NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Merck Sharp & Dohme**
   a. Response form
   b. Appendices of new evidence

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Kidney Cancer UK
   b. Kidney Cancer Support Network
   c. National Cancer Research Institute-Association of Cancer Physicians-Royal College of Physicians-Royal College of Radiologists

   Comments on the Appraisal Consultation Document from experts:
   None

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

5. **Evidence Review Group critique of company comments on the ACD**

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

Appraisal title

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

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

Type of stakeholder:

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 Social Care 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 document (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 and Social Care, 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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	Merck Sharp & Dohme	**General comment on content of the Appraisal Consultation Document and MSD's key concerns** MSD is encouraged that the Appraisal Consultation Document acknowledges the following: • Data from the KEYNOTE-426 clinical trial demonstrates that pembrolizumab with axitinib is more effective than sunitinib for people with untreated renal cell carcinoma. • People with untreated renal cell carcinoma would welcome a new treatment option as reported by the patient expert who contributed at the committee meeting, and who had also been a participant in the KEYNOTE-426 clinical trial. • The Committee recognised that for advanced renal cell carcinoma, there is a high unmet need for both patients and healthcare professionals, and an option that improves survival and reduces side effects would be welcomed by patients and clinicians to allow a greater choice of treatments and individualised care plans. Despite the above, MSD is concerned by the conclusions reached by the Committee in relation to the outstanding issues that were initially raised in the Technical Report and now further discussed in the Appraisal Consultation Document. Our main considerations are as follows: • MSD understands that the potential reimbursement of pembrolizumab with axitinib would have an impact on the existing renal cell carcinoma treatment pathway. However, the Appraisal Consultation Document fails to acknowledge that the renal cell carcinoma treatment landscape is evolving, and other new and different combination regimens recently approved for funding via the Cancer Drug Fund already have had the same impact on the current first-line and second-line treatment options (see Comment 2). • MSD acknowledges the Committee's view that there are certain areas of clinical uncertainty, due to the limited follow-up in the KEYNOTE-426 data which informed the company submission (first interim analysis; data cut-off date August 2018). Yet MSD considers it unfortunate that clinical expert input has not been utilised appropriately to better inform the Committee's conclusions. o The clinical expert input that was elicited during the appraisal process, in order to inform some of the key areas of uncertainty, is broadly supportive of the	Comments noted. Please see individual responses to comments number 2 – 10 below.

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			modelling approach and assumptions made by MSD in our base case concerning overall survival extrapolation and long-term duration of treatment effect. However much of this input has seemingly been disregarded by the Committee (see comment 3). MSD urges the Committee to place greater emphasis on utilising clinical expert opinion to inform the conclusions that the Committee reaches during the appraisal process. • MSD believes that all clinical input throughout the appraisal process, alongside biological plausibility, has supported the original base case assumptions outlined within the company submission; justifying the use of alternative parametric distributions and a lifetime treatment effect. MSD has provided an updated base case; selecting conservative overall survival distributions. • MSD believes that an ICER threshold of £30,000 per QALY gained should apply in this appraisal. We do not consider the level of uncertainty to be of such magnitude to warrant a decreased and much more restrictive cost-effectiveness threshold of £20,000 per QALY gained (see comment 8). • MSD strongly believes that the combination of pembrolizumab with axitinib for treating advanced renal cell carcinoma is a suitable candidate for the Cancer Drugs Fund. Additional information, provided as part of this response to the Appraisal Consultation Document (see comment 9), including details about a proposed further data-cut from the KEYNOTE-426 study, supports the consideration of pembrolizumab with axitinib as an eligible candidate for the Cancer Drugs Fund. • The apparent inconsistency in the approach taken by two NICE Committees, appraising (in parallel) two immuno-oncology/tyrosine-kinase inhibitor combination therapies in the same patient population, is of great concern to MSD [1, 2] (see comment 10). We are yet to see any documentation released by NICE following the first committee meeting for ID1547; if standard process had been followed and the result of the first committee meeting was an Appraisal Consultation Document, we would have expected this to enter the public domain week commencing 27th January 2020. The apparent different conclusions reached by the NICE committees appraising these two topics at this time results in a divergence with clinical consensus on these therapies, as detailed in the ESMO guideline published in February 2020 [3], which recommends the combination of pembrolizumab and axitinib as front-line/treatment-naïve therapy for advanced disease. Avelumab with axitinib (ID1547) is not included in the ESMO guideline, since the combination has not yet demonstrated a significant OS advantage over sunitinib as detailed in the guideline.	
2	Consultee (company)	Merck Sharp & Dohme	**Introduction of pembrolizumab with axitinib into the treatment pathway, and potential**	Comment noted. The committee was aware of

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			impact on eligibility for subsequent therapies ***MSD recognises that the introduction of pembrolizumab with axitinib in the first-line setting for the treatment of advanced renal cell carcinoma would have an impact on the current treatment pathway and eligibility for subsequent treatments. However, this is not a situation specific to pembrolizumab with axitinib; it would also apply (and has previously applied) to the introduction of any new immuno-oncology containing treatment regimen in the first-line setting.*** Pages 6-7, Section 3.2 of the Appraisal Consultation Document states that "*The Committee concluded that the introduction of pembrolizumab with axitinib was likely to have a substantial effect on the care pathway*". However, this statement, alongside the rest of Section 3.2 of the Appraisal Consultation Document, fails to recognise some important considerations, as follows: • In addition to pembrolizumab with axitinib, the renal cell carcinoma landscape will inevitably change in the future due to the development of further effective treatment options for this patient population; • Acknowledgment should be given to the fact that new treatment options will give patients the opportunity to receive benefits from more efficacious treatments earlier in the disease pathway, rather than focusing on reducing the options available in the second-line setting; • Other treatment regimens either currently funded or likely to be funded in the near future via the Cancer Drug Fund, such as nivolumab plus ipilimumab and avelumab plus axitinib, would have the same impact as pembrolizumab plus axitinib on the subsequent therapies used in the treatment pathway, given their modes of action [2, 4]; • As stated by NHS England in the committee papers for public consultation "*the 2nd line treatment rate is currently approximately 50-60% and so a combination of these 2 therapies [pembrolizumab and axitinib] employed as 1st line treatment removes concern that patients might miss out on one important type of 2nd line therapy if they receive the other important type as 1st line treatment*"; • The Committee's use of the word "*eligible*" in the context of subsequent therapy is inappropriate since, in theory and in practice, every patient would be eligible to receive treatment but their suitability for a specific intervention in the second-line setting may vary based on individual disease characteristics. It would be at the discretion of clinicians after discussion with patients, to make a final recommendation on the most appropriate intervention. There remains an unmet need for novel agents to treat advanced renal cell carcinoma, which	the unmet need in this population and that a positive recommendation would allow more choice of treatment and individualised care plans. See FAD section 3.1. Comments noted. Section 3.2 of the FAD has been updated to reflect some of your comments accordingly. FAD section 3.2 has been amended to read: *The committee concluded that pembrolizumab with axitinib was likely to have a substantial effect on the care pathway. But, this effect would be similar to that of other immunotherapy combinations for first-line renal cell cancer.* Wording has been amended to remove reference to eligibility: *'If*

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			have durable clinical benefit and potential curative effects. The combination of pembrolizumab with axitinib investigated in KEYNOTE-426 is the first immuno-oncology combination therapy regimen to demonstrate statistically significant and clinically meaningful improvements in overall survival, progression free survival and objective response rate in renal cell carcinoma patients, irrespective of risk group classification [5]. MSD encourages NICE to acknowledge that the anticipated changes within the treatment pathway for patients with advanced renal cell carcinoma that may result following the introduction of pembrolizumab with axitinib, are not unexpected. Such impact on the treatment pathway has already been considered acceptable in light of other aforementioned new therapeutic options coming to market and recently approved via the Cancer Drug Fund.	*recommended. pembrolizumab with axitinib is likely to affect access to subsequent treatments"*
3	Company	Merck Sharp & Dohme	**Value of clinical expert opinion to help address the uncertainty in survival estimates due to the limited duration of follow-up in the KEYNOTE-426 data which informed the company submission** ***Several sections of the Appraisal Consultation Document refer to the 'uncertainty' that remains in terms of overall survival estimates (page 13, section 3.14), and due to the immaturity of the evidence from the KEYNOTE-426 study (page 10, section 3.9; page 13, section 3.15). MSD considers that the clinical expert opinions provided during the committee meeting should have served to address some of the areas of uncertainty; however the expert input provided appears to have been largely disregarded.*** MSD urges the Committee to give due consideration to all information detailed below: *Clinical expert opinion provided during the appraisal process to date* In MSD's company submission, two data-cuts from the KEYNOTE-426 trial were presented, dated August 2018 (first-interim analysis) and January 2019 (second unplanned interim-analysis); these data-cuts reported a median follow-up of 13.2 months and 17.4 months respectively (maximum follow-up of 22 and 27 months respectively). With acceptance of the limited follow-up based on the data currently available from the KEYNOTE-426 study, MSD considers the opinions of clinical experts to be of paramount importance, in order to help address some key areas of uncertainty. The eminent clinical experts who participated in the technical engagement and the committee meeting not only have experience of treating this patient population in real-world practice, but also direct experience of using pembrolizumab with axitinib. MSD urges the NICE Committee to place a greater emphasis on utilising clinical expert opinion to inform the conclusions that the Committee reach during the	Comment noted. The NICE process guide states that *'Evidence is obtained from a range of sources, including randomised controlled trials, observational studies and expert opinion (of clinical professionals and/or patients or carers)….. Experts are invited to help clarify issues about the submitted evidence and attend committee meetings'.* In light of your comments that clinical expert opinion has been disregarded, NICE ensured that experts were invited to the second committee meeting. The issue was presented to the committee and it considered expert views provided in the second

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			appraisal process. In the context of a NICE appraisal, the "Guide to the processes of technology appraisal" [6] outlines the role of clinical experts in helping to clarify *"issues about the submitted evidence and to provide advice before, during and after committee meetings*"; clinical experts can also comment on the technical report, with the main purpose of providing "*views on the judgements made by the technical team*". MSD would therefore like to draw attention to the below clinical experts' opinions received during the technical engagement phase and the first committee meeting [7]. <u>Clinical expert comments concerning long-term efficacy and duration of response:</u> • From "<u>ID1426 Pembrolizumab Committee papers for consultation</u>" – Dr. Tom Waddell: o *"Due to the mechanism of action of checkpoint inhibitors, it is also observed that more patients achieve deep responses (>80% reduction in tumour volume) or complete responses (disappearance of all visible tumour) with the combination compared to standard of care. Some of these patients will have long-term durable remissions that may even equate to cure. This effect is not seen with use of VEGF TKIs where all patients will eventually progress and die as a result of the disease".* o *"would estimate that approximately 15% of patients will achieve long-term durable remission / cure with use of Pembrolizumab plus Axitinib. Due to the relatively early follow-up this plateau effect in the OS curve will not be seen for some time but should be considered"* o *"In addition, due to the 'tail of the curve' effect with the combination approach, it is likely that Pembrolizumab and Axitinib will result in long-term remissions for some patients. For these patients the threat of dying from their cancer will be almost entirely negated. This does not happen with single agent VEGF TKIs."* • From "<u>ID1426 Pembrolizumab Committee papers for consultation</u>" – Dr. Balaji Venugopal: o *"There are a proportion of patients treated with immune checkpoint inhibitors who can achieve durable clinical benefit that could last years, which is referred as "tail of the curve" in Kaplan Meier survival curves. This effect is proven in melanoma and early evidence with ipilimumab/nivolumab also supports this hypothesis"* o *"There are a proportion of patients treated with this technology who can achieve durable clinical response and this response does not come with significant adverse*	meeting in its decision making. <u>Long-term efficacy and duration of response</u> The committee noted that a durable response was clinically plausible with checkpoint inhibitors, but that immaturity of the data meant there was no evidence to support the size or duration of this effect. Expert opinion on long-term survival with pembrolizumab and axitinib varied (estimates for 5-year survival ranged between 50% and 35%) and a large amount of uncertainty surrounded the estimates at 10 and 20 years. Given the short follow up for KEYNOTE-426, the committee concluded that the treatment effect duration was uncertain. The

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			events as noticed in the patients treated with ipilimumab/nivolumab which is now one of the standard of care in aRCC of intermediate or poor risk group." • From technical report (page 18): "*Two clinical experts commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only)*". • From technical report (page 18): "*With regard to long term survival estimates for pembrolizumab with axitinib, the company clinical experts estimated a 50% survival at 5 years. An ERG clinical expert thought this may be optimistic. A clinical expert for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years*" • From technical report (page 24): "*Two clinical experts have commented that a "tail of the curve" effect is likely to be observed for survival curves on combination immunotherapy. This could suggest a long duration of treatment effect is expected for pembrolizumab with axitinib. One expert commented that the effect of treatment could be durable (potentially lifelong) and beyond the duration of therapy in patients achieving long-term control. Another expert commented on a potential continued treatment effect on survival due to persistent activation of immuno-surveillance, but was unclear about the potential duration of effect*". <u>Clinical expert comments concerning effectiveness of pembrolizumab in combination with axitinib, in the context of other available treatment options:</u> • From "<u>ID1426 Pembrolizumab Committee papers for consultation</u>" – Dr. Tom Waddell: o *"It would be expected that this combination would be more effective than standard of care options for all patients with metastatic RCC. In particular this effect has been confirmed across all prognostic groups (favourable, intermediate and poor) and would be expected regardless of the histological subtype of RCC (clear and non-clear cell patient groups)".* o *"Additionally, in comparison to combination with Ipilimumab and Nivolumab, there will be fewer severe immune-related side-effects with Pembrolizumab and Axitinib. This will lead to fewer hospital admissions for management of toxicity"* o *"All of the above parameters represent a huge step forwards in the treatment of metastatic RCC compared to using single agent VEGF TKIs such as Sunitinib. The durability of these responses for some patients is completely transformative, and*	committee agreed that there was not enough evidence to assume a lifetime treatment effect. Therefore, treatment benefit waning effects should be applied in the economic model. See FAD section 3.10. The committee considered scenarios where treatment effect waned after 3 years, 5 years and 10 years (i.e. 1 year, 3 years and 7 years after stopping pembrolizumab).It concluded that a waning effect after 5 years was most plausible based on clinical expert opinion, the evidence presented and consistency with previous NICE appraisals of checkpoint inhibitors that included stopping rules. See FAD section 3.11 <u>Effectiveness versus comparators:</u> The committee agreed that pembrolizumab with axitinib extended progression free survival, but noted that the data were too immature to determine the overall

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			therefore this combination significantly reduces the unmet need for responding patients" o *"With any treatment there will be a group of patients who do not respond at all (so called 'primary progressers'). These patients have the highest unmet need as they have treatment-resistant tumours and have very poor outcomes compared to other patients. From the Keynote-426 data, the % of patients who have primary disease progression on Pembrolizumab plus Axitinib is only 10.9%"* o *"For patients, the most important outcome is the overall survival and this was the primary outcome being evaluated (and significantly improved) with this technology"* • From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Balaji Venugopal: o *"The overall survival data based on the first interim analysis indicates a 47% reduction in risk of death in patient treated with the technology compared to patients treated with sunitinib. Although the data is based on the first interim analysis, the statistically significant improvement in overall survival will translate in increasing the length of life than current care."* o *"This technology would be first of its kind to combine immune checkpoint inhibitor and VEGF TKI, which has shown improvement in all clinical relevant end points of progression free survival, overall survival and overall response rate."* Based on the conclusions reached by the Committee as detailed in the Appraisal Consultation Document, it would appear that the above input from clinical experts, who have experience of using pembrolizumab with axitinib for the treatment of patients with advanced renal cell carcinoma, has not been taken into consideration by the Committee. This is reflected by the statement on page 10, section 3.10 of the Appraisal Consultation Document which states *"Although the committee thought a durable response was possible, immaturity of the data meant that this was based on clinical opinion, scientific reasoning and short-term anecdotal evidence"*. The implication of this statement is that assumptions cannot be made about the appropriateness of overall survival extrapolations and duration of treatment effect, unless long-term data is already available to evidence the approach taken in the economic modelling. MSD consider this completely at odds with the ambition to bring early access to promising, innovative treatments, with the acknowledgment that where there is uncertainty, this can potentially be addressed with further data collection via mechanisms such as the Cancer Drugs Fund. The purpose of clinical expert opinion is to inform areas of uncertainty, so that in the	survival benefit. It also heard from patient experts that pembrolizumab with axitinib had a tolerable side effect profile, but concluded that all benefits had been captured in the QALY. See FAD section 3.3 and 3.21.

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			absence of data, appropriate judgements can be made based on scientific and clinical rationale. Nevertheless, in this case, it appears that little value has been placed on clinical experts' opinions when evaluating issues associated with clinical uncertainty. Additionally, page 9 of the Appraisal Consultation Document states, "*The committee noted that clinical estimations might not factor in assumptions about treatment duration or a stopping rule. So, they may not be directly comparable or suitable to inform the model.*" MSD considers this statement made within the document to be no more than conjecture. We consider it inappropriate for the Committee to make a comment that seemingly dismisses clinical expert opinion without solid justification, considering that the vast majority of phase III clinical trials investigating pembrolizumab have included a 2-year stopping rule which clinical experts would undoubtedly be aware of. Furthermore, as some of the clinical experts who have provided input during this appraisal are investigators on the KEYNOTE-426 trial, it appears somewhat presumptuous to suggest they may be unaware of the details of the clinical trial. MSD would urge the Committee to reconsider this statement.	FAD section 3.6 has been amended to remove the statement: "*The committee noted that clinical estimations might not factor in assumptions about treatment duration or a stopping rule. So, they may not be directly comparable or suitable to inform the model'.*
4	Consultee (company)	Merck Sharp & Dohme	**<u>Robustness of the network meta-analysis used for the intermediate and poor-risk subgroup analysis</u>** ***MSD asserts that the analyses conducted represent the most robust analyses that could have been done with the available evidence.*** MSD acknowledges the relatively small sample size of the CABOSUN trial compared to KEYNOTE 426. However, due to the lack of head-to-head data comparing cabozantinib to pembrolizumab or access to patient-level data for CABOSUN, the analyses conducted represent the most robust analyses possible with the available evidence. Other than some imbalance in the distribution of ethnicity between CABOSUN and KEYNOTE 426, the two trials were sufficiently comparable in terms of patient population, therefore an anchored indirect treatment comparison is a valid method to compare cabozantinib to pembrolizumab in the intermediate/poor risk population despite the limitation of small sample size [8].	Comment noted. The committee was aware of the limitations in the comparison with carbozantinib (small size of the CABOSAN trial, lack of head to head data with pembrolizumab + axitinib) and considered ICERs from the poor/intermediate IMDC risk group at both committee meetings. However, it concluded that the evidence in this

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				subgroup was weak and the ICERs were not cost-effective for routine commissioning. See FAD section 3.4.
5	Consultee (company)	Merck Sharp & Dohme	**Overall Survival Extrapolation and Treatment Effect Duration** ***MSD acknowledges the Committee's uncertainty surrounding the extrapolation of overall survival of both treatments owing to the immaturity of data from KEYNOTE-426. MSD believes that all clinical input throughout the appraisal process, alongside biological plausibility, has supported the original base case assumptions outlined within the company submission; justifying the use of alternative parametric distributions and a lifetime treatment effect. MSD has provided an updated base case; selecting conservative overall survival distributions.*** Clinical expert opinion throughout ID1426 MSD consider the issues of overall survival extrapolation and treatment effect duration to be intrinsically linked due to the impact on long term overall survival estimates. MSD is aware that for both issues the Committee considers there is a large degree of uncertainty owing to the immaturity of the data, and in the face of such uncertainty it is pivotal to consider clinical expert opinion: • From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Tom Waddell o *"would estimate that approximately 15% of patients will achieve long-term durable remission / cure with use of Pembrolizumab plus Axitinib. Due to the relatively early follow-up this plateau effect in the OS curve will not be seen for some time but should be considered"* • From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Balaji Venugopal o *"There are a proportion of patients treated with immune checkpoint inhibitors who can achieve durable clinical benefit that could last years, which is referred as "tail of the curve" in Kaplan Meier survival curves. This effect is proven in melanoma and early evidence with ipilimumab/nivolumab also supports this hypothesis"* • From technical report (page 18): "*Two clinical experts commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only)*". • From technical report (page 18): "*With regard to long term survival estimates for*	Comments noted. See responses below. Clinical expert opinion/mechanism of action Clinical experts were invited to attend the second committee meeting, where the committee considered their views on the technology. The company's comments on disregard of clinical expert opinion were also presented to the committee. It was aware that clinical experts expected immunotherapy to provide a durable response after stopping the treatment because of its mode of action but that this has not been

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			pembrolizumab with axitinib, the company clinical experts estimated a 50% survival at 5 years. An ERG clinical expert thought this may be optimistic. A clinical expert for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years" • From technical report (page 24): "*Two clinical experts have commented that a "tail of the curve" effect is likely to be observed for survival curves on combination immunotherapy. This could suggest a long duration of treatment effect is expected for pembrolizumab with axitinib. One expert commented that the effect of treatment could be durable (potentially lifelong) and beyond the duration of therapy in patients achieving long-term control. Another expert commented on a potential continued treatment effect on survival due to persistent activation of immuno-surveillance, but was unclear about the potential duration of effect*". It is important to note that **all** clinical expert input within this appraisal has suggested the strong probability of a lifetime treatment effect of pembrolizumab in combination with axitinib. <u>Mechanism of action</u> The rationale for this is due to the mechanism of action of pembrolizumab in combination with axitinib, which is outlined on page 8 of the Appraisal Consultation Document, which states "*They suggested that a different survival trajectory between pembrolizumab with axitinib and sunitinib could be expected. This was because of the differences in the biological mode of action between an immunotherapy and a TKI. The clinical experts explained that immunotherapy was expected to not only attack and kill the cancer cells, but also re-programme the immune system to recognise and adapt to attack and kill future cancer cells. This mode of action differed from a single TKI. The clinical experts supported an expected durable sustained response after treatment that was not expected with treatment from a single TKI.*" As previously mentioned within MSD's Technical Engagement consultation, from a biochemical point of view the mechanism of action of PD-L blockers like pembrolizumab, enables cytotoxic CD8+ T-cells to avoid an exhausted state, which allows them to keep the disease in a state of cancer-immune equilibrium that can potentially be maintained for up to several decades even in the absence of continued therapy [9] [10]. <u>Longer term KEYNOTE data</u> Longer term data from other KEYNOTE clinical trials has shown a continued treatment effect post discontinuation of pembrolizumab treatment at 2 years. In KEYNOTE-006 a long-term survival benefit has been observed in patients with advanced melanoma who were treated with pembrolizumab for up to 2 years [11]. In patients who ceased treatment after completing 35 doses of pembrolizumab at 2 years, 78.4% remained in progression-free survival for at least 24 months (censored) following discontinuation [11]. The long-term outcome seen in KEYNOTE-006 is generally consistent with the outcome seen in the melanoma cohort of KEYNOTE-001, which	confirmed with clinical evidence as yet. It concluded that there is not enough evidence to assume a lifetime treatment effect. See section 3.10 of FAD. <u>Longer-term KEYNOTE-data</u> The committee considered longer-term data from other KEYNOTE trials. It noted that data in KEYNOTE-006 and -010 were

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			did not include a 2-year stopping rule [12]. The cumulative and log-cumulative hazard plots below show that there is no structural difference between the hazards in these two trials. This can also be seen in the digitised KM data shown in Figures 1-3. This data points towards a sustained treatment effect post discontinuation of pembrolizumab in melanoma patients. **Figure 1 Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001**  **Figure 2 Cumulative and log-cumulative hazard plots for OS in KEYNOTE-006**	collected in different cancer types and used pembrolizumab as a monotherapy. Based on long-term follow up data from other checkpoint inhibitors, the committee believed it was reasonable to assume some duration of response. However, it agreed that it could not generalise the size of this effect from 1 cancer to another. It agreed that the long-term follow up data from KEYNOTE-035 were encouraging, but was concerned that the trial wasn't powered to assess overall survival. The committee maintained that the log-logistic distribution produced optimistic survival estimates based on the evidence provided. See FAD sections 3.6 and 3.11.

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			 **Figure 3 Comparison of Overall Survival curves of KEYNOTE-001 and KEYNOTE-006 in melanoma**  Appendix 1 provides a summary of the Phase 1b KEYNOTE-035 study, which provides the longest follow-up data in a population of patients with advanced renal cell carcinoma treated with pembrolizumab with axitinib. The long-term treatment effect of pembrolizumab post-	

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			discontinuation has been demonstrated in KEYNOTE-035, where, similarly to the KEYNOTE-426 study, pembrolizumab therapy ceased after 35 cycles (as per the trial protocol [13]) and axitinib therapy continued. At the latest cut-off date of KEYNOTE-035 (accruing almost 5-years of follow-up), [redacted] Consistency with previous appraisals of immunotherapy in RCC MSD would again draw comparison with TA581 (nivolumab and ipilimumab for untreated advanced renal cell carcinoma) when considering treatment effect duration [14]. The Evidence Review Group's comments on the company's response to the technical report are in agreement with the company position stating, "*The ERG agrees with the statement in the technical report that "the immaturity of data means that the long term treatment effect of the drug is unclear." We also agree with the company's statement (in reference to previous NICE pembrolizumab/immunotherapy-oncology appraisals in which a treatment waning effect had been included) that they "see no rationale for maintaining consistency with approaches adopted in appraisals concerning completely different indications" and that "a greater focus should be placed with maintaining consistency with precedent in previous appraisal of IO therapies for renal cell carcinoma". As noted by the company, in the appraisal of nivolumab and ipilimumab for untreated advanced renal cell carcinoma (NICE TA581), no reduction in treatment effect was included. For this reason, we did not include treatment waning in the ERG base case, but included it as a scenario analysis to allow for the possibility that a waning effect could be possible*." MSD acknowledges that there was no stopping rule implemented for nivolumab within TA581, in contrast to the pembrolizumab component of the combination therapy; however, it is fundamental then to consider the proportion of patients expected to receive long-term treatment. The median time on treatment for patients treated within CHECKMATE-214 (intermediate/poor patients) was only 7.4 months, in comparison to KEYNOTE-426 (all-comer population) with median time on treatment of 9.1 months [15]. In addition, to maintain the treatment effect from the TKI component in pembrolizumab in combination with axitinib in the long term, patients continued axitinib treatment until progression with 5.7% of patients modelled to continue to receive axitinib beyond 5 years. MSD would also like to recognise that within TA581, treatment of ipilimumab ceased after four cycles however a continued treatment effect was accepted by the respective Committee. Overall Survival estimates outlined in the Appraisal Consultation Document Page 10, section 3.9 of the Appraisal Consultation Document outlines the Committee's expected	Consistency with previous RCC appraisals The committee considered that the trial evidence was immature and that previous appraisals of checkpoint inhibitors where treatment length was capped at 2 years did not assume lifetime treatment effect. With regards to the mention of consistency with TA581, this was an appraisal on a subgroup of a different population (intermediate poor-risk IMDC population). The committee concluded that applying a treatment benefit waning effect was appropriate for decision making. Treatment waning effect The committee

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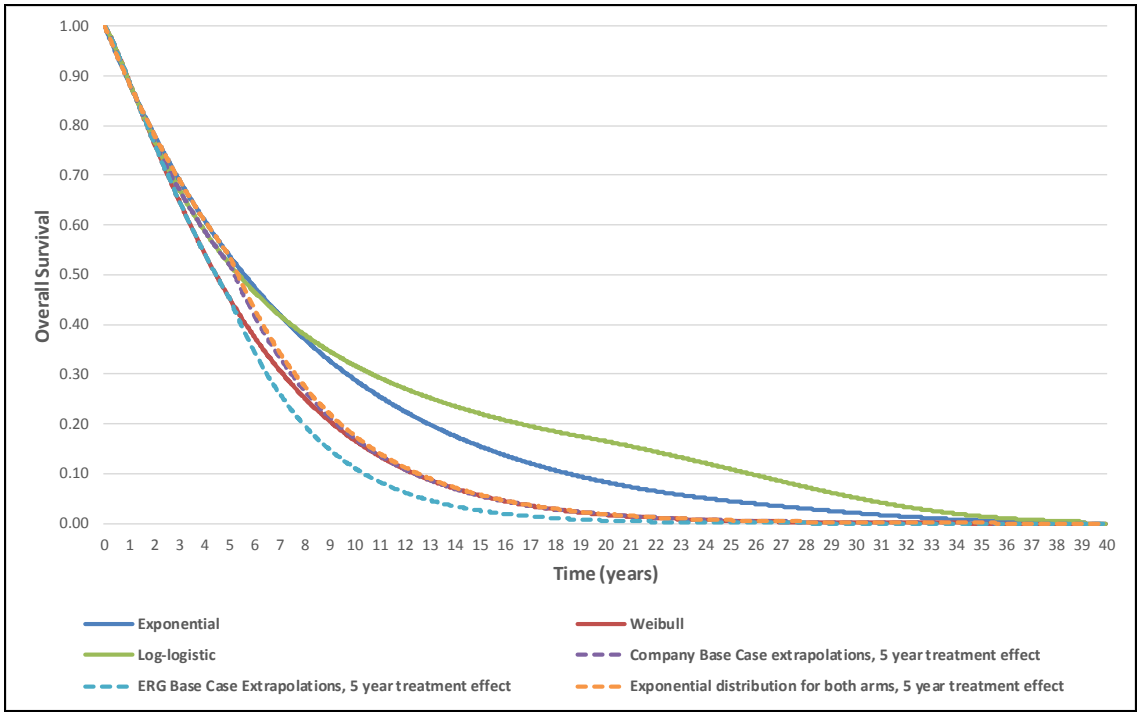
			overall survival range for pembrolizumab in combination with axitinib, stating: "*The committee concluded that the most plausible survival estimates were likely to fall within the range created by the log-logistic and Weibull distribution used in the company base case and the ERG and technical team base cases respectively. It agreed to take both into account in its decision making. However, it noted that considerable uncertainty remained because of the immaturity of the evidence.*" However, when a treatment effect cap of 5 years is implemented, regardless of extrapolation used, the overall survival curve produces estimates at, or below, the lower bound of the range established by the committee. This can be seen in Figure 4 below. **Figure 4 Overall survival extrapolations for pembrolizumab + axitinib, with and without 5 year treatment effect**  As such, MSD consider the implementation of a 5-year treatment effect to be both contradictory of all clinical expert opinion, but also produces implausibly low long term survival estimates.	considered a range of treatment effect duration assumptions. It concluded that a waning effect after 5 years was most plausible based on clinical expert opinion, the evidence presented and consistency with previous NICE appraisals of checkpoint inhibitors that included stopping rules. See FAD section 3.11.

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			<u>The use of different distributions to extrapolate survival for each of the trial arms</u> MSD agree that the immaturity of the KEYNOTE-426 trial data causes considerable uncertainty for the extrapolation of overall survival over the time horizon. The Appraisal Consultation Document gives a thorough account of the biological plausibility and clinical expert support for the use of different distributions to extrapolate survival for each of the trial arms, concluding on page 8 "*There was theoretical justification to use different distributions for each of the trial arms*". Despite this, page 8 the Appraisal Consultation Document states, "*However, it [the committee] concluded that there was insufficient robust evidence to justify using different distributions to extrapolate survival for each of the trial arms.*" MSD is disappointed with this decision by the Committee as, in the absence of mature data and more robust evidence, MSD consider clinical expert opinion and theoretical justification of the biological plausibility for using different distributions for each trial arm to be the 'next best' source of evidence. Furthermore, in relation to clinical validity and external data, TSD 14 states [16], "*It is likely that long-term external data will only be available for the control treatment, as by definition the experimental intervention is new… Hence, clinically valid and justifiable assumptions on issues such as duration of treatment effect are required to extrapolate long-term survival for the experimental treatment. These could be informed by clinical expert opinion and biological plausibility, and such assumptions should be subject to scenario analysis.*" Therefore, MSD considers that, in the context of this appraisal, the original base case assumption of using different distributions for each trial arm to be entirely justifiable if the model outcomes are aligned to clinical expectations. <u>The log-logistic distribution produces realistic overall survival estimates for pembrolizumab in combination with axitinib</u> Page 9, section 3.6 of the Appraisal Consultation Document states, "*Overall the committee considered the survival estimates from the log-logistic distribution used in the company base case [for the pembrolizumab in combination with axitinib arm] to be optimistic*". Table 1 below summarises the long-term overall survival estimates using the log-logistic distribution. **Table 1 Long-term OS estimates for pembrolizumab in combination with axitinib using the log-logistic distribution** **Year** | **Pembrolizumab / axitinib**	<u>Overall survival distributions</u> The committee considered both MSD's original base case (using the log-logistic distribution for pembrolizumab + axitinib and exponential distribution for sunitinib) and new base case at ACM2 (using the exponential distribution for both). The committee acknowledged that the overall survival data were immature and therefore that it was appropriate to consider various scenarios presented, including analyses when different distributions were applied. However, it concluded that there was insufficient robust evidence to justify using different distributions to extrapolate survival for each of the trial arms. See FAD section 3.5.

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1	88.5%
2	76.8%
3	66.7%
5	51.9%
10	31.6%
15	22.0%
20	16.5%

MSD is uncertain as to the Committee's rationale for the log-logistic curve providing optimistic long-term overall survival estimates for pembrolizumab in combination with axitinib. Although there is limited long-term data, clinical expert opinion throughout this appraisal process has been in line with these estimates:

- From technical report (page 17): "*Two clinical experts commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only)*".
- From technical report (page 17): "*With regard to long term survival estimates for pembrolizumab with axitinib, the company clinical experts estimated a 50% survival at 5 years. An ERG clinical expert thought this may be optimistic. A clinical expert for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years*"

In addition to Table 1, the use of the log-logistic model implicitly assumes that 17.4% of patients treated with pembrolizumab in combination with axitinib are effectively 'cured', as this is the proportion of patients alive at the intersection of the log-logistic hazard curve with the general population mortality rate. Although this assumption is implicit within the model, the proportion of patients who revert to general population mortality is in line with clinical opinion, as mentioned by Dr Tom Waddell's clinical expert statement, "*I would estimate that approximately 15% of patients will achieve longterm durable remission / cure with use of Pembrolizumab plus Axitinib. Due to the relatively early follow-up this plateau effect in the OS curve will not be seen for some time but should be considered. This 'tail of the curve' effect has been seen at a lower % level with single agent Nivolumab in RCC and is well described with immunotherapy in metastatic melanoma.*" Dr Balaji Venugopal's clinical expert statement also reflected this sentiment, "*There are a proportion of patients treated with immune checkpoint inhibitors who can achieve durable clinical benefit that could last years, which is referred as "tail of the curve" in Kaplan Mier survival curves.*"

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Statements made within the technical report also elude to a tail of the curve effect, synonymous with an implicit assumption of cure for a proportion of patients.

Therefore, according to extensive clinical expert opinion, the aforementioned biological plausibility owing to immune checkpoint inhibitor's mechanism of action, and additional data from KEYNOTE-035 trial, MSD does not consider the overall survival estimates produced by the log-logistic curve to be optimistic. MSD maintain that the log-logistic curve produces overall survival estimates in line with the clinical expectation that this innovative therapy will be step-changing in the treatment of advanced renal cell carcinoma.

<u>The Weibull distribution produces clinically implausible overall survival estimates for pembrolizumab in combination with axitinib</u>

Page 10 of the Appraisal Consultation Document states, "Clinical experts confirmed that a rising hazard rate, which was a characteristic of the chosen Weibull distribution, was not expected for people who had pembrolizumab with axitinib. Therefore, the committee agreed that the chosen Weibull distribution was likely to give pessimistic survival estimates." MSD agrees with this statement, however considers that the survival estimates produced by the Weibull curve are not only pessimistic but clinically implausible.

As mentioned in the Appraisal Consultation Document, the increasing hazard rate (in this instance) of the Weibull curve does not align with clinical opinion, resulting in no patients receiving a long-term durable benefit and consequently no tail of the curve effect. Table 2 below summarises the long-term overall survival estimates for the pembrolizumab in combination with axitinib arm.

Table 2 Long-term OS estimates for pembrolizumab in combination with axitinib using the Weibull distribution
<table>
<tr><th>Year</th><th>Pembrolizumab / axitinib</th></tr>
<tr><td>1</td><td>88.6%</td></tr>
<tr><td>2</td><td>76.2%</td></tr>
<tr><td>3</td><td>64.3%</td></tr>
<tr><td>5</td><td>44.9%</td></tr>
<tr><td>10</td><td>16.5%</td></tr>
<tr><td>15</td><td>5.5%</td></tr>
<tr><td>20</td><td>1.7%</td></tr>
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Although there is minimal variation between the 5-year overall survival estimates of the log-logistic and Weibull distributions, beyond 5 years the curves diverge and the Weibull distribution consequently produce incredibly pessimistic overall survival expectations. This is exemplified by comparing with expected life years gained for nivolumab in combination with ipilimumab. Although MSD recognises there are differences between the appraisals, within TA581 (in an intermediate/poor patient population only) the mean life years for nivolumab in combination with ipilimumab in the original ERG base case equalled 5.26 years [15]. However, the NICE Technical Team and ERG's preferred Weibull curve estimates 4.89 years in this appraisal of pembrolizumab with axitinib, in a patient population with a more favourable prognosis. This demonstrates the extent to which the Weibull curve underestimates the long-term benefit of pembrolizumab in combination with axitinib, and hence should not be considered as an appropriate distribution for modelling overall survival.

<u>The exponential curve could be considered a conservative estimate for pembrolizumab in combination with axitinib</u>

Page 10 of the Appraisal Consultation Document stated, "The committee concluded that the most plausible survival estimates were likely to fall within the range created by the log-logistic and Weibull distribution used in the company base case and the ERG and technical team base cases respectively. It agreed to take both into account in its decision making. However, it noted that considerable uncertainty remained because of the immaturity of the evidence."
As the Committee established, there is a high degree of uncertainty surrounding the extrapolation of overall survival. As outlined above, MSD considers the log-logistic distribution to provide overall survival estimates for pembrolizumab in combination with axitinib that are in line with clinical opinion and biological plausibility, whereas the Weibull curve greatly underestimates expected overall survival. As a conservative alternative, MSD considers the exponential curve to produce a 'lower bound' of expected overall survival estimates. The exponential curve was chosen within MSD's original base case for the extrapolation of overall survival as the estimates produced were broadly in line (slightly higher) with clinical expert opinion. Although it has been frequently noted throughout this appraisal that patients treated with pembrolizumab in combination with axitinib will experience a 'tail of the curve' or 'cure' effect, the exponential distribution assumes no such effect. Please see Table 3 for the overall survival estimates using the exponential distribution for both arms.

Table 3 Long-term OS estimates for pembrolizumab in combination with axitinib using the exponential distribution
<table>
<tr><th>Year</th><th>Pembrolizumab / axitinib</th><th>Sunitinib</th></tr>
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<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>1</td><td>88.3%</td><td>79.9%</td></tr>
<tr><td>2</td><td>78.0%</td><td>63.9%</td></tr>
<tr><td>3</td><td>68.7%</td><td>50.9%</td></tr>
<tr><td>5</td><td>53.5%</td><td>32.5%</td></tr>
<tr><td>10</td><td>28.7%</td><td>10.6%</td></tr>
<tr><td>15</td><td>15.4%</td><td>3.4%</td></tr>
<tr><td>20</td><td>8.2%</td><td>1.1%</td></tr>
</table>
Please see Appendix 2 for additional analyses surrounding overall survival extrapolation and treatment effect duration, including the updated base case using the exponential curve to extrapolate overall survival for both arms.</td><td></td></tr>
<tr><td>6</td><td>Consultee (company)</td><td>Merck Sharp & Dohme</td><td><u>Appropriateness of 2-year stopping rule for the pembrolizumab component of the combination therapy regimen in clinical practice, and inappropriateness of including re-treatment in the economic model, in order to be reflective of the stopping rule in clinical practice.</u>

If pembrolizumab with axitinib is recommended for the treatment of advanced renal cell carcinoma, MSD would support the implementation of a 2-year stopping rule for the pembrolizumab component of the combination therapy regimen in clinical practice, in line with KEYNOTE-426 study protocol [17]. Although the KEYNOTE-426 protocol permits certain patients (who meet a strict eligibility criteria), to be re-treated with pembrolizumab for a maximum of 17 cycles, MSD maintain our position that at present, it would be neither appropriate nor informative to include re-treatment in the economic modelling based on the KEYNOTE-426 data currently available.

As reflected on page 11, section 3.12 of the Appraisal Consultation Document, the KEYNOTE-426 protocol “applied a stopping rule after 35 cycles (approximately 2 years of continuous treatment). It allowed treatment to stop and restart within the 35 cycles, and allowed for another 17 cycles of retreatment because of relapse if the patient had stopped at 35 cycles or stopped because of complete remission.” This section of the Appraisal Consultation Document later goes on to confirm “The committee concluded that a 2-year treatment stopping rule in line with the clinical- and cost-effectiveness evidence was appropriate”.

Re-treatment has been an option in many pembrolizumab study protocols for previously approved</td><td>Comment noted. The committee was aware that no patients had received pembrolizumab retreatment and noted the limitations and complexities of modelling the effect on the ICER. It considered the scenario presented by the company, which based retreatment rates on those seen in the KEYNOTE-006 (melanoma) and KEYNOTE-010 (non-small cell lung cancer) but agreed that data from a different indication using pembrolizumab monotherapy were not generalisable to RCC. The committee concluded that the retreatment scenario presented in</td></tr>
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Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			indications [18-22]. However, a 2-year stopping rule has been implemented in clinical practice, reflective of the maximum duration of initial therapy, as per the respective study protocols. In keeping with MSD's approach in previous pembrolizumab submissions, the company's economic model did not include re-treatment in this submission for pembrolizumab plus axitinib for advanced renal cell carcinoma. We believe this approach is appropriate given the intention to apply a two-year stopping rule for the pembrolizumab component of the combination therapy regimen in clinical practice. The Appraisal Consultation Document correctly notes that the follow up of 20 months, based on the first interim analysis (August 2018 data cut), was shorter than the 2-year stopping rule, which means that the data which informed the submission did not provide evidence on the likely effect of the 2-year stopping rule, the proportion of patients who would restart treatment with pembrolizumab after having had 35 cycles, or the effectiveness of retreatment. In their response to Technical engagement, MSD notes that NHS England stated that they "*would wish such information or at least a range of assumptions which could reflect this information to be incorporated into the economic modelling as at least some patients in Keynote 426 will have had this protocol-specified re-treatment*" [7]. MSD would like to highlight some important considerations regarding the above statements: • As already acknowledged, KEYNOTE-426 follow-up it is not sufficiently long enough for any patients to have been re-treated. As further described in Comment 9, neither the August 2018 or January 2019 data-cuts included any patients who had a second course of pembrolizumab; therefore, not including the cost of re-treatment, is reflective of the clinical data informing the model. o However, if pembrolizumab with axitinib were to successfully gain access through the Cancer Drugs Fund (see comment 9), after completion of the data collection period, MSD will provide a cost-effectiveness analysis with appropriate adjustments to provide a plausible boundary of results as sensitivity analyses to address potential re-treatment with pembrolizumab (currently not observed in KEYNOTE-426) in a small number of patients. Modelling is complex due to study-specific circumstances, especially where longer-term data beyond those used in regulatory filing, and data after the initial public disclosure of the study results are of concerns because of the biases being introduced beyond the key timepoint. MSD share NICE's concerns and acknowledge that naïve and crude analyses would only introduce more biases and more noise into the decision-making process. MSD therefore strongly discourage such analyses at this stage, but recognise that it is an important methodological research topic to be explored	response to ACD was not appropriate for decision making. See FAD section 3.13 and 3.14.

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			in the near future. • Attempting to model re-treatment without any evidence of re-treatment from the January 2019 data-cut is strongly discouraged by MSD since: o There is insufficient data to support any assumptions on re-treatment in MSD trials, or in real-world practice o Any assumptions made in statistical models cannot be fully explored and justified without relevant data o There is currently no robust statistical methodology to address this issue in the presence of other biases and confounders, whether internally or in scientific literature	
7	Consultee (company)	Merck Sharp & Dohme	**Health-related quality of life** ***MSD maintains our base case assumption of using the time-to-death utility approach estimated using EQ-5D data from KEYNOTE-426.*** The justification of time-to-death based utilities is supported by page 12, section 3.13 of the Appraisal Consultation Document, which states "*Clinical experts confirmed that markers of disease progression, such as tumour size, may not have a strong correlation with quality of life. This suggests that a time-to-death approach to estimate health-related quality of life could be reasonable.*" MSD maintains that a time-to-death approach models the decline of a patient's health-related quality of life more accurately than using a health-state based approach. Page 12, section 3.13 of the Appraisal Consultation Document also states, "*Utilities were calculated by progression status and differentiated by treatment. They were higher for pembrolizumab with axitinib than those calculated for sunitinib for each respective health state.*" MSD considers this statement to be unclear. A scenario was presented within the company submission where utilities were modelled using a health-state based approach and differentiated by treatment, and upon request of the ERG a scenario where utilities were modelled using a time-to-death approach and differentiated by treatment was also provided. However, in the company and ERG base case, utilities were calculated by a time-to-death approach and were not differentiated by treatment. MSD believes it is important to recognise that in all previous Technology Appraisals of pembrolizumab across a variety of indications, health-related quality of life data from the relevant KEYNOTE studies has always been used, to some degree, to inform the economic model. In the vast majority of appraisals, the only source of utility data has been the respective KEYNOTE trial, despite in all cases EQ-5D questionnaires having limited distribution post patient progression. As such, MSD consider the best source of utility data to inform this appraisal should be derived	Comment noted. The committee was aware of the paucity of post-progression data in untreated advanced RCC. It was concerned that data collection on health-related quality of life stopped shortly after progression, which may have led to informative censoring bias in the clinical trial data. However, without further evidence, it concluded at the second meeting that post-progression utility values from both the literature and KEYNOTE-426 were acceptable for decision making. See FAD section 3.15. Section 3.15 has been amended to read '*The committee compared the utility values used for the*

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			solely from KEYNOTE-426 despite the limitations. Page 13, section 3.13 of the Appraisal Consultation Document states, "*The committee concluded that using values from the published literature for the progressed health state would be preferable to using the trial data.*" Although it is not established within the Appraisal Consultation Document which source of data could be more appropriate than using KEYNOTE-426 data, MSD has given consideration to the two sources which were considered as scenario analyses within the ERG report: TA215 (Pazopanib for the first-line treatment of advanced renal cell carcinoma) and TA512 (tivozanib for treating advanced renal cell carcinoma) [23] [24]. There were similar limitations with how utilities were derived in these appraisals to that of KEYNOTE-426: • TA215 [23]: o Company submission Page 173, "*HRQL was assessed using EQ-5D and the EORTC-QLQ-C30 questionnaires at baseline and at Weeks 8, 16, 24 and 48, following randomization in the pivotal trial VEG105192.*" o Company submission Page 209, "*Data on utility post-progression from VEGF105192 was not available and this was therefore estimated based on data from a secondary source.*" • TA512 [24]: o Company submission Page 132, "*In the TIVO-1 study, all patients were asked to complete the EQ-5D-3L questionnaire on the first day of each treatment cycle.*" o Company submission Page 133, "*Post-progression: for 275 patients who experienced progression on treatment, subsequent EQ-5D results were available. The estimate for post-progression utility was derived from the results from the first treatment cycle following the diagnosis of progression.*" It is therefore evident that the issue of limited post-progression data-collection on utilities is consistent across the sources identified by the ERG, and as such, MSD considers the utility values sourced from the literature to be less valid. The NICE reference case stipulates a preference for utility values to be obtained directly from the clinical trial when possible; hence MSD considers the base case assumption of time-to-death utilities sourced from the KEYNOTE-426 trial to be the most appropriate data source upon which to model health-related quality of life within this appraisal.	*progression-free and progressed states against those using the time-to-death approach in the company base case. The company also provided a scenario where utilities were calculated by progression status and differentiated by treatment.'*
8	Consultee (company)	Merck Sharp & Dohme	**<u>ICER threshold of £20,000 per QALY</u>** ***MSD believes that an ICER threshold of £30,000 per QALY gained should apply in this***	Comment noted. The FAD has been updated accordingly. See FAD

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			appraisal. We do not consider the level of uncertainty to be of such magnitude to warrant a decreased and much more restrictive cost-effectiveness threshold of £20,000 per QALY gained Page 13, section 3.15 of the Appraisal Consultation Document states, "*Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be at the lower end of the acceptable range (that is, around £20,000 per QALY gained).*" MSD appreciates that this is technically within process as per the NICE's guide to the methods of technology appraisal. However, MSD contests that the level of uncertainty founded within this appraisal is greater than the uncertainty seen in other appraisals seeking a CDF recommendation by NICE. On review of previous NICE appraisals which have been recommended for use within the CDF, and not meeting the End of Life criteria, MSD found that there were no other occurrences that the Committee had opted for the lower end of the acceptable range [25-30]. Furthermore, as the technology being appraised is a combination therapy with a high level of drug acquisition cost, MSD considers this decision by NICE to be directly preventative of patients gaining access to innovative new therapies with expected improvement to patient outcomes.	section 3.17.
9	Consultee (company)	Merck Sharp & Dohme	**Suitability of pembrolizumab with axitinib for the treatment of advanced renal cell carcinoma as a candidate for the Cancer Drugs Fund, and proposal to provide an additional data-cut, beyond the pre-specified final analysis, in order to provide further data which will address the clinical uncertainty identified over long-term survival.** ***Data from KEYNOTE-426 demonstrates that pembrolizumab with axitinib offers clinically meaningful and statistically significant overall survival and progression free survival benefits in patients affected with advanced renal cell carcinoma. MSD strongly believes that pembrolizumab with axitinib for treating advanced renal cell carcinoma should be considered as a suitable candidate for the Cancer Drugs Fund. Longer-term follow-up data from the KEYNOTE-426 study will become available in the future, which will address any uncertainties in the clinical and economic evidence. MSD wishes to underline that the aim of our submission fits with the ambition of the Cancer Drugs Fund, which is to "provide patients with faster access to the most promising new cancer treatments", while further evidence is collected to address clinical uncertainty.*** MSD is extremely disappointed that the NICE Committee reached a conclusion that *"pembrolizumab with axitinib did not meet the criteria to be considered for inclusion in the CDF*", as stated on page 16, section 3.1.8 of the Appraisal Consultation Document. The NICE website confirms that recommendations for use within the Cancer Drugs Fund can	Comment noted. The committee was aware of the company's offer to conduct a further analysis that could provide a further 3.5 years of data (giving around 5 years' worth of data in total) in the typical CDF timeframe of 2 years. Further analysis using this data would help reduce uncertainty on the fraction of people 'cured' for use in a 'mixture' cure model. However, there was no potential for routine use because all plausible ICERs were above £30,000 per QALY gained when commercial

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			be made when "*there is plausible potential for the drug to satisfy the criteria for routine commissioning, but <u>there is significant remaining clinical uncertainty which needs more investigation</u>, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid long delays, but we need more information on its effectiveness before it can be considered for routine commissioning"* [31]. As mentioned in previous comments, MSD acknowledges that currently, limited follow-up is available based on data from the first interim-analysis of KEYNOTE-426 (August 2018 data cut) which informs the economic modelling. Nevertheless, MSD urges the Committee to reconsider its opinion, as we strongly believe that with further data collection, clinical uncertainty would be reduced. We also assert that there is potential for this combination therapy to be cost-effective if the Committee and the Evidence Review Group take into consideration the robustness of the base case assumptions made within the economic model, based on the new evidence provided (Comment 5 / Appendix 2), which would make pembrolizumab with axitinib an eligible candidate for the Cancer Drugs Fund. It is worth noting that in the NICE appraisal of nivolumab with ipilimumab (TA581) for renal cell carcinoma, the Committee decided to recommend the combination therapy via the Cancer Drugs Fund despite recognition that "*When using the analysis that most closely reflected the committee's preferred assumptions the ICER was higher than would normally be considered a cost-effective use of NHS resources*" [32]. With this precedent in mind, MSD urges the Committee to revisit their negative recommendation in order to fund this combination therapy through the Cancer Drugs fund based on: • Clinically and statistically significant overall survival results from KEYNOTE-426 based on both data-cuts included in the company submission (August 2018 and January 2019). • Additional evidence provided in Appendix 1 and further described in Comment 5 which further supports a persistent and sustainable duration of treatment effect of pembrolizumab with axitinib at five years in patients with advanced renal cell carcinoma, further reducing the clinical uncertainties • The company cost-effectiveness base case is hugely and negatively impacted by the clinical uncertainties identified by the Committee; the further evidence provided in this response to the Appraisal Consultation Document robustly validates some of the assumptions used in the company's economic model (e.g. Further scenario analyses presented within Appendix 2 on alternative methods of modelling treatment effect duration and retreatment of pembrolizumab) Page 16, section 3.18 of the Appraisal Consultation Document lists the specific reasons for the draft recommendation on the unsuitability of pembrolizumab with axitinib as a candidate for the	arrangements were included in the analyses. Hence pembrolizumab with axitinib could not be recommended for use in the CDF. See FAD section 3.19.

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			Cancer Drugs Fund. MSD has responded to each point below, and request this be taken into consideration ahead of the second committee meeting: • "*The modelling of overall survival data was uncertain. There was no evidence to confirm that pembrolizumab with axitinib would have a durable response and the size of response is highly uncertain*" o As detailed in Comment 5, evidence to confirm that pembrolizumab with axitinib has a durable response are provided (Appendix 1) from the KEYNOTE-035 study. This not only validates the results obtained from the KEYNOTE-426 interim analyses (August 2018 and January 2019) and the economic model base case, but adds further clarity around the expected, and therefore correctly assumed, duration of response of pembrolizumab with axitinib for treating advanced renal cell carcinoma. • *"Further information could reduce this uncertainty: The number of people who complete 2 years of therapy or stop because of complete remission; The proportion of these 2 groups that relapse and when they do; The response to retreatment"* o The original data-cut from the first interim analysis of KEYNOTE-426 (dated August 2018) had a maximum follow-up of 22 months; consequently, this data cannot inform the above-mentioned areas of uncertainty identified by the Committee and NHS England, as reflected within the Committee papers for consultation. However, as detailed within MSD company submission, the subsequent KEYNOTE-426 database lock dated January 2019, which was not pre-specified but instead produced for the Food and Drug Administration to meet regulatory requirements, had a median follow-up of 17.4 months and a maximum follow-up of 27 months. This provides supportive evidence that pembrolizumab in combination with axitinib continued to demonstrate a statistically significant and clinically meaningful improvement in overall survival (HR 0.59) and progression free survival (HR 0.69) compared with sunitinib for the first-line treatment of participants with advanced renal cell carcinoma. Based on the January 2019 data cut, the percentage of subjects who discontinued study treatment by the data cut-off date [redacted] in the pembrolizumab + axitinib group [redacted] compared to the sunitinib group [redacted]. Of those who discontinued study treatment, [redacted] subjects in the pembrolizumab + axitinib group discontinued for complete response. [redacted] of subjects in the ITT population in the sunitinib group [redacted] discontinued the study due to death, compared to the pembrolizumab + axitinib group [redacted]. Of the [redacted] subjects who discontinued for complete response, [redacted] had progression of disease after treatment discontinuation based on BICR assessment per RECIST	

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			1.1. [redacted] had received the second course of pembrolizumab re-treatment (see Appendix 3 for additional information). • "*The company stated that further data cuts were expected from KEYNOTE-426. While further analysis using this data would help reduce uncertainty, the committee did not believe that the uncertainty would be resolved in the proposed timeframe with these data*". o At the time of the submission, MSD provided NICE with the confidential timeline concerning the estimated study completion date for KEYNOTE-426. However, based on the Committee's concerns around this timeframe and the consequent probability of being able to adequately reduce uncertainty, MSD is willing to conduct a further data cut for the KEYNOTE-426 study, beyond the pre-specified final-analysis. [redacted]. MSD is confident that the new proposed timeframe would meet the Committee's requirements to ensure that, after the potential data collection period within the Cancer Drugs Fund, the clinical uncertainty is resolved. • "*The Committee considered whether further information about progression-free survival would be useful to collect through the CDF. If everyone's disease had progressed by the end of the CDF data collection period, then it could be rule out a long-term immunotherapeutic effect with pembrolizumab*" o MSD disagrees with the assertion that disease progression by the end of the CDF data collection period would rule out a long-term immunotherapeutic effect, as radiological progression is not the only readout of immunotherapeutic effect. Arguably overall survival is a more clinically relevant readout; radiological progression would not preclude an extension of overall survival. • "*There is no plausible potential for routine use because all plausible ICERS were above £30,000 per QALY gained when commercial arrangements were included in the analyses'*" o As MSD is not aware of confidential discounts available to the NHS, it is not possible to comment where all plausible ICERs fall when the confidential discounts are accounted for. MSD maintains that pembrolizumab in combination with axitinib is step-changing in the treatment paradigm of advanced renal cell carcinoma and therefore would like to stress that the expected life year and QALY gain will be in line with the estimates provided by the company. With this taken into consideration, MSD believes that pembrolizumab in combination with	For clarity, section 3.19 of FAD has been amended to read: *'The committee considered whether further information about progression-free survival would be useful to collect through the CDF. If everyone's disease had progressed by the end of the CDF data collection period, then a long-term immunotherapeutic effect with pembrolizumab would be less likely.'*

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			axitinib is a cost-effective therapy that provides good value to the NHS. The significant survival results already obtained from the early data from KEYNOTE-426, alongside the 5 years' worth of evidence of long-term response derived from KEYNOTE-035, and MSD's commitment to providing further follow-up data from KEYNOTE-426 beyond the prespecified final analysis to resolve clinical uncertainty, all support MSD's belief that the combination of pembrolizumab with axitinib for treating advanced renal cell carcinoma meets the criteria to be funded through the Cancer Drugs Fund.	
10	Consultee (company)	Merck Sharp & Dohme	**Apparent inconsistencies in NICE appraisal committees' approaches when appraising, in parallel, two immuno-oncology/tyrosine kinase inhibitor combination therapy regimens, in the same patient population.** ***The focus on the 'uncertainty' of the KEYNOTE-426 data is also particularly questionable, in the context of no Appraisal Consultation Document being released for avelumab with within the same patient population (ID1547), which is also based on an early interim analysis with limited follow-up data. The apparent inconsistency in approach between two separate NICE committees appraising, in parallel, two immuno-oncology/tyrosine-kinase inhibitor combination therapies in the same patient population, is of great concern to MSD. The divergent NICE positions on these two combination therapy regimens is misaligned with current clinical opinion on these two combination therapy regimes, as reflected in the updated ESMO guideline*** It is important to note that both ID1426 and ID1547 have been running almost in parallel, with the first committee meeting for ID1547 occurring one week prior to the first committee meeting for ID1426. Following the first committee meeting for avelumab with axitinib (ID1547) which took place on 15 January 2020, if standard process had been followed and the result of the first committee meeting was an Appraisal Consultation Document, we would have expected this to enter the public domain week commencing 27th January 2020. As an Appraisal Consultation Document has not been released it would appear that areas of clinical uncertainty and the resultant implications for the economic modelling have been dealt with very differently by Committee C, in the context of pembrolizumab with axitinib (ID1426), as opposed to Committee B for avelumab with axitinib (ID1547). The manufacturer of avelumab plus axitinib (ID1547) presented results from two interim analyses of the JAVELIN renal 101 trial; the first dated June 2018 and the second dated January 2019. These data-cuts reported [redacted]. When the two	Comment noted. The committee considers an appraisal with respect its evidence base. Each appraisal is different and each committee considers the data presented to it on an individual basis to ascertain the clinical and cost effectiveness. ID1547 is still ongoing.

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			median follow-ups for KEYNOTE-426 and JAVELIN renal 101 are compared, it is evident that the KEYNOTE-426 data presented in ID1426 has a longer duration of follow-up. Additionally, KEYNOTE-426 is the only study to demonstrate a statistically significant overall survival advantage (for pembrolizumab with axitinib). In contrast for avelumab with axitinib, the overall survival endpoint in JAVELIN renal 101 was not met; consequently, the clinical uncertainty in relation to the longer-term survival associated with avelumab with axitinib is greater than the uncertainty in longer-term overall survival for pembrolizumab with axitinib for patients with untreated advanced renal cell carcinoma. The divergent NICE positions on these two combination therapy regimens also results in a misalignment with current clinical opinion on these two combination therapy regimes, as reflected in the updated European Society of Medical Oncology guideline [3] (published February 2020). This states that based on KEYNOTE-426 data, the combination of pembrolizumab and axitinib is recommended as front-line/treatment-naïve therapy for advanced disease. It is noteworthy that the guideline also states the following: "*Randomised trials of axitinib/avelumab and bevacizumab/atezolizumab have also been reported in the front-line/treatment-naïve setting [4, 5]. Both combinations were tested against sunitinib. Both achieved their pre-defined PFS co-primary endpoint, but neither have achieved the significant OS advantage over sunitinib. For this reason, neither combination features in the guidelines despite axitinib and avelumab having EMA approval. Final OS data are awaited."* As a general comment, MSD would urge the NICE Committees to adopt a more consistent approach to dealing with similar areas of uncertainty across appraisals.	
1	Consultee	[NCRI Bladder and Renal Clinical Research Group]	The committee have considered all the directly relevant evidence within the scope of the TA	Comment noted.
2	Consultee	[NCRI Bladder and Renal Clinical Research Group]	The summary of clinical effectiveness is a reasonable interpretation of the data.	Comment noted.
3	Consultee	[NCRI	I am unable to comment in any detail on the summary of cost effectiveness as this is outside my	Comment noted.

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		Bladder and Renal Clinical Research Group]	area of expertise and key components of the assessment are not available to me.	
4	Consultee	[NCRI Bladder and Renal Clinical Research Group]	The recommendation will be disappointing to patients and clinicians as this combination is among the most active treatments trialled to date in this condition and is likely to become the gold standard treatment globally where it is affordable.	Comment noted.
1	Consultee	Kidney cancer UK	We are concerned that although you state there is uncertainty in the data, we believe this would be resolved with further data collection within Cancer drugs fund and this should be a consideration.	Comment noted. The committee agreed that pembrolizumab + axitinib did not meet the criteria for inclusion in the Cancer Drugs Fund. This was because there was no plausible potential to be cost-effective for routine commissioning when commercial arrangements were considered. See FAD section 3.19.
2	Consultee	Kidney cancer UK	We are concerned that you have stated negatively that pembrolizumab and axitinib would have a substantial effect on the pathway. From a patient and professional point of view this combination would have a highly positive effect on the pathway giving patients the opportunity the best of two treatments, working together up front and therefore giving better outcomes in the long term.	Comment noted. The committee was aware of the impact of a positive recommendation on the pathway and noted that clinicians and patients would welcome a choice of treatment in first line RCC. See FAD section 3.1 and 3.2. Potential negative implications of a positive

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				recommendation on the pathway have been removed from FAD section 3.2, the first sentence of which now reads: *'The committee considered the current treatment pathway for renal cell carcinoma'*
3	Consultee	Kidney cancer UK	We are concerned that you are disregarding the clinical and patients' experts in this area and their expertise using these drugs and the real effects it is having on patient's tumour response and quality of life.	Comment noted. The committee was aware that combination therapies offer improved tolerability and longer duration of disease control than current first-line therapies. It noted that some people had little to no side effects with the technology and that side effects of standard treatment could substantially affect quality of life. See FAD section 3.1 and 3.2. To ensure their views were captured, clinical and patient experts were invited back to the second committee meeting. Their opinions were considered by the committee when making a recommendation.
4	Consultee	Kidney cancer UK	We are concerned that you are not considering the benefit of a treatment that is three weekly with a definite number of doses. This is beneficial to hospital resources and time for the patient. Additional this treatment does not need any pre-medications and has a low infusion reaction profile. This therefore makes it a cost-effective treatment. As stated by our patient and others we	Comment noted. The committee considered patient and clinical expert experience of using the

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			have talked to the side effect profile is also low and therefore is effective to bring quality of life to patients as well as response.	combination alongside the quality of life gain from the KEYNOTE-426 clinical trial. It agreed that no evidence of any additional benefits had been presented that could not be captured in the measurement of QALYs. The committee concluded that pembrolizumab with axitinib did not have plausible potential for routine commissioning, as all ICERs were over £30,000 when taking into consideration commercial arrangements. See FAD section 3.1, 3.15 and 3.21.
1	Consultee	Kidney Cancer Support Network	The committee, ERG and company agreed that pembrolizumab with axitinib does not meet end-of-life criteria for the overall renal cell carcinoma population. The committee agreed that the first end-of-life criterion (that treatment is indicated for patients with a short life expectancy, normally less than 24 months) in the intermediate and poor risk group was not met because the median overall survival in the sunitinib arm of CheckMate-214 was 26 months. We consider this observation of overall survival for sunitinib from CheckMate-214 to be an over-estimate, since it was taken from a clinical trial with pre-selected patients. A more realistic estimate of survival could be taken from real-world data to determine whether the pembrolizumab/axitinib combination meets the end-of-life criteria. A recent paper published in The Oncologist analysed real-world data to further evaluate the effectiveness of first line sunitinib in patients with metastatic RCC with favourable, intermediate or poor risk disease according to the International Metastatic RCC Database Consortium (IMDC) risk criteria. The study included 1769 patients; 318 (18.0%) had favourable risk, 1031 (58.3%) had intermediate risk, and 420 (23.7%) had poor risk disease. The median overall survival was 52.1 months in favourable risk patients versus 9.8 months in poor risk patients. In the intermediate risk group, overall survival was 35.1 months for those with one risk factor and 21.9 months for those with two risk factors.	Comment noted. The committee was aware that a range of estimates exist for overall survival with sunitinib. However, it noted that there was no robust overall survival evidence for cabozantinib, the standard of care comparator in the NHS for the poor/intermediate IMDC risk population. The committee concluded there was no evidence to support that the first end-of-life criterion (short life expectancy) had been

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			https://theoncologist.onlinelibrary.wiley.com/doi/epdf/10.1634/theoncologist.2019-0605 We feel that the pembrolizumab with axitinib combination should be considered an end-of-life treatment for patients with untreated metastatic RCC categorised as intermediate or poor risk according to IMDC risk criteria.	met in any of the IMDC risk groups, See FAD section 3.18.
2	Consultee	Kidney Cancer Support Network	The committee is not willing to consider the pembrolizumab/axitinib combination for inclusion in the Cancer Drugs Fund (CDF) due to uncertainty about the overall survival data and uncertainty about a potential durable response to treatment. Inclusion of the combination in the CDF for up to 3 years would enable collection of further survival data and resolve the uncertainty regarding a durable response to immunotherapy, while at the same time allow access to the treatment for patients looking for an effective and tolerable immunotherapy/VEGFR inhibitor treatment offering a potential long-term response.	Comment noted. The committee agreed that pembrolizumab + axitinib did not meet the criteria for inclusion in the Cancer Drugs Fund. This was because there was no plausible potential to be cost-effective for routine commissioning when commercial arrangements were considered. See FAD section 3.19.
3	Consultee	Kidney Cancer Support Network	The pembrolizumab/axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in advanced RCC and has been granted priority review status by the FDA. Having priority review status, the pembrolizumab/axitinib combination has been fast tracked for approval in a number of countries, including the USA, Canada and Europe, based on the phase 3 clinical trial data.	Comment noted.
4	Consultee	Kidney Cancer Support Network	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 patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these 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 the rest of Europe and North America.	Comment noted. The committee considered whether pembrolizumab + axitinib was innovative. It concluded that no evidence had been presented to suggest that additional benefits over current first-line treatment for RCC had not been captured in the measurement of QALYs. See FAD section 3. 21.
5	Consultee	Kidney Cancer Support	The pembrolizumab/axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to undergo NICE appraisal for untreated advanced RCC. Previous drug combinations have proven to be unsuccessful as a result of unacceptable side effects. However,	Comment noted. The committee was aware of the clinical evidence from

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		Network	the pembrolizumab/axitinib combination seems to be well tolerated, as well as proven to be more effective at extending survival compared to single agent therapy with sunitinib in the first line.	KEYNOTE-425 and concluded that pembrolizumab + axitinib was more effective than sunitinib for untreated renal cell cancer. It also noted clinical expert opinion that pembrolizumab + axitinib had a favourable side effect profile compare with other combination treatments. See FAD section 3.3 and 3.21.
6	Consultee	Kidney Cancer Support Network	Current first line treatments have proven to shrink tumours and delay disease progression in some patients; however, these treatment options are not effective for everyone. Choice in the first line, and access to new innovative treatments remains paramount to managing the progression of this disease. Undue restrictions in accessing the pembrolizumab/axitinib combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Having a choice of treatment would enable patients and oncologists to better control this disease and individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.	Comment noted. The committee was aware of the unmet need in this population and that a positive recommendation would allow more choice of treatment and individualised care plans. However, it concluded that the uncertainty in long-term overall survival meant it could not recommend the combination for use in the NHS. See FAD section 3.1.
7	Consultee	Kidney Cancer Support Network	Some immunotherapies have been shown to be effective in the treatment of non-clear cell RCC, especially papillary RCC. If recommended, the pembrolizumab/axitinib combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC. Inclusion of the pembrolizumab/axitinib combination in the CDF would enable collection of efficacy and tolerability data for the treatment of nonclear cell RCC to address this unmet need. https://meetinglibrary.asco.org/record/169447/abstract	Comment noted. The committee was aware that there is an unmet need for treating non-clear cell renal cancer and that further treatment options would be welcomed by clinicians and patients.

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				However, it concluded that pembrolizumab + axitinib was not cost effective so could not be recommended for use in the NHS. See FAD section 3.1.
1	Web comment	Robert Jones	"(Response on behalf of 15 senior oncology consultants) We believe the company (MSD) were justified in choosing different models for extrapolating long-term survival outcomes in the intervention group and the comparator group. The rationale comes from the high likelihood that a subgroup of patients will derive live-long benefit from an immune checkpoint inhibitor and that this subgroup will be considerably larger in patients who receive immune checkpoint inhibitors as first line therapy than in those who receive sunitinib (or another tyrosine kinase inhibitor) as first line. A hazard ratio for survival of 0.53 with high durable response rates makes the possibility of long - term outcomes plausible (1-3). The combined effect of the lower proportion of patients achieving durable response to second line nivolumab, and the fact that 30 – 40% of patients never receive a checkpoint inhibitor in the comparator group is likely to result in a different pattern of decay in the comparator arm (4-6) refs: 1 Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Alekseev B, Soulières D, Melichar B, Vynnychenko I, Kryzhanivska A, Bondarenko I, Azevedo SJ, Borchiellini D, Szczylik C, Markus M, McDermott RS, Bedke J, Tartas S, Chang YH, Tamada S, Shou Q, Perini RF, Chen M, Atkins MB, Powles T; KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.N Engl J Med. 2019 Feb 16. doi: 10.1056/NEJMoa1816714. 2 Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.N Engl J Med. 2018 Apr 5;378(14):1277-1290 3 Motzer RJ, Rini BI, McDermott DF, Arén Frontera O, Hammers HJ, Carducci MA, Salman P, Escudier B, Beuselinck B, Amin A, Porta C, George S, Neiman V, Bracarda S, Tykodi SS, Barthélémy P, Leibowitz-Amit R, Plimack ER, Oosting SF, Redman B, Melichar B, Powles T, Nathan P, Oudard S, Pook D, Choueiri TK, Donskov F, Grimm MO, Gurney H, Heng DYC,	Comment noted. The committee was aware that clinical experts expected pembrolizumab + axitinib to have a durable response, but that the size of this response was unknown. It acknowledged that the overall survival data were immature and therefore that it was appropriate to consider various scenarios presented, including analyses when different distributions were applied. However, it concluded that there was insufficient robust evidence to justify using different distributions to extrapolate survival for each of the trial arms. See FAD section 3.5.

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			Kollmannsberger CK, Harrison MR, Tomita Y, Duran I, Grünwald V, McHenry MB, Mekan S, Tannir NM Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019 Oct;20(10):1370-1385. 4 Final analysis of the CheckMate 025 trial comparing nivolumab (NIVO) versus everolimus (EVE) with >5 years of follow-up in patients with advanced renal cell carcinoma (aRCC) Motzer R et al. ASCO GO 2020. Rapid Abstract Session, Sat, 11:35 AM-12:30 PM and Poster Session (Board #D3), 5 CheckMate 025 Randomized Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma. Escudier B, Sharma P, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Gurney H, Donskov F, Peltola K, Wagstaff J, Gauler TC, Ueda T, Zhao H, Waxman IM, Motzer RJ; CheckMate 025 investigators. Eur Urol. 2017 Dec;72(6):962-971 6 Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN, Choueiri TK. Pazopanib versus sunitinib in metastatic renal-cell carcinoma.N Engl J Med. 2013 Aug 22;369(8):722-31."	
2	Web comment	Robert Jones	"(Response on behalf of 15 senior consultant oncologists) We believe it is very likely that there is a lifetime benefit from first line pembrolizumab with axitinib which is not seen in patients receiving sunitinib (or another first line tyrosine kinase inhibitor as monotherapy). None of the trials of first line checkpoint inhibitors has been followed up sufficiently to demonstrate this, but we believe there is good evidence that immune checkpoint inhibitors alter the natural history of cancer in some patients in such a way that lifelong immune control is likely (ie. that some patients are 'cured'). The KN-426 trial sponsor's estimate that 17% of patients experience such life-long control is, in our opinion, plausible. We believe the (admittedly short follow up) data from KN-426 are in keeping with a dramatic effect on survival and that the longer term follow up data from other first line immune checkpoint inhibitor trials in renal cancer (most notably the first line trial of ipilimumab plus nivolumab) strongly point to a subgroup of patients experiencing long-term disease control [1-3]. In contrast, patients who start their treatment pathway with a tyrosine kinase inhibitor appear to have a much lower chance of a durable response to immune checkpoint inhibitor where this is only accessed in the second (or subsequent) line [3,4]. We therefore do not agree with The Committee's opinion that it is appropriate to consider a 5-year waning effect	The committee noted that a durable response was clinically plausible with checkpoint inhibitors, but that immaturity of the data meant there was no evidence to support the size or duration of this effect. Expert opinion on long-term survival with pembrolizumab and axitinib was not consistent (estimates for 5-year survival ranged between 50% and 35%) and a

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			scenario to estimate cost effectiveness, but, rather, consider a life-long effect to be more likely, even when the duration of pembrolizumab is capped at two years. 1 Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Alekseev B, Soulières D, Melichar B, Vynnychenko I, Kryzhanivska A, Bondarenko I, Azevedo SJ, Borchiellini D, Szczylik C, Markus M, McDermott RS, Bedke J, Tartas S, Chang YH, Tamada S, Shou Q, Perini RF, Chen M, Atkins MB, Powles T; KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.N Engl J Med. 2019 Feb 16. doi: 10.1056/NEJMoa1816714. 2 Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.N Engl J Med. 2018 Apr 5;378(14):1277-1290 3 Motzer RJ, Rini BI, McDermott DF, Arén Frontera O, Hammers HJ, Carducci MA, Salman P, Escudier B, Beuselinck B, Amin A, Porta C, George S, Neiman V, Bracarda S, Tykodi SS, Barthélémy P, Leibowitz-Amit R, Plimack ER, Oosting SF, Redman B, Melichar B, Powles T, Nathan P, Oudard S, Pook D, Choueiri TK, Donskov F, Grimm MO, Gurney H, Heng DYC, Kollmannsberger CK, Harrison MR, Tomita Y, Duran I, Grünwald V, McHenry MB, Mekan S, Tannir NM Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019 Oct;20(10):1370-1385. 4 Final analysis of the CheckMate 025 trial comparing nivolumab (NIVO) versus everolimus (EVE) with >5 years of follow-up in patients with advanced renal cell carcinoma (aRCC) Motzer R et al. ASCO GO 2020. Rapid Abstract Session, Sat, 11:35 AM-12:30 PM and Poster Session (Board #D3),""	large amount of uncertainty surrounded the estimates at 10 and 20 years. The committee considered scenarios where treatment effect waned after 3 years, 5 years and 10 years (i.e. 1 year, 3 years and 7 years after stopping pembrolizumab).It concluded that a waning effect after 5 years was most plausible based on clinical expert opinion, the evidence presented and consistency with previous NICE appraisals of checkpoint inhibitors that included 2 year stopping rules. See FAD section 3.10 and 3.11.
3	Web comment	Robert Jones	(Response on behalf of a group of 15 senior consultant oncologists) We do agree with the Committee's view that the currently-available data from the pivotal trial (Keynote-426) are immature. However, we believe that every effort should be made to make this seemingly transformational treatment available to patients despite this uncertainty. We believe that planned updated analyses of the trial in the next two years will add significantly to our understanding of these data and will reduce uncertainty in the assumptions made in the health economic analysis sufficiently to allow a good understanding of the true cost effectiveness of this intervention. In particular, over this timeframe, we will see the impact of the 2-year stopping rule for	Comment noted. The committee agreed that pembrolizumab + axitinib did not meet the criteria for inclusion in the Cancer Drugs Fund. This was because there was no plausible potential to be

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			pemrolizumab. We therefore believe that the combination of pembrolizumab and axitinib should be considered potentially suitable for inclusion by the Cancer Drugs Fund.	cost-effective for routine commissioning when commercial arrangements were considered. See FAD section 3.19.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments
ID1426 Pembrolizumab ACD consult comments v0.1 040320 PS [ACIC].doc	Merck Sharp & Dohme	None	10	
ID1426 Pembrolizumab ACD cons response RCP-RCR 200220 PS [noACIC].doc	[NCRI Bladder and Renal Clinical Research Group] .doc	[None]	4	
ID1426 Pembrolizumab ACD consult response KCUK 28022020 LJ [noACIC].doc	Kidney cancer UK	None to decalre	4	
ID1426 Pembrolizumab ACD consult response KCSN 030320 PS [noACIC]	Kidney Cancer Support Network	None	7	
ID1426 ACD Compiled Web Comments.doc	Robert Jones	None	3	

NICE National Institute for Health and Care Excellence

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 4 March 2020 **email:** TACommC@nice.org.uk

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Merck Sharp & Dohme
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Kalpana D'Oca

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NICE National Institute for Health and Care Excellence

Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**General comment on content of the Appraisal Consultation Document and MSD's key concerns** MSD is encouraged that the Appraisal Consultation Document acknowledges the following: • Data from the KEYNOTE-426 clinical trial demonstrates that pembrolizumab with axitinib is more effective than sunitinib for people with untreated renal cell carcinoma. • People with untreated renal cell carcinoma would welcome a new treatment option as reported by the patient expert who contributed at the committee meeting, and who had also been a participant in the KEYNOTE-426 clinical trial. • The Committee recognised that for advanced renal cell carcinoma, there is a high unmet need for both patients and healthcare professionals, and an option that improves survival and reduces side effects would be welcomed by patients and clinicians to allow a greater choice of treatments and individualised care plans. Despite the above, MSD is concerned by the conclusions reached by the Committee in relation to the outstanding issues that were initially raised in the Technical Report and now further discussed in the Appraisal Consultation Document. Our main considerations are as follows: • MSD understands that the potential reimbursement of pembrolizumab with axitinib would have an impact on the existing renal cell carcinoma treatment pathway. However, the Appraisal Consultation Document fails to acknowledge that the renal cell carcinoma treatment landscape is evolving, and other new and different combination regimens recently approved for funding via the Cancer Drug Fund already have had the same impact on the current first-line and second-line treatment options (see Comment 2). • MSD acknowledges the Committee's view that there are certain areas of clinical uncertainty, due to the limited follow-up in the KEYNOTE-426 data which informed the company submission (first interim analysis; data cut-off date August 2018). Yet MSD considers it unfortunate that clinical expert input has not been utilised appropriately to better inform the Committee's conclusions. o The clinical expert input that was elicited during the appraisal process, in order to inform some of the key areas of uncertainty, is broadly supportive of the modelling approach and assumptions made by MSD in our base case concerning overall survival extrapolation and long-term duration of treatment effect. However much of this input has seemingly been disregarded by the Committee (see comment 3). MSD urges the Committee to place greater emphasis on utilising clinical expert opinion to inform the conclusions that the Committee reaches during the appraisal process. • MSD believes that all clinical input throughout the appraisal process, alongside biological plausibility, has supported the original base case assumptions outlined within the company submission; justifying the use of alternative parametric distributions and a lifetime treatment effect. MSD has provided an updated base case; selecting conservative overall survival distributions. • MSD believes that an ICER threshold of £30,000 per QALY gained should apply in this appraisal. We do not consider the level of uncertainty to be of such magnitude to warrant a decreased and much more restrictive cost-effectiveness threshold of £20,000 per QALY gained (see comment 8).

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	• MSD strongly believes that the combination of pembrolizumab with axitinib for treating advanced renal cell carcinoma is a suitable candidate for the Cancer Drugs Fund. Additional information, provided as part of this response to the Appraisal Consultation Document (see comment 9), including details about a proposed further data-cut from the KEYNOTE-426 study, supports the consideration of pembrolizumab with axitinib as an eligible candidate for the Cancer Drugs Fund. • The apparent inconsistency in the approach taken by two NICE Committees, appraising (in parallel) two immuno-oncology/tyrosine-kinase inhibitor combination therapies in the same patient population, is of great concern to MSD [1, 2] (see comment 10). We are yet to see any documentation released by NICE following the first committee meeting for ID1547; if standard process had been followed and the result of the first committee meeting was an Appraisal Consultation Document, we would have expected this to enter the public domain week commencing 27th January 2020. The apparent different conclusions reached by the NICE committees appraising these two topics at this time results in a divergence with clinical consensus on these therapies, as detailed in the ESMO guideline published in February 2020 [3], which recommends the combination of pembrolizumab and axitinib as front-line/treatment-naïve therapy for advanced disease. Avelumab with axitinib (ID1547) is not included in the ESMO guideline, since the combination has not yet demonstrated a significant OS advantage over sunitinib as detailed in the guideline.
2	**Introduction of pembrolizumab with axitinib into the treatment pathway, and potential impact on eligibility for subsequent therapies** ***MSD recognises that the introduction of pembrolizumab with axitinib in the first-line setting for the treatment of advanced renal cell carcinoma would have an impact on the current treatment pathway and eligibility for subsequent treatments. However, this is not a situation specific to pembrolizumab with axitinib; it would also apply (and has previously applied) to the introduction of any new immuno-oncology containing treatment regimen in the first-line setting.*** Pages 6-7, Section 3.2 of the Appraisal Consultation Document states that "*The Committee concluded that the introduction of pembrolizumab with axitinib was likely to have a substantial effect on the care pathway*". However, this statement, alongside the rest of Section 3.2 of the Appraisal Consultation Document, fails to recognise some important considerations, as follows: • In addition to pembrolizumab with axitinib, the renal cell carcinoma landscape will inevitably change in the future due to the development of further effective treatment options for this patient population; • Acknowledgment should be given to the fact that new treatment options will give patients the opportunity to receive benefits from more efficacious treatments earlier in the disease pathway, rather than focusing on reducing the options available in the second-line setting; • Other treatment regimens either currently funded or likely to be funded in the near future via the Cancer Drug Fund, such as nivolumab plus ipilimumab and avelumab plus axitinib, would have the same impact as pembrolizumab plus axitinib on the subsequent therapies used in the treatment pathway, given their modes of action [2, 4]; • As stated by NHS England in the committee papers for public consultation "*the 2nd line treatment rate is currently approximately 50-60% and so a combination of these 2 therapies [pembrolizumab and axitinib] employed as 1st line treatment removes concern that patients might miss out on one important type of 2nd line therapy if they receive the other important type as 1st line treatment*"; • The Committee's use of the word "*eligible*" in the context of subsequent therapy is inappropriate since, in theory and in practice, every patient would be eligible to receive treatment but their suitability for a specific intervention in the second-line setting may vary based on individual disease characteristics. It would be at the discretion of clinicians after

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	discussion with patients, to make a final recommendation on the most appropriate intervention. There remains an unmet need for novel agents to treat advanced renal cell carcinoma, which have durable clinical benefit and potential curative effects. The combination of pembrolizumab with axitinib investigated in KEYNOTE-426 is the first immuno-oncology combination therapy regimen to demonstrate statistically significant and clinically meaningful improvements in overall survival, progression free survival and objective response rate in renal cell carcinoma patients, irrespective of risk group classification [5]. MSD encourages NICE to acknowledge that the anticipated changes within the treatment pathway for patients with advanced renal cell carcinoma that may result following the introduction of pembrolizumab with axitinib, are not unexpected. Such impact on the treatment pathway has already been considered acceptable in light of other aforementioned new therapeutic options coming to market and recently approved via the Cancer Drug Fund.
3	**Value of clinical expert opinion to help address the uncertainty in survival estimates due to the limited duration of follow-up in the KEYNOTE-426 data which informed the company submission** ***Several sections of the Appraisal Consultation Document refer to the 'uncertainty' that remains in terms of overall survival estimates (page 13, section 3.14), and due to the immaturity of the evidence from the KEYNOTE-426 study (page 10, section 3.9; page 13, section 3.15). MSD considers that the clinical expert opinions provided during the committee meeting should have served to address some of the areas of uncertainty; however the expert input provided appears to have been largely disregarded.*** MSD urges the Committee to give due consideration to all information detailed below: *Clinical expert opinion provided during the appraisal process to date* In MSD's company submission, two data-cuts from the KEYNOTE-426 trial were presented, dated August 2018 (first-interim analysis) and January 2019 (second unplanned interim-analysis); these data-cuts reported a median follow-up of 13.2 months and 17.4 months respectively (maximum follow-up of 22 and 27 months respectively). With acceptance of the limited follow-up based on the data currently available from the KEYNOTE-426 study, MSD considers the opinions of clinical experts to be of paramount importance, in order to help address some key areas of uncertainty. The eminent clinical experts who participated in the technical engagement and the committee meeting not only have experience of treating this patient population in real-world practice, but also direct experience of using pembrolizumab with axitinib. MSD urges the NICE Committee to place a greater emphasis on utilising clinical expert opinion to inform the conclusions that the Committee reach during the appraisal process. In the context of a NICE appraisal, the "Guide to the processes of technology appraisal" [6] outlines the role of clinical experts in helping to clarify *"issues about the submitted evidence and to provide advice before, during and after committee meetings*"; clinical experts can also comment on the technical report, with the main purpose of providing "*views on the judgements made by the technical team*". MSD would therefore like to draw attention to the below clinical experts' opinions received during the technical engagement phase and the first committee meeting [7].

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Clinical expert comments concerning long-term efficacy and duration of response:

- From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Tom Waddell:
  - *"Due to the mechanism of action of checkpoint inhibitors, it is also observed that more patients achieve deep responses (>80% reduction in tumour volume) or complete responses (disappearance of all visible tumour) with the combination compared to standard of care. Some of these patients will have long-term durable remissions that may even equate to cure. This effect is not seen with use of VEGF TKIs where all patients will eventually progress and die as a result of the disease".*
  - *"would estimate that approximately 15% of patients will achieve long-term durable remission / cure with use of Pembrolizumab plus Axitinib. Due to the relatively early follow-up this plateau effect in the OS curve will not be seen for some time but should be considered"*
  - *"In addition, due to the 'tail of the curve' effect with the combination approach, it is likely that Pembrolizumab and Axitinib will result in long-term remissions for some patients. For these patients the threat of dying from their cancer will be almost entirely negated. This does not happen with single agent VEGF TKIs."*

- From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Balaji Venugopal:
  - *"There are a proportion of patients treated with immune checkpoint inhibitors who can achieve durable clinical benefit that could last years, which is referred as "tail of the curve" in Kaplan Meier survival curves. This effect is proven in melanoma and early evidence with ipilimumab/nivolumab also supports this hypothesis"*
  - *"There are a proportion of patients treated with this technology who can achieve durable clinical response and this response does not come with significant adverse events as noticed in the patients treated with ipilimumab/nivolumab which is now one of the standard of care in aRCC of intermediate or poor risk group."*

- From technical report (page 18): "*Two clinical experts commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only)*".
- From technical report (page 18): "*With regard to long term survival estimates for pembrolizumab with axitinib, the company clinical experts estimated a 50% survival at 5 years. An ERG clinical expert thought this may be optimistic. A clinical expert for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years*"
- From technical report (page 24): "*Two clinical experts have commented that a "tail of the curve" effect is likely to be observed for survival curves on combination immunotherapy. This could suggest a long duration of treatment effect is expected for pembrolizumab with axitinib. One expert commented that the effect of treatment could be durable (potentially lifelong) and beyond the duration of therapy in patients achieving long-term control. Another expert commented on a potential continued treatment effect on survival due to persistent activation of immuno-surveillance, but was unclear about the potential duration of effect*".

Clinical expert comments concerning effectiveness of pembrolizumab in combination with axitinib, in the context of other available treatment options:

- From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Tom Waddell:
  - *"It would be expected that this combination would be more effective than standard of care options for all patients with metastatic RCC. In particular this effect has been*

confirmed across all prognostic groups (favourable, intermediate and poor) and would be expected regardless of the histological subtype of RCC (clear and non-clear cell patient groups)".

- *"Additionally, in comparison to combination with Ipilimumab and Nivolumab, there will be fewer severe immune-related side-effects with Pembrolizumab and Axitinib. This will lead to fewer hospital admissions for management of toxicity"*
- *"All of the above parameters represent a huge step forwards in the treatment of metastatic RCC compared to using single agent VEGF TKIs such as Sunitinib. The durability of these responses for some patients is completely transformative, and therefore this combination significantly reduces the unmet need for responding patients"*
- *"With any treatment there will be a group of patients who do not respond at all (so called 'primary progressers'). These patients have the highest unmet need as they have treatment-resistant tumours and have very poor outcomes compared to other patients. From the Keynote-426 data, the % of patients who have primary disease progression on Pembrolizumab plus Axitinib is only 10.9%"*
- *"For patients, the most important outcome is the overall survival and this was the primary outcome being evaluated (and significantly improved) with this technology"*

- From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Balaji Venugopal:

  - *"The overall survival data based on the first interim analysis indicates a 47% reduction in risk of death in patient treated with the technology compared to patients treated with sunitinib. Although the data is based on the first interim analysis, the statistically significant improvement in overall survival will translate in increasing the length of life than current care."*
  - *"This technology would be first of its kind to combine immune checkpoint inhibitor and VEGF TKI, which has shown improvement in all clinical relevant end points of progression free survival, overall survival and overall response rate."*

Based on the conclusions reached by the Committee as detailed in the Appraisal Consultation Document, it would appear that the above input from clinical experts, who have experience of using pembrolizumab with axitinib for the treatment of patients with advanced renal cell carcinoma, has not been taken into consideration by the Committee.

This is reflected by the statement on page 10, section 3.10 of the Appraisal Consultation Document which states *"Although the committee thought a durable response was possible, immaturity of the data meant that this was based on clinical opinion, scientific reasoning and short-term anecdotal evidence"*. The implication of this statement is that assumptions cannot be made about the appropriateness of overall survival extrapolations and duration of treatment effect, unless long-term data is already available to evidence the approach taken in the economic modelling. MSD consider this completely at odds with the ambition to bring early access to promising, innovative treatments, with the acknowledgment that where there is uncertainty, this can potentially be addressed with further data collection via mechanisms such as the Cancer Drugs Fund. The purpose of clinical expert opinion is to inform areas of uncertainty, so that in the absence of data, appropriate judgements can be made based on scientific and clinical rationale. Nevertheless, in this case, it appears that little value has been placed on clinical experts' opinions when evaluating issues associated with clinical uncertainty.

Additionally, page 9 of the Appraisal Consultation Document states, "*The committee noted that clinical estimations might not factor in assumptions about treatment duration or a stopping rule. So, they may not be directly comparable or suitable to inform the model.*" MSD considers this statement made within the document to be no more than conjecture. We consider it inappropriate for the Committee to make a comment that seemingly dismisses clinical expert opinion without solid justification, considering that the vast majority of phase III clinical trials investigating pembrolizumab have included a 2-year stopping rule which clinical experts would undoubtedly be aware of.

	Furthermore, as some of the clinical experts who have provided input during this appraisal are investigators on the KEYNOTE-426 trial, it appears somewhat presumptuous to suggest they may be unaware of the details of the clinical trial. MSD would urge the Committee to reconsider this statement.
4	**Robustness of the network meta-analysis used for the intermediate and poor-risk subgroup analysis** ***MSD asserts that the analyses conducted represent the most robust analyses that could have been done with the available evidence.*** MSD acknowledges the relatively small sample size of the CABOSUN trial compared to KEYNOTE 426. However, due to the lack of head-to-head data comparing cabozantinib to pembrolizumab or access to patient-level data for CABOSUN, the analyses conducted represent the most robust analyses possible with the available evidence. Other than some imbalance in the distribution of ethnicity between CABOSUN and KEYNOTE 426, the two trials were sufficiently comparable in terms of patient population, therefore an anchored indirect treatment comparison is a valid method to compare cabozantinib to pembrolizumab in the intermediate/poor risk population despite the limitation of small sample size [8].
5	**Overall Survival Extrapolation and Treatment Effect Duration** ***MSD acknowledges the Committee's uncertainty surrounding the extrapolation of overall survival of both treatments owing to the immaturity of data from KEYNOTE-426. MSD believes that all clinical input throughout the appraisal process, alongside biological plausibility, has supported the original base case assumptions outlined within the company submission; justifying the use of alternative parametric distributions and a lifetime treatment effect. MSD has provided an updated base case; selecting conservative overall survival distributions.*** Clinical expert opinion throughout ID1426 MSD consider the issues of overall survival extrapolation and treatment effect duration to be intrinsically linked due to the impact on long term overall survival estimates. MSD is aware that for both issues the Committee considers there is a large degree of uncertainty owing to the immaturity of the data, and in the face of such uncertainty it is pivotal to consider clinical expert opinion: • From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Tom Waddell o *"would estimate that approximately 15% of patients will achieve long-term durable remission / cure with use of Pembrolizumab plus Axitinib. Due to the relatively early follow-up this plateau effect in the OS curve will not be seen for some time but should be considered"* • From "ID1426 Pembrolizumab Committee papers for consultation" – Dr. Balaji Venugopal o *"There are a proportion of patients treated with immune checkpoint inhibitors who can achieve durable clinical benefit that could last years, which is referred as "tail of the curve" in Kaplan Meier survival curves. This effect is proven in melanoma and early evidence with ipilimumab/nivolumab also supports this hypothesis"* • From technical report (page 18): "*Two clinical experts commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only)*". • From technical report (page 18): "*With regard to long term survival estimates for pembrolizumab with axitinib, the company clinical experts estimated a 50% survival at 5 years. An ERG clinical expert thought this may be optimistic. A clinical expert for the*

technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years"

- From technical report (page 24): "*Two clinical experts have commented that a "tail of the curve" effect is likely to be observed for survival curves on combination immunotherapy. This could suggest a long duration of treatment effect is expected for pembrolizumab with axitinib. One expert commented that the effect of treatment could be durable (potentially lifelong) and beyond the duration of therapy in patients achieving long-term control. Another expert commented on a potential continued treatment effect on survival due to persistent activation of immuno-surveillance, but was unclear about the potential duration of effect*".

It is important to note that **all** clinical expert input within this appraisal has suggested the strong probability of a lifetime treatment effect of pembrolizumab in combination with axitinib.

Mechanism of action

The rationale for this is due to the mechanism of action of pembrolizumab in combination with axitinib, which is outlined on page 8 of the Appraisal Consultation Document, which states "*They suggested that a different survival trajectory between pembrolizumab with axitinib and sunitinib could be expected. This was because of the differences in the biological mode of action between an immunotherapy and a TKI. The clinical experts explained that immunotherapy was expected to not only attack and kill the cancer cells, but also re-programme the immune system to recognise and adapt to attack and kill future cancer cells. This mode of action differed from a single TKI. The clinical experts supported an expected durable sustained response after treatment that was not expected with treatment from a single TKI.*" As previously mentioned within MSD's Technical Engagement consultation, from a biochemical point of view the mechanism of action of PD-L blockers like pembrolizumab, enables cytotoxic CD8+ T-cells to avoid an exhausted state, which allows them to keep the disease in a state of cancer-immune equilibrium that can potentially be maintained for up to several decades even in the absence of continued therapy [9] [10].

Longer term KEYNOTE data

Longer term data from other KEYNOTE clinical trials has shown a continued treatment effect post discontinuation of pembrolizumab treatment at 2 years. In KEYNOTE-006 a long-term survival benefit has been observed in patients with advanced melanoma who were treated with pembrolizumab for up to 2 years [11]. In patients who ceased treatment after completing 35 doses of pembrolizumab at 2 years, 78.4% remained in progression-free survival for at least 24 months (censored) following discontinuation [11]. The long-term outcome seen in KEYNOTE-006 is generally consistent with the outcome seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule [12]. The cumulative and log-cumulative hazard plots below show that there is no structural difference between the hazards in these two trials. This can also be seen in the digitised KM data shown in Figures 1-3. This data points towards a sustained treatment effect post discontinuation of pembrolizumab in melanoma patients.

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Figure 1 Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001

Figure 2 Cumulative and log-cumulative hazard plots for OS in KEYNOTE-006

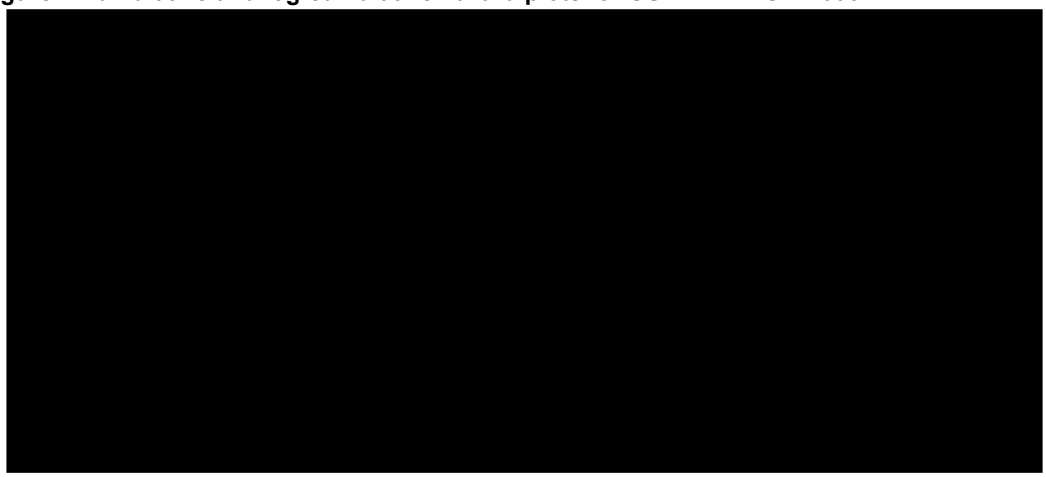

Figure 3 Comparison of Overall Survival curves of KEYNOTE-001 and KEYNOTE-006 in melanoma

Appendix 1 provides a summary of the Phase 1b KEYNOTE-035 study, which provides the longest follow-up data in a population of patients with advanced renal cell carcinoma treated with

	pembrolizumab with axitinib. The long-term treatment effect of pembrolizumab post-discontinuation has been demonstrated in KEYNOTE-035, where, similarly to the KEYNOTE-426 study, pembrolizumab therapy ceased after 35 cycles (as per the trial protocol [13]) and axitinib therapy continued. At the latest cut-off date of KEYNOTE-035 (accruing almost 5-years of follow-up), [redacted] Consistency with previous appraisals of immunotherapy in RCC MSD would again draw comparison with TA581 (nivolumab and ipilimumab for untreated advanced renal cell carcinoma) when considering treatment effect duration [14]. The Evidence Review Group's comments on the company's response to the technical report are in agreement with the company position stating, "*The ERG agrees with the statement in the technical report that "the immaturity of data means that the long term treatment effect of the drug is unclear." We also agree with the company's statement (in reference to previous NICE pembrolizumab/immunotherapy-oncology appraisals in which a treatment waning effect had been included) that they "see no rationale for maintaining consistency with approaches adopted in appraisals concerning completely different indications" and that "a greater focus should be placed with maintaining consistency with precedent in previous appraisal of IO therapies for renal cell carcinoma". As noted by the company, in the appraisal of nivolumab and ipilimumab for untreated advanced renal cell carcinoma (NICE TA581), no reduction in treatment effect was included. For this reason, we did not include treatment waning in the ERG base case, but included it as a scenario analysis to allow for the possibility that a waning effect could be possible.*" MSD acknowledges that there was no stopping rule implemented for nivolumab within TA581, in contrast to the pembrolizumab component of the combination therapy; however, it is fundamental then to consider the proportion of patients expected to receive long-term treatment. The median time on treatment for patients treated within CHECKMATE-214 (intermediate/poor patients) was only 7.4 months, in comparison to KEYNOTE-426 (all-comer population) with median time on treatment of 9.1 months [15]. In addition, to maintain the treatment effect from the TKI component in pembrolizumab in combination with axitinib in the long term, patients continued axitinib treatment until progression with 5.7% of patients modelled to continue to receive axitinib beyond 5 years. MSD would also like to recognise that within TA581, treatment of ipilimumab ceased after four cycles however a continued treatment effect was accepted by the respective Committee. Overall Survival estimates outlined in the Appraisal Consultation Document Page 10, section 3.9 of the Appraisal Consultation Document outlines the Committee's expected overall survival range for pembrolizumab in combination with axitinib, stating: "*The committee concluded that the most plausible survival estimates were likely to fall within the range created by the log-logistic and Weibull distribution used in the company base case and the ERG and technical team base cases respectively. It agreed to take both into account in its decision making. However, it noted that considerable uncertainty remained because of the immaturity of the evidence.*" However, when a treatment effect cap of 5 years is implemented, regardless of extrapolation used, the overall survival curve produces estimates at, or below, the lower bound of the range established by the committee. This can be seen in Figure 4 below.

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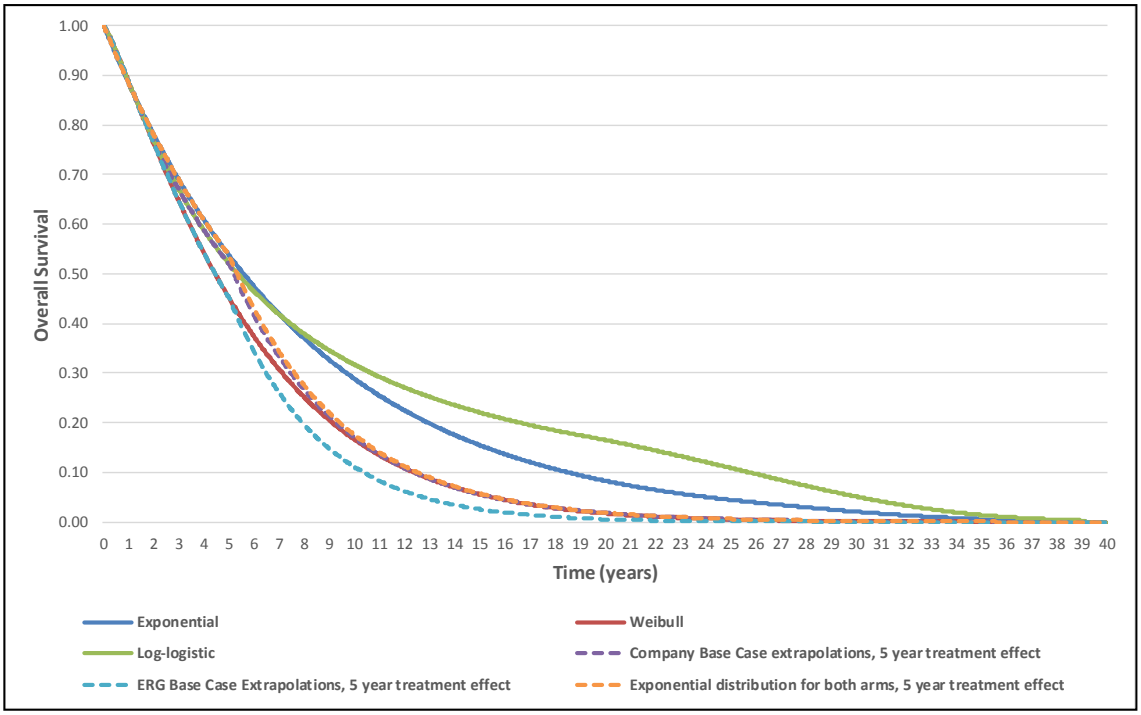
Figure 4 Overall survival extrapolations for pembrolizumab + axitinib, with and without 5 year treatment effect



As such, MSD consider the implementation of a 5-year treatment effect to be both contradictory of all clinical expert opinion, but also produces implausibly low long term survival estimates.

<u>The use of different distributions to extrapolate survival for each of the trial arms</u>

MSD agree that the immaturity of the KEYNOTE-426 trial data causes considerable uncertainty for the extrapolation of overall survival over the time horizon. The Appraisal Consultation Document gives a thorough account of the biological plausibility and clinical expert support for the use of different distributions to extrapolate survival for each of the trial arms, concluding on page 8 "*There was theoretical justification to use different distributions for each of the trial arms*". Despite this, page 8 the Appraisal Consultation Document states, "*However, it [the committee] concluded that there was insufficient robust evidence to justify using different distributions to extrapolate survival for each of the trial arms.*"

MSD is disappointed with this decision by the Committee as, in the absence of mature data and more robust evidence, MSD consider clinical expert opinion and theoretical justification of the biological plausibility for using different distributions for each trial arm to be the 'next best' source of evidence. Furthermore, in relation to clinical validity and external data, TSD 14 states [16], "*It is likely that long-term external data will only be available for the control treatment, as by definition the experimental intervention is new… Hence, clinically valid and justifiable assumptions on issues such as duration of treatment effect are required to extrapolate long-term survival for the experimental treatment. These could be informed by clinical expert opinion and biological plausibility, and such assumptions should be subject to scenario analysis.*"

Therefore, MSD considers that, in the context of this appraisal, the original base case assumption of using different distributions for each trial arm to be entirely justifiable if the model outcomes are aligned to clinical expectations.

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The log-logistic distribution produces realistic overall survival estimates for pembrolizumab in combination with axitinib

Page 9, section 3.6 of the Appraisal Consultation Document states, "*Overall the committee considered the survival estimates from the log-logistic distribution used in the company base case [for the pembrolizumab in combination with axitinib arm] to be optimistic*". Table 1 below summarises the long-term overall survival estimates using the log-logistic distribution.

Table 1 Long-term OS estimates for pembrolizumab in combination with axitinib using the log-logistic distribution

Year	Pembrolizumab / axitinib
1	88.5%
2	76.8%
3	66.7%
5	51.9%
10	31.6%
15	22.0%
20	16.5%

MSD is uncertain as to the Committee's rationale for the log-logistic curve providing optimistic long-term overall survival estimates for pembrolizumab in combination with axitinib. Although there is limited long-term data, clinical expert opinion throughout this appraisal process has been in line with these estimates:

- From technical report (page 17): "*Two clinical experts commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only)*".
- From technical report (page 17): "*With regard to long term survival estimates for pembrolizumab with axitinib, the company clinical experts estimated a 50% survival at 5 years. An ERG clinical expert thought this may be optimistic. A clinical expert for the technical team estimated a 30% survival at 5 years and a plateau of 25% survival at 10 and 20 years*"

In addition to Table 1, the use of the log-logistic model implicitly assumes that 17.4% of patients treated with pembrolizumab in combination with axitinib are effectively 'cured', as this is the proportion of patients alive at the intersection of the log-logistic hazard curve with the general population mortality rate. Although this assumption is implicit within the model, the proportion of patients who revert to general population mortality is in line with clinical opinion, as mentioned by Dr Tom Waddell's clinical expert statement, "*I would estimate that approximately 15% of patients will achieve longterm durable remission / cure with use of Pembrolizumab plus Axitinib. Due to the relatively early follow-up this plateau effect in the OS curve will not be seen for some time but should be considered. This 'tail of the curve' effect has been seen at a lower % level with single agent Nivolumab in RCC and is well described with immunotherapy in metastatic melanoma.*" Dr Balaji Venugopal's clinical expert statement also reflected this sentiment, "*There are a proportion of patients treated with immune checkpoint inhibitors who can achieve durable clinical benefit that could last years, which is referred as "tail of the curve" in Kaplan Mier survival curves.*" Statements made within the technical report also elude to a tail of the curve effect, synonymous with an implicit assumption of cure for a proportion of patients.

Therefore, according to extensive clinical expert opinion, the aforementioned biological plausibility owing to immune checkpoint inhibitor's mechanism of action, and additional data from KEYNOTE-035 trial, MSD does not consider the overall survival estimates produced by the log-logistic curve to

be optimistic. MSD maintain that the log-logistic curve produces overall survival estimates in line with the clinical expectation that this innovative therapy will be step-changing in the treatment of advanced renal cell carcinoma.

The Weibull distribution produces clinically implausible overall survival estimates for pembrolizumab in combination with axitinib

Page 10 of the Appraisal Consultation Document states, "*Clinical experts confirmed that a rising hazard rate, which was a characteristic of the chosen Weibull distribution, was not expected for people who had pembrolizumab with axitinib. Therefore, the committee agreed that the chosen Weibull distribution was likely to give pessimistic survival estimates.*" MSD agrees with this statement, however considers that the survival estimates produced by the Weibull curve are not only pessimistic but clinically implausible.

As mentioned in the Appraisal Consultation Document, the increasing hazard rate (in this instance) of the Weibull curve does not align with clinical opinion, resulting in no patients receiving a long-term durable benefit and consequently no tail of the curve effect. Table 2 below summarises the long-term overall survival estimates for the pembrolizumab in combination with axitinib arm.

Table 2 Long-term OS estimates for pembrolizumab in combination with axitinib using the Weibull distribution

Year	Pembrolizumab / axitinib
1	88.6%
2	76.2%
3	64.3%
5	44.9%
10	16.5%
15	5.5%
20	1.7%

Although there is minimal variation between the 5-year overall survival estimates of the log-logistic and Weibull distributions, beyond 5 years the curves diverge and the Weibull distribution consequently produce incredibly pessimistic overall survival expectations. This is exemplified by comparing with expected life years gained for nivolumab in combination with ipilimumab. Although MSD recognises there are differences between the appraisals, within TA581 (in an intermediate/poor patient population only) the mean life years for nivolumab in combination with ipilimumab in the original ERG base case equalled 5.26 years [15]. However, the NICE Technical Team and ERG's preferred Weibull curve estimates 4.89 years in this appraisal of pembrolizumab with axitinib, in a patient population with a more favourable prognosis. This demonstrates the extent to which the Weibull curve underestimates the long-term benefit of pembrolizumab in combination with axitinib, and hence should not be considered as an appropriate distribution for modelling overall survival.

The exponential curve could be considered a conservative estimate for pembrolizumab in combination with axitinib

Page 10 of the Appraisal Consultation Document stated, "*The committee concluded that the most plausible survival estimates were likely to fall within the range created by the log-logistic and Weibull distribution used in the company base case and the ERG and technical team base cases respectively. It agreed to take both into account in its decision making. However, it noted that considerable uncertainty remained because of the immaturity of the evidence."*
As the Committee established, there is a high degree of uncertainty surrounding the extrapolation of overall survival. As outlined above, MSD considers the log-logistic distribution to provide overall survival estimates for pembrolizumab in combination with axitinib that are in line with clinical opinion and biological plausibility, whereas the Weibull curve greatly underestimates expected overall

survival. As a conservative alternative, MSD considers the exponential curve to produce a 'lower bound' of expected overall survival estimates. The exponential curve was chosen within MSD's original base case for the extrapolation of overall survival as the estimates produced were broadly in line (slightly higher) with clinical expert opinion. Although it has been frequently noted throughout this appraisal that patients treated with pembrolizumab in combination with axitinib will experience a 'tail of the curve' or 'cure' effect, the exponential distribution assumes no such effect. Please see Table 3 for the overall survival estimates using the exponential distribution for both arms.

Table 3 Long-term OS estimates for pembrolizumab in combination with axitinib using the exponential distribution

Year	Pembrolizumab / axitinib	Sunitinib
1	88.3%	79.9%
2	78.0%	63.9%
3	68.7%	50.9%
5	53.5%	32.5%
10	28.7%	10.6%
15	15.4%	3.4%
20	8.2%	1.1%

Please see Appendix 2 for additional analyses surrounding overall survival extrapolation and treatment effect duration, including the updated base case using the exponential curve to extrapolate overall survival for both arms.

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6	**Appropriateness of 2-year stopping rule for the pembrolizumab component of the combination therapy regimen in clinical practice, and inappropriateness of including re-treatment in the economic model, in order to be reflective of the stopping rule in clinical practice.** ***If pembrolizumab with axitinib is recommended for the treatment of advanced renal cell carcinoma, MSD would support the implementation of a 2-year stopping rule for the pembrolizumab component of the combination therapy regimen in clinical practice, in line with KEYNOTE-426 study protocol [17]. Although the KEYNOTE-426 protocol permits certain patients (who meet a strict eligibility criteria), to be re-treated with pembrolizumab for a maximum of 17 cycles, MSD maintain our position that at present, it would be neither appropriate nor informative to include re-treatment in the economic modelling based on the KEYNOTE-426 data currently available.*** As reflected on page 11, section 3.12 of the Appraisal Consultation Document, the KEYNOTE-426 protocol *"applied a stopping rule after 35 cycles (approximately 2 years of continuous treatment). It allowed treatment to stop and restart within the 35 cycles, and allowed for another 17 cycles of retreatment because of relapse if the patient had stopped at 35 cycles or stopped because of complete remission."* This section of the Appraisal Consultation Document later goes on to confirm *"The committee concluded that a 2-year treatment stopping rule in line with the clinical- and cost-effectiveness evidence was appropriate".* Re-treatment has been an option in many pembrolizumab study protocols for previously approved indications [18-22]. However, a 2-year stopping rule has been implemented in clinical practice, reflective of the maximum duration of initial therapy, as per the respective study protocols. In keeping with MSD's approach in previous pembrolizumab submissions, the company's economic model did not include re-treatment in this submission for pembrolizumab plus axitinib for advanced renal cell carcinoma. We believe this approach is appropriate given the intention to apply a two-year stopping rule for the pembrolizumab component of the combination therapy regimen in clinical practice. The Appraisal Consultation Document correctly notes that the follow up of 20 months, based on the first interim analysis (August 2018 data cut), was shorter than the 2-year stopping rule, which means that the data which informed the submission did not provide evidence on the likely effect of the 2-year stopping rule, the proportion of patients who would restart treatment with pembrolizumab after having had 35 cycles, or the effectiveness of retreatment. In their response to Technical engagement, MSD notes that NHS England stated that they "*would wish such information or at least a range of assumptions which could reflect this information to be incorporated into the economic modelling as at least some patients in Keynote 426 will have had this protocol-specified re-treatment*" [7]. MSD would like to highlight some important considerations regarding the above statements: • As already acknowledged, KEYNOTE-426 follow-up it is not sufficiently long enough for any patients to have been re-treated. As further described in Comment 9, neither the August 2018 or January 2019 data-cuts included any patients who had a second course of pembrolizumab; therefore, not including the cost of re-treatment, is reflective of the clinical data informing the model. o However, if pembrolizumab with axitinib were to successfully gain access through the Cancer Drugs Fund (see comment 9), after completion of the data collection period, MSD will provide a cost-effectiveness analysis with appropriate adjustments to provide a plausible boundary of results as sensitivity analyses to address potential re-treatment with pembrolizumab (currently not observed in KEYNOTE-426) in a small number of patients. Modelling is complex due to study-specific circumstances, especially where longer-term data beyond those used in regulatory filing, and data after the initial public disclosure of the study results are of concerns

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	because of the biases being introduced beyond the key timepoint. MSD share NICE's concerns and acknowledge that naïve and crude analyses would only introduce more biases and more noise into the decision-making process. MSD therefore strongly discourage such analyses at this stage, but recognise that it is an important methodological research topic to be explored in the near future. • Attempting to model re-treatment without any evidence of re-treatment from the January 2019 data-cut is strongly discouraged by MSD since: o There is insufficient data to support any assumptions on re-treatment in MSD trials, or in real-world practice o Any assumptions made in statistical models cannot be fully explored and justified without relevant data o There is currently no robust statistical methodology to address this issue in the presence of other biases and confounders, whether internally or in scientific literature
7	**Health-related quality of life** ***MSD maintains our base case assumption of using the time-to-death utility approach estimated using EQ-5D data from KEYNOTE-426.*** The justification of time-to-death based utilities is supported by page 12, section 3.13 of the Appraisal Consultation Document, which states "*Clinical experts confirmed that markers of disease progression, such as tumour size, may not have a strong correlation with quality of life. This suggests that a time-to-death approach to estimate health-related quality of life could be reasonable.*" MSD maintains that a time-to-death approach models the decline of a patient's health-related quality of life more accurately than using a health-state based approach. Page 12, section 3.13 of the Appraisal Consultation Document also states, "*Utilities were calculated by progression status and differentiated by treatment. They were higher for pembrolizumab with axitinib than those calculated for sunitinib for each respective health state.*" MSD considers this statement to be unclear. A scenario was presented within the company submission where utilities were modelled using a health-state based approach and differentiated by treatment, and upon request of the ERG a scenario where utilities were modelled using a time-to-death approach and differentiated by treatment was also provided. However, in the company and ERG base case, utilities were calculated by a time-to-death approach and were not differentiated by treatment. MSD believes it is important to recognise that in all previous Technology Appraisals of pembrolizumab across a variety of indications, health-related quality of life data from the relevant KEYNOTE studies has always been used, to some degree, to inform the economic model. In the vast majority of appraisals, the only source of utility data has been the respective KEYNOTE trial, despite in all cases EQ-5D questionnaires having limited distribution post patient progression. As such, MSD consider the best source of utility data to inform this appraisal should be derived solely from KEYNOTE-426 despite the limitations. Page 13, section 3.13 of the Appraisal Consultation Document states, "*The committee concluded that using values from the published literature for the progressed health state would be preferable to using the trial data.*" Although it is not established within the Appraisal Consultation Document which source of data could be more appropriate than using KEYNOTE-426 data, MSD has given consideration to the two sources which were considered as scenario analyses within the ERG report: TA215 (Pazopanib for the first-line treatment of advanced renal cell carcinoma) and TA512 (tivozanib for treating advanced renal cell carcinoma) [23] [24]. There were similar limitations with how utilities were derived in these appraisals to that of KEYNOTE-426: • TA215 [23]: o Company submission Page 173, "*HRQL was assessed using EQ-5D and the EORTC-QLQ-C30 questionnaires at baseline and at Weeks 8, 16, 24 and 48, following randomization in the pivotal trial VEG105192.*"

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	o Company submission Page 209, "*Data on utility post-progression from VEGF105192 was not available and this was therefore estimated based on data from a secondary source.*" • TA512 [24]: o Company submission Page 132, "*In the TIVO-1 study, all patients were asked to complete the EQ-5D-3L questionnaire on the first day of each treatment cycle.*" o Company submission Page 133, "*Post-progression: for 275 patients who experienced progression on treatment, subsequent EQ-5D results were available. The estimate for post-progression utility was derived from the results from the first treatment cycle following the diagnosis of progression.*" It is therefore evident that the issue of limited post-progression data-collection on utilities is consistent across the sources identified by the ERG, and as such, MSD considers the utility values sourced from the literature to be less valid. The NICE reference case stipulates a preference for utility values to be obtained directly from the clinical trial when possible; hence MSD considers the base case assumption of time-to-death utilities sourced from the KEYNOTE-426 trial to be the most appropriate data source upon which to model health-related quality of life within this appraisal.
8	**ICER threshold of £20,000 per QALY** ***MSD believes that an ICER threshold of £30,000 per QALY gained should apply in this appraisal. We do not consider the level of uncertainty to be of such magnitude to warrant a decreased and much more restrictive cost-effectiveness threshold of £20,000 per QALY gained*** Page 13, section 3.15 of the Appraisal Consultation Document states, "*Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be at the lower end of the acceptable range (that is, around £20,000 per QALY gained).*" MSD appreciates that this is technically within process as per the NICE's guide to the methods of technology appraisal. However, MSD contests that the level of uncertainty founded within this appraisal is greater than the uncertainty seen in other appraisals seeking a CDF recommendation by NICE. On review of previous NICE appraisals which have been recommended for use within the CDF, and not meeting the End of Life criteria, MSD found that there were no other occurrences that the Committee had opted for the lower end of the acceptable range [25-30]. Furthermore, as the technology being appraised is a combination therapy with a high level of drug acquisition cost, MSD considers this decision by NICE to be directly preventative of patients gaining access to innovative new therapies with expected improvement to patient outcomes.
9	**Suitability of pembrolizumab with axitinib for the treatment of advanced renal cell carcinoma as a candidate for the Cancer Drugs Fund, and proposal to provide an additional data-cut, beyond the pre-specified final analysis, in order to provide further data which will address the clinical uncertainty identified over long-term survival.** ***Data from KEYNOTE-426 demonstrates that pembrolizumab with axitinib offers clinically meaningful and statistically significant overall survival and progression free survival benefits in patients affected with advanced renal cell carcinoma. MSD strongly believes that pembrolizumab with axitinib for treating advanced renal cell carcinoma should be considered as a suitable candidate for the Cancer Drugs Fund. Longer-term follow-up data from the KEYNOTE-426 study will become available in the future, which will address any uncertainties in the clinical and economic evidence. MSD wishes to underline that the aim of our submission fits with the ambition of the Cancer Drugs Fund, which is to "provide patients with faster access to the most promising new cancer treatments", while further evidence is collected to address clinical uncertainty.***

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	MSD is extremely disappointed that the NICE Committee reached a conclusion that *"pembrolizumab with axitinib did not meet the criteria to be considered for inclusion in the CDF*", as stated on page 16, section 3.1.8 of the Appraisal Consultation Document. The NICE website confirms that recommendations for use within the Cancer Drugs Fund can be made when "*there is plausible potential for the drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation, through data collection in the NHS or clinical studies. This means the CDF will fund the drug, to avoid long delays, but we need more information on its effectiveness before it can be considered for routine commissioning"* [31]. As mentioned in previous comments, MSD acknowledges that currently, limited follow-up is available based on data from the first interim-analysis of KEYNOTE-426 (August 2018 data cut) which informs the economic modelling. Nevertheless, MSD urges the Committee to reconsider its opinion, as we strongly believe that with further data collection, clinical uncertainty would be reduced. We also assert that there is potential for this combination therapy to be cost-effective if the Committee and the Evidence Review Group take into consideration the robustness of the base case assumptions made within the economic model, based on the new evidence provided (Comment 5 / Appendix 2), which would make pembrolizumab with axitinib an eligible candidate for the Cancer Drugs Fund. It is worth noting that in the NICE appraisal of nivolumab with ipilimumab (TA581) for renal cell carcinoma, the Committee decided to recommend the combination therapy via the Cancer Drugs Fund despite recognition that "*When using the analysis that most closely reflected the committee's preferred assumptions the ICER was higher than would normally be considered a cost-effective use of NHS resources*" [32]. With this precedent in mind, MSD urges the Committee to revisit their negative recommendation in order to fund this combination therapy through the Cancer Drugs fund based on: • Clinically and statistically significant overall survival results from KEYNOTE-426 based on both data-cuts included in the company submission (August 2018 and January 2019). • Additional evidence provided in Appendix 1 and further described in Comment 5 which further supports a persistent and sustainable duration of treatment effect of pembrolizumab with axitinib at five years in patients with advanced renal cell carcinoma, further reducing the clinical uncertainties • The company cost-effectiveness base case is hugely and negatively impacted by the clinical uncertainties identified by the Committee; the further evidence provided in this response to the Appraisal Consultation Document robustly validates some of the assumptions used in the company's economic model (e.g. Further scenario analyses presented within Appendix 2 on alternative methods of modelling treatment effect duration and retreatment of pembrolizumab) Page 16, section 3.18 of the Appraisal Consultation Document lists the specific reasons for the draft recommendation on the unsuitability of pembrolizumab with axitinib as a candidate for the Cancer Drugs Fund. MSD has responded to each point below, and request this be taken into consideration ahead of the second committee meeting: • "*The modelling of overall survival data was uncertain. There was no evidence to confirm that pembrolizumab with axitinib would have a durable response and the size of response is highly uncertain*" o As detailed in Comment 5, evidence to confirm that pembrolizumab with axitinib has a durable response are provided (Appendix 1) from the KEYNOTE-035 study. This not only validates the results obtained from the KEYNOTE-426 interim analyses (August 2018 and January 2019) and the economic model base case, but adds further clarity around the expected, and therefore correctly assumed, duration of response of pembrolizumab with axitinib for treating advanced renal cell carcinoma.

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- *"Further information could reduce this uncertainty: The number of people who complete 2 years of therapy or stop because of complete remission; The proportion of these 2 groups that relapse and when they do; The response to retreatment"*
  - The original data-cut from the first interim analysis of KEYNOTE-426 (dated August 2018) had a maximum follow-up of 22 months; consequently, this data cannot inform the above-mentioned areas of uncertainty identified by the Committee and NHS England, as reflected within the Committee papers for consultation. However, as detailed within MSD company submission, the subsequent KEYNOTE-426 database lock dated January 2019, which was not pre-specified but instead produced for the Food and Drug Administration to meet regulatory requirements, had a median follow-up of 17.4 months and a maximum follow-up of 27 months. This provides supportive evidence that pembrolizumab in combination with axitinib continued to demonstrate a statistically significant and clinically meaningful improvement in overall survival (HR 0.59) and progression free survival (HR 0.69) compared with sunitinib for the first-line treatment of participants with advanced renal cell carcinoma. Based on the January 2019 data cut, the percentage of subjects who discontinued study treatment by the data cut-off date [redacted] in the pembrolizumab + axitinib group [redacted] compared to the sunitinib group [redacted]. Of those who discontinued study treatment, [redacted] subjects in the pembrolizumab + axitinib group discontinued for complete response. [redacted] of subjects in the ITT population in the sunitinib group [redacted] discontinued the study due to death, compared to the pembrolizumab + axitinib group [redacted]. Of the [redacted] subjects who discontinued for complete response, [redacted] had progression of disease after treatment discontinuation based on BICR assessment per RECIST 1.1. [redacted] had received the second course of pembrolizumab re-treatment (see Appendix 3 for additional information).

- "*The company stated that further data cuts were expected from KEYNOTE-426. While further analysis using this data would help reduce uncertainty, the committee did not believe that the uncertainty would be resolved in the proposed timeframe with these data*".
  - At the time of the submission, MSD provided NICE with the confidential timeline concerning the estimated study completion date for KEYNOTE-426. However, based on the Committee's concerns around this timeframe and the consequent probability of being able to adequately reduce uncertainty, MSD is willing to conduct a further data cut for the KEYNOTE-426 study, beyond the pre-specified final-analysis. [redacted]. MSD is confident that the new proposed timeframe would meet the Committee's requirements to ensure that, after the potential data collection period within the Cancer Drugs Fund, the clinical uncertainty is resolved.

- "*The Committee considered whether further information about progression-free survival would be useful to collect through the CDF. If everyone's disease had progressed by the end of the CDF data collection period, then it could be rule out a long-term immunotherapeutic effect with pembrolizumab*"
  - MSD disagrees with the assertion that disease progression by the end of the CDF data collection period would rule out a long-term immunotherapeutic effect, as radiological progression is not the only readout of immunotherapeutic effect. Arguably overall survival is a more clinically relevant readout; radiological progression would not preclude an extension of overall survival.

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	• "*There is no plausible potential for routine use because all plausible ICERS were above £30,000 per QALY gained when commercial arrangements were included in the analyses*"" o As MSD is not aware of confidential discounts available to the NHS, it is not possible to comment where all plausible ICERs fall when the confidential discounts are accounted for. MSD maintains that pembrolizumab in combination with axitinib is step-changing in the treatment paradigm of advanced renal cell carcinoma and therefore would like to stress that the expected life year and QALY gain will be in line with the estimates provided by the company. With this taken into consideration, MSD believes that pembrolizumab in combination with axitinib is a cost-effective therapy that provides good value to the NHS. The significant survival results already obtained from the early data from KEYNOTE-426, alongside the 5 years' worth of evidence of long-term response derived from KEYNOTE-035, and MSD's commitment to providing further follow-up data from KEYNOTE-426 beyond the prespecified final analysis to resolve clinical uncertainty, all support MSD's belief that the combination of pembrolizumab with axitinib for treating advanced renal cell carcinoma meets the criteria to be funded through the Cancer Drugs Fund.
10	**Apparent inconsistencies in NICE appraisal committees' approaches when appraising, in parallel, two immuno-oncology/tyrosine kinase inhibitor combination therapy regimens, in the same patient population.** ***The focus on the 'uncertainty' of the KEYNOTE-426 data is also particularly questionable, in the context of no Appraisal Consultation Document being released for avelumab with within the same patient population (ID1547), which is also based on an early interim analysis with limited follow-up data. The apparent inconsistency in approach between two separate NICE committees appraising, in parallel, two immuno-oncology/tyrosine-kinase inhibitor combination therapies in the same patient population, is of great concern to MSD. The divergent NICE positions on these two combination therapy regimens is misaligned with current clinical opinion on these two combination therapy regimes, as reflected in the updated ESMO guideline*** It is important to note that both ID1426 and ID1547 have been running almost in parallel, with the first committee meeting for ID1547 occurring one week prior to the first committee meeting for ID1426. Following the first committee meeting for avelumab with axitinib (ID1547) which took place on 15 January 2020, if standard process had been followed and the result of the first committee meeting was an Appraisal Consultation Document, we would have expected this to enter the public domain week commencing 27th January 2020. As an Appraisal Consultation Document has not been released it would appear that areas of clinical uncertainty and the resultant implications for the economic modelling have been dealt with very differently by Committee C, in the context of pembrolizumab with axitinib (ID1426), as opposed to Committee B for avelumab with axitinib (ID1547). The manufacturer of avelumab plus axitinib (ID1547) presented results from two interim analyses of the JAVELIN renal 101 trial; the first dated June 2018 and the second dated January 2019. These data-cuts reported [redacted] When the two median follow-ups for KEYNOTE-426 and JAVELIN renal 101 are compared, it is evident that the KEYNOTE-426 data presented in ID1426 has a longer duration of follow-up. Additionally, KEYNOTE-426 is the only study to demonstrate a statistically significant overall survival advantage (for pembrolizumab with axitinib). In contrast for avelumab with axitinib, the overall survival endpoint in JAVELIN renal 101 was not met; consequently, the clinical uncertainty in relation to the longer-term survival associated with avelumab with axitinib is greater than the uncertainty in longer-term

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	overall survival for pembrolizumab with axitinib for patients with untreated advanced renal cell carcinoma. The divergent NICE positions on these two combination therapy regimens also results in a misalignment with current clinical opinion on these two combination therapy regimes, as reflected in the updated European Society of Medical Oncology guideline [3] (published February 2020). This states that based on KEYNOTE-426 data, the combination of pembrolizumab and axitinib is recommended as front-line/treatment-naïve therapy for advanced disease. It is noteworthy that the guideline also states the following: "*Randomised trials of axitinib/avelumab and bevacizumab/atezolizumab have also been reported in the front-line/treatment-naïve setting [4, 5]. Both combinations were tested against sunitinib. Both achieved their pre-defined PFS co-primary endpoint, but neither have achieved the significant OS advantage over sunitinib. For this reason, neither combination features in the guidelines despite axitinib and avelumab having EMA approval. Final OS data are awaited.*" As a general comment, MSD would urge the NICE Committees to adopt a more consistent approach to dealing with similar areas of uncertainty across appraisals.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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APPENDIX 1: KEYNOTE-035 - LONGER TERM DATA CONCERNING PEMBROLIZUMAB IN COMBINATION WITH AXITINIB IN PATIENTS WITH TREATMENT-NAIVE ADVANCED RENAL CELL CARCINOMA (RCC)

The KEYNOTE-035 study is an open-label phase 1b, multicentre study that evaluated the safety and efficacy of axitinib in combination with pembrolizumab in patients with treatment-naive advanced renal cell carcinoma (RCC). The study consisted of two phases: a dose-finding phase to estimate the maximum tolerated dose and select a recommended phase 2 dose, and a dose-expansion phase. The study is registered with the ClinicalTrials.gov Identifier NCT02133742 and a description of the study with its initial results were published by Atkins and colleagues in 2018 (https://doi.org/10.1016/S1470-2045(18)30081-0).

Study design

KEYNOTE-035 was a phase 1b, open-label, multi-centre, multiple-dose, safety, pharmacokinetic and pharmacodynamic study of axitinib in combination with pembrolizumab in adult patients with previously untreated advanced RCC. This clinical study was composed of a *Dose Finding Phase* and a *Dose Expansion Phase*. The Dose Finding Phase estimated the maximum tolerated dose (MTD) in patients with advanced RCC patients with clear cell histology who did not receive any prior systemic therapy for their advanced disease, using the modified toxicity probability interval (mTPI) method.

The *Dose Finding Phase* lead to the identification of an *Expansion Test Dose* for axitinib in combination with pembrolizumab in patients with advanced RCC who did not receive prior systemic therapy. The *Expansion Test Dose* will be either the MTD (i.e. the highest dose of axitinib and pembrolizumab associated with the occurrence of dose-limiting toxicity [DLTs] in <33% of patients) or the recommended phase 2 dose (RP2D), i.e. the highest tested dose that is declared safe and tolerable by the Investigators and Sponsor. Once the *Expansion Test Dose* was identified, the *Dose Expansion Phase* opened and axitinib in combination with pembrolizumab was tested in patients with previously untreated advanced RCC. Approximately 60 patients were planned to be enrolled in the study.

The primary objective of the study was:

- To assess the safety and tolerability of axitinib in combination with pembrolizumab in patients with previously untreated advanced RCC in order to estimate the MTD and select the RP2D.

The secondary objectives of the study were:

- To evaluate the overall safety profile of axitinib in combination with pembrolizumab.
- To assess the anti-tumor activity of axitinib in combination with pembrolizumab in patients with advanced RCC in the first-line treatment setting.
- To characterize the pharmacokinetics (PK) of axitinib and axitinib plus pembrolizumab when administered in combination, and to assess the effect of pembrolizumab on the PK of axitinib.
- To characterize, using translational approaches, genes and proteins such as PD-L1, VEGF-A and IL-8 relevant to angiogenesis drug target pathway, renal cell carcinoma biology, and sensitivity/resistance mechanisms to axitinib in combination with pembrolizumab in tumor and/or blood.
- To explore the pharmacodynamic effect of axitinib in combination with pembrolizumab in blood and tumor by assessment of gene, RNAs and proteins including but not limited to VEGF-A, IL-8 and VEGFR2 and T-cell receptors.
- To assess the immunogenicity of pembrolizumab.

The primary endpoint was investigator-assessed dose-limiting toxicity during the first two treatment cycles (6 weeks) of the dose-finding phase to estimate the maximum tolerated dose and recommended phase 2 dose. Dose-limiting toxicity was classified as any of the following: grade 4 neutropenia or thrombocytopenia, grade 3 or worse neutropenic infection or thrombocytopenia with bleeding, or febrile neutropenia; non-haematological grade 3 or worse toxicity; and inability to complete at least 75% of axitinib dosing or two infusions of pembrolizumab due to treatment-related toxicity occurring during the 6-week observation period for dose-limiting toxicities and attributable to one or both study drugs.

Secondary endpoints were adverse events (AEs), laboratory abnormalities, vital signs, PD-L1 biomarker status, pharmacokinetics, immunogenicity (anti-drug antibodies), serum and whole blood biomarkers, and antitumour activity. Antitumour activity was assessed as the proportion of patients who achieved an objective response, defined as those who achieved a confirmed complete response or confirmed partial response according to RECIST version 1.1 definitions (≥30% decrease in tumour size from baseline), and as duration of response (defined as the time from the first documentation of objective tumour response [complete or partial response] that was subsequently confirmed until the first documentation of objective tumour progression or death due to any cause, whichever occurred first), progression-free survival (PFS, defined as time from first pembrolizumab dose to first documentation of objective tumour progression, or on-study death due to any cause, whichever occurred first), and overall survival (OS, defined as the time from the first dose of study treatment to the date of death due to any cause). Patients who were taken off treatment because of toxicity, without evidence of disease progression, had their progression-free survival censored at the time of their last on-study CT scan assessment.

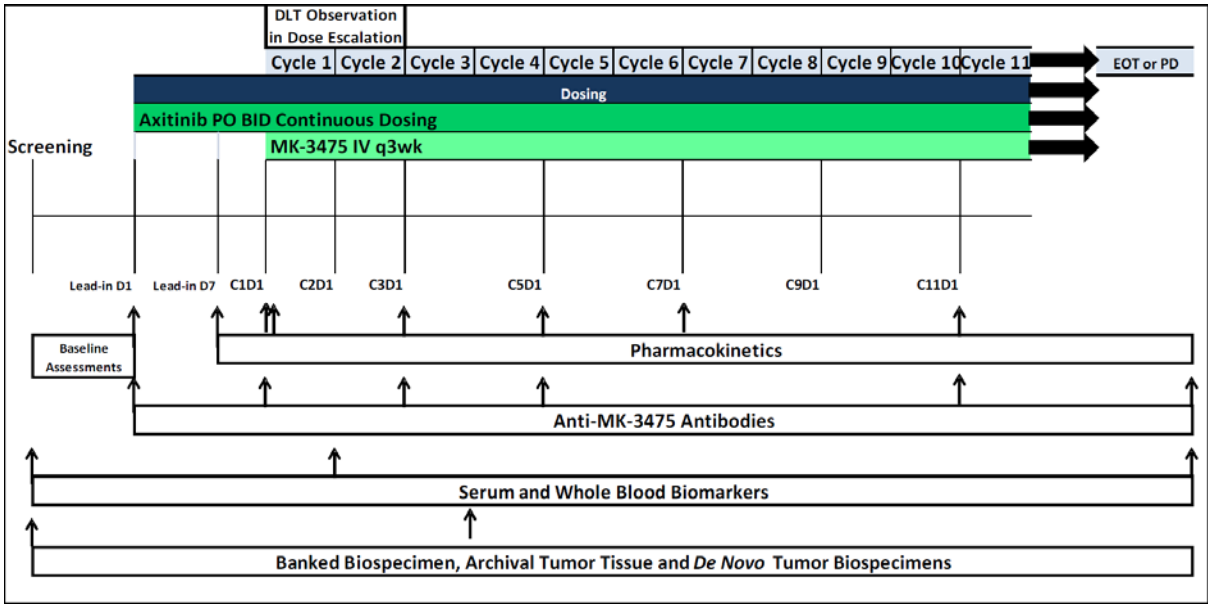
Eligible patients were aged 18 years or older with histologically or cytologically confirmed advanced RCC, predominantly clear cell subtype, who had undergone resection of their primary tumour; with at least one measurable lesion, defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; controlled hypertension (baseline blood pressure ≤150/90 mm Hg); and adequate bone marrow, renal, and liver function. Patients enrolled also had to provide an archival tumour biospecimen and undergo a baseline de-novo biopsy from a metastatic lesion. Patients were excluded if they had previous systemic therapy for metastatic RCC; disease progression or relapse within 12 months after completing adjuvant or neoadjuvant treatment; or previous treatment with axitinib, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 antibody. Additionally, patients were excluded if they had a diagnosis of immunodeficiency, active or documented history of autoimmune disease, gastrointestinal abnormalities, active or documented history of bleeding disorder, or a history of known active seizure disorder.

Axitinib was administered orally (starting dose 5 mg twice daily) beginning on day –7 (ie, 7 days before the start of cycle 1), and pembrolizumab 2 mg/kg intravenously on day 1 of each 3-week cycle. The possible dose-finding scenarios based on the starting dose level tolerability were: dose level 1, axitinib 5 mg twice daily plus pembrolizumab 2 mg/kg on day 1 of each 3-week cycle and dose level –1, axitinib 3 mg twice daily plus pembrolizumab 2 mg/kg on day 1 of each 3-week cycle. Dose level –1 was to be explored only if the maximum tolerated dose was exceeded at dose level 1. No intra-patient dose escalation was permitted during the dose-finding phase. Planned treatment duration with pembrolizumab was 2 years based on its use in other studies, calculated from the first dose of pembrolizumab. After completing treatment with pembrolizumab, patients who achieved an objective response or stable disease were able to continue treatment with single-drug axitinib until confirmed disease progression, patient refusal, or unacceptable toxicity, whichever occurred first. Per

the protocol and according to the investigator's judgment, if patients with evidence of disease progression were still deriving clinical benefit, they were eligible for continued treatment. Retreatment with pembrolizumab for patients who discontinued treatment because they attained a confirmed complete response and then had radiological disease progression was allowed. No planned breaks of axitinib treatment or alternative axitinib treatment schedules were used in this study. Treatment with axitinib was paused as necessary in the case of toxicity and then resumed at the dose indicated by the protocol when the toxicity was resolved.

The expansion-phase dose was the recommended phase 2 dose. During the dose-finding phase, the study design did not allow testing doses higher than the recommended dose of axitinib 5 mg twice daily and pembrolizumab 2 mg/kg. In the expansion phase, intra-patient dose escalation of axitinib was permitted after 12 weeks of treatment based on tolerability and axitinib prescribing information. Patients who tolerated the starting dose with no grade 2 or worse drug-related adverse events had the option to have their axitinib dose increased from 5 mg twice daily to 7 mg twice daily, and then to a maximum of 10 mg twice daily (unless their blood pressure was >150/90 mm Hg or the patient was receiving antihypertensive medication).

Figure 1 KEYNOTE-035 study schema



BID: twice a day, DLT: dose-limiting toxicity, EOT: end of trial, MK-3475: pembrolizumab, PD: disease progression, IV: intravenously, PO: administered orally, q3wk: every 3 weeks.

Source: KEYNOTE-035 Study Protocol (https://clinicaltrials.gov/ProvidedDocs/42/NCT02133742/Prot_000.pdf).

Study results (longer term)

Between 23-SEP2014, and 25-MAR-2015, 11 patients with previously untreated advanced RCC were enrolled in the dose-finding phase. Between 03-JUN-2015, and 13-OCT-2015, 41 patients with previously untreated advanced RCC were enrolled in the dose-expansion phase. The baseline characteristics of the 52 patients enrolled are shown in Table 1.The study results from the 31-MAR-2017 data cut-off date were published by Atkins and colleagues in 2018 (https://doi.org/10.1016/S1470-2045(18)30081-0).

Longer term results data are available from the 03-JUL-2019 cut-off date:

Table 1 KEYNOTE-035 patient demographics and baseline characteristics

	All participants (n=52)
Age (years)	
Mean	61·2 (9·2)
Median	63·0 (57·0–67·5)
<65 years	29 (56%)
≥65 years	23 (44%)
Sex	
Male	41 (79%)
Female	11 (21%)
Race	
White	45 (87%)
Black	1 (2%)
Asian	4 (8%)
Other	2 (4%)
ECOG performance status	
0	39 (75%)
1	10 (19%)
Not reported	3 (6%)
IMDC criteria risk group	
Favourable	24 (46%)
Intermediate	23 (44%)
Poor	3 (6%)
Unknown	2 (4%)
Fuhrman grade	
1	2 (4%)
2	12 (23%)
3	18 (35%)
4	14 (27%)
Not done	6 (12%)
Histology	
Clear cell renal cell carcinoma	52 (100%)
Sarcomatoid features	1 (2%)
Sites of metastasis	
Lung	30 (58%)
Liver	7 (14%)
Adrenal	7 (14%)
Pancreas	5 (10%)
Lymph nodes	26 (50%)
Other	22 (42%)
Time since initial pathological diagnosis	
Patients (n)	46
Median (months)	20·3 (7·4–65·4)
Unspecified (n)	6

Data are n (%), mean (SD), median (IQR), or as specified. ECOG=Eastern Cooperative Oncology Group. IMDC=International Metastatic Database Consortium.

Source: Atkins 2018 (https://doi.org/10.1016/S1470-2045(18)30081-0).

APPENDIX 2: ADDITIONAL SCENARIO ANALYSES

Page 10 of the Appraisal Consultation Document states, "*The committee concluded that the most plausible survival estimates were likely to fall within the range created by the log-logistic and Weibull distribution used in the company base case and the ERG and technical team base cases respectively. It agreed to take both into account in its decision making. However, it noted that considerable uncertainty remained because of the immaturity of the evidence"*

Page 16 of the Appraisal Consultation Document states, "*The modelling of overall survival data was uncertain. There was no evidence to confirm that pembrolizumab with axitinib would have a durable response and the size of response is highly uncertain. Further information could reduce this uncertainty, in particular:*
− the number of people who complete 2 years of therapy or stop because of complete remission
− the proportion of these 2 groups that relapse and when they do
− the response to retreatment."

A key issue of uncertainty for the committee was the extrapolation of overall survival coupled with treatment effect duration, as outlined by the two quotes above.

MSD have responded formally to the ACD through the ACD consultation process, however would like to take this opportunity to amend the Base Case as well as exploring alternative, plausible, treatment waning scenarios and re-treatment scenarios to help alleviate areas of uncertainty.

MSD's original base-case adjusted for ERG preferences

Table 2 presents MSD's original base-case deterministic results which has been adjusted to include certain ERG preferences. Our adjusted, original base-case is based on the following assumptions:

- Overall survival extrapolated using the log-logistic distribution for pembrolizumab in combination with axitinib and the exponential distribution for sunitinib
- Lifetime treatment effect
- Time-to-death utility approach
- Time on treatment extrapolated using the Weibull distribution for all therapies (ERG preference)
- Removal of administration costs of oral therapies (ERG preference)
- Terminal care cost amended to £8,073 to reflect TA542 (ERG preference)
- Change in the distribution of subsequent therapies as per the ERG base case (ERG preference)

Table 2. Deterministic results for original MSD base-case (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	[redacted]	5.331	-	-	-
Sunitinib	[redacted]	[redacted]	3.011	144,723	2.320	62,390
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

MSD's new Base-Case

MSD recognise the Committee's uncertainty surrounding the extrapolation of overall survival. As outlined by the Appraisal Consultation Document, "*There was theoretical justification to use different distributions for each of the trial arms. However, there is no robust evidence to support the argument that the different mode of action of the drugs would result in different survival trajectories.*" Although MSD consider the use of different distributions for each of the trial arms to be fully justifiable (as explained in our response to Technical Engagement and Appraisal Consultation Document response), and that the log-logistic distribution provides survival estimates in line with clinical expert opinion and biological plausibility, MSD recognises the Committee's discomfort in accepting MSD's justification, and deviating from the standard approach as outlined in NICE DSU TSD 14.

In order to address the conclusions reached by Committee as per the Appraisal Consultation Document, MSD would like to propose a new base case for the Committee's consideration. The new base case takes into account the above-mentioned statement taken from the Appraisal Consultation Document, outlining the Committee's opinion that the most plausible survival estimates would fall between an 'upper bound' as per the log-logistic curve, and a 'lower bound' as per the Weibull curve. During the entire appraisal process to date, and again with the company response to the Appraisal Consultation Document, MSD has expressed our opinion that the Weibull curve is not only a poor fit to the observed data, but more importantly, also produces long term-overall survival estimates that are thoroughly implausible according to all clinical opinion as per the increasing hazard rate of the distribution and lack of 'tail of the curve' effect. However, the exponential curve intersects the range outlined by the Committee and, as such, MSD considers the exponential curve (with lifetime treatment effect) to produce conservative overall survival estimates for pembrolizumab in combination with axitinib. When considering the log-logistic curve for extrapolation of pembrolizumab in combination with axitinib, the Appraisal Consultation Document states, "*Overall the committee considered that*

overall survival for pembrolizumab and axitinib may have been overestimated because of having a switch to the same mortality as the general population at approximately 20 years." However, using the exponential curve to extrapolate overall survival negates the uncertainty around this issue, as a negligible proportion of patients are 'cured'.

Please see Figure 2 which shows long-term overall survival for pembrolizumab in combination with axitinib using different distributions, and Figure 3 which shows long-term overall survival for both the intervention and comparator using the exponential curve.

Figure 2. Overall survival extrapolations for pembrolizumab + axitinib

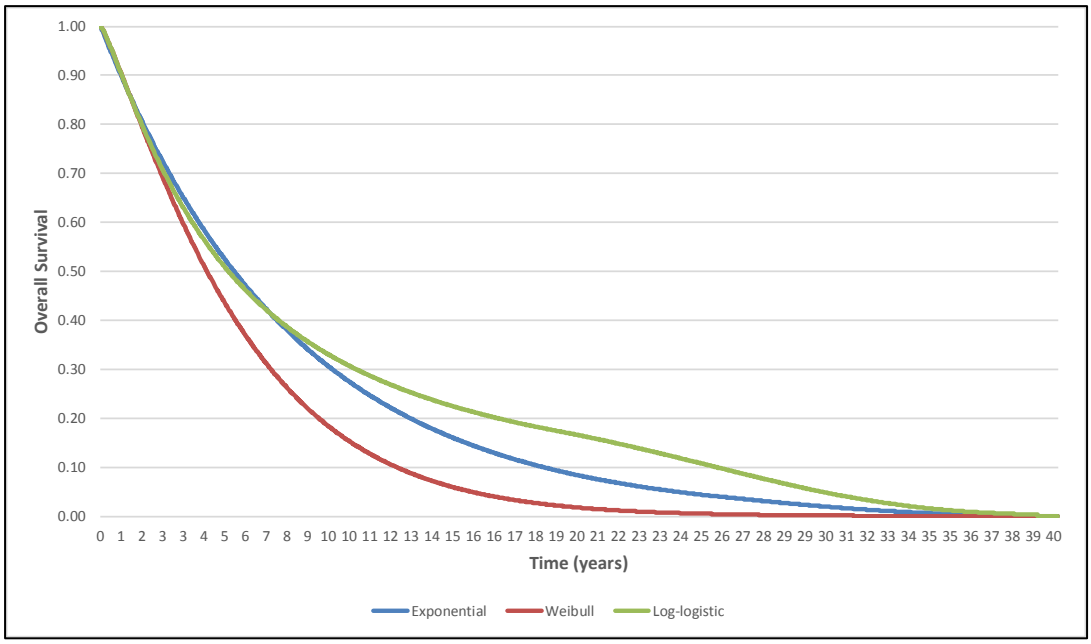
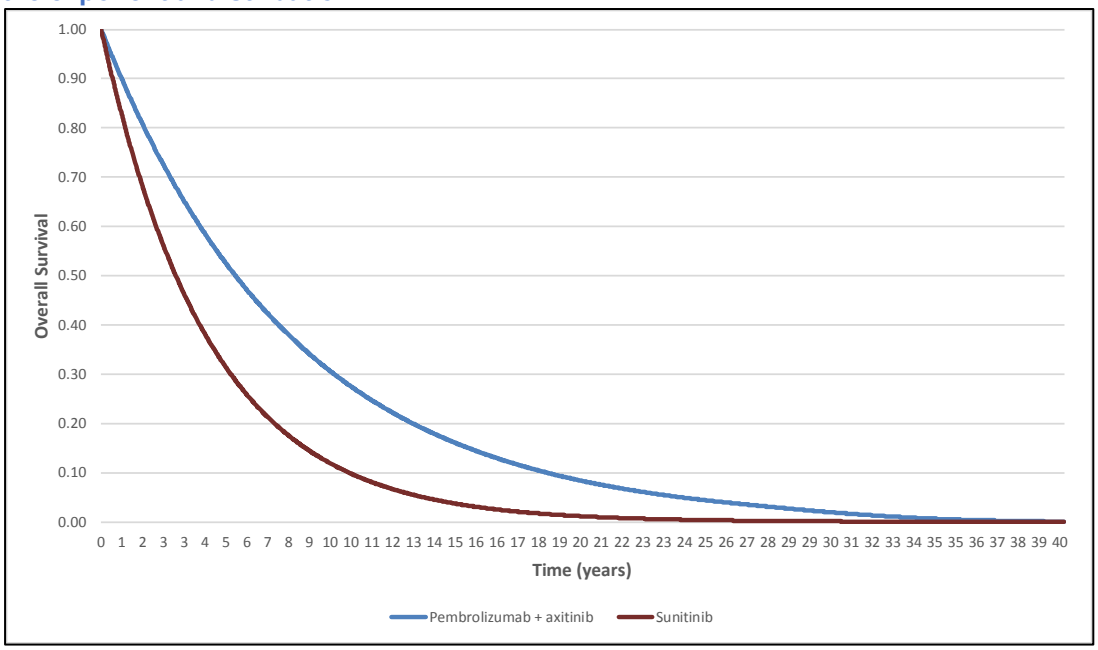


Figure 3. Overall Survival extrapolation for pembrolizumab + axitinib versus sunitinib using the exponential distribution



Please see the analysis below which provides list price deterministic and probabilistic analysis of the new company base case. As MSD maintain the original base case presented in the company submission (adjusted for ERG preferences) is wholly plausible, scenario analyses have been conducted using both base cases.

Table 3. Deterministic results for new MSD base-case (list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	[redacted]	4.872	-	-	-
Sunitinib	[redacted]	[redacted]	3.011	143,209	1.861	76,972
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Probabilistic Sensitivity Analysis

Table 4. Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator sunitinib (list price)

Technologies	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	143,075	1.88	76,222
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Figure 4. Scatterplot of PSA results (1,000 simulations) versus trial comparator sunitinib (list price)

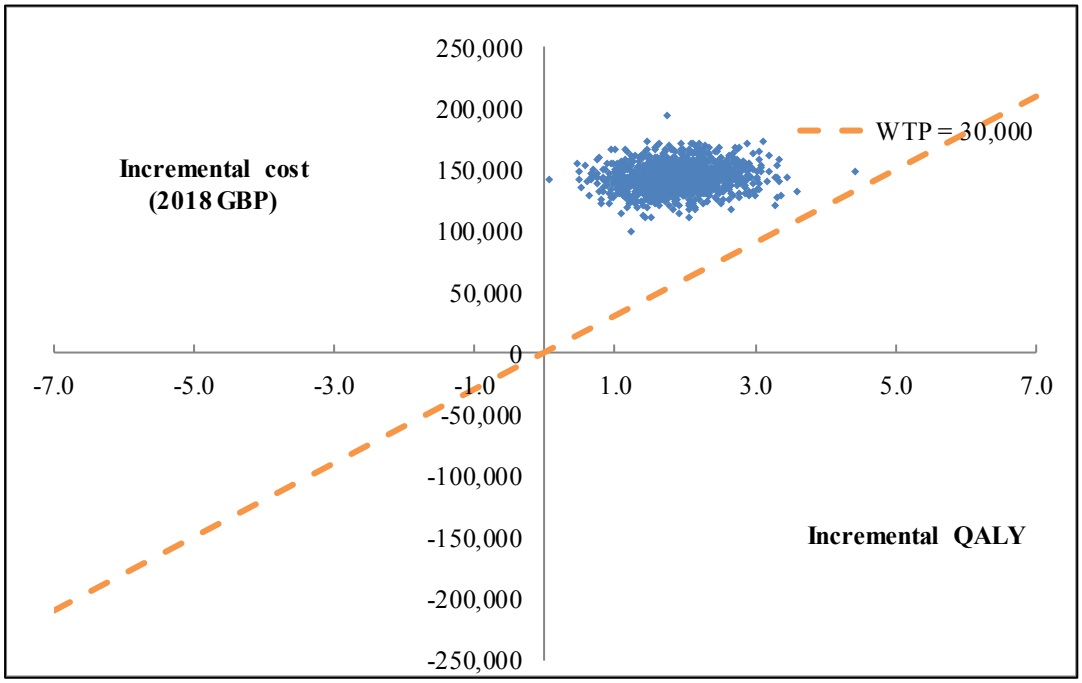
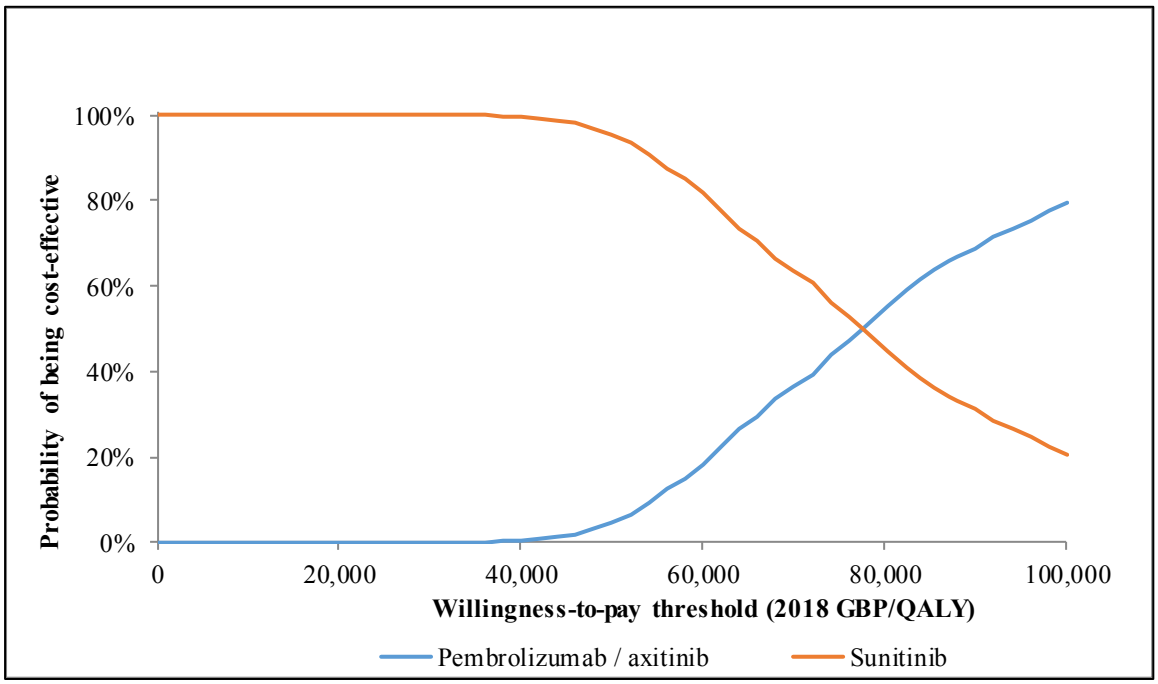
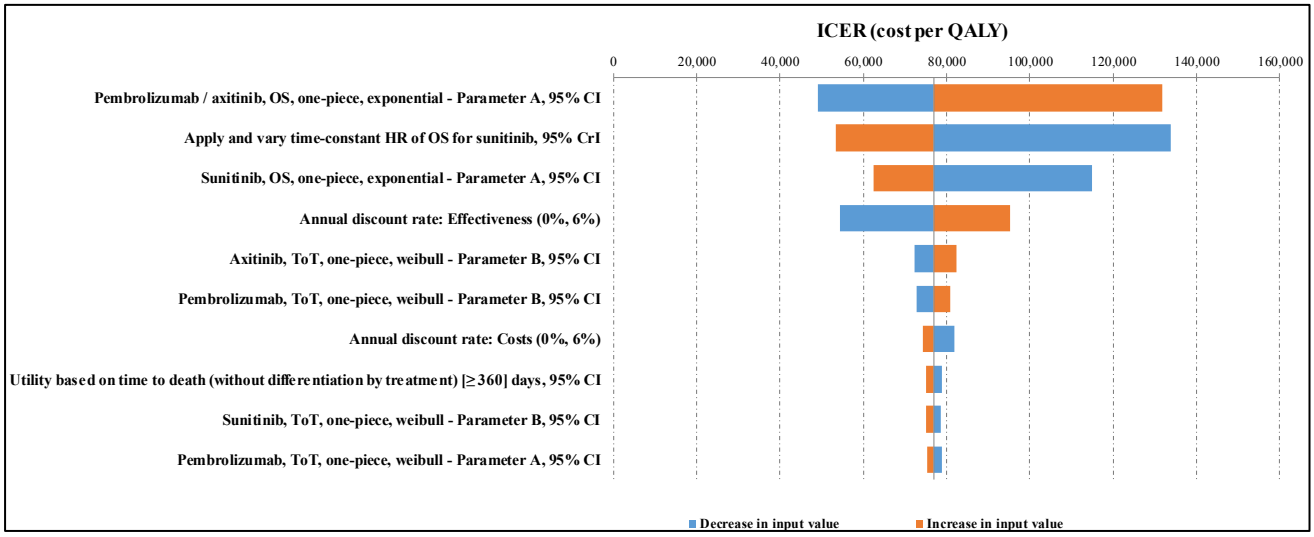


Figure 5. Cost-effectiveness acceptability curve versus trial comparator sunitinib (list price)



Deterministic Sensitivity Analysis

Figure 6. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensible variables versus trial comparator sunitinib (list price)



*Indicates sensitivity analyses in which pembrolizumab / axitinib is dominant over the comparator

**Indicates sensitivity analyses in which pembrolizumab / axitinib is dominated by the comparator

***Indicates sensitivity analyses in which pembrolizumab /axitinib ranges from dominated to dominant (or vice versa) over the range of the parameter input

Additional scenario analysis

Scenario analysis: Overall Survival and treatment effect duration

MSD acknowledges that overall survival extrapolation and the duration of treatment effect is an area of uncertainty within this appraisal. To address this issue, MSD has conducted further scenario analysis to address this issue, as described below:

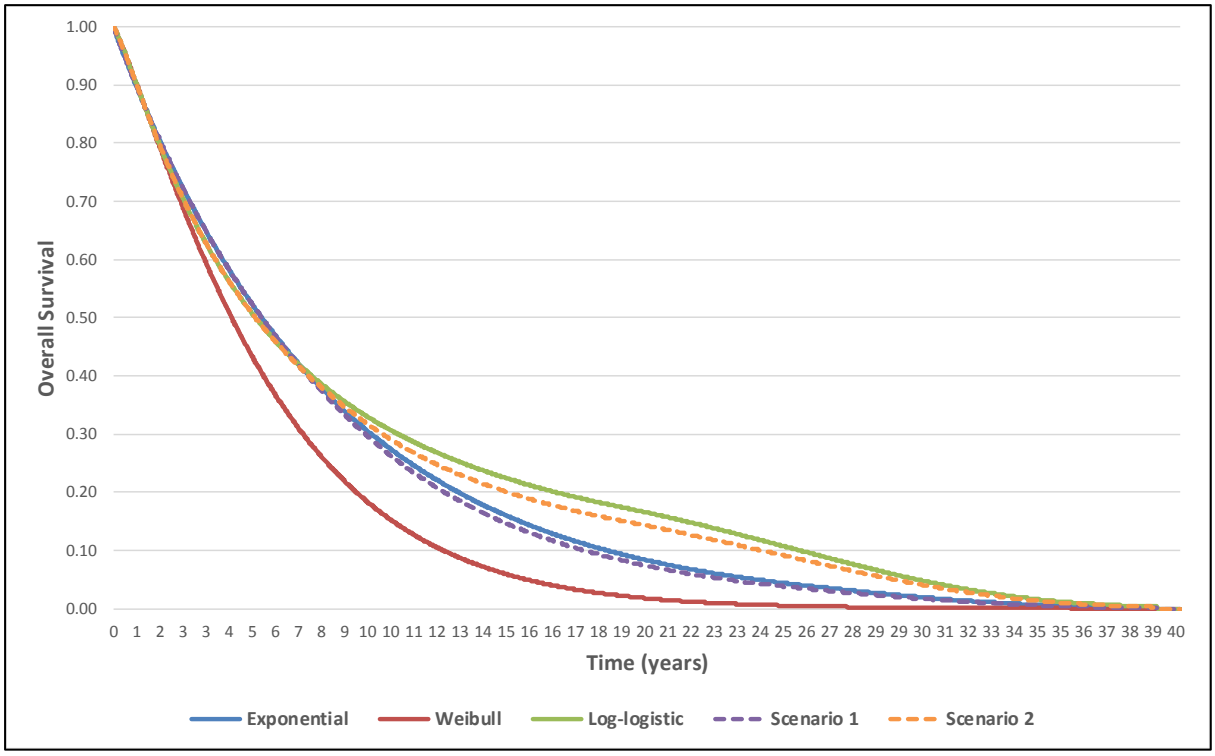
In the base-case analysis, PFS and OS in the pembrolizumab plus axitinib arm were extrapolated based on parametric curves fitted directly to within-trial survival trends. In line with the recent appraisal of nivolumab plus ipilimumab (TA581), treatment waning assumptions were not incorporated into the base case given clinical experts' expectations that a percentage of patients would derive a long-term survival benefit from immunotherapy.

The duration and magnitude of the treatment effect beyond the trial period are nevertheless subject to uncertainty and could have an important influence on cost-effectiveness findings over a lifetime horizon. A scenario analysis was therefore conducted to explore the possibility of a waning treatment effect of pembrolizumab/axitinib vs. sunitinib. Under this scenario, the base-case efficacy estimation approach was modified according to the following assumptions:

For patients who achieved a best overall response of complete response (5.8%), partial response (53.5%), or stable disease (24.5%), base-case hazard rates of PFS and OS failure were used until the end of the model horizon. This approach may be considered conservative, as the base-case parametric models of progression-free survival and overall survival were determined by all patients randomised to pembrolizumab plus axitinib, regardless of response achievement. In fact, initial response to pembrolizumab/axitinib is a strong prognostic factor for survival outcomes. Moreover, due to better prognosis, patients who achieved at least stable disease would likely represent a larger percentage of patients who survive to the point that treatment waning takes effect.

The remaining proportion of patients (16.2%) were modelled to experience a gradual treatment waning effect in the pembrolizumab plus axitinib arm. For these patients, hazard rates of progression-free survival and overall survival failure were assumed to linearly converge towards those of sunitinib between years 5 and 10, equalling those of sunitinib starting from the 10-year time point until the end of the model horizon.

Figure 7. Overall survival extrapolations for pembrolizumab + axitinib using alternative treatment effect duration assumptions



The results of this analysis are presented below using both the original base case overall survival distributions and the new base case overall survival distributions.

Table 5. Scenario analyses exploring alternative treatment effect duration (list price)

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 1- New Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	4.783	-	-	-
	Sunitinib	[redacted]	[redacted]	3.011	140,572	1.772	79,333
Scenario 2- Original Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	5.161	-	-	-
	Sunitinib	[redacted]	[redacted]	3.011	141,822	2.150	65,963

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Scenario analysis: Retreatment

As outlined in MSD's response to the Appraisal Consultation Document, based on the duration of follow-up in the data cuts currently available from the KEYNOTE-426 study (August 2018 and January 2019), no patients have currently received a second course of treatment with pembrolizumab after initially discontinuing therapy due to either complete response or completing 2 years of treatment. Therefore, it is not possible to use data from KEYNOTE-426 to alleviate the uncertainty outlined by the committee. To address this issue, MSD has since conducted further analysis utilising data from KEYNOTE-006 [1] and KEYNOTE-010 [2], as described below:

Within the scenario analysis, it is assumed that a percentage of patients in the pembrolizumab in combination with axitinib arm who either progressed after ceasing therapy due to a complete response or progressed after completing 2 years of treatment, will receive a re-treatment course. This percentage is based on the pooled percentages of patients from the KEYNOTE-006 [1] and KEYNOTE-010 trials [2], i.e., 14.3%=(12+14)/(103+79), who received re-treatment after completing 2 years of pembrolizumab.

By this approach, a lump-size re-treatment cost is applied to 14.3% of patients in the pembrolizumab in combination with axitinib arm who newly progress in each cycle after the 2-year mark. The lump-sum cost of a re-treatment course is based on the estimated mean duration of re-treatment assuming constant hazards, given the 9-month median re-treatment duration reported in KEYNOTE-006 and the 12-month maximum re-treatment duration (median length of re-treatment was not reported) [1, 2]. MSD believes this is a conservative approach to the issue of retreatment and should help alleviate the Committee's concerns around the impact on the economic analyses when considering retreatment. MSD acknowledges that as the proportion of patients treated and the length of treatment is not informed by KEYNOTE-426, this analysis has limitations. However, if a CDF recommendation were to be made, analysis could subsequently be conducted using the KEYNOTE-426 data and included in a CDF guidance review, in order to further understand the impact of retreatment on a renal cell carcinoma patient population.

The results of this analysis are presented below using both the original base case overall survival distributions and the new base case overall survival distributions.

Table 6. Scenario analyses exploring retreatment (list price)

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 3- New Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	4.872	-	-	-
	Sunitinib	[redacted]	[redacted]	3.011	145,616	1.861	78,266
Scenario 4- Original Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	5.331	-	-	-
	Sunitinib	[redacted]	[redacted]	3.011	147,136	2.320	63,430
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

As shown in Table 6, the impact of modelling retreatment costs has a negligible impact on the overall ICER, therefore MSD hope this scenario analysis will alleviate the Committee's concerns surrounding the impact of retreatment upon the economic analysis.

APPENDIX 3: POST-TREATMENT DISCONTINUATION PROGRESSION OF DISEASE AND RE-TREATMENT STATUS (JANUARY 2019 DATA-CUT)

Provided below are analysis results to support the NICE submission in UK. The specific objectives of this report are:

- To descriptively summarize the disposition of subjects;
- descriptively summarize the subjects who had a progression of disease after treatment discontinuation for complete response or for completing first course of pembrolizumab;
- To descriptively summarize the time to progression of disease for subjects who had a progression of disease after treatment discontinuation for complete response or for completing first course of pembrolizumab; and
- To descriptively summarize the subjects re-treated with pembrolizumab in subjects initially treated with pembrolizumab + axitinib after treatment discontinuation for complete response or for completing first course of pembrolizumab.

Efficacy Endpoints

Progression of disease is defined as the subjects in the analysis population who have a progression of disease per RECIST 1.1 based on BICR assessment.

Analysis Populations

The Intention-to-Treat (ITT) population serves as the population for the primary efficacy analyses. All randomized subjects are included in this population. Subjects are analysed in the treatment group to which they are randomized.

The All Subjects as Treated (ASaT) population is used for the analysis in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects are analysed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this would be the treatment group to which they are randomized.

Data Used in the Analyses

The results presented in this report are based on the data from the Safety Update Report (SUR) Database Lock. The analyses that are not pre-specified in the study protocol [are exploratory only, the results are descriptive only, and p-values are strictly nominal.

Table 7: List of Protocols and DBLs Used in the Submission

MK Number	Protocol number	Database Cutoff date
MK-3475	P426	JAN 02, 2019

RESULTS

A total of [redacted] subjects in the ITT population, and [redacted] subjects in the AsaT population were included in the analysis.

Disposition of subjects, treatment discontinuation and subsequent progression of disease

The percentage of subjects who discontinued study treatment by the data cutoff date was [redacted] in the pembrolizumab + axitinib group [redacted] compared to the sunitinib group [redacted] Of those who discontinued study treatment, [redacted] subjects in the pembrolizumab + axitinib group discontinued for complete response. [redacted] of subjects in the ITT population in the sunitinib group [redacted] discontinued the study due to death, compared to the pembrolizumab + axitinib group [redacted] (Table 8)

Of the [redacted] subjects who discontinued for complete response, [redacted] had progression of disease after treatment discontinuation based on BICR assessment per RECIST 1.1. [redacted] had received the second course of pembrolizumab re-treatment (Table 9)

Table 8: Disposition of Subjects (ITT Population)

	Pembrolizumab + Axitinib		Sunitinib		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]					
Status for Trial						
Discontinued						
Death						
Lost To Follow-Up						
Withdrawal By Subject						
Trial Ongoing						
Status for Study Medication in Trial						
Started						
Discontinued						
Adverse Event						
Clinical Progression						
Complete Response						
Excluded Medication						
Non-Compliance With Study Drug						
Physician Decision						
Progressive Disease						
Withdrawal By Subject						
Treatment Ongoing						

Each subject is counted once for Trial Status based on the latest Survival Follow-up record.

Each subject is counted once for Study Medication Status based on the latest corresponding disposition record.

Database Cutoff Date: 02Jan2019.

Table 9: Summary of Treatment Discontinuation and Subsequent Progression of Disease (ASaT Population)

Characteristic	**Study: 3475-426**	
	Pembrolizumab + Axitinib N[a]=429	**Sunitinib** N[a]=425
Progression of Disease after Last Dose[b]		
Yes	[redacted]	
No		
NA		
Time to Progression (Days) after Last Dose[b]		
Subjects with data	[redacted]	
Mean (SD)		
Received Second Course Treatment		
Yes	[redacted]	
No		

a: Number of subjects: all subjects as treated
b: For subjects who completed first course of study treatment, or discontinued study treatment for a complete response per investigator assessment. Progression of disease is based on BICR assessment per RECIST 1.1
NA: Not Applicable; BICR: Blinded Independent Central Review; RECIST: Response Evaluation Criteria in Solid Tumors
Database Cutoff Date: 02Jan2019.

References

1. Robert, C., et al., *Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study*. The Lancet Oncology, 2019. **20**(9): p. 1239-1251.

2. Herbst, R.S., et al., *Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1Positive, Advanced NonSmall-Cell Lung Cancer in the KEYNOTE-010 Study*. J Clin Oncol, 2020: p. JCO1902446.

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Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [ID1426]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney cancer UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None to decalre
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that although you state there is uncertainty in the data, we believe this would be resolved with further data collection within Cancer drugs fund and this should be a consideration.
2	We are concerned that you have stated negatively that pembrolizumab and axtinib would have a substantial effect on the pathway. From a patient and professional point of view this combination would have a highly positive effect on the pathway giving patients the opportunity the best of two treatments, working together up front and therefore giving better outcomes in the long term.
3	We are concerned that you are disregarding the clinical and patients' experts in this area and their expertise using these drugs and the real effects it is having on patient's tumour response and quality of life.
4	We are concerned that you are not considering the benefit of a treatment that is three weekly with a definite number of doses. This is beneficial to hospital resources and time for the patient. Additional this treatment does not need any pre-medications and has a low infusion reaction profile. This therefore makes it a cost-effective treatment. As stated by our patient and others we have talked to the side effect profile is also low and therefore is effective to bring quality of life to patients as well as response.
5	
6	

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Cancer Support Network
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1	The committee, ERG and company agreed that **pembrolizumab with axitinib does not meet end-of-life criteria for the overall renal cell carcinoma population**. The committee agreed that the first end-of-life criterion (that treatment is indicated for patients with a short life expectancy, normally less than 24 months) in the intermediate and poor risk group was not met because the median overall survival in the sunitinib arm of CheckMate-214 was 26 months. We consider this observation of overall survival for sunitinib from CheckMate-214 to be an over-estimate, since it was taken from a clinical trial with pre-selected patients. A more realistic estimate of survival could be taken from real-world data to determine whether the pembrolizumab/axitinib combination meets the end-of-life criteria. A recent paper published in *The Oncologist* analysed real-world data to further evaluate the effectiveness of first line sunitinib in patients with metastatic RCC with favourable, intermediate or poor risk disease according to the International Metastatic RCC Database Consortium (IMDC) risk criteria. The study included 1769 patients; 318 (18.0%) had favourable risk, 1031 (58.3%) had intermediate risk, and 420 (23.7%) had poor risk disease. The median overall survival was 52.1 months in favourable risk patients versus 9.8 months in poor risk patients. In the intermediate risk group, overall survival was 35.1 months for those with one risk factor and 21.9 months for those with two risk factors. https://theoncologist.onlinelibrary.wiley.com/doi/epdf/10.1634/theoncologist.2019-0605 We feel that the pembrolizumab with axitinib combination should be considered an end-of-life treatment for patients with untreated metastatic RCC categorised as intermediate or poor risk according to IMDC risk criteria.
2	The committee is not willing to consider the pembrolizumab/axitinib combination for inclusion in the Cancer Drugs Fund (CDF) due to uncertainty about the overall survival data and uncertainty about a potential durable response to treatment. Inclusion of the combination in the CDF for up to 3 years would enable collection of further survival data and resolve the uncertainty regarding a durable response to immunotherapy, while at the same time allow access to the treatment for patients looking for an effective and tolerable immunotherapy/VEGFR inhibitor treatment offering a potential long-term response.
3	The pembrolizumab/axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to show efficacy in advanced RCC and has been granted priority review status by the FDA. Having priority review status, the pembrolizumab/axitinib combination has been fast tracked for approval in a number of countries, including the USA, Canada and Europe, based on the phase 3 clinical trial data.
4	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 patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these 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 the rest of Europe and North America.
5	The pembrolizumab/axitinib combination is one of the first immunotherapy/VEGFR inhibitor combinations to undergo NICE appraisal for untreated advanced RCC. Previous drug combinations have proven to be unsuccessful as a result of unacceptable side effects. However, the pembrolizumab/axitinib combination seems to be well tolerated, as well as proven to be more effective at extending survival compared to single agent therapy with sunitinib in the first line.
6	Current first line treatments have proven to shrink tumours and delay disease progression in some patients; however, these treatment options are not effective for everyone. Choice in the first line, and access to new innovative treatments remains paramount to managing the progression of this disease. Undue restrictions in accessing the pembrolizumab/axitinib combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Having a choice of treatment would enable patients and oncologists to better control this disease and individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.
7	Some immunotherapies have been shown to be effective in the treatment of non-clear cell RCC, especially

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	papillary RCC. If recommended, the pembrolizumab/axitinib combination could be used to address an area of significant unmet need in the treatment of non-clear cell RCC. Inclusion of the pembrolizumab/axitinib combination in the CDF would enable collection of efficacy and tolerability data for the treatment of non-clear cell RCC to address this unmet need. https://meetinglibrary.asco.org/record/169447/abstract

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[NCRI Bladder and Renal Clinical Research Group]
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Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The committee have considered all the directly relevant evidence within the scope of the TA
2	The summary of clinical effectiveness is a reasonable interpretation of the data.
3	I am unable to comment in any detail on the summary of cost effectiveness as this is outside my area of expertise and key components of the assessment are not available to me.
4	The recommendation will be disappointing to patients and clinicians as this combination is among the most active treatments trialled to date in this condition and is likely to become the gold standard treatment globally where it is affordable.
5	
6	

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Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Consultant Oncologist
Organisation	*"We are not an organisation: but we are a group of who specialise in the treatment of renal cancer* [redacted]

Comments on the ACD:

Chapter name:
Committee discussion

Section:
'There is not robust evidence to support the use of different distributions to extrapolate survival for each of the trial arms'

Comment 1:

"(Response on behalf of 15 senior oncology consultants) We believe the company (MSD) were justified in choosing different models for extrapolating long-term survival outcomes in the intervention group and the comparator group. The rationale comes from the high likelihood that a subgroup of patients will derive live-long benefit from an immune checkpoint inhibitor and that this subgroup will be considerably larger in patients who receive immune checkpoint inhibitors as first line therapy than in those who receive sunitinib (or another tyrosine kinase inhibitor) as first line. A hazard ratio for survival of 0.53 with high durable response rates makes the possibility of long -term outcomes plausible (1-3). The combined effect of the lower proportion of patients achieving durable response to second line nivolumab, and the fact that 30 – 40% of patients never receive a checkpoint inhibitor in the comparator group is likely to result in a different pattern of decay in the comparator arm (4-6)

refs: 1 Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Alekseev B, Soulières D, Melichar B, Vynnychenko I, Kryzhanivska A, Bondarenko I, Azevedo SJ, Borchiellini D, Szczylik C, Markus M, McDermott RS, Bedke J, Tartas S, Chang YH, Tamada S, Shou Q, Perini RF, Chen M, Atkins MB, Powles T; KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.N Engl J Med. 2019 Feb 16. doi: 10.1056/NEJMoa1816714.

2 Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.N Engl J Med. 2018 Apr 5;378(14):1277-1290

3 Motzer RJ, Rini BI, McDermott DF, Arén Frontera O, Hammers HJ, Carducci MA, Salman P, Escudier B, Beuselinck B, Amin A, Porta C, George S, Neiman V, Bracarda S, Tykodi SS, Barthélémy P, Leibowitz-Amit R, Plimack ER, Oosting SF, Redman B, Melichar B, Powles T, Nathan P, Oudard S, Pook D, Choueiri TK, Donskov F, Grimm MO, Gurney H, Heng DYC, Kollmannsberger CK, Harrison MR, Tomita Y, Duran I, Grünwald V, McHenry MB, Mekan S, Tannir NM Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019 Oct;20(10):1370-1385.

4 Final analysis of the CheckMate 025 trial comparing nivolumab (NIVO) versus everolimus (EVE) with >5 years of follow-up in patients with advanced renal cell carcinoma (aRCC) Motzer R et al. ASCO GO 2020. Rapid Abstract Session, Sat, 11:35 AM-12:30 PM and Poster Session (Board #D3),

5 CheckMate 025 Randomized Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma.
Escudier B, Sharma P, McDermott DF, George S, Hammers HJ, Srinivas S, Tykodi SS, Sosman JA, Procopio G, Plimack ER, Castellano D, Gurney H, Donskov F, Peltola K, Wagstaff J, Gauler TC, Ueda T, Zhao H, Waxman IM, Motzer RJ; CheckMate 025 investigators.
Eur Urol. 2017 Dec;72(6):962-971

6 Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, Nathan P, Staehler M, de Souza P, Merchan JR, Boleti E, Fife K, Jin J, Jones R, Uemura H, De Giorgi U, Harmenberg U, Wang J, Sternberg CN, Deen K, McCann L, Hackshaw MD, Crescenzo R, Pandite LN, Choueiri TK. Pazopanib versus sunitinib in metastatic renal-cell carcinoma.N Engl J Med. 2013 Aug 22;369(8):722-31."

Section:
Because of the immaturity of data, it is appropriate to consider a 5-year waning effect scenario to estimate cost effectiveness

Comment 2:

"(Response on behalf of 15 senior consultant oncologists) We believe it is very likely that there is a lifetime benefit from first line pembrolizumab with axitinib which is not seen in patients receiving sunitinib (or another first line tyrosine kinase inhibitor as monotherapy). None of the trials of first line checkpoint inhibitors has been followed up sufficiently to demonstrate this, but we believe there is good evidence that immune checkpoint inhibitors alter the natural history of cancer in some patients in such a way that lifelong immune control is likely (ie. that some patients are 'cured'). The KN-426 trial sponsor's estimate that 17% of patients experience such life-long control is, in our opinion, plausible. We believe the (admittedly short follow up) data from KN-426 are in keeping with a dramatic effect

on survival and that the longer term follow up data from other first line immune checkpoint inhibitor trials in renal cancer (most notably the first line trial of ipilimumab plus nivolumab) strongly point to a subgroup of patients experiencing long-term disease control [1-3]. In contrast, patients who start their treatment pathway with a tyrosine kinase inhibitor appear to have a much lower chance of a durable response to immune checkpoint inhibitor where this is only accessed in the second (or subsequent) line [3,4]. We therefore do not agree with The Committee's opinion that it is appropriate to consider a 5-year waning effect scenario to estimate cost effectiveness, but, rather, consider a life-long effect to be more likely, even when the duration of pembrolizumab is capped at two years.

1 Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, Pouliot F, Alekseev B, Soulières D, Melichar B, Vynnychenko I, Kryzhanivska A, Bondarenko I, Azevedo SJ, Borchiellini D, Szczylik C, Markus M, McDermott RS, Bedke J, Tartas S, Chang YH, Tamada S, Shou Q, Perini RF, Chen M, Atkins MB, Powles T; KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.N Engl J Med. 2019 Feb 16. doi: 10.1056/NEJMoa1816714.

2 Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, Plimack ER, Barthélémy P, Porta C, George S, Powles T, Donskov F, Neiman V, Kollmannsberger CK, Salman P, Gurney H, Hawkins R, Ravaud A, Grimm MO, Bracarda S, Barrios CH, Tomita Y, Castellano D, Rini BI, Chen AC, Mekan S, McHenry MB, Wind-Rotolo M, Doan J, Sharma P, Hammers HJ, Escudier B; CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.N Engl J Med. 2018 Apr 5;378(14):1277-1290

3 Motzer RJ, Rini BI, McDermott DF, Arén Frontera O, Hammers HJ, Carducci MA, Salman P, Escudier B, Beuselinck B, Amin A, Porta C, George S, Neiman V, Bracarda S, Tykodi SS, Barthélémy P, Leibowitz-Amit R, Plimack ER, Oosting SF, Redman B, Melichar B, Powles T, Nathan P, Oudard S, Pook D, Choueiri TK, Donskov F, Grimm MO, Gurney H, Heng DYC, Kollmannsberger CK, Harrison MR, Tomita Y, Duran I, Grünwald V, McHenry MB, Mekan S, Tannir NM Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019 Oct;20(10):1370-1385.

4 Final analysis of the CheckMate 025 trial comparing nivolumab (NIVO) versus everolimus (EVE) with >5 years of follow-up in patients with advanced renal cell carcinoma (aRCC) Motzer R et al. ASCO GO 2020. Rapid Abstract Session, Sat, 11:35 AM-12:30 PM and Poster Session (Board #D3),"

Section:
Cancer Drugs Fund

Comment 3:

"(Response on behalf of a group of 15 senior consultant oncologists) We do agree with the Committee's view that the currently-available data from the pivotal trial (Keynote-426) are immature. However, we believe that every effort should be made to make this seemingly transformational treatment available to patients despite this uncertainty. We believe that planned updated analyses of the trial in the next two years will add significantly to our understanding of these data and will reduce uncertainty in the assumptions made in the health economic analysis sufficiently to allow a good understanding of the true cost effectiveness of this

intervention. In particular, over this timeframe, we will see the impact of the 2-year stopping rule for pemrolizumab. We therefore believe that the combination of pembrolizumab and axitinib should be considered potentially suitable for inclusion by the Cancer Drugs Fund".

CONFIDENTIAL

Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

Pembrolizumab in combination with axitinib for untreated advanced renal cell carcinoma

Consultation on the appraisal consultation document: ERG critique of company's response

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Dr Keith Cooper, Senior Research Fellow, SHTAC
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Date **16th June 2020**

[redacted]

1. Introduction

This document is the ERG's critique of the response by the company (Merck Sharp & Dohme, MSD) to the appraisal consultation document (ACD) issued by NICE to stakeholders on 5th February 2020. The ERG received the company's response on 11th March 2020.

Below we take the key issues raised by the NICE appraisal committee at their meeting in January 2020, as described in the ACD, and we comment on the company's response to them.

The company conducted further cost effectiveness analyses to address key uncertainties discussed in the ACD. They present the following additional cost effectiveness analyses (Appendix 2 of their response):

1. The company's original base case, incorporating ERG's preferred assumptions.
2. The company's updated base case, incorporating ERG's preferred assumptions, and using an alternative parametric overall survival distribution.
3. Scenario analyses exploring the waning of treatment effect over time.
4. Scenario analyses exploring the impact of retreating patients whose disease has progressed after cessation of pembrolizumab treatment.

The ERG has verified and replicated the results of the above analyses, with the exception of Table 5 in the company's Appendix 2 (scenario analyses exploring alternative treatment effect duration - discussed below in section 3.1).

2. Overall survival extrapolation

The company updated their base case with some of their assumptions based on ERG preferences, as follows:

- Overall survival extrapolated using the log-logistic distribution for pembrolizumab in combination with axitinib and using the exponential distribution for sunitinib
- Lifetime treatment effect
- Time-to-death utility approach
- Time on treatment extrapolated using the Weibull distribution for all therapies (ERG preference)
- Removal of administration costs of oral therapies (ERG preference)

- Terminal care cost amended to £8,073 to reflect the cost used in NICE TA542 (cabozantinib for untreated advanced renal cell carcinoma) (ERG preference)
- Change in the distribution of subsequent line therapies as per the ERG base case (ERG preference)

The results of the company's original base case analysis, adjusted to incorporate the ERG's preferences, are shown in Table 2 of the company's appendix and are reproduced in Table 1 below (overall treatment population – all RCC risk levels).

Table 1 Deterministic results for original company base case (list price) adjusted for ERG preferences, overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	144,723	2.320	62,390

Although the company considers the use of different parametric survival distributions for trial arms to be fully justified, they propose an updated base case for the committee's consideration which uses the same distribution for each trial arm. The company proposes using the exponential distribution for both trial arms as the exponential curve intersects the range of plausible survival estimates in the opinion of the appraisal committee (The committee concluded that this would be within the range of estimates created by the log-logistic and Weibull distributions). The results of the company's updated base case are shown in Table 3 of the company's ACD response appendix 2 and are reproduced in Table 2 below.

Table 2 Deterministic results for updated company base case (list price) for overall population, exponential distribution

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	143,209	1.861	76,972

The company provided updated base case results for the overall RCC patient population but not for the sub-group of patients with poor / intermediate RCC risk status (for which the most relevant comparator treatment is cabozantinib). The ERG therefore repeated the company's updated base case analyses (as presented in Table 2 above) for the poor / intermediate RCC risk population, for the comparison of pembrolizumab + axitinib versus cabozantinib (Table 3 log-logistic distribution and
Table **4** exponential distribution).

Table 3 Deterministic results for updated company base case (list price) for the poor / intermediate RCC risk population, log-logistic distribution (ERG replication of company analyses)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	46,040	1.543	29,835

Table 4 Deterministic results for updated company base case (list price) for the poor / intermediate RCC risk population, exponential distribution (ERG replication of company analyses)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	46,146	1.203	38,346

The ACD states that the Weibull distribution is likely to give pessimistic survival estimates because the rising hazard rate (a characteristic of this distribution) was not expected for people who had pembrolizumab + axitinib. The company considers that the survival estimates produced by the Weibull curve are not only pessimistic but also clinically implausible.

We previously commented that *"the ERG notes that the OS survival data is immature and for pembrolizumab plus axitinib the data does not demonstrate an underlying hazard that is similar to the log-logistic. Furthermore, the underlying hazard is similar to sunitinib"* (section 4.3.5.1 of the ERG report). Below we show the diagram of the hazard for pembrolizumab

and axitinib (Figure 1). On the evidence available, the hazard (smoothed line) appears to be increasing (see trendline in the figure) which suggests the Weibull is not implausible.

Figure 1 Hazard (smoothed line) for the pembrolizumab + axitinib trial arm from KEYNOTE-426

As stated in the ERG report (section 4.5.1), we consider the exponential distribution is also plausible to estimate overall survival for pembrolizumab + axitinib. Therefore, we consider the company's approach in their updated base case (i.e. exponential distribution for both trial arms) to be reasonable.

In an appendix to their response to the ACD (Appendix 1), the company provided a summary of long-term data from the phase 1b, open-label, multiple-dose safety, pharmacokinetic KEYNOTE-035 trial. The key finding of relevance is that at almost 5 years of follow-up . The company suggests this supports their assumption of a continued treatment effect for pembrolizumab + axitinib in RCC. The company does not, however, use these data to inform their cost effectiveness modelling. The ERG acknowledges the long-term survival results from KEYNOTE-035 are clinically encouraging, but we note some of the limitations of the evidence presented: a phase 1b open-label study with the primary aim of assessing safety and tolerability; survival was one of a number of secondary outcomes. These results cannot necessarily be generalised to the modelled patient population in this appraisal.

3. Additional scenario analyses

3.1 Treatment effect duration

The company conducted further analyses on the duration of treatment effect. They modelled a gradual waning of the treatment effect in a proportion of patients (16.2%) in the pembrolizumab plus axitinib arm. This appears to be the proportion of patients in KEYNOTE 426 who did not exhibit any tumour response (i.e. they were not classified as having complete response, partial response or stable disease). For these patients "*hazard rates of progression-free survival and overall survival failure were assumed to linearly converge towards those of sunitinib between years 5 and 10, equalling those of sunitinib starting from the 10-year time point until the end of the model horizon"* (page 13, appendix 2 of company's ACD response).

The ERG notes that previously the modelling of treatment effect assumed that the probability of progression and death became equal between the two trial arms at a specified time duration. We are unclear why the company has chosen to model only patients with no response (progressive disease) to be subject to treatment effect waning. We note that after five years follow-up the majority of patients have progressed so we are unclear why the treatment waning effect is restricted to this group.

The results of this scenario are shown in Table 5 of the company's Appendix 2. We were unable to replicate these results exactly (although the results are similar). We present the ERG's replicated results for this scenario in Table 5 below.

Table 5 Company's scenario analysis of alternative treatment effect duration (list price) for the overall population (ERG replication of company analyses)

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 1- New base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
	Sunitinib	[redacted]	[redacted]	[redacted]	140,572	1.772	80,661
Scenario 2- Original base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
	Sunitinib	[redacted]	[redacted]	[redacted]	141,822	2.150	67,058
Scenario 1 - exponential distribution for both trial arms; Scenario 2 - log-logistic distribution for pembrolizumab + axitinib; exponential distribution for sunitinib							

For illustration, the ERG has run the company's scenario with a treatment waning effect applied to all patients, rather than the sub-group of 16.2% patients with no tumour response. The results show substantial increases in the ICERs, exceeding £100,000 per QALY (Table 6).

Table 6 ERG's scenario analysis of alternative treatment effect duration (list price) for the overall population

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 1- New Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]			
	Sunitinib	[redacted]	[redacted]	[redacted]	141,467	1.314	107,693
Scenario 2- Original Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]			
	Sunitinib	[redacted]	[redacted]	[redacted]	141,347	1.273	111,064
Scenario 1 - exponential distribution for both trial arms; Scenario 2 - log-logistic distribution for pembrolizumab + axitinib; exponential distribution for sunitinib							

The ERG have repeated the analyses reported in Table 5 and Table 6 above, for the poor / intermediate RCC risk population, comparing pembrolizumab + axitinib versus cabozantinib (Table 7 and Table 8, respectively).

Table 7 Company's scenario analysis of alternative treatment effect duration (list price) for the poor / intermediate RCC risk population (ERG replication of company analyses)

Scenario	Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 1- New Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
	Cabozantinib	[redacted]	[redacted]	[redacted]	43,883	1.143	38,410
Scenario 2- Original Base Case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
	Cabozantinib	[redacted]	[redacted]	[redacted]	43,471	1.388	31,321
Scenario 1 - exponential distribution for both trial arms; Scenario 2 - log-logistic distribution for pembrolizumab + axitinib; exponential distribution for sunitinib							

Table 8 ERG's scenario analysis of alternative treatment effect duration (list price) for the poor / intermediate RCC risk population

Scenario	Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 1- New base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]			
	Cabozantinib	[redacted]	[redacted]	[redacted]	42,891	0.827	51,836
Scenario 2- Original base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	
	Cabozantinib	[redacted]	[redacted]	[redacted]	40,896	0.585	69,910
Scenario 1 - exponential distribution for both trial arms; Scenario 2 - log-logistic distribution for pembrolizumab + axitinib; exponential distribution for sunitinib							

3.2 Retreatment of patients progressing after stopping pembrolizumab

One of the key uncertainties identified by the NICE appraisal committee is the effectiveness of retreating patients whose disease has progressed after cessation of pembrolizumab treatment. Retreatment was not included in the company's original economic model and at the time of the appraisal consultation none of the patients in KEYNOTE-426 had yet been retreated with a second course of pembrolizumab.[1] The committee's view is that information on the effects of retreatment could help to reduce the uncertainty around the estimation of overall survival.

The company responded by providing a scenario analysis modelling retreatment with pembrolizumab + axitinib in patients whose disease progressed following discontinuation of their original course of pembrolizumab (i.e. discontinuing therapy due to either a complete response during treatment or from completing the maximum permitted two years (35 cycles) of pembrolizumab treatment). To inform this scenario the company used long-term follow up data from the KEYNOTE -006 and KEYNOTE-010 trials, which evaluated pembrolizumab (monotherapy) treatment for patients with advanced melanoma and advanced non-small cell lung cancer, respectively. Both of these were phase III multicentre randomised controlled trials sponsored by the company. The company pooled the percentage of patients from these trials who received re-treatment after completing 2 years of pembrolizumab.

[1] [NB. Appendix 3 of the company's response provides information on the disposition of patients, treatment discontinuation and subsequent progression of disease. This is based on an (unplanned) data cut taken in January 2019 for US Food and Drug Administration (FDA) regulatory purposes. The ERG notes that [redacted] patients in the pembrolizumab + axitinib arm discontinued because of a complete response, compared to [redacted] patients in the sunitinib arm. None of the five patients discontinuing pembrolizumab + axitinib had subsequent progression of disease.

Based on these trials, a re-treatment cost was applied to 14.3% of patients in the pembrolizumab and axitinib arm whose disease progressed after 2-years treatment. The ERG notes that in the economic model about a third of patients have not progressed at 2 years. Therefore, in this analysis, the 14.3% of retreated patients is a proportion of this sub-group, rather than the whole trial population (4.8%). The results of these analyses shows that this has a negligible impact on the ICER (Table 9, reproduced from Table 6 of the company's Appendix).

Table 9 Company's scenario analyses exploring retreatment (list price) for the overall population

Scenario	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 3- New base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
	Sunitinib	[redacted]	[redacted]	[redacted]	145,616	1.861	78,266
Scenario 4- Original base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
	Sunitinib	[redacted]	[redacted]	[redacted]	147,136	2.320	63,430
Scenario 1 - exponential distribution for both trial arms; Scenario 2 - log-logistic distribution for pembrolizumab + axitinib; exponential distribution for sunitinib							

The ERG repeated this analysis for the poor/intermediate RCC population, for the comparison of pembrolizumab + axitinib versus cabozantinib, as shown in Table 10.

Table 10 Company's scenario analysis exploring retreatment (list price) for the poor / intermediate RCC risk population (ERG replication of company analyses)

Scenario	Technologies	Total costs (£)	Total LYG	Total QALY	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Scenario 3- New base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	
	Cabozantinib	[redacted]	[redacted]	[redacted]	46,144	1.203	38,344
Scenario 4- Original base case assumptions	Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]			
	Cabozantinib	[redacted]	[redacted]	[redacted]	48,112	1.543	31,178
Scenario 1 - exponential distribution for both trial arms; Scenario 2 - log-logistic distribution for pembrolizumab + axitinib; exponential distribution for sunitinib							

Although the trials in the company's KEYNOTE clinical trial programme share certain design characteristics (e.g. two-year treatment stopping rules for pembrolizumab), it cannot necessarily be assumed that retreatment rates in trials for other cancers are generalisable to renal cell carcinoma. There may be other potential sources of clinical heterogeneity between the trials, such as differences in patient characteristics, which could limit generalisability to the current appraisal. A further factor is that pembrolizumab was given as monotherapy in the KEYNOTE -006 and KEYNOTE-010 trials, but was given in combination with axitinib in KEYNOTE-426. In their submission to NICE, the company highlights the innovative nature this immune-oncology (TKI) combination in targeting both angiogenesis and immune-checkpoint pathways. The proposed mechanism of action of pembrolizumab + axitinib combination therapy is, therefore, different from the mechanism for pembrolizumab monotherapy. This difference may indicate that the rate of retreatment is not necessarily comparable with that seen with pembrolizumab monotherapy.

The ERG therefore suggests caution in the interpretation of the results of this scenario analysis. The company likewise acknowledges the limitations of their analysis and propose that, if pembrolizumab + axitinib were to be included in the Cancer Drugs Fund (CDF), it would allow retreatment data from KEYNOTE-426 to be included in the CDF guidance review.

4. Summary

The ERG considers that the company's approach in their new base case (i.e. use of an exponential distribution for both trial arms) to be reasonable. For the company's scenario analyses exploring alternative treatment effect duration, we do not understand the rationale of restricting this assumption only to a small proportion of patients. Furthermore, we are unclear how generalisable the retreatment rates from KEYNOTE trials in melanoma and in non-small cell lung cancer are to renal cell carcinoma. The results of the scenario analyses should be interpreted with caution.