and initially showed a good response, but the second scan showed that there was a much more mixed response. We were advised again that we should get our affairs in order. We were devastated. But we were offered a lifeline. At this time a clinical trial had opened at Addenbrookes for Nivolumab which he was offered.

[redacted] began on Nivolumab in March and has felt really well on it. He has had no side affects, except some tiredness. This Friday, [redacted] had his second set of scans and we found out that ALL of his tumours have reduced in size! Almost a miracle, something we hadn't dared hope for. He has been brought precious time and is feeling really well. Well enough to work full time, play with the children, cycle, run, play on the beach, go on holiday and enjoy precious family time. If we hadn't been offered this clinical trial, I can't bear to think where we would be. The prospect of this life line drug not being available when his year on the trial finishes is awful. [redacted] is my soulmate, my best friend, a wonderful Dad, much loved son and brother. Nivolumab means he is still here with us. It needs to be made available to people who have this awful illness to give them a chance.

We would be happy to answer any further questions from a patient and his family perspective, though would not wish to go public due to our young boys.

Please consider how Nivolumab has really helped people like [redacted], live a relatively normal life when we thought this would never be the case again, when making your decision whether to licence this drug for NHS use. We know money is a huge problem within the NHS, but it really does make a difference.

Name	[redacted]

Role	Carer

Comments on the ACD:

My husband is stage IV kidney cancer patient with secondaries to lungs, lymph nodes, pancreas and maxilla area.
He had a radical nephrectomy and after a trial on BIBF1120 (Nintedanib) he then had a maxillectomy. Stability was achieved in the secondaries at the time except in the maxilla area. After the surgery he started Pazopanib and this resulted in near stability except in the maxilla area and so had further surgery to de-bulk the tumour in that area. During the time on the drugs he managed to work part-time and financially support his family. Fatigue was an issue and everything had to be planned around knowing where he could rest and had access to toilet facilities. Other prescription drugs were needed to deal with the side effects caused by the kidney cancer drug. The stress of wondering if a drug was working or not cannot be underestimated but the knowledge that there are other options available was very important and reassuring.

My husband has now started Axitinib due to Pazopanib not controlling the facial tumour. The fatigue is considerably worse and he is now unable to work. His whole body seems to ache and bones hurt. The side effects of Axitinib appear for him to be much tougher than on Pazopanib. The stress on the whole family seeing him so unwell and knowing there are no more drugs available to him if this treatment fails is immense. There seems to be no consideration given to rarer cancer patients with secondaries in unusual places or in bones. No research seems to look at patients where the secondaries are in places the TKIs do not appear to work, where patients do not tolerate these drugs or for those patients for whom the drugs for kidney cancer simply do not work. Why should my husband not have access to a drug which may work for his unusual circumstances instead of a type of drug which is not achieving the desired outcome for all his metastases? An immunotherapy drug such as Nivolumab with a different mode of action could allow him to participate actively in family life and to enable him to return to work and surely this has to be taken into account – to us it is so important. Quality of life is vitally important. Independence from daily drug routines so that we don't have to make sure we get home in time or take pills with us so we can change plans. Every day our lives revolve around drug regime and his fatigue.
Financial independence and ability to work is important for his self-esteem and confidence and plays a vital part in his battle and that every cancer patient has to fight.
Having kidney cancer is difficult and trying to support my husband and our family is upsetting enough without the added stress of financial worries and not knowing whether he can access the latest clinically effective treatments.
Please reconsider your preliminary decision and allow patients with rarer cancers to access Nivolumab, a drug which has already been approved for melanoma patients.

Name	[redacted]

Comments on the ACD:

Yes, we understand the NHS is a finite resource , it is patronising to tell us so, we are not ignorant, we were brought up by parents born in the 20s & 30s who taught us respect and values.
To do our part when we can ,both of us pay for private services for treatment relating to side effects from the cancer drugs. [redacted] 's feet need a lot of tlc due to the axitinib, we pay privately for this. He was referred for heart investigations, again due to axitinib use, we paid privately.
I was on watch & wait for my lymphoma last year but the hospital weren't listening to my concerns .....so I paid £1200 for MRI scan at private hospital and guess what, the pain in my leg (I had moaned of for a year) was that a large tumour had eaten away my femur. The NHS then went into a spin and fitted a titanium rod in my leg , a cost that would never have been had they listened to begin with. No apology, no refund of my £1200 .....money that yes we can afford because we saved for our old age.....but we may as well spend it now as there won't be old age, the cancer will finish us before the govt pension age.
A good "medicine " for cancer is "hope". [redacted] was given that last year when told of nivolumab. Exact words of the consultant were "hold on until next year".... ie, survive, cope with the awful side effects of axitinib , then a committee decides to take away the hope and the improved new treatment.
Oh, and finally, when you tell us the NHS is a finite resource , try telling that to all those who access

our free at the point of service facilities the moment they arrive here either illegally or from countries the NHS could invoice but don't.
Then there's the appalling waste of equipment , mobility aids, given for free (oh very nice) but when you bother to return them a jobsworth refuses to take them ....
No smoking signs outside hospital seem to be there simply for patients to stand by leaning on their drip, tubes in, pjs on and having a fag.....do staff move them on , no, they wander back in, bringing germs on their often bare feet or socks, and have some more treatment before putting up a proverbial 2 fingers as they go out for another fag.
I could tell you about one of the hospital wards [redacted] was on & the night there was a "do " to go to but all staff could not attend due to being on shift. Just the same as [redacted] 's 32 years of Police shifts, you put your shifts in the diary , go to work , then do your activities on time off. Oh no, not in the NHS, ward sister drafted in agency and every single member of staff could attend the "do".
Not only a "cost" on the finite resource but leaving patients vulnerable too.
My case rests at this point, but there is plenty more, I have bitten my tongue for 3 years and it's starting to hurt.

Nivolumab for previously treated advanced renal cell carcinoma

ERG's review of the company's comments on ACD

This report was commissioned by the NIHR HTA Programme as project number 15/69/20

BMJ Technology Assessment Group

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SUMMARY

The company manufacturing nivolumab (Opdivo®) submitted additional analyses as part of their comments on the Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for nivolumab for previously treated advanced renal cell carcinoma (RCC).

As part of the comments on the ACD, the company provided:

- Economic results from the company's interpretation of the committee's preferred analysis. In particular, the results relied on the company's assumption about the proportion of delayed doses of nivolumab that would not represent a cost to the National Health Service (NHS);
- CheckMate 025 trial data about the length of nivolumab dose delays;
- A proposed patient access scheme (PAS) for nivolumab, and the economic results obtained from its application to the company's interpretation of the committee's preferred analysis;
- Scenario analyses assuming that patients on nivolumab who had not progressed at 3 or 5 years would have the same mortality rates as the general age- and gender-matched population (i.e. the "immunotherapy survival tail") based on the company's interpretation of the committee's preferred analysis;
- Scenario analyses assuming that the likelihood of the 3-year or 5-year "immunotherapy survival tail" would be 50% based on the company's interpretation of the committee's preferred analysis.

In this document, the Evidence Review Group (ERG) summarises the appraisal committee's preferred analysis in Section 1, and reviews the company's analyses provided as comments on the ACD from Section 2 to Section 4. The results of the economic scenarios based on the company's analyses and further analyses requested by NICE are reported in Section 6.

1 Company's interpretation of the committee's preferred analysis

Section 4.21 of the ACD summarises the committee's preferred analysis as reported in Box 1.

Box 1. Committee's preferred analysis (ACD, Section 4.21)

The committee's preferred analysis:

- assumed axitinib was as effective as everolimus for progression-free survival and overall survival […]
- used a log-normal distribution to model time-to-stopping treatment […]
- assumed utility values for axitinib and everolimus were equal […]
- included the costs of subsequent therapy […]

The ERG notes that the summary of the committee's preferred analysis in the ACD did not specify clearly (i.e. numerically) the committee's view on the inclusion or exclusion of the delayed doses of nivolumab. The ACD reported the committee's concern that, "if a planned dose was delayed for a short time, the dose would still be given and this would incur a cost for the NHS [National Health Service]" (ACD, Section 4.17), and additionally that, "The committee concluded that the true cost to the NHS of providing nivolumab probably lay between the assumptions used by the company (excluding missed and delayed doses) and the ERG (including missed and delayed doses)" (ACD, Section 4.17).

The company presented a new scenario based on their own interpretation of the committee's opinion. The scenario was based on additional data provided as part of the ACD comments, and detailed in Section 2.

2 Doses delays in the CheckMate 025 trial

The base case economic model presented in the company's submission (CS) relied on the assumption that the proportion of planned doses of nivolumab which were either missed (2.500%) or delayed (5.075%) would not represent a cost for the NHS. As a result, 7.575% of the total treatment acquisition costs for nivolumab were excluded. It is reported in the ACD that, "The committee concluded that the true cost to the NHS of providing nivolumab probably lay between the assumptions used by the company (excluding missed and delayed doses) and the ERG (including missed and delayed doses)" (ACD, Section 4.17).

In the ERG's opinion, the company seems to have interpreted this statement as if the committee's preferred analysis excluded missed doses entirely from the economic analysis, and that the proportion of the delayed doses to be considered as a cost incurred by the NHS would lay between the 0% in the ERG's preferred analysis and the 5.075% (proportion of delayed doses on planned doses) proposed by the company. An average between the two values, in addition to excluding the missed doses from the total costs, would yield 5.038%[a]. In the ERG's opinion, the statement from the ACD reports uncertainty between the 0% used in the ERG's preferred analysis and the 7.575% (proportion of missed and delayed doses on planned doses) proposed by the company. The average between the two values is 3.788%.

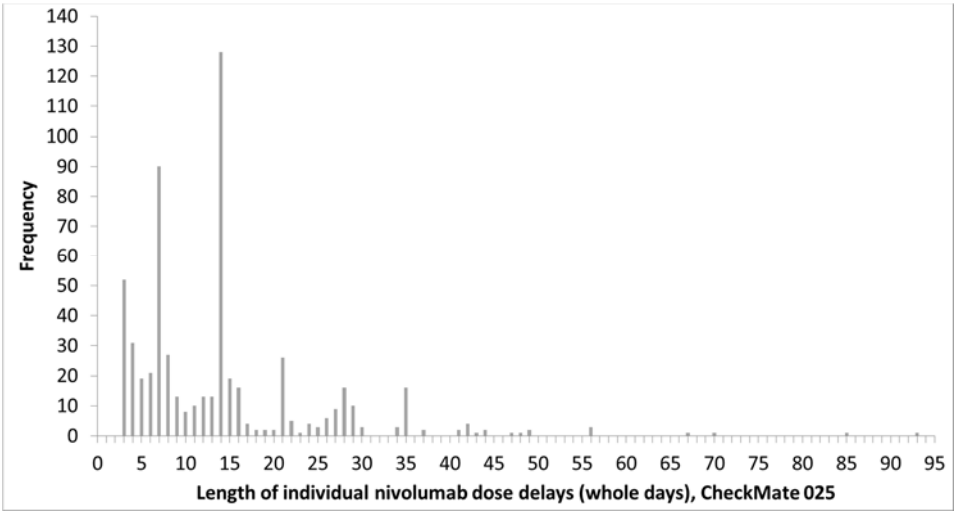
The main driver of the cost-effectiveness was the increased treatment acquisition cost associated to nivolumab when compared to axitinib, everolimus and best supportive care (BSC). The ERG notes

[a] Calculated as $100(0.025 + 0.5 \cdot (0.05075))\%$.

that even a small difference in the cost of nivolumab might have a substantial impact on the resulting incremental cost-effectiveness ratio (ICER).

The company presented additional analyses based on the CheckMate 025 trial and included the histogram showing the length of individual nivolumab dose delays, reported in Figure 1.

Figure 1. Histogram of dose delays, CheckMate 025 nivolumab patients (company's comments on ACD, Figure 1)



The company then argued that, "in order to adopt a cautious approach, [they] propose excluding the cost of delayed doses if the delay is at least 7 days" (company's comments on the ACD, Section 1.1). While the total proportion of delayed doses on planned doses was 5.075%, the same proportion if the delay was at least 7 days was 4.002% in the CheckMate 025 trial. Given the different interpretations of Section 4.17 of the ACD already highlighted, the ERG argues that this approach is neither cautious nor conservative. The total discount on the planned dose of nivolumab would be 6.502%, which is greater than the values resulting from both the interpretations of the ACD statement reported previously, i.e. 5.038% and 3.788%.

As the company did not provide the raw data for the calculation, the ERG digitised the data in the histogram in Figure 1 in order to re-estimate the proportion of delayed doses on the planned doses, based on the assumption that the total delayed doses were 5.075% on the total planned doses. The results are reported in Table 1.

Table 1. Proportion of delayed doses on planned doses by duration of delay considered

Length of delay excluded	Proportion of excluded delayed doses on planned doses
All delays (company's base case)	5.075% (company's analysis)
At least 7 days (company's interpretation of the committee's preferred analysis)	4.002% (company's analysis) 4.026% (ERG's re-estimation)

Length of delay excluded	Proportion of excluded delayed doses on planned doses
More than 7 days	3.258% (ERG's re-estimation)
At least 14 days	2.542% (ERG's re-estimation)
More than 14 days	1.450% (ERG's re-estimation)
No delays excluded (ERG's preferred base case)	0.000%

The 7 days threshold assumed by the company seems to be arbitrarily chosen, as no rationale for the selection of this particular duration was provided. Additionally, the ERG notes that a significant proportion of dose delays lasted exactly 7 days in the trial (as shown in Figure 1). Based on the ERG's re-estimation of the proportion of delayed doses on planned doses, the consequence of the arbitrariness of the choice would result in discounting the total treatment acquisition costs of nivolumab by 0.80% if changing the definition of the threshold by as little as a single day.

The impact on the economic results of the delay thresholds and interpretation of the ACD is reported in Section 6. The combinations analysed are listed in Table 2. It is worth noting that, in all analyses, the RDI applied to axitinib was 102% as in the company's base case analysis.

Table 2. Scenarios analysed around the proportion of planned doses paid by the NHS

Scenario*	Rationale	Cost reduction applied	
		Nivolumab	Everolimus
Base case	Average between ERG's preferred analysis and company's base case RDIs	3.788%	0.000%
Scenario 3	ERG's preferred analysis	0.000%	0.000%
Scenario 4	Average between ERG's and company's assumption on delayed doses	5.038%	0.000%
Scenario 5	Company's interpretation of committee's preferred analysis	6.502%	0.000%
Scenario 6	Assessment of the impact of everolimus RDI observed in the CheckMate 025 trial	3.788%	5.760%
Scenario 7 (6+4)		5.038%	5.760%
Scenario 8 (6+5)		6.502%	5.760%

Abbreviations in table: ERG, Evidence Review Group; RDI, reduced drug intensity.
* The numbers refer to the scenarios described in Section 6.

3 Long-term survival benefits of immunotherapy

In Section 1.2 of their comments on the ACD, the company argued that the CheckMate 025 trial data are too immature to demonstrate a survival plateau in renal cell carcinoma (RCC) patients, which was deemed plausible by the committee's clinical experts. The company stated that data from CheckMate 003 (phase 1b dose-escalation trial, N=34) and CheckMate 010 (phase 2 dose-ranging trial, N=150) support the hypothesis of an 'immunotherapeutic tail'.

The company stated that, "from 2 years after randomisation, where CheckMate 003, 010 and 025 OS [overall survival] estimates are broadly similar, the economic model underpredicts long-term RCC data from CheckMate 003 from 3 years onwards" (company's comments on ACD, Section 1.2). The company compared the trial outcomes to the economic model, as presented in Table 3. The ERG notes that the company did not report the updated 3-year estimate for the CheckMate 003 trial (41% instead of 44%). This was amended in the table.

Table 3. Summary of evidence on overall survival from nivolumab in RCC clinical trial programme in comparison to the base case economic submission (modified from the company's comments on ACD, Table 2)

Study	Phase	Outcome	Value	Reference
CheckMate 003	Ib	2-year OS	48%	McDermott *et al.* 2015 [1]
CheckMate 010	II		48% (42-52% depending on dose)	Plimack *et al.* 2015 [2]
CheckMate 025	III		52%	Motzer *et al.* 2015 [3]
Base case model			53%	Figure 28, CS
CheckMate 003	Ib	3-year OS	41%*	McDermott *et al.* 2016*[4]
CheckMate 010	II		35% (33-40% depending on dose)	Plimack *et al.* 2015 [2]
Base case model			38%	Figure 28, CS
CheckMate 003	Ib	4-year OS	38%	McDermott *et al.* 2015[1]
CheckMate 010	II		29%	McDermott et *al.* 2016[4]
Base case model			28%	Figure 28, CS
CheckMate 003	Ib	5-year OS	34%	McDermott et *al.* 2016[4]
Base case model			21%	Figure 28, CS

Abbreviations in table: ASCO, American Society of Clinical Oncology; CS, company submission; OS, overall survival; RCC, renal cell carcinoma.
* Based on the updated results reported by McDermott *et al*. 2016[4]

The ERG notes that the company's comparison is potentially misleading, as they did not report any measure to quantify the uncertainty associated to the estimates in Table 3 such as a confidence interval, or even the number of patients included in the trials. Given the substantial difference in sample sizes (among other characteristics), a comparison between mean estimates is unlikely to be informative.

The ERG does not deem the number of patients in the CheckMate 003 trial, relative to the sample size in CheckMate 025, to be sufficient to substantiate a key component such as the long-term survival extrapolation. The ERG also notes that the trials were different in many other aspects, first of all the doses of drug received by patients, which cannot be considered not to have an impact of the results without an in-depth analysis. In addition, the company did not comment on why the observed CheckMate 010 trial, reporting data for substantially more patients than the CheckMate 003 trial, showed a survival proportion 9% lower. The CheckMate 010 trial, albeit providing an estimate almost identical to the base case model estimate and based on the observation of 167 patients (compared to the 34 in the phase 1 trial CheckMate 003), was not considered by the company in this analysis.

Heuristically, assuming that the 5-year OS estimate of 21% predicted in the economic model and of 34% observed in the CheckMate 003 trial are different, and basing a scenario analysis on the results of the phase 1 trial, would imply ignoring the trends observed in a large phase 3 trial and base the long-term survival in the model on the outcome of 5 out of 34 patients, based on the sample size of CheckMate 003[b], while ignoring the outcomes observed on 167 patients in the CheckMate 010 trial and on 410 patients (considering the nivolumab arm only) in the CheckMate 025 trial. The ERG stresses the extreme amount of uncertainty, which was unaccounted for in the company's analysis, associated with extrapolating outcomes from a robust phase 3 trial using a dose-ranging, uncontrolled phase 1 trial following up 34 patients.

Assuming no censoring for simplicity, the estimated variance of the empirical survivor function $\hat{S}(t)$ at time t can be estimated as $\hat{V}\left[\hat{S}(t)\right] = \hat{S}(t)\left[1 - \hat{S}(t)\right]/n_1$. It follows that the approximated $100(1 - \alpha)\% = 95\%$ confidence interval for the survival estimate at 3 years from the CheckMate 003 trial is approximately [0.181, 0.499].[(5)] Albeit a crude approximation of the uncertainty associated with the estimate, confidence interval does not support the hypothesis that the survival estimate based on the trial is different from the one projected in the model (based on the outcomes in the phase 3 trial).

In conclusion, given the amount of uncertainty likely to be associated with the 3-year OS estimate from the CheckMate 003 trial, the ERG does not consider the estimate from the economic model to be inconsistent with the trial results. In the ERG's opinion, after accounting for uncertainty and taking into account the very limited data available, the two estimates do not seem inconsistent. Therefore, the ERG considers that the company's statement that the committee's preferred analysis, "substantially underestimates the overall survival estimates from CheckMate 003 RCC patients" (company's comments on ACD, Section 1.2) is not based on robust evidence, as stated in Section 4.15 of the ACD.

The company presented scenarios proposing a weighted approach, attributing a 50% chance to the 'immunotherapeutic tail' scenario at either 3 or 5 years, and the remaining 50% to the committee's preferred analysis (i.e. excluding the 'immunotherapeutic tail'). The ERG does not deem the company's justification for the scenario reasonable, as discussed above, and thus the 50% chance is considered highly liberal. As the company is effectively proposing to extrapolate the results of the CheckMate 025 phase 3 trial (N=821) using the CheckMate 003 phase 1 trial (N=34), an extremely simplistic and liberal data-driven weighting might be based on the proportion of information given by each trial and calculated suing the relative sample size. This would yield a $\frac{34}{34+821} = 3.98\%$ weight to

[b] The difference between the expected events based on the OS estimate in CheckMate 003 and in the economic model in a cohort of 34 patients.

the 'immunotherapeutic tail' and a 96.02% to the committee's preferred analysis. The economic results of this sample size-based weighting are explored in Section 6.

4 Proposed patients access scheme

The company proposed a patients access scheme (PAS) in the form of a simple discount to the acquisition cost of nivolumab. In Section 1.3 of the comments on the ACD, the company provided scenario analyses applying the PAS discount to the drug acquisition cost of nivolumab, as well as providing threshold analyses based on the PAS discount applied to axitinib. The results are reported in Section 6.

The ERG notes that the company's analysis including the PAS for axitinib is affected by an error in calculations, as the company did not take into account the cost reduction of axitinib when used as third-line therapy, while the PAS discount would still apply, as confirmed by NICE in internal communications.

The company stated the scenarios not including the 'immunotherapeutic tail' were "highly conservative" (company's comments on ACD, Section 1.3). The ERG strongly disagrees, as discussed in Section 3. Conversely, the 'immunotherapeutic tail' scenarios were based on phase 1 trial data and expert opinion, noting that the expectancy of the survival plateau for nivolumab originates from the outcomes associated to treatment with different drug (i.e. ipilimumab) in a different disease area (i.e. melanoma), and as such should be deemed speculative.

5 Additional analyses requested by NICE

NICE requested the ERG provide an opinion on the independent curve fit for OS, as per Section 4.14 of the ACD; and to provide a graphical summary of OS predicted in the 'immunotherapeutic tail' weighed scenarios proposed by the company. It must be noted that, given the very limited time available, the ERG was unable to validate the survival analysis and the selection of parametric models used for the extrapolation of the outcomes with clinical experts.

5.1 Independent curve fits for the overall survival

The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the independent curves fitted to the CheckMate 025 overall survival (OS) data are reported in Table 4.

Table 4. Relative goodness of fit, independent curve for the overall survival (CheckMate 025)

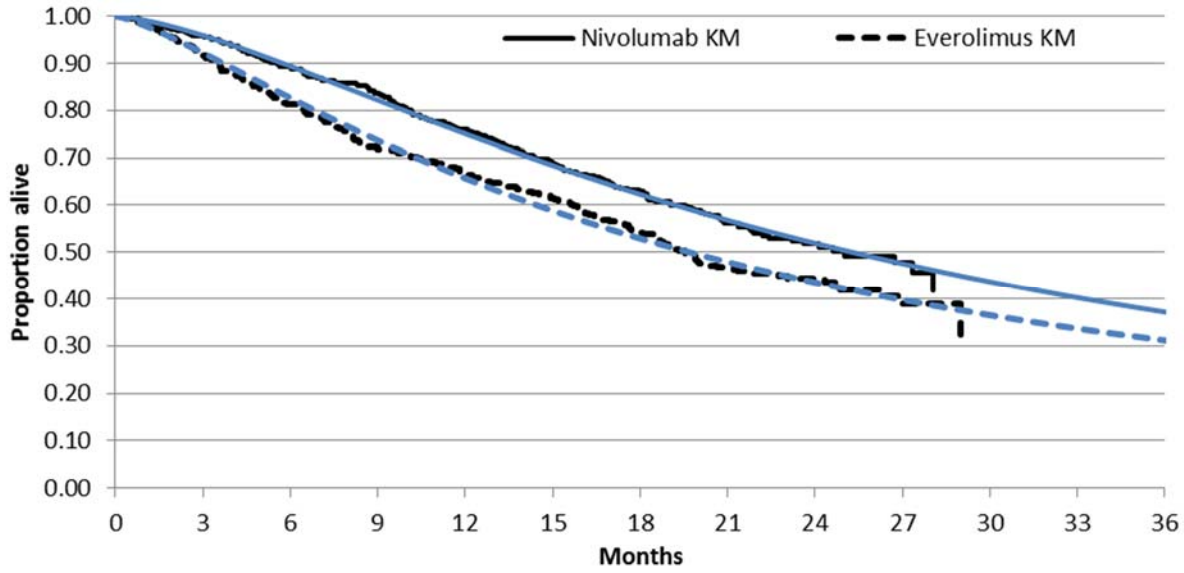
Parametric model	Nivolumab		Everolimus	
	AIC	BIC	AIC	BIC
Log-logistic	1689.087	1697.120	1875.948	1883.986
Generalised Gamma	1690.403	1702.451	1875.466	1887.522
Log-normal	1696.451	1704.484	1874.610	1882.647

Parametric model	Nivolumab		Everolimus	
	AIC	BIC	AIC	BIC
Weibull	1688.628	1696.660	1880.544	1888.581
Gompertz	1692.759	1700.791	1878.987	1883.006
Exponential	1699.373	1703.389	1878.987	1883.006
Abbreviations in table: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.				

The best-fitting models for nivolumab and everolimus on the AIC scale were the Weibull and the lognormal models, respectively. However, a strong rationale is needed to support the choice of very different parametric forms as these two models for the two treatment arms. These two models were also crossing and predicting clearly implausible results, and thus different parametric models were not considered.

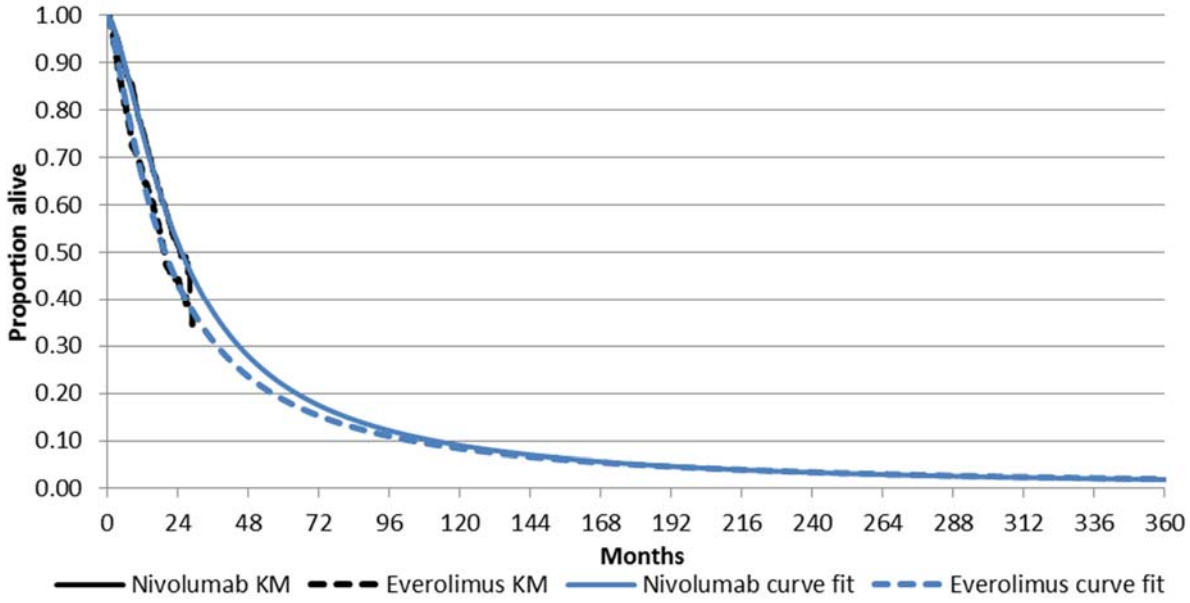
In the ERG's opinion, the log-logistic models seem to provide a reasonable fit both visually and in terms of AIC and BIC measures; therefore, a scenario using independently fitted log-logistic curves was explored. Graphically, the models were a good fit to the observed data, as shown in Figure 2.

Figure 2. Log-logistic curves independently fitted to CheckMate 025 OS data



The extrapolation of the OS over the time horizon of the model, based on the independently fitted log-logistic curves, is shown in Figure 3. The curves crossed at year 15 at a value of 0.05, but the differences between the curves were minimal and practically null for the rest of the time horizon, with a maximum difference of 0.002, observed at the end of the time horizon.

Figure 3. Log-logistic independent curves, extrapolation over 30 years

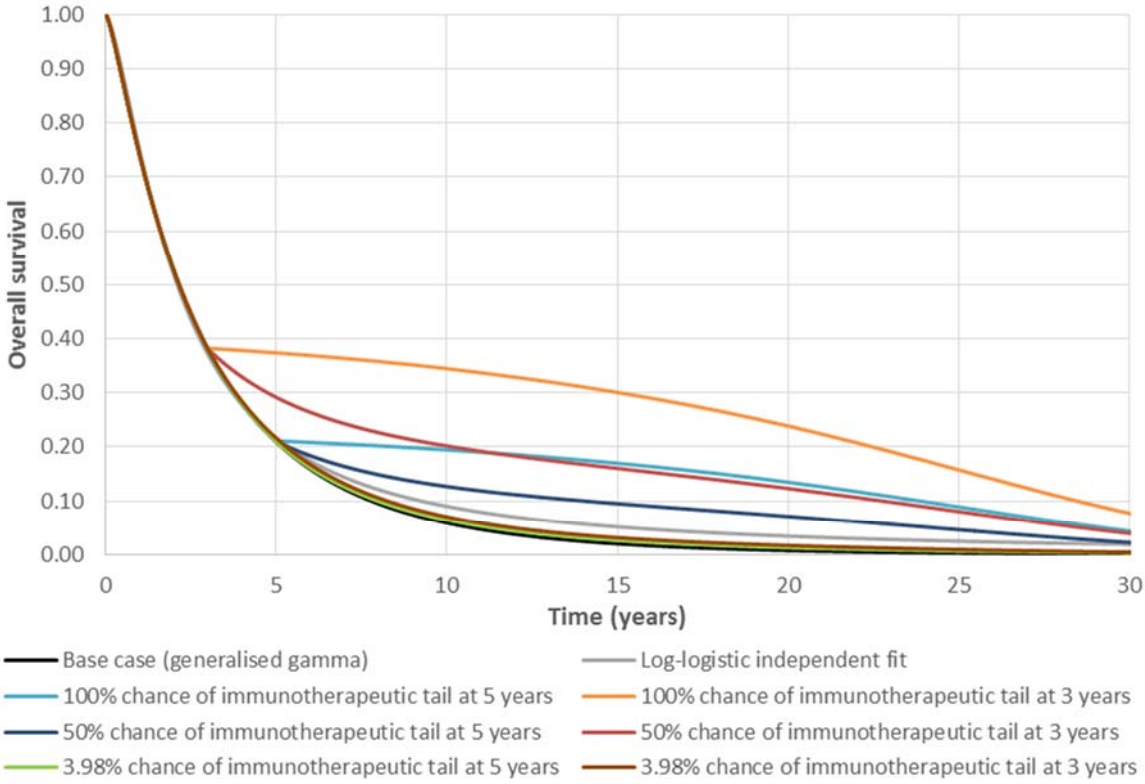


The results for the independent OS curves scenario are reported in Section 6.

5.2 Overall survival projections in alternative scenarios

A graphical summary of the overall survival projections, comparing the base case model predictions and the scenarios based on the 'immunotherapeutic tail' survival, is shown in Figure 4.

Figure 4. Overall survival projections for nivolumab, alternative scenarios



The survival outcomes at different time points, as well as the average life years projected, are reported in Table 5 for all the immunotherapeutic tail scenarios explored.

Table 5. OS endpoints by scenario

Model	Average LYs	5-year OS	10-year OS	20-year OS
Nivolumab				
Base case	3.41	21.13%	5.95%	0.79%
Log-logistic, independent fit	4.03	21.80%	9.05%	3.43%
100% chance of immunotherapeutic tail at 3 years	9.08	37.39%	34.50%	23.90%
100% chance of immunotherapeutic tail at 5 years	6.13	21.13%	19.50%	13.51%
50% chance of immunotherapeutic tail at 3 years	6.24	29.26%	20.23%	12.35%
50% chance of immunotherapeutic tail at 5 years	4.77	21.13%	12.73%	7.15%
3.98% chance of immunotherapeutic tail at 3 years	3.63	21.78%	7.09%	1.71%
3.98% chance of immunotherapeutic tail at 5 years	3.51	21.13%	6.49%	1.30%
Everolimus				
Base case	2.57	13.53%	2.89%	0.26%
Log-logistic, independent fit	3.66	18.80%	8.49%	3.59%
Abbreviations in table: LYs, life years; OS, overall survival.				

Table 6 reports the proportions of patients alive at different time points in the trials and in the different OS extrapolation scenarios. Scenarios assuming 5-year immunotherapeutic tails were not included, as they would not have been different from the base case model in the first 5 years of the simulation.

Table 6. Overall survival by trial or OS assumption up to 5 years

Years	Study / model	Value
2	CheckMate 003 (Ib)	48%
	CheckMate 010 (II)	48% (42-52% depending on dose)
	CheckMate 025 (III)	52%
	Base case model	**53%**
3	CheckMate 003 (Ib)	41%*
	CheckMate 010 (II)	35% (33-40% depending on dose)
	Base case model	**38%**
4	CheckMate 003 (Ib)	38%
	CheckMate 010 (II)	29%
	Base case model	**28%**
	100% chance of immunotherapeutic tail at 3 years	38%
	50% chance of immunotherapeutic tail at 3 years	33%
	3.98% chance of immunotherapeutic tail at 3 years	28%
5	CheckMate 003 (Ib)	34%
	Base case model	**21%**
	100% chance of immunotherapeutic tail at 3 years	37%
	50% chance of immunotherapeutic tail at 3 years	29%
	3.98% chance of immunotherapeutic tail at 3 years	22%

6 Economic results of the scenarios analysed

In this Section, the ERG reports the results of the analyses proposed by the company and requested by NICE. As already mentioned in Section 1, the ERG's and the company's interpretations of the committee's preferred analysis were different, particularly in relation to the proportion of delayed doses on planned doses which would not represent a cost to the NHS. The ERG therefore uses an average scenario as the basis of the application of all aspects of the requested analyses, discounting the total cost of nivolumab by 3.788%, accounting for both missed and delayed doses. Given the limited time available and the relatively small impact of minor variations, extensive scenario analyses for all proportions were not carried out, as they would have multiplied substantially the number of analyses.

The base case scenario considers:

- Axitinib as effective as everolimus for both PFS and OS;
- A lognormal distribution for time to treatment discontinuation (TTD);
- Equal utility values for axitinib and everolimus, and equal to the values calculated based on the values observed in the everolimus arm of the CheckMate 025 trial;
- Inclusion of the costs of subsequent therapy;
- Inclusion of the reduced drug intensity (RDI) for nivolumab, everolimus and axitinib. The proportion of total drug quantity representing a cost to the NHS is assumed equal to 96.212% (calculated as $100(1-0.03788)\%$), 100% (excluding reduced drug intensity) and 102.000% (as reported by the company) respectively for nivolumab, everolimus and axitinib.

The results of the base case scenario are reported in Table 7.

Table 7. Base case scenario results

Treatment	Cost	QALYs	LYs*	Incremental costs Nivolumab versus	Incremental LYs Nivolumab versus	Incremental QALYs Nivolumab versus	ICER Nivolumab versus
Nivolumab	£93,593.84	2.30	3.39	-	-	-	-
Axitinib	£52,707.41	1.69	2.55	£40,886.44	0.84	0.61	**£67,218.53**
Everolimus	£41,916.93	1.69	2.55	£51,676.92	0.84	0.61	**£84,958.40**
BSC	£10,525.24	1.00	1.47	£83,068.61	1.92	1.30	**£64,129.53**

Abbreviations used in the table: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year. Note: *, undiscounted.

6.1 Results: list prices

Table 8 summarises the results of the scenarios at list prices for both nivolumab and axitinib.

Table 8. Scenario results, list prices

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
0	**Base case**							
	Total costs (£)	£93,593.84	£52,707.41	£41,916.93	£10,525.24	£40,886.44	£51,676.92	£83,068.61
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£67,218.53**	**£84,958.40**	**£64,129.53**
1	**Generalised gamma model for TTD**							
	Total costs (£)	£97,893.62	£52,707.41	£43,777.45	£10,525.24	£45,186.22	£54,116.17	£87,368.39
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£74,287.50**	**£88,968.62**	**£67,448.99**
2	**Independently fitted log-logistic curves for OS**							
	Total costs (£)	£94,868.38	£55,142.48	£44,355.88	-[a]	£39,725.89	£50,512.50	-[a]
	QALYs	2.56	2.18	2.18	-[a]	0.38	0.38	-[a]
	LYs	4.01	3.64	3.64	-[a]	0.37	0.37	-[a]
	ICER					**£103,716.30**	**£131,877.94**	-[a]
3	**Missed and delayed doses - proportion of nivolumab costs not paid for by NHS: 0%**							
	Total costs (£)	£96,292.06	£52,707.41	£41,916.93	£10,525.24	£43,584.65	£54,375.13	£85,766.82
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£71,654.48**	**£89,394.35**	**£66,212.57**
4	**Missed and delayed doses - proportion of nivolumab costs not paid for by NHS: 5.038%**							

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
	Total costs (£)	£92,703.46	£52,707.41	£41,916.93	£10,525.24	£39,996.05	£50,786.53	£82,178.22
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£65,754.71**	**£83,494.58**	**£63,442.14**
5	**Missed and delayed doses - proportion of nivolumab costs not paid for by NHS: 6.502%**							
	Total costs (£)	£91,660.64	£52,707.41	£41,916.93	£10,525.24	£38,953.23	£49,743.71	£81,135.40
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£64,040.29**	**£81,780.16**	**£62,637.08**
6	**Everolimus RDI: 5.760% (CheckMate 025 trial)**							
	Total costs (£)	£93,488.51	£52,682.58	£40,658.59	£10,525.24	£40,805.94	£52,829.92	£82,963.27
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£67,086.18**	**£86,853.98**	**£64,048.21**
7	**6+4**							
	Total costs (£)	£92,598.13	£52,682.58	£40,658.59	£10,525.24	£39,915.55	£51,939.54	£82,072.89
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£65,622.37**	**£85,390.16**	**£63,360.83**
8	**6+5**							
	Total costs (£)	£91,555.31	£52,682.58	£40,658.59	£10,525.24	£38,872.73	£50,896.72	£81,030.07
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£63,907.94**	**£83,675.73**	**£62,555.76**
9	**100% chance of immunotherapeutic tail at 3 years**							
	Total costs (£)	£105,761.69	£52,707.41	£41,916.93	£10,525.24	£53,054.28	£63,844.76	£95,236.45

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
	QALYs	4.83	1.69	1.69	1.00	3.14	3.14	3.83
	LYs	9.06	2.55	2.55	1.47	6.51	6.51	7.59
	ICER					**£16,883.76**	**£20,317.67**	**£24,869.87**
10	**100% chance of immunotherapeutic tail at 5 years**							
	Total costs (£)	£99,101.36	£52,707.41	£41,916.93	£10,525.24	£46,393.95	£57,184.43	£88,576.12
	QALYs	3.46	1.69	1.69	1.00	1.77	1.77	2.46
	LYs	6.11	2.55	2.55	1.47	3.56	3.56	4.64
	ICER					**£26,202.27**	**£32,296.49**	**£36,040.66**
11	**50% chance of immunotherapeutic tail at 3 years**							
	Total costs (£)	£99,677.77	£52,707.41	£41,916.93	£10,525.24	£46,970.36	£57,760.84	£89,152.53
	QALYs	3.56	1.69	1.69	1.00	1.88	1.88	2.56
	LYs	6.22	2.55	2.55	1.47	3.67	3.67	4.76
	ICER					**£25,046.93**	**£30,800.95**	**£34,793.16**
12	**50% chance of immunotherapeutic tail at 5 years**							
	Total costs (£)	£96,347.60	£52,707.41	£41,916.93	£10,525.24	£43,640.19	£54,430.67	£85,822.36
	QALYs	2.88	1.69	1.69	1.00	1.19	1.19	1.88
	LYs	4.75	2.55	2.55	1.47	2.20	2.20	3.28
	ICER					**£36,689.86**	**£45,761.80**	**£45,735.37**
13	**3.98% chance of immunotherapeutic tail at 3 years**							
	Total costs (£)	£94,078.12	£52,707.41	£41,916.93	£10,525.24	£41,370.72	£52,161.20	£83,552.89
	QALYs	2.40	1.69	1.69	1.00	0.71	0.71	1.40
	LYs	3.61	2.55	2.55	1.47	1.06	1.06	2.14
	ICER					**£58,341.15**	**£73,557.93**	**£59,843.87**
14	**3.98% chance of immunotherapeutic tail at 5 years**							
	Total costs (£)	£93,813.04	£52,707.41	£41,916.93	£10,525.24	£41,105.63	£51,896.11	£83,287.80
	QALYs	2.34	1.69	1.69	1.00	0.65	0.65	1.34

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
	LYs	3.49	2.55	2.55	1.47	0.95	0.95	2.03
	ICER					**£62,802.45**	**£79,288.47**	**£62,081.56**
15	**AXIS HSUVs**							
	Total costs (£)	£93,593.84	£52,707.41	£41,916.93	£10,525.24	£40,886.44	£51,676.92	£83,068.61
	QALYs	2.05	1.49	1.49	0.88	0.56	0.56	1.17
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					**£73,605.51**	**£93,030.99**	**£71,046.17**

Abbreviations in table: BSC, best supportive care; HSUV, health-state utility value; ICER, incremental cost-effectiveness ratio; LY, life year; NHS, National Health Service; OS, overall survival; QALY, quality-adjusted life year; RDI, reduced dose intensity; TTD, time to (treatment) discontinuation.

[a] As mentioned in the ERG report, the company's comparison with BSC is affected by a methodological error (i.e. application of an hazard ratio to a non-PH model). While this effect might be considered somewhat alleviated from not using independently fitted curve, the results from a scenario testing independently fitted and extrapolated curves would not be acceptable.

6.2 Results: nivolumab PAS

Table 9 summarises the results of the scenarios when applying the proposed [redacted] PAS discount to the price of nivolumab. The cost of axitinib is at list price.

Table 9. Scenario results, nivolumab PAS and axitinib list price

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
0	**Base case**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
1	**Generalised gamma model for TTD**							
	Total costs (£)	[redacted]	£52,707.41	£43,777.45	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
2	**Independently fitted log-logistic curves for OS**							
	Total costs (£)	[redacted]	£55,142.48	£44,355.88	-[a]	[redacted]	[redacted]	-[a]
	QALYs	2.56	2.18	2.18	-[a]	0.38	0.38	-[a]
	LYs	4.01	3.64	3.64	-[a]	0.37	0.37	-[a]
	ICER					[redacted]	[redacted]	**-[a]**
3	**Missed and delayed doses - proportion of nivolumab costs not paid for by NHS: 0%**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
4	**Missed and delayed doses - proportion of nivolumab costs not paid for by NHS: 5.038%**							

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
5	**Missed and delayed doses - proportion of nivolumab costs not paid for by NHS: 6.502%**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
6	**Everolimus RDI: 5.760% (CheckMate 025 trial)**							
	Total costs (£)	[redacted]	£52,682.58	£40,658.59	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
7	**6+4**							
	Total costs (£)	[redacted]	£52,682.58	£40,658.59	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
8	**6+5**							
	Total costs (£)	[redacted]	£52,682.58	£40,658.59	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.30	1.69	1.69	1.00	0.61	0.61	1.30
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]
9	**100% chance of immunotherapeutic tail at 3 years**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
	QALYs	4.83	1.69	1.69	1.00	3.14	3.14	3.83
	LYs	9.06	2.55	2.55	1.47	6.51	6.51	7.59
	ICER					[redacted]	[redacted]	[redacted]
10	**100% chance of immunotherapeutic tail at 5 years**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	3.46	1.69	1.69	1.00	1.77	1.77	2.46
	LYs	6.11	2.55	2.55	1.47	3.56	3.56	4.64
	ICER					[redacted]	[redacted]	[redacted]
11	**50% chance of immunotherapeutic tail at 3 years**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	3.56	1.69	1.69	1.00	1.88	1.88	2.56
	LYs	6.22	2.55	2.55	1.47	3.67	3.67	4.76
	ICER					[redacted]	[redacted]	[redacted]
12	**50% chance of immunotherapeutic tail at 5 years**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.88	1.69	1.69	1.00	1.19	1.19	1.88
	LYs	4.75	2.55	2.55	1.47	2.20	2.20	3.28
	ICER					[redacted]	[redacted]	[redacted]
13	**3.98% chance of immunotherapeutic tail at 3 years**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.40	1.69	1.69	1.00	0.71	0.71	1.40
	LYs	3.61	2.55	2.55	1.47	1.06	1.06	2.14
	ICER					[redacted]	[redacted]	[redacted]
14	**3.98% chance of immunotherapeutic tail at 5 years**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.34	1.69	1.69	1.00	0.65	0.65	1.34

	Results per patient	Nivolumab	Axitinib	Everolimus	BSC	Incremental value		
		(1)	(2)	(3)	(4)	(1-2)	(1-3)	(1-4)
	LYs	3.49	2.55	2.55	1.47	0.95	0.95	2.03
	ICER					[redacted]	[redacted]	[redacted]
15	**AXIS HSUVs**							
	Total costs (£)	[redacted]	£52,707.41	£41,916.93	£10,525.24	[redacted]	[redacted]	[redacted]
	QALYs	2.05	1.49	1.49	0.88	0.56	0.56	1.17
	LYs	3.39	2.55	2.55	1.47	0.84	0.84	1.92
	ICER					[redacted]	[redacted]	[redacted]

Abbreviations in table: BSC, best supportive care; HSUV, health-state utility value; ICER, incremental cost-effectiveness ratio; LY, life year; NHS, National Health Service; OS, overall survival; QALY, quality-adjusted life year; RDI, reduced dose intensity; TTD, time to (treatment) discontinuation.

[a] As mentioned in the ERG report, the company's comparison with BSC is affected by a methodological error (i.e. application of an hazard ratio to a non-PH model). While this effect might be considered somewhat alleviated from not using independently fitted curve, the results from a scenario testing independently fitted and extrapolated curves would not be acceptable.

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