NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

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 (MSD)**
   a. Comments on the Appraisal Consultation Document
   b. Additional evidence

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. *Joint response from* the Royal College of Physicians

4. **Evidence Review Group critique of company additional evidence**

There were no comments received through the website facility or from the invited experts.

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

Appraisal title

Single Technology Appraisal

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	NCRI-ACP-RCP-RCR	The evidence for this drug in this indication remains the only level one evidence for immunotherapy in urothelial cancer within product label. By contrast, the phase III study supporting the marketing authorisation for atezolizumab in this indication failed to meet its primary objectives (although the data were considered sufficient for the marketing authorisation to remain). The marketing authorisations for both atezolizumab and pembrolizumab in the first line, non-cisplatin-fit populations are currently based on non-randomised phase II data. The Research Group considers level of evidence to be an important consideration in clinical decision making. The NICE appraisal, by its nature, has not adequately considered this factor. However, the Research Group believes that it is undesirable that clinicians may prescribe a drug without level I evidence (atezolizumab, docetaxel, paclitaxel) where there is an alternative where such evidence exists (pembrolizumab). The Research Group urges the Appraisal Committee to consider this factor in weighing up other causes of uncertainty in the economic analysis.	Comment noted. As described in the Guide to the methods of technology appraisal section 6.2.17, the committee considers a number of factors in making its judgements on cost effectiveness, including: • The strength of the supporting clinical-effectiveness evidence. • The robustness and appropriateness of the structure of the economic models. The plausibility of the inputs into, and the assumptions made, in the economic models. • The committee's preferred modelling approach, taking into account all of the economic evidence submitted. • The range and plausibility of the ICERs generated by the models reviewed. • The likelihood of decision error and its consequences. In this appraisal, the committee considered that the most plausible ICER was above the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It therefore concluded not to recommend

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
				pembrolizumab.
2	Consultee	NCRI-ACP-RCP-RCR	Whilst acknowledging the uncertainty regarding the long-term survival benefits of pembrolizumab in this indication, there is insufficient follow up of the pivotal (or any other) data to resolve this one way or the other. Given the transformational effects of pembrolizumab for some patients observed by members of the group in their own practices, the Research Group urges to the Appraisal Committee to permit more 'benefit of doubt' to the optimistic case. The most recent updated analysis of Keynote-045 demonstrates that 20.7% of patients are still alive 36 months after starting pembrolizumab and that the median duration of response is 29.7 months with pembrolizumab (compared to 4.4 months for chemotherapy) (Necchi et al. poster 919P, ESMO meeting ,Barcelona, 30 Sep 2019). The Research Group considers these data to be consistent with more positive long term survival estimates than those assumed by the Appraisal Committee, noting similarities with survival curves seen in other cancers at a similar stage of follow up where long term data supported higher 10 year survival figures than those assumed for urothelial cancer by The Committee.	Comment noted. The committee considered the data on survival at 36 months and median duration of response. It considered that these figures suggested the relative treatment effect of pembrolizumab might continue beyond 3 years. However, it also agreed that the Kaplan–Meier evidence did not suggest a long-term difference in hazard rates between the 2 treatment arms. It concluded that a 3- to 5-year treatment effect from the start of pembrolizumab treatment could be plausible. See FAD section 3.18. The range of treatment effect durations was taken into account in the committee's consideration of the cost-effectiveness estimates. See FAD section 3.22.
3	Consultee	NCRI-ACP-RCP-RCR	Member of the Research Group are in no doubt that for most patients, immune checkpoint inhibitors such as pembrolizumab, are the technologies which are most likely to meet the needs of patients in this indication. This encompasses patients' expectations around safety and tolerability and also efficacy when compared to the cytotoxic comparators.	Comment noted. The committee heard that that chemotherapy is associated with unpleasant side effects such as fatigue, nausea and vomiting and puts people at a greater risk of infection. It understood that pembrolizumab was well tolerated and that patients considered it to have fewer severe adverse events than chemotherapy. See FAD section 3.1 and 3.9.
4	Consultee	NCRI-ACP-RCP-RCR	Paclitaxel and docetaxel, though widely offered in this indication, are of limited efficacy with only low-level evidence. The Research Group is keen to ensure that the standard of evidence in treatment pathways in the UK is aligned to the best available evidence in the world. It would be a backward step if clinicians	Comment noted. The committee takes into account a number of factors in its decision making, including the level of evidence available for the intervention. See response to earlier comment. In this appraisal, the

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
			were to revert to less-evidence based medicine by using these cytotoxic drugs in this indication where previously they were permitted to use pembrolizumab.	committee concluded that pembrolizumab was more clinically effective than docetaxel or paclitaxel. However the most plausible ICER was above the range that NICE normally considers to be a cost-effective use of NHS resources for a life-extending treatment at the end of life. It therefore concluded not to recommend pembrolizumab.
5	Company	Merck Sharp & Dohme	**General comment on content and tone of the Appraisal Consultation Document** MSD is encouraged that the Appraisal Consultation Document confirms that: • Clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with docetaxel and paclitaxel. • Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. • Pembrolizumab is well tolerated. Despite the above, MSD is disappointed by the overall tone of the Appraisal Consultation Document. Our key concerns are as follows: • MSD considers that the Appraisal Consultation Document fails to reflect the strong clinical and patient group advocacy for pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy, which was apparent at the NICE appraisal committee meeting which took place on 22 October 2019. o The clinical and patient group representatives at the committee meeting clearly described pembrolizumab as the current standard of care for this patient population. They also highlighted the improvement offered by pembrolizumab in terms of quality of life, and clearly recognised the value of the product as an effective treatment option which produces durable responses, in a patient population for which there are limited	Comments noted. The committee understood that pembrolizumab is well tolerated and that patients considered it to have fewer severe adverse events than chemotherapy. See FAD section 3.9.

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
			alternative effective treatments. • MSD is concerned with apparent inconsistencies in the decision-making approach of Committee D, when compared to other appraisals conducted by this Committee (see comment 3, 4, 5, 6, 7, 8, and 12) • MSD is concerned by the inclusion of inaccurate statements in the Appraisal Consultation Document which we do not consider aid decision-making. These are further outlined in comments that follow (see comments 2, 3,9, 10 and 11).	Comment noted. For detailed responses, please see responses below. Thank you for highlighting the perceived inaccurate statements in the ACD. The FAD has been amended in line with some of these comments.
6	Company	Merck Sharp & Dohme	**<u>Rationale for the recommendations as stated in the Appraisal Consultation Document</u>** ***MSD believes that the current availability of atezolizumab should have no bearing and is irrelevant in the context of the decision-making in this appraisal of pembrolizumab for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum containing therapy.*** Section 1, page 3 of the Appraisal Consultation Document under the subheading "*Why the committee made these recommendations*" states (5th paragraph) "*Atezolizumab is now also a possible treatment. But it was not established clinical practice in the NHS at the time of the original appraisal, so is not included in the scope*". MSD strongly believes that it is inappropriate to include this statement as a part-justification for the recommendations made in the Appraisal Consultation Document. As reported in the Appraisal Consultation Document, atezolizumab was not included in the scope at the time of the original appraisal of pembrolizumab in this indication. Consequently, it was not considered a comparator of relevance in the context of this Cancer Drug Fund guidance review of pembrolizumab. MSD considers it is misleading to include reference to availability of atezolizumab at this stage of the Cancer Drug Fund guidance review process. This should not provide part-justification for the NICE Committee's provisional recommendation to not recommend pembrolizumab for baseline commissioning through the NHS for the treatment of patients with	Comment noted. The paragraph in section 1 explains to readers why atezolizumab is not considered as a comparator in this Cancer Drugs Fund review and is not a comment on current practice in the NHS.

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
			locally advanced or metastatic urothelial carcinoma who have had platinum-containing therapy. In addition to the above-mentioned reference to atezolizumab in the Appraisal Consultation Document, Section 3.2 (page 6) also reports that atezolizumab "*was not established clinical practice in the NHS at the time of the original appraisal*". MSD would query the definition of "established clinical practice" accredited to atezolizumab in the Appraisal Consultation Document. Data collected from Ipsos' Global Oncology Monitor shows that, as of the Moving Annual Total ending in September 2019 [1], 39% of reported drug-treated patients in their sample affected with metastatic urothelial cancer in a second-line setting were prescribed with pembrolizumab (following 1st line platinum-containing chemotherapy); this reflects a 17% higher usage share for pembrolizumab compared to atezolizumab (22% patient usage share) among this reported patient sample cohort The 17% difference in favour of pembrolizumab is, in MSD's opinion, reflective of the clinical confidence in pembrolizumab as a suitable and effective treatment option when it comes to clinicians making a therapeutic choice for a urothelial cancer patient after failure of platinum-containing chemotherapy. As mentioned in comment 1, this clinical confidence was apparent at the NICE committee meeting which took place in October 2019, and the above data is reflective of the clinical expert's description of pembrolizumab as current standard of care.	Final guidance for atezolizumab was not published at the time of the original appraisal and therefore atezolizumab was not considered to be in established clinical practice in this indication. As described in the Guide to the methods of technology appraisal, section 6.2.3, the committee will normally be guided by established practice in the NHS when identifying the appropriate comparator.
7	Company	Merck Sharp & Dohme	**Inconsistencies in NICE appraisal approach between pembrolizumab and atezolizumab technology appraisals for previously treated advanced or metastatic urothelial cancer** ***MSD has identified inconsistencies in Committee D's interpretation of key issues that inform the cost-effectiveness assessment of pembrolizumab in this Cancer Drugs Fund guidance review, as compared to how these issues were considered within the context of the appraisal of atezolizumab (TA525) [2]. The inconsistency in approach applied to these issues are key drivers in the Committee's disappointing preliminary conclusion that pembrolizumab would not be a cost-effective option for NHS***	Comment noted. The committee was aware of a number of differences between the company submissions for atezolizumab and pembrolizumab. There was no 2-year stopping rule in the trial of atezolizumab or its summary of product characteristics and the modelling of duration of treatment presented to the committee was different to the modelling presented in this appraisal of pembrolizumab. Considering the company's new evidence, the committee agreed that a 3- to 5-year treatment effect

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
			resources in patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy. Atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy was recommended by NICE following its appraisal by Committee D in June 2018 (TA525) for baseline commissioning [2]. The same Committee (Committee D) conducted the original appraisal of pembrolizumab in this indication following our company submission in February 2017. At the time of the original MSD submission, atezolizumab was not yet recommended by NICE and therefore neither it was considered established clinical practice nor deemed a relevant comparator in the scope of the pembrolizumab appraisal. Pembrolizumab was subsequently recommended within the Cancer Drugs Fund. The same Committee (Committee D) is now undertaking this CDF guidance review of pembrolizumab, which is the subject of this Appraisal Consultation Document. The key areas of inconsistency are discussed in turn below: <u>*Approach to modelling duration of treatment effect*</u> Different approaches have been applied by Committee D between the two appraisals regarding the assumption of duration of treatment effect: • In the atezolizumab appraisal, in the absence of data regarding treatment effect after atezolizumab is stopped (median follow-up data of 17.4 months and maximum follow-up data of 24.5 months) [2], the NICE Committee applied a 3-year cap on duration of treatment effect **after treatment is stopped** (in effect a 5-year duration of treatment effect from start of treatment). This arbitrary timeframe was based on prior appraisals of immunotherapies where a stopping rule was applied (please also refer to Comment 12). • In contrast based on the updated data-cut from KEYNOTE-045 which informs this Cancer Drugs Fund guidance review (median follow-up data of 40.9 months and maximum follow-up data of 48.9 months) [3], the Committee preferred assumption for pembrolizumab is a 3-year cap on duration of treatment effect **from the start of treatment.**, disregarding the greater	from the start of pembrolizumab treatment could be plausible. See FAD section 3.18. The range of treatment effect durations was taken into account in the committee's consideration of the cost-effectiveness estimates. See FAD section 3.22. Comment noted. In TA525, the committee noted that there was not enough evidence to support a specific duration of benefit (see TA535 FAD section 3.12).

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
			Validity of 2-stage model • Criticisms concerning treatment switching have been levelled by the Evidence Review Group during their critique of the pembrolizumab submission that informs this Cancer Drugs Fund guidance review. This issue was not an area of concern during the atezolizumab appraisal. ○ With regards to treatment switching, the Evidence Review Group cites data from vinflunine (Bellmunt et al. [4]) to argue for the harshness of the acceleration factor adversely affecting the UK standard of care arm when the 2-stage method was applied. However, vinflunine is not used in UK clinical practice and should not be used as a proxy for UK clinical treatment (please also refer to Comment 6). *Disregard of evidence of treatment effect duration from other pembrolizumab trials* • MSD had presented evidence from pembrolizumab studies KEYNOTE-001 [5, 6] (melanoma, non-small cell lung cancer), KEYNOTE-006 [7] (melanoma) and KEYNOTE-024 [8] (non-small cell lung cancer) as supportive of a long-term duration of treatment effect with our response to the technical engagement. However, section 3.14 (page 13) of the Appraisal Consultation Document states "*Evidence of treatment effect duration from other pembrolizumab trials is not appropriate for decision making*". The document further elaborates, stating that the Committee agreed that *"the results from those trials were not generalisable to urothelial carcinoma".* • However, in the case of atezolizumab where there was a dearth of clinical evidence, the Committee applied a 3-year cap on duration of treatment effect after 2 years of treatment (i.e. 5 years from starting treatment) based on appraisals of other immunotherapies where a stopping cap was applied. • A duration of treatment effect of >3 years has been accepted by NICE committees on several other pembrolizumab appraisals (and appraisals of other	Comment noted. Treatment switching was not raised as an issue in the appraisal of atezolizumab. For this appraisal, the committee concluded that both the results with and without the 2-stage adjustment for treatment switching should be taken into account. See FAD section 3.6. Comment noted. The committee considered the company's new evidence and agreed that a 3- to 5-year treatment effect from the start of pembrolizumab treatment could be plausible. See FAD section 3.18. The range of treatment effect durations was taken into account in the committee's consideration of the cost-effectiveness estimates. See FAD section 3.22.

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
			immuno-oncology therapies) [9-16]. MSD further discusses these specific issues in greater detail in this response (Comments 4,5,6,7,8 and 12). We urge the NICE Committee to apply a consistent approach when dealing with these issues in the context of this Cancer Drugs Fund guidance review of pembrolizumab, as applied at the time of the appraisal of TA525 [2]. This will aid transparency and ensure consistency in the decision-making framework when applied across appraisals. MSD would like to highlight that, if the approach accepted in TA525 [2] was consistently applied in this assessment of pembrolizumab, it would be proven that this intervention is a cost-effective option for patients affected by locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy.	
8	Company	Merck Sharp & Dohme	**Appropriateness of the 2-stage method to adjust for subsequent therapy in the UK Standard of Care arm** ***MSD strongly disagrees that the unadjusted analysis should be used for decision making in this appraisal, and considers results based on the 2-stage method to be robust, reliable and generated using methodology previously accepted as appropriate by NICE Committees.*** Section 3.5, page 8 of the Appraisal Consultation Document states "*New KEYNOTE-045 data shows that the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account*". MSD is concerned that the 2-stage model has been disproportionately criticised by the Evidence Review Group and the NICE technical team in the context of this Cancer Drug Fund guidance review appraisal, as opposed to when this method has been utilised (and accepted as appropriate) in previous NICE appraisals [3]. Based on the content of the Appraisal Consultation Document, it seems that the key driver for the concern over the appropriateness of the 2-	Comment noted. The main concern was not the magnitude of the acceleration factor, but that the increased magnitude meant the adjustment had more influence and therefore existing uncertainties associated with the 2-stage method were more important to consider, compared with TA519. These uncertainties were: • The wide confidence interval around the acceleration factor showed a high degree of uncertainty • The adjustment method assumed an average adjustment for all people switching and it is unlikely that all patients who switched benefitted equally from the anti-PD-L1 or PD-1 treatment • With the adjustment, the benefit would have been the same as if patients had anti-PD-L1 or PD-1

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
			stage method is the magnitude of the acceleration factor which is generated when running this method, based on the November 2018 data-cut of KEYNOTE-045. As a result of the magnitude of the acceleration factor, it appears that the Evidence Review Group has subsequently questioned other aspects of the 2-stage methodology, which has translated into additional concerns with this approach for the NICE Committee, centred on a lack of confidence in the general acceptability of this adjustment method for treatment switching and the external validity of the adjusted results. MSD strongly disagrees that the unadjusted analysis should be used for decision making in this appraisal. MSD has attempted to sequentially address these concerns below, and in our subsequent comments (from 5 to 8): *Precedent set in TA519 [17]* As acknowledged in the Appraisal Consultation Document, the 2-stage method to adjust for subsequent therapy usage in the UK standard of care arm was used in the original appraisal of TA519 [17], and was considered by the Committee as the most appropriate patient population upon which to base decision making. The Evidence Review Group report confirms that alternative methods of adjusting for treatment switching were discussed in the previous review of this indication and were deemed not beneficial (Rank-preserving structural failure time and Inverse probability of censoring weighted). The approach taken by MSD when applying the 2-stage adjustment method is entirely consistent with the approach taken in TA519 [17]; consequently, MSD believes that it continues to be appropriate to base decision making on the comparison between pembrolizumab and the 2-stage adjusted UK standard of care population. The same variables (age, gender, Eastern Cooperative Oncology Group at secondary baseline [0, ≥1], time to progression, liver metastases, time from last prior chemotherapy [<3 vs. ≥3 months], haemoglobin at secondary baseline and site of primary tumour) have been used as per the original submission. The method has been followed appropriately, with adjustment made based on whether patients switched at the time of disease progression (which is a mandatory requirement to create a	therapy earlier in their disease pathway. The KEYNOTE-045 trial data did not support this. • There was potential for selection bias in relation to switching, and unmeasured prognostic factors could affect the data. The committee considered the most plausible ICERs lay somewhere between those including the 2-stage adjustment for treatment switching in the UK SoC arm, and those without the adjustment, and took both into account in its consideration of the cost-effectiveness estimates. See FAD sections 3.6 and 3.22.

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
			secondary baseline within the model) or not, with an average effect applied accordingly to all patients classified as eligible for having their survival time adjusted under the 2-stage method. <u>*Precedent set in other appraisals of pembrolizumab*</u> The use of the 2-stage method has been used , in all other NICE appraisals of pembrolizumab [17-19] when it has been necessary to adjust data in the comparator arm due to within trial switching or subsequent therapy usage which was inconsistent with standard UK clinical practice. This approach has been accepted as appropriate by various NICE committees in these appraisals. <u>*Response to specific concerns centred on 2-stage methodology*</u> MSD considers that most of the concerns highlighted by the Evidence Review Group in their report, and again reiterated in the Appraisal Consultation Document, are standard disadvantages and/or assumptions of the 2-stage methodology and are not correlated to the KEYNOTE-045 data. In our subsequent comments, MSD has attempted to address each issue in turn (Comments 5 to 8). MSD strongly disagrees that it would be appropriate to use the unadjusted analysis for decision making in this appraisal. As mentioned in the Technical Report, the Evidence Review Group acknowledges that failing to adjust for subsequent therapy is "*not ideal, as it is likely that some patients who switched did receive a benefit from the treatment*." The Evidence Review Group also states that "*not adjusting for this benefit introduces bias which favours the control arm*". In the Evidence Review Group report, it had been stated that this bias favouring the control arm "*may be stronger than the potential biases when the 2-stage method is used*". We would urge the Committee to take all the presented evidence in this response into consideration, which provides strong support for the use of the adjusted results based on the 2-stage method as the basis for decision making and determining the cost-effectiveness of pembrolizumab for the treatment of locally advanced or metastatic urothelial cancer for adults who received platinum-containing	Comments noted. The main concern was not the magnitude of the acceleration factor, but that the increased magnitude meant the adjustment had more influence and therefore existing uncertainties associated with the 2-stage method were more important to consider, compared with TA519. These uncertainties were: • The wide confidence interval around the acceleration factor showed a high degree of uncertainty • The adjustment method assumed an average adjustment for all people switching and it is unlikely that all patients who switched benefitted equally from the anti-PD-L1 or PD-1 treatment • With the adjustment, the benefit would have been the same as if patients had anti-PD-L1 or PD-1 therapy earlier in their disease pathway. The KEYNOTE-045 trial data did not support this. • There was potential for selection bias in relation to switching, and unmeasured prognostic factors could affect the data. The committee considered the most plausible ICERs lay somewhere between

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
			chemotherapy	those including the 2-stage adjustment for treatment switching in the UK SoC arm, and those without the adjustment, and took both into account in its consideration of the cost-effectiveness estimates. See FAD sections 3.6 and 3.22.
9	Company	Merck Sharp & Dohme	**<u>Calculation and application of acceleration factor in the 2-stage model</u>** ***MSD considers that the acceleration factor of 5.37 based on the November 2018 data-cut of KEYNOTE-045 is a more precise and reliable estimate of the acceleration factor than that generated at the time of the original appraisal of TA519 [17].*** The acceleration factor is a multiplicative factor, which quantifies the increase in survival time due to pembrolizumab compared to UK standard of care. In our Cancer Drug Fund guidance review submission, the calculated acceleration factor of 5.37 was calculated using a standard approach, that is estimated based on the effect of switching from control to anti-PD-1/PD-L1 treatment. The 2-stage method has been applied to the November 2018 data-cut using the same methodology as previously employed in the original appraisal of TA519 [17], **when it was deemed by both the Evidence Review Group and NICE Committee as the most appropriate method to use, and appropriate for decision making**. Page 8 (paragraph 2) of the Appraisal Consultation Document reports "*The November 2018 data cut from KEYNOTE-045 showed that the acceleration factor had a higher magnitude and applied to more people in the trial. This meant the 2-stage adjustment had a greater influence on overall survival than it did in the original appraisal. The acceleration factor was 5.37 (95% confidence interval [CI] 3.23 to 10.09) (based on 25 patients) after the November 2018 data cut, compared with 3.86 (95% CI 1.79 to 11.68) (based on 14 patients) using previous data".* MSD acknowledges that the acceleration factor generated using the trial data from the November 2018 data-cut is higher in magnitude compared to the acceleration factor provided in the original submission.	Comment noted. The main concern was not the magnitude of the acceleration factor, but that the increased magnitude meant the adjustment had more influence and therefore existing uncertainties associated with the 2-stage method were more important to consider. The committee considered the company's analysis where the acceleration factor was applied to all 40 patients. However the calculation of the acceleration factor was not adjusted to include the additional 15 patients. See FAD section 3.6.

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
			However, MSD feels that the Committee should not simply consider the magnitude of the acceleration factor in isolation, without also considering other important factors; for example, differences between the results of the two data-cuts (September 2016 and November 2018) in terms of sample sizes, accuracy of the acceleration factor and range of the confidence intervals. • The very small sample size used in the original appraisal (N=14) resulted in a smaller acceleration factor (3.87) and a wider confidence interval (difference between upper and lower confidence interval = 9.89). It is recognised widely, that any statically inference applied to such small sample sizes may produce uncertain results, therefore the width of the confidence interval is not surprising. • Based on the November 2018 data-cut which informs this Cancer Drug Fund guidance review, the acceleration factor is higher in magnitude (5.37) but the confidence interval generated is narrower as compared to that generated in the original submission (November 2018 data-cut difference between upper and lower CIs = 6.86). • **It is noteworthy that the confidence interval obtained using the November 2018 data-cut (3.23 to 10.09) is not only narrower, but also falls entirely within the range of the confidence interval of the original acceleration factor based on the previous data cut at the time of the original appraisal (1.79 to 11.68).** • Based on the above, MSD urges the Committee to consider, that based on the higher sample size with the November 2018 data-cut (N = 25), the acceleration factor of 5.37 actually represents a more precise estimate of the true value gained when switching from UK standard of care to an anti-PD-1/PD-L1 therapy, compared to the acceleration factor generated at the time of the original appraisal. During the clarification question phase of the Cancer Drug Fund guidance review appraisal, the Evidence Review Group had requested that MSD estimates the acceleration factor including vinflunine patients in the standard of care arm, in an attempt to reduce uncertainty. The results of this analysis (provided in our response to clarification questions) were deemed "*consistent"* with the original analysis	The committee was aware that the company considered the updated acceleration factor to be more reliable than the original acceleration factor, because it was calculated from a larger sample size and the confidence intervals were narrower and within the range of the originally calculated confidence intervals. However the main concern was not with the value of the acceleration factor. See FAD section 3.6.

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
			presented by the Company (i.e. acceleration factor = 5.32, confidence intervals: 3.44, 8.446). Thus, even by increasing the sample size to assess variability and check for accuracy of the generated acceleration factor, the results are stable. Page 8 (paragraph 2) of the Appraisal Consultation Document goes on to report "*The acceleration factor was calculated from the 25 people who switched when progression of their diseases was documented. The acceleration factor was not applied to the overall survival time of 15 patients which switched at different times. It is not known how including these 15 patients in an adjustment would have affected the estimated incremental cost-effectiveness ratio (ICER)*". • The *"15 patients who switched at different times"* refer to patients who (unlike the 25 'eligible' patients) did not switch based on documented disease progression (defined centrally by Response evaluation criteria in solid tumours). ○ Examples of the reason for switching for these 15 patients may include but not be limited to having had documented disease progression defined by the investigator (i.e. rather than by central review per Response evaluation criteria in solid tumours) or following discontinuation due to adverse events. It is at the investigator's and subject's discretion as to how to treat following discontinuation from study treatment. As a result, eligibility for subsequent therapy, outside of subjects that qualified for switching (according to the criteria of documented disease progression defined centrally by Response evaluation criteria in solid tumours) was not captured in the KEYNOTE-045 trial. • In order to address the above uncertainty identified in the Appraisal Consultation Document, a sensitivity analysis has been conducted to show the results of the 2-stage adjustment when applying the same acceleration factor of 5.37 to <u>all</u> switchers including the 15 patients who switched at a time other than documented disease progression defined centrally by Response evaluation criteria in solid tumours.	

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
			○ The results are presented in Appendix 1, and show that with the inclusion of these 15 patients, the hazard ratio for the comparison of pembrolizumab versus UK standard of care is 0.55 (CI 0.41, 0.69) ○ This improved hazard ratio shows that MSD's original approach, of not including these 15 patients in the 2-stage adjusted analysis, is a more conservative approach: it results in the survival times of fewer patients in the UK standard of care arm being adjusted downwards, and therefore a less favourable hazard ratio for the comparison of pembrolizumab with UK standard of care. MSD reiterates that the November 2018 data-cut and the extra analyses provided, demonstrate robustness in the generated acceleration factor of 5.37. Based on the rationale described above, we consider this point estimate to be more precise and reliable than the acceleration factor generated at the time of the original appraisal of TA519 [17].	
10	Company	Merck Sharp & Dohme	**External validity of 2-stage adjusted results in the UK standard of care arm** ***MSD considers 2-stage adjusted results to be reliable, and entirely disagrees with the view that the 2-stage model overly underestimates survival time in the UK standard of care arm. We also believe it is inappropriate to consider data on the non-UK recommended drug, vinflunine from the Bellmunt (2013) study [4], as a proxy for expected efficacy in the UK standard of care arm.*** Page 8 (paragraph 2) of the Appraisal Consultation Document reports "*It advised that the true overall survival benefit would be somewhere between the results of the 2 approaches. Using an approach without the adjustment might overestimate survival time in the UK SoC arm, but the 2-stage model might underestimate survival time in this arm too much*". In response to the above statement, MSD restates that the approach used in this Cancer Drug Fund guidance review appraisal is entirely consistent with that used at the time of the original appraisal of TA519 [17], whereby results are presented, and economic evaluation is based	Comment noted. The main concerns with the 2-stage adjustment method were: • The wide confidence interval around the acceleration factor showed a high degree of uncertainty. • The adjustment method assumed an average adjustment for all people switching to anti PD L1 or PD 1 therapy. The ERG considered it unlikely that all patients who switched benefitted equally from the anti-PD-L1 or PD-1 treatment. This was because evidence from KEYNOTE-045 suggested pembrolizumab was inferior to UK SoC for the first 3 months of follow-up, and because immunotherapies

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
			on results of the 2-stage model, adjusting for treatment switching in the UK standard of care arm. MSD strongly supports the use of this method, since failing to do so (i.e. using only results of unadjusted analyses) will misrepresent the clinical benefit and true treatment effect associated with pembrolizumab versus UK standard of care in the urothelial cancer population investigated within KEYNOTE-045 [3]. MSD entirely disagrees with the premise that the 2-stage model overly underestimates survival time in the UK standard of care arm. Most of the rationale for this conclusion, as had been previously described in the Evidence review Group and NICE technical reports, was based on a perceived discrepancy when comparing 2-stage adjusted results from the UK standard of care arm of KEYNOTE-045, with vinflunine data (Bellmunt et al. [4]), which the Evidence Review Group were using as a proxy to validate the 2-stage adjusted UK standard of care results from KEYNOTE-045. MSD reiterates that the conclusions reached by the NICE committee for this comparison should be interpreted with extreme caution since: • Although the median overall survival in the vinflunine arm of the Bellmunt et al study [4] is closer to the median overall survival from the UK standard of care arm of the KEYNOTE-045 population without adjustment for treatment switching, it is noteworthy that in terms of the reported 12, 24 and 30 month overall survival in the Bellmunt et al study [4], there is better consistency with the UK standard of care arm of the 2-stage adjusted population from KEYNOTE-045. • Bellmunt et al. [4] presented in their publication limited patient characteristics thus, it is inappropriate to consider the two study populations as analogous. • Some heterogeneity exists between the population included in the Bellmunt paper [4] and KEYNOTE-045 populations with regards to the age of the patients at the time of enrolment, the Eastern Cooperative Oncology Group Performance Status and prior therapies reported. • These differences could have impacted the outcomes of the studies in several ways (e.g. heterogeneity of the results, over or underestimation of treatment effect). • The aim of the Bellmunt study [4] was to investigate the efficacy	have not been shown to benefit everyone. • With the adjustment, the benefit would have been the same as if patients had anti-PD-L1 or PD-1 therapy earlier in their disease pathway. The KEYNOTE 045 trial data did not support this. • There was potential for selection bias in relation to switching, and unmeasured prognostic factors could affect the data. The committee considered that the true overall survival benefit was probably between that seen with an adjustment for treatment switching and that without an adjustment. The committee took both into account it its consideration of the cost-effectiveness estimates. See FAD sections 3.6 and 3.22.

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
			of vinflunine in combination with best supportive care versus best supportive care alone. It is important to note that vinflunine is not recommended by NICE in England and is not established clinical practice in the UK; consequently, the comparison made between the two studies by the Evidence Review Group seems inappropriate. In the absence of more appropriate evidence in the second-line setting for established UK standard of care treatments (e.g. taxanes), the results of KEYNOTE-045 trial [3], which directly investigated the efficacy of pembrolizumab versus currently approved UK standard of care (e.g. docetaxel and paclitaxel), should be considered as the best available evidence, since head-to-head trials are considered the gold standard in delivering high quality data.	
11	Company	Merck Sharp & Dohme	**Committee's additional concerns with 2-stage methodology** ***The 2-stage model assumes an average adjustment for eligible subjects receiving subsequent therapy rather than the same overall survival benefits for all people switching to anti-PD-L1 or PD-1 therapy.*** Page 9 (paragraph 1) of the Appraisal Consultation Document states *"The ERG explained that the adjustment method assumed that all people switching to anti-PD-L1 or PD-1 therapy had the same overall survival benefits".* MSD believes that this statement is misleading and that it incorrectly represents some of the assumptions used in the 2-stage model. The 2-stage model assumes an 'average adjustment for eligible subjects receiving subsequent therapy' and not "*the same overall survival benefits"*. These two concepts are not interchangeable, and the misuse of the latter in this situation can lead to inaccurate conclusions being drawn. "*The same overall survival benefits"* implies that all patients who switched to any anti- PD-1/PD-L1 therapies were treated as if they received the same benefit in terms of survival (equal hazard ratio). This consideration is imprecise and unrealistic.	Comment noted. The FAD has been amended to clarify this statement. See FAD section 3.6.

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
			The average adjustment estimates an average of the effect and benefits seen in some patients, equally balanced by including those patients who benefitted less from switching. Therefore, patients who benefitted less or not at all from switching therapy are included in the 2-stage model, which better reflects clinical practice. The ratio of those patients who switched and did not switch is then used to generate the acceleration factor which is uniformly applied to all switchers. Concluding, it is incorrect to state that this model assumes the same overall survival benefits. Additionally, within the context of this study, more complex modelling approaches would be inadvisable and perhaps not possible, given the very small sample size of patients who switched (N = 40). It is also true that considering unadjusted analysis (i.e. disregarding adjustment for treatment switching) will overly penalise pembrolizumab as described in comment 6 of this document.	
12	Company	Merck Sharp & Dohme	**<u>Impact on economic model when using 2-stage adjusted analysis</u>** ***MSD confirms there is no error in the economic model.*** Page 9 (paragraph 1) of the Appraisal Consultation Document reports *"Although the company stated that the same methodology was used in other submissions for pembrolizumab, the committee noted that the model for this appraisal appeared to incorrectly change outcomes for the pembrolizumab arm when survival for the UK SoC arm was adjusted, and these changes favoured pembrolizumab. The committee concluded that, while the ICERs using the 2-stage adjustment for treatment switching were not robust because of the apparent error in the model and the other issues above, the true overall survival benefit was probably between that seen with an adjustment for treatment switching and that without an adjustment."* MSD believes this statement is misleading, and incorrectly casts doubt on the accuracy of the incremental cost-effectiveness ratio estimates produced by the economic model. The '*apparent issue*' of the change in outcomes for the pembrolizumab arm when survival for the UK standard of care is adjusted, is due to the implementation of the treatment effect cap within the economic model.	Comment noted. This has been removed from the FAD. See FAD section 3.6.

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
			The introduction of a treatment effect cap results in a change in the hazard rate from the pembrolizumab arm to the UK standard of care arm at a defined time point. When the adjustment method is changed for the UK standard of care arm, this implicitly alters the hazard rate in the standard of care arm and hence leads to a change in outcomes in the pembrolizumab arm, due to the treatment effect cap associating the two. There is no error in the model - this can be seen when selecting a lifetime treatment effect and switching between adjusted and unadjusted analyses; there is no impact on the outcomes within the pembrolizumab arm.	
13	Company	Merck Sharp & Dohme	**Availability of clinical effectiveness data for the PD-L1 positive subgroups** ***MSD confirms that clinical effectiveness data for the PD-L1 positive subgroups were provided by the company during this cancer drugs fund guidance review.*** Page 10 (paragraph 2) of the Appraisal Consultation Document states "*The company did not present clinical effectiveness data for the PD-L1 positive subgroups using data from the November 2018 cut-off*". The above-mentioned statement is incorrect since MSD provided this information upon request from the Evidence Review Group as part of the clarification questions process. MSD is concerned that the consequence of this misrepresentation in the Appraisal Consultation Document is a failure to reflect MSD's willingness to resolve uncertainty around the issues identified by the Evidence Review Group and the NICE technical team during the course of the appraisal.	Comment noted. This has been amended in the FAD. See FAD section 3.7.
14	Company	Merck Sharp & Dohme	**Indirect comparison of pembrolizumab with best supportive care** ***MSD does not consider clinical or cost-effectiveness evidence comparing pembrolizumab with best supportive care to be of relevance within the context of this Cancer Drug Fund guidance review.***	Comment noted. This has been amended in the FAD. See FAD section 3.8.

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
			Page 11 (paragraph 1) of the Appraisal Consultation Document states: "*For the original appraisal, the company provided an indirect comparison of pembrolizumab with best supportive care, but the committee concluded that this was not useful for decision making. The company had not presented any new clinical or cost-effectiveness evidence comparing pembrolizumab with best supportive care*". MSD would like to highlight that the above is yet another misrepresentation of the evidence provided during the original appraisal of TA519 [17], and during the course of this Cancer Drug Fund guidance review. • During the course of the original appraisal of TA519 [17], MSD clarified, on several occasions, that best supportive care was not a relevant comparator in the population of interest, as alternative active treatments (e.g. docetaxel and paclitaxel) are available; consequently, an indirect comparison of pembrolizumab with best supportive care was **not** provided. o Taxanes are offered only in people with a good performance status, which is the population included in KEYNOTE-045. Best supportive care is a valid option for people with a poorer PS (Eastern Cooperative Oncology Group Performance Status >2). o Since KEYNOTE-045 only included patients with PS≤2, MSD did not include evidence in our original submission on the clinical effectiveness of pembrolizumab in people who would otherwise be offered best supportive care. o Given that the KEYNOTE-045 is the only trial that evaluated pembrolizumab in people with locally advanced or metastatic urothelial cancer after platinum-containing chemotherapy, there is no evidence to compare pembrolizumab to best supportive care in patients with Eastern Cooperative Oncology Group Performance Status >2 either directly or indirectly.	

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

			• The value of an indirect comparison of pembrolizumab with best supportive care, if it had been conducted would have been of little value given the heterogeneity in patient populations receiving either pembrolizumab or best supportive care
			  ○ During the original appraisal of TA519 [17], the Evidence Review Group mentioned that there was "*a phase 3 randomised controlled trial (RCT) which compared vinflunine + BSC with BSC alone. This trial could have been used to compare pembrolizumab to BSC indirectly but the relevance is questionable given that the trial only included people with PS 0-1*".
			  ○ The Final Appraisal Document for TA519 [17] states that "*the ERG highlighted that an indirect comparison would be inappropriate because the performance status of people in the trials (KEYNOTE-045) would be much better than in people having best supportive care in clinical practice"* and that *"The committee noted that there was no evidence for people who would be likely to have best supportive care, and therefore concluded that it was unable to make a recommendation for this population".*
			
			In light of the consensus reached at the time of the original appraisal, MSD questions the relevance of now including, within this Appraisal Consultation Document, a statement which highlights that MSD has not submitted any new clinical or cost effectiveness evidence to compare pembrolizumab with best supportive care. We are again concerned that the inclusion of such a statement serves no purpose but to suggest an apparent unwillingness of MSD to provide all necessary evidence to support our Cancer Drug Fund guidance review.
			
			The Terms of Engagement document developed by NICE for this Cancer Drug Fund guidance review outlined all areas of outstanding uncertainty, based on the evidence provided at the time of the original submission. It should be noted that:
			
			• There were no uncertainties highlighted concerning the	

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
			comparative clinical or cost-effectiveness of pembrolizumab with best supportive care. • At no stage of the Cancer Drug Fund guidance review to date has there been any requests made by NICE for MSD to present further clinical or cost-effectiveness analyses for this comparison. It is worth mentioning that the approach taken by MSD in respect to a comparison between pembrolizumab and best supportive care is consistent with that taken during the appraisal of atezolizumab (TA525) [2]. The wording in the atezolizumab Final Appraisal Document [9] confirms that although the Committee would have liked to see a comparison with BSC, "*The comparison with taxanes is sufficient for decision-making"* and also acknowledged that *"a lack of data would have made this [comparison with BSC] difficult".*	
15	Company	Merck Sharp & Dohme	**Additional inaccuracies in the Appraisal Consultation Document** ***Reference to Nivolumab in in this Appraisal Consultation Document is of no relevance.*** Page 11 (paragraph 3) of the ACD states "*For pembrolizumab for other indications, and for both atezolizumab and nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy, a 2-year stopping rule applied*". MSD considers the inclusion of nivolumab here as of no relevance, since nivolumab for treating locally advanced unresectable or metastatic urothelial cancer is **not** recommended by NICE [20] and it is not established practice in the UK.	Comment noted. This has been removed from the FAD. See FAD section 3.10.
16	Company	Merck Sharp & Dohme	**Duration of treatment effect** ***MSD considers that a duration of treatment effect of 5 years is a conservative assumption for pembrolizumab and is consistent with precedent accepted by this Committee for atezolizumab in this same patient population. Clinical consensus and KEYNOTE-045 data are also strongly supportive of a long-term treatment effect***.	Comment noted. The committee considered the company's new evidence and agreed that a 3- to 5-year treatment effect duration could be plausible. It considered a 3-year duration could be plausible because after 3 years, only 1 death occurred in the unadjusted UK SoC arm and none in the adjusted population, and the evidence did not suggest the

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
			Page 15 of the Appraisal Consultation Document states, "*The committee considered that there was robust evidence to support a 3-year treatment effect after starting pembrolizumab (2 years of treatment plus 1 year of follow up). However, there was no strong evidence to support a 5-year or longer treatment effect, and no more than 5% of people treated with pembrolizumab might be alive after 10 years*." MSD considers a 3-year treatment effect cap both implausible and inappropriate, for the following reasons: *KEYNOTE-045 has median follow-up of 40.9 months [3]* • The follow-up period in KEYNOTE-045 is greater than three years (maximum follow-up was 48.9 months). Time varying hazard ratio data was presented, within the appendices of the company submission, for pembrolizumab versus UK standard of care using both adjusted and unadjusted analysis. The Evidence Review Group claims that the upper confidence limit rising above 1, "*is strong evidence of some degree of waning effect within the observed follow-up*". MSD considers this the only evidence pertaining to a loss of treatment effect, albeit the time varying hazard ratio estimate remaining constant and below 1 post ~60 weeks in both the adjusted and unadjusted analyses, numerically showing a continued treatment effect beyond 3 and even 5 years. • With the upper confidence limit rising above 1, the Technical Report states that the Evidence Review Group has indicated that this "*may have been partially due to the small number of patients remaining at risk, so this wasn't strong evidence of a loss of effect".* To observe a narrower confidence interval at the tail of the hazard ratio curve, it would require a larger trial sample size. Please note that the time varying hazard ratio analysis is a post-hoc analysis, and KEYNOTE-045 trial was not designed to significantly detect the long-term hazard ratio for pembrolizumab vs chemotherapy, thus it is plausible the trial lacks power to detect the difference in the hazard level due to an insufficient sample size. • MSD does not consider that there is any robust evidence of a loss of treatment effect. Furthermore, as highlighted during the	hazard rate for long-term response was different across the treatment arms after 2 years. However the committee also considered the company's comment that the trial was not designed to show a treatment benefit at 3 years. It considered up to a 5-year duration could be plausible based on the company's new evidence and clinical opinion. The committee did not consider the company's new scenario analyses to be plausible because responders and non-responders had the same response to pembrolizumab for the first 3 or 5 years, and because the analysis was not also applied to the UK SoC arm. In TA525, the committee noted that there was not enough evidence to support a specific duration of benefit. See FAD sections 3.15 to 3.18. The range of treatment effect durations was taken into account in the committee's consideration of the cost-effectiveness estimates. See FAD section 3.22.

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
			technical engagement consultation and at the Appraisal Committee Meeting, a 3-year treatment effect cap causes the parametric fitting to visually deviate to below the observed overall survival data. <u>*Clinical opinion suggests a long tail when treated with pembrolizumab*</u> • All clinical input in the company submission and Evidence Review Group report suggested the expectation of a long tail for overall survival when treated with pembrolizumab. The Evidence Review Group report states "*that some sustained long-term benefit could be plausible for patients receiving pembrolizumab"* which supported both the company and Evidence Review Group 's preference for the log-logistic, as the distribution for extrapolation, as the Evidence Review Group report stated *"both of the log models have a sharply decreasing hazard over time, which means a small number of patients will live for a long time".* By introducing a 3-year treatment effect cap, this is a direct contradiction to the Evidence Review Group's rationale for selection of the log-logistic curve. Furthermore, by the nature of the log-logistic curves, fitted to each arm, there is convergence over time; hence there is a reduction in the relative treatment effect over time. This could be considered gradual treatment waning effect. • MSD considers the Appraisal Consultation Document to be contradictory, stating both, "*The clinical expert… found it plausible that 5% to 10% of people having pembrolizumab might survive to 10 years after starting treatment (with a 2-year stopping rule)"*, but later mentions that the Committee concluded "*no more than 5% of people treated with pembrolizumab might be alive after 10 years.*" It is unclear why the committee disagreed with the clinical expert. • As noted in the Appraisal Consultation Document "*The company indicated that with their preferred log-logistic curve for extrapolation of overall survival (see section 3.16), 4.5% of people having pembrolizumab were modelled to still be alive 10 years after starting treatment*." Hence, the use of a 3-year treatment effect cap produces lower estimates for overall	

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
			survival than the lower bound of the clinical experts' range for 10-year overall survival when treated with pembrolizumab. Using the same extrapolation curve (log-logistic), 10-year overall survival estimates would be 5.48% and 6.92% with a 5-year treatment effect cap and infinite treatment effect, respectively, which is in line, or even conservative, with clinical opinion. *In TA525 [2], atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy, the committee chose a treatment effect cap synonymous to 5 years* • As stated within the Final Appraisal Document of TA525 [9], "*the committee agreed that it should take into account in its decision-making the analysis including a treatment effect cap at 3 years **after stopping***". The Evidence Review Group comments on the MSD's response to technical engagement during this Cancer Drug Fund guidance review stated "*TA584 [corrected to TA525] is at least for the same indication so can be considered more relevan*t. The Evidence Review Group was unable to scrutinise the evidence underlying the committee's decision at the time of the atezolizumab appraisal to prefer a 3-year post-stopping-treatment duration effect of atezolizumab." Despite this, the Evidence review Group makes the claim that "*the company's (MSD's) assumption that this is equivalent to a 5-year stopping rule is likely to be incorrect."* MSD strongly dispute this conclusion reached by the Evidence Review Group, based on the following facts: o On page 28 of the 3rd set of committee papers for TA525 [21] (i.e. page 2 of the company submitted additional analyses), it states "*Consistent with the appraisal atezolizumab in second-line non-small cell lung cancer in [ID970/TA520], we provide additional analyses incorporating a 2-year treatment stopping rule and a range of treatment benefit duration scenarios*". Page 552 of the first set of committee papers for TA520 [22], includes the Evidence Review Group report analysis of how the treatment effect cap is implemented, *"If the duration of treatment effect is set to be 'x' months in the model, then the hazard rate for*	

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
			atezolizumab is set to be equal to docetaxel at 'x' months after the start of the model." Therefore the 3-year treatment effect cap post maximum treatment duration applied within TA525 is equal to a 5-year treatment effect cap after treatment initiation. ○ The data used to inform the economic model in TA525 [2] had median follow-up data of 17.4 months and maximum follow-up data of 24.5 months, at the time of their submission as opposed to the median follow-up of 40.9 months for pembrolizumab. • Therefore, the decision by the Committee to accept a 5-year treatment effect cap in TA525 [2], in the absence of data suggesting a continued treatment effect of at least 5 years, is entirely inconsistent with the approach of the Evidence Review Group and NICE committee within this Cancer Drug Fund guidance review. • The Appraisal Consultation Document states, "*The committee recalled that in the technology appraisal of atezolizumab, analyses with a treatment effect cap at 3 years after stopping were taken into account in its decision making but there was not enough evidence to support a specific duration of benefit*." Be this the case as it may, the committee did not investigate the impact of a treatment effect cap at 1 year after stopping treatment, regardless of the much less mature overall survival data used to inform the model. Hence the approach, by the same committee (Committee D), to establish a treatment effect duration has been **fundamentally different** between the two appraisals, both of which are assessing an immune-oncology therapy in previously treated urothelial carcinoma patients. *Long-term data availability for pembrolizumab from KEYNOTE-045 and across different tumour types are good evidence to inform decision-making and accept a sustained duration of treatment effect* Section 3.14, page 13 of the Appraisal Consultation Document is entitled "*Evidence of treatment effect duration from other pembrolizumab trials is not appropriate for decision making"* and also reports that (page 14) "*It [the Committee] recognised that the evidence suggests that treatment effect duration varies in different types of*	The committee noted that the new figures from KEYNOTE-045 suggested the relative treatment effect of pembrolizumab might continue beyond 3 years. It concluded that a 3-year to 5-year treatment effect from start of pembrolizumab treatment could be plausible. See FAD section 3.18.

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
			cancers. It therefore agreed that the results from those trials were not generalisable to urothelial carcinoma". MSD considers it inappropriate to entirely disregard longer-term follow-up data from clinical trials investigating the efficacy of pembrolizumab in other tumour types, which provide supportive evidence on the long-term treatment benefit of this therapy. As highlighted previously (see comment 3) NICE has set a precedent of accepting evidence from trials in other tumour types to inform their decision making in the absence of direct evidence; hence we cannot understand why consideration of such evidence in the context of this CDF guidance review is seemingly being disregarded as irrelevant. A clear example can be found in this Cancer Drug Fund review of pembrolizumab whereby the NICE Committee rejected the appropriateness of considering long-term data from KEYNOTE-001 [5, 6], KEYNOTE-006 [7] and KEYNOTE-024 [8], as these were trials in other tumour types. However, in the case of atezolizumab (TA525) [2] where there was a lack of clinical evidence, the Committee decided to use a five-year cap on duration of treatment effect, based on previous immunotherapies appraisals where a stopping rule was applied, even though the evidence did not directly support such choice. In contrast, MSD has presented results from KEYNOTE-045 [3] which is the only randomised clinical trial of an immunotherapy for the second-line treatment of urothelial cancer with more than 3 years of follow-up data, which shows a benefit in overall survival when compared to UK standard of care. Given the long-term treatment effect data of pembrolizumab in melanoma (KEYNOTE-006) and lung cancers (KEYNOTE-001) alongside KEYNOTE-045 follow-up, it is not clinically plausible to assume that the effect of pembrolizumab treatment would simply cease 3 years after starting therapy as suggested by the Evidence Review Group. This was already acknowledged by MSD's and the Evidence Review Group's clinical experts who stated that, "*although it is very difficult to ascertain how many patients will be alive after 10 years since no-one has experience of this scenario, it is plausible that for a handful of patients who continue to respond after few years, they would 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
			expected to remain in response and alive when treated with pembrolizumab" (clinical expert statement from MSD technical engagement response). The longer duration of response (i.e. beyond 3 years) in partial/complete responders and stable disease patients treated with pembrolizumab, was recognised to be "*consistent to other immune-oncology therapies for treating urothelial cancer and across different tumour types" (clinical expert statement from MSD technical engagement response)*. This is supported by KEYNOTE-045 data published by Fradet et al. [23], which shows that overall survival by objective response was prolonged among patients with complete or partial response to pembrolizumab compared with those who responded to standard of care; and that among patients with stable disease as best response, median overall survival was greater with pembrolizumab than with chemotherapy. The sustained and prolonged treatment effect derived from the administration of immune-oncology therapies is also recognised in literature. Several papers [24-26] clearly explain that the mechanism of action of checkpoint inhibitors, such as pembrolizumab, help cytotoxic T-cells avoiding an exhausted state which in turn, enables to maintain the disease in a sort of cancer-immune equilibrium that can be potentially sustained for up to several decades even in the absence of continued therapy. Again, this clinical and biological explanation is translated into reality when take into consideration the results from KEYNOTE-001 [5, 6], KEYNOTE-006 [7], KEYNOTE-024 [8] and KEYNOTE-045 [3]. In light of the above evidence, MSD urges the Committee to recognise the validity of the clinical data from KEYNOTE-045, the long-term duration of treatment effect and a 5-year duration of treatment effect as a conservative assumption which is also consistent with precedent accepted by this Committee for atezolizumab in this same patient population. MSD has provided additional scenario analyses (please refer to Appendix 2) exploring an alternative method of implementing the treatment waning effect to further reduce the uncertainty around the duration of response of pembrolizumab in this indication and also to	

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
			prove that the results of such scenario analyses generate stable results that further confirm the robustness of the base-case approach use in MSD submission for this Cancer Drug Fund review.	

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	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:	[redacted]

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

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	**<u>General comment on content and tone of the Appraisal Consultation Document</u>** MSD is encouraged that the Appraisal Consultation Document confirms that: • Clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with docetaxel and paclitaxel. • Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. • Pembrolizumab is well tolerated. Despite the above, MSD is disappointed by the overall tone of the Appraisal Consultation Document. Our key concerns are as follows: • MSD considers that the Appraisal Consultation Document fails to reflect the strong clinical and patient group advocacy for pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy, which was apparent at the NICE appraisal committee meeting which took place on 22 October 2019. o The clinical and patient group representatives at the committee meeting clearly described pembrolizumab as the current standard of care for this patient population. They also highlighted the improvement offered by pembrolizumab in terms of quality of life, and clearly recognised the value of the product as an effective treatment option which produces durable responses, in a patient population for which there are limited alternative effective treatments. • MSD is concerned with apparent inconsistencies in the decision-making approach of Committee D, when compared to other appraisals conducted by this Committee (see comment 3, 4, 5, 6, 7, 8, and 12) • MSD is concerned by the inclusion of inaccurate statements in the Appraisal Consultation Document which we do not consider aid decision-making. These are further outlined in comments that follow (see comments 2, 3,9, 10 and 11).
2	**<u>Rationale for the recommendations as stated in the Appraisal Consultation Document</u>** ***MSD believes that the current availability of atezolizumab should have no bearing and is irrelevant in the context of the decision-making in this appraisal of pembrolizumab for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum containing therapy.*** Section 1, page 3 of the Appraisal Consultation Document under the subheading "*Why the committee made these recommendations*" states (5th paragraph) "*Atezolizumab is now also a possible treatment. But it was not established clinical practice in the NHS at the time of the original appraisal, so is not included in the scope*". MSD strongly believes that it is inappropriate to include this statement as a part-justification for the recommendations made in the Appraisal Consultation Document. As reported in the Appraisal Consultation Document, atezolizumab was not included in the scope at the time of the original appraisal of pembrolizumab in this indication. Consequently, it was not considered a comparator of relevance in the context of this Cancer Drug Fund guidance review of pembrolizumab. MSD

	considers it is misleading to include reference to availability of atezolizumab at this stage of the Cancer Drug Fund guidance review process. This should not provide part-justification for the NICE Committee's provisional recommendation to not recommend pembrolizumab for baseline commissioning through the NHS for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have had platinum-containing therapy. In addition to the above-mentioned reference to atezolizumab in the Appraisal Consultation Document, Section 3.2 (page 6) also reports that atezolizumab "*was not established clinical practice in the NHS at the time of the original appraisal*". MSD would query the definition of "established clinical practice" accredited to atezolizumab in the Appraisal Consultation Document. Data collected from Ipsos' Global Oncology Monitor shows that, as of the Moving Annual Total ending in September 2019 [1], 39% of reported drug-treated patients in their sample affected with metastatic urothelial cancer in a second-line setting were prescribed with pembrolizumab (following 1st line platinum-containing chemotherapy); this reflects a 17% higher usage share for pembrolizumab compared to atezolizumab (22% patient usage share) among this reported patient sample cohort The 17% difference in favour of pembrolizumab is, in MSD's opinion, reflective of the clinical confidence in pembrolizumab as a suitable and effective treatment option when it comes to clinicians making a therapeutic choice for a urothelial cancer patient after failure of platinum-containing chemotherapy. As mentioned in comment 1, this clinical confidence was apparent at the NICE committee meeting which took place in October 2019, and the above data is reflective of the clinical expert's description of pembrolizumab as current standard of care.
3	**<u>Inconsistencies in NICE appraisal approach between pembrolizumab and atezolizumab technology appraisals for previously treated advanced or metastatic urothelial cancer</u>** ***MSD has identified inconsistencies in Committee D's interpretation of key issues that inform the cost-effectiveness assessment of pembrolizumab in this Cancer Drugs Fund guidance review, as compared to how these issues were considered within the context of the appraisal of atezolizumab (TA525) [2]. The inconsistency in approach applied to these issues are key drivers in the Committee's disappointing preliminary conclusion that pembrolizumab would not be a cost-effective option for NHS resources in patients with locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy.*** Atezolizumab for the treatment of locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy was recommended by NICE following its appraisal by Committee D in June 2018 (TA525) for baseline commissioning [2]. The same Committee (Committee D) conducted the original appraisal of pembrolizumab in this indication following our company submission in February 2017. At the time of the original MSD submission, atezolizumab was not yet recommended by NICE and therefore neither it was considered established clinical practice nor deemed a relevant comparator in the scope of the pembrolizumab appraisal. Pembrolizumab was subsequently recommended within the Cancer Drugs Fund. The same Committee (Committee D) is now undertaking this CDF guidance review of pembrolizumab, which is the subject of this Appraisal Consultation Document. The key areas of inconsistency are discussed in turn below: <u>*Approach to modelling duration of treatment effect*</u> Different approaches have been applied by Committee D between the two appraisals regarding the assumption of duration of treatment effect:

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

- In the atezolizumab appraisal, in the absence of data regarding treatment effect after atezolizumab is stopped (median follow-up data of 17.4 months and maximum follow-up data of 24.5 months) [2], the NICE Committee applied a 3-year cap on duration of treatment effect **after treatment is stopped** (in effect a 5-year duration of treatment effect from start of treatment). This arbitrary timeframe was based on prior appraisals of immunotherapies where a stopping rule was applied (please also refer to Comment 12).
- In contrast based on the updated data-cut from KEYNOTE-045 which informs this Cancer Drugs Fund guidance review (median follow-up data of 40.9 months and maximum follow-up data of 48.9 months) [3], the Committee preferred assumption for pembrolizumab is a 3-year cap on duration of treatment effect **from the start of treatment.**, disregarding the greater

Validity of 2-stage model

- Criticisms concerning treatment switching have been levelled by the Evidence Review Group during their critique of the pembrolizumab submission that informs this Cancer Drugs Fund guidance review. This issue was not an area of concern during the atezolizumab appraisal.
    - With regards to treatment switching, the Evidence Review Group cites data from vinflunine (Bellmunt et al. [4]) to argue for the harshness of the acceleration factor adversely affecting the UK standard of care arm when the 2-stage method was applied. However, vinflunine is not used in UK clinical practice and should not be used as a proxy for UK clinical treatment (please also refer to Comment 6).

Disregard of evidence of treatment effect duration from other pembrolizumab trials

- MSD had presented evidence from pembrolizumab studies KEYNOTE-001 [5, 6] (melanoma, non-small cell lung cancer), KEYNOTE-006 [7] (melanoma) and KEYNOTE-024 [8] (non-small cell lung cancer) as supportive of a long-term duration of treatment effect with our response to the technical engagement. However, section 3.14 (page 13) of the Appraisal Consultation Document states "*Evidence of treatment effect duration from other pembrolizumab trials is not appropriate for decision making*". The document further elaborates, stating that the Committee agreed that *"the results from those trials were not generalisable to urothelial carcinoma".*
- However, in the case of atezolizumab where there was a dearth of clinical evidence, the Committee applied a 3-year cap on duration of treatment effect after 2 years of treatment (i.e. 5 years from starting treatment) based on appraisals of other immunotherapies where a stopping cap was applied.
- A duration of treatment effect of >3 years has been accepted by NICE committees on several other pembrolizumab appraisals (and appraisals of other immuno-oncology therapies) [9-16].

MSD further discusses these specific issues in greater detail in this response (Comments 4,5,6,7,8 and 12). We urge the NICE Committee to apply a consistent approach when dealing with these issues in the context of this Cancer Drugs Fund guidance review of pembrolizumab, as applied at the time of the appraisal of TA525 [2]. This will aid transparency and ensure consistency in the decision-making framework when applied across appraisals.

MSD would like to highlight that, if the approach accepted in TA525 [2] was consistently applied in this assessment of pembrolizumab, it would be proven that this intervention is a cost-effective option for patients affected by locally advanced or metastatic urothelial carcinoma after prior platinum-containing chemotherapy.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

4	**Appropriateness of the 2-stage method to adjust for subsequent therapy in the UK Standard of Care arm** ***MSD strongly disagrees that the unadjusted analysis should be used for decision making in this appraisal, and considers results based on the 2-stage method to be robust, reliable and generated using methodology previously accepted as appropriate by NICE Committees.*** Section 3.5, page 8 of the Appraisal Consultation Document states "*New KEYNOTE-045 data shows that the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account*". MSD is concerned that the 2-stage model has been disproportionately criticised by the Evidence Review Group and the NICE technical team in the context of this Cancer Drug Fund guidance review appraisal, as opposed to when this method has been utilised (and accepted as appropriate) in previous NICE appraisals [3]. Based on the content of the Appraisal Consultation Document, it seems that the key driver for the concern over the appropriateness of the 2-stage method is the magnitude of the acceleration factor which is generated when running this method, based on the November 2018 data-cut of KEYNOTE-045. As a result of the magnitude of the acceleration factor, it appears that the Evidence Review Group has subsequently questioned other aspects of the 2-stage methodology, which has translated into additional concerns with this approach for the NICE Committee, centred on a lack of confidence in the general acceptability of this adjustment method for treatment switching and the external validity of the adjusted results. MSD strongly disagrees that the unadjusted analysis should be used for decision making in this appraisal. MSD has attempted to sequentially address these concerns below, and in our subsequent comments (from 5 to 8): *Precedent set in TA519 [17]* As acknowledged in the Appraisal Consultation Document, the 2-stage method to adjust for subsequent therapy usage in the UK standard of care arm was used in the original appraisal of TA519 [17], and was considered by the Committee as the most appropriate patient population upon which to base decision making. The Evidence Review Group report confirms that alternative methods of adjusting for treatment switching were discussed in the previous review of this indication and were deemed not beneficial (Rank-preserving structural failure time and Inverse probability of censoring weighted). The approach taken by MSD when applying the 2-stage adjustment method is entirely consistent with the approach taken in TA519 [17]; consequently, MSD believes that it continues to be appropriate to base decision making on the comparison between pembrolizumab and the 2-stage adjusted UK standard of care population. The same variables (age, gender, Eastern Cooperative Oncology Group at secondary baseline [0, ≥1], time to progression, liver metastases, time from last prior chemotherapy [<3 vs. ≥3 months], haemoglobin at secondary baseline and site of primary tumour) have been used as per the original submission. The method has been followed appropriately, with adjustment made based on whether patients switched at the time of disease progression (which is a mandatory requirement to create a secondary baseline within the model) or not, with an average effect applied accordingly to all patients classified as eligible for having their survival time adjusted under the 2-stage method. *Precedent set in other appraisals of pembrolizumab* The use of the 2-stage method has been used , in all other NICE appraisals of pembrolizumab [17-19] when it has been necessary to adjust data in the comparator arm due to within trial switching or

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	subsequent therapy usage which was inconsistent with standard UK clinical practice. This approach has been accepted as appropriate by various NICE committees in these appraisals. *Response to specific concerns centred on 2-stage methodology* MSD considers that most of the concerns highlighted by the Evidence Review Group in their report, and again reiterated in the Appraisal Consultation Document, are standard disadvantages and/or assumptions of the 2-stage methodology and are not correlated to the KEYNOTE-045 data. In our subsequent comments, MSD has attempted to address each issue in turn (Comments 5 to 8). MSD strongly disagrees that it would be appropriate to use the unadjusted analysis for decision making in this appraisal. As mentioned in the Technical Report, the Evidence Review Group acknowledges that failing to adjust for subsequent therapy is "*not ideal, as it is likely that some patients who switched did receive a benefit from the treatment*." The Evidence Review Group also states that "*not adjusting for this benefit introduces bias which favours the control arm*". In the Evidence Review Group report, it had been stated that this bias favouring the control arm "*may be stronger than the potential biases when the 2-stage method is used*". We would urge the Committee to take all the presented evidence in this response into consideration, which provides strong support for the use of the adjusted results based on the 2-stage method as the basis for decision making and determining the cost-effectiveness of pembrolizumab for the treatment of locally advanced or metastatic urothelial cancer for adults who received platinum-containing chemotherapy
5	**Calculation and application of acceleration factor in the 2-stage model** ***MSD considers that the acceleration factor of 5.37 based on the November 2018 data-cut of KEYNOTE-045 is a more precise and reliable estimate of the acceleration factor than that generated at the time of the original appraisal of TA519 [17].*** The acceleration factor is a multiplicative factor, which quantifies the increase in survival time due to pembrolizumab compared to UK standard of care. In our Cancer Drug Fund guidance review submission, the calculated acceleration factor of 5.37 was calculated using a standard approach, that is estimated based on the effect of switching from control to anti-PD-1/PD-L1 treatment. The 2-stage method has been applied to the November 2018 data-cut using the same methodology as previously employed in the original appraisal of TA519 [17], **when it was deemed by both the Evidence Review Group and NICE Committee as the most appropriate method to use, and appropriate for decision making**. Page 8 (paragraph 2) of the Appraisal Consultation Document reports "*The November 2018 data cut from KEYNOTE-045 showed that the acceleration factor had a higher magnitude and applied to more people in the trial. This meant the 2-stage adjustment had a greater influence on overall survival than it did in the original appraisal. The acceleration factor was 5.37 (95% confidence interval [CI] 3.23 to 10.09) (based on 25 patients) after the November 2018 data cut, compared with 3.86 (95% CI 1.79 to 11.68) (based on 14 patients) using previous data".* MSD acknowledges that the acceleration factor generated using the trial data from the November 2018 data-cut is higher in magnitude compared to the acceleration factor provided in the original submission. However, MSD feels that the Committee should not simply consider the magnitude of the acceleration factor in isolation, without also considering other important factors; for example, differences between the results of the two data-cuts (September 2016 and November 2018) in terms of sample sizes, accuracy of the acceleration factor and range of the confidence intervals.

- The very small sample size used in the original appraisal (N=14) resulted in a smaller acceleration factor (3.87) and a wider confidence interval (difference between upper and lower confidence interval = 9.89). It is recognised widely, that any statically inference applied to such small sample sizes may produce uncertain results, therefore the width of the confidence interval is not surprising.
- Based on the November 2018 data-cut which informs this Cancer Drug Fund guidance review, the acceleration factor is higher in magnitude (5.37) but the confidence interval generated is narrower as compared to that generated in the original submission (November 2018 data-cut difference between upper and lower CIs = 6.86).
- **It is noteworthy that the confidence interval obtained using the November 2018 data-cut (3.23 to 10.09) is not only narrower, but also falls entirely within the range of the confidence interval of the original acceleration factor based on the previous data cut at the time of the original appraisal (1.79 to 11.68).**
- Based on the above, MSD urges the Committee to consider, that based on the higher sample size with the November 2018 data-cut (N = 25), the acceleration factor of 5.37 actually represents a more precise estimate of the true value gained when switching from UK standard of care to an anti-PD-1/PD-L1 therapy, compared to the acceleration factor generated at the time of the original appraisal.

During the clarification question phase of the Cancer Drug Fund guidance review appraisal, the Evidence Review Group had requested that MSD estimates the acceleration factor including vinflunine patients in the standard of care arm, in an attempt to reduce uncertainty. The results of this analysis (provided in our response to clarification questions) were deemed "*consistent"* with the original analysis presented by the Company (i.e. acceleration factor = 5.32, confidence intervals: 3.44, 8.446). Thus, even by increasing the sample size to assess variability and check for accuracy of the generated acceleration factor, the results are stable.

Page 8 (paragraph 2) of the Appraisal Consultation Document goes on to report "*The acceleration factor was calculated from the 25 people who switched when progression of their diseases was documented. The acceleration factor was not applied to the overall survival time of 15 patients which switched at different times. It is not known how including these 15 patients in an adjustment would have affected the estimated incremental cost-effectiveness ratio (ICER)*".

- The *"15 patients who switched at different times"* refer to patients who (unlike the 25 'eligible' patients) did not switch based on documented disease progression (defined centrally by Response evaluation criteria in solid tumours).
    - Examples of the reason for switching for these 15 patients may include but not be limited to having had documented disease progression defined by the investigator (i.e. rather than by central review per Response evaluation criteria in solid tumours) or following discontinuation due to adverse events. It is at the investigator's and subject's discretion as to how to treat following discontinuation from study treatment. As a result, eligibility for subsequent therapy, outside of subjects that qualified for switching (according to the criteria of documented disease progression defined centrally by Response evaluation criteria in solid tumours) was not captured in the KEYNOTE-045 trial.
- In order to address the above uncertainty identified in the Appraisal Consultation Document, a sensitivity analysis has been conducted to show the results of the 2-stage adjustment when applying the same acceleration factor of 5.37 to <u>all</u> switchers including the 15 patients who switched at a time other than documented disease progression defined centrally by Response evaluation criteria in solid tumours.
    - The results are presented in Appendix 1, and show that with the inclusion of these 15 patients, the hazard ratio for the comparison of pembrolizumab versus UK standard of care is 0.55 (CI 0.41, 0.69)

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	○ This improved hazard ratio shows that MSD's original approach, of not including these 15 patients in the 2-stage adjusted analysis, is a more conservative approach: it results in the survival times of fewer patients in the UK standard of care arm being adjusted downwards, and therefore a less favourable hazard ratio for the comparison of pembrolizumab with UK standard of care. MSD reiterates that the November 2018 data-cut and the extra analyses provided, demonstrate robustness in the generated acceleration factor of 5.37. Based on the rationale described above, we consider this point estimate to be more precise and reliable than the acceleration factor generated at the time of the original appraisal of TA519 [17].
6	**External validity of 2-stage adjusted results in the UK standard of care arm** ***MSD considers 2-stage adjusted results to be reliable, and entirely disagrees with the view that the 2-stage model overly underestimates survival time in the UK standard of care arm. We also believe it is inappropriate to consider data on the non-UK recommended drug, vinflunine from the Bellmunt (2013) study [4], as a proxy for expected efficacy in the UK standard of care arm.*** Page 8 (paragraph 2) of the Appraisal Consultation Document reports "*It advised that the true overall survival benefit would be somewhere between the results of the 2 approaches. Using an approach without the adjustment might overestimate survival time in the UK SoC arm, but the 2-stage model might underestimate survival time in this arm too much*". In response to the above statement, MSD restates that the approach used in this Cancer Drug Fund guidance review appraisal is entirely consistent with that used at the time of the original appraisal of TA519 [17], whereby results are presented, and economic evaluation is based on results of the 2-stage model, adjusting for treatment switching in the UK standard of care arm. MSD strongly supports the use of this method, since failing to do so (i.e. using only results of unadjusted analyses) will misrepresent the clinical benefit and true treatment effect associated with pembrolizumab versus UK standard of care in the urothelial cancer population investigated within KEYNOTE-045 [3]. MSD entirely disagrees with the premise that the 2-stage model overly underestimates survival time in the UK standard of care arm. Most of the rationale for this conclusion, as had been previously described in the Evidence review Group and NICE technical reports, was based on a perceived discrepancy when comparing 2-stage adjusted results from the UK standard of care arm of KEYNOTE-045, with vinflunine data (Bellmunt et al. [4]), which the Evidence Review Group were using as a proxy to validate the 2-stage adjusted UK standard of care results from KEYNOTE-045. MSD reiterates that the conclusions reached by the NICE committee for this comparison should be interpreted with extreme caution since: • Although the median overall survival in the vinflunine arm of the Bellmunt et al study [4] is closer to the median overall survival from the UK standard of care arm of the KEYNOTE-045 population without adjustment for treatment switching, it is noteworthy that in terms of the reported 12, 24 and 30 month overall survival in the Bellmunt et al study [4], there is better consistency with the UK standard of care arm of the 2-stage adjusted population from KEYNOTE-045. • Bellmunt et al. [4] presented in their publication limited patient characteristics thus, it is inappropriate to consider the two study populations as analogous.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	• Some heterogeneity exists between the population included in the Bellmunt paper [4] and KEYNOTE-045 populations with regards to the age of the patients at the time of enrolment, the Eastern Cooperative Oncology Group Performance Status and prior therapies reported. • These differences could have impacted the outcomes of the studies in several ways (e.g. heterogeneity of the results, over or underestimation of treatment effect). • The aim of the Bellmunt study [4] was to investigate the efficacy of vinflunine in combination with best supportive care versus best supportive care alone. It is important to note that vinflunine is not recommended by NICE in England and is not established clinical practice in the UK; consequently, the comparison made between the two studies by the Evidence Review Group seems inappropriate. In the absence of more appropriate evidence in the second-line setting for established UK standard of care treatments (e.g. taxanes), the results of KEYNOTE-045 trial [3], which directly investigated the efficacy of pembrolizumab versus currently approved UK standard of care (e.g. docetaxel and paclitaxel), should be considered as the best available evidence, since head-to-head trials are considered the gold standard in delivering high quality data.
7	**<u>Committee's additional concerns with 2-stage methodology</u>** ***The 2-stage model assumes an average adjustment for eligible subjects receiving subsequent therapy rather than the same overall survival benefits for all people switching to anti-PD-L1 or PD-1 therapy.*** Page 9 (paragraph 1) of the Appraisal Consultation Document states *"The ERG explained that the adjustment method assumed that all people switching to anti-PD-L1 or PD-1 therapy had the same overall survival benefits".* MSD believes that this statement is misleading and that it incorrectly represents some of the assumptions used in the 2-stage model. The 2-stage model assumes an 'average adjustment for eligible subjects receiving subsequent therapy' and not "*the same overall survival benefits"*. These two concepts are not interchangeable, and the misuse of the latter in this situation can lead to inaccurate conclusions being drawn. "*The same overall survival benefits"* implies that all patients who switched to any anti- PD-1/PD-L1 therapies were treated as if they received the same benefit in terms of survival (equal hazard ratio). This consideration is imprecise and unrealistic. The average adjustment estimates an average of the effect and benefits seen in some patients, equally balanced by including those patients who benefitted less from switching. Therefore, patients who benefitted less or not at all from switching therapy are included in the 2-stage model, which better reflects clinical practice. The ratio of those patients who switched and did not switch is then used to generate the acceleration factor which is uniformly applied to all switchers. Concluding, it is incorrect to state that this model assumes the same overall survival benefits. Additionally, within the context of this study, more complex modelling approaches would be inadvisable and perhaps not possible, given the very small sample size of patients who switched (N = 40). It is also true that considering unadjusted analysis (i.e. disregarding adjustment for treatment switching) will overly penalise pembrolizumab as described in comment 6 of this document.
8	**<u>Impact on economic model when using 2-stage adjusted analysis</u>**

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	MSD confirms there is no error in the economic model. Page 9 (paragraph 1) of the Appraisal Consultation Document reports *"Although the company stated that the same methodology was used in other submissions for pembrolizumab, the committee noted that the model for this appraisal appeared to incorrectly change outcomes for the pembrolizumab arm when survival for the UK SoC arm was adjusted, and these changes favoured pembrolizumab. The committee concluded that, while the ICERs using the 2-stage adjustment for treatment switching were not robust because of the apparent error in the model and the other issues above, the true overall survival benefit was probably between that seen with an adjustment for treatment switching and that without an adjustment."* MSD believes this statement is misleading, and incorrectly casts doubt on the accuracy of the incremental cost-effectiveness ratio estimates produced by the economic model. The '*apparent issue*' of the change in outcomes for the pembrolizumab arm when survival for the UK standard of care is adjusted, is due to the implementation of the treatment effect cap within the economic model. The introduction of a treatment effect cap results in a change in the hazard rate from the pembrolizumab arm to the UK standard of care arm at a defined time point. When the adjustment method is changed for the UK standard of care arm, this implicitly alters the hazard rate in the standard of care arm and hence leads to a change in outcomes in the pembrolizumab arm, due to the treatment effect cap associating the two. There is no error in the model - this can be seen when selecting a lifetime treatment effect and switching between adjusted and unadjusted analyses; there is no impact on the outcomes within the pembrolizumab arm.
9	**<u>Availability of clinical effectiveness data for the PD-L1 positive subgroups</u>** ***MSD confirms that clinical effectiveness data for the PD-L1 positive subgroups were provided by the company during this cancer drugs fund guidance review.*** Page 10 (paragraph 2) of the Appraisal Consultation Document states "*The company did not present clinical effectiveness data for the PD-L1 positive subgroups using data from the November 2018 cut-off*". The above-mentioned statement is incorrect since MSD provided this information upon request from the Evidence Review Group as part of the clarification questions process. MSD is concerned that the consequence of this misrepresentation in the Appraisal Consultation Document is a failure to reflect MSD's willingness to resolve uncertainty around the issues identified by the Evidence Review Group and the NICE technical team during the course of the appraisal.
10	**<u>Indirect comparison of pembrolizumab with best supportive care</u>** ***MSD does not consider clinical or cost-effectiveness evidence comparing pembrolizumab with best supportive care to be of relevance within the context of this Cancer Drug Fund guidance review.*** Page 11 (paragraph 1) of the Appraisal Consultation Document states: "*For the original appraisal, the company provided an indirect comparison of pembrolizumab with best supportive care, but the committee concluded that this was not useful for decision making. The company had not presented any new clinical or cost-effectiveness evidence comparing pembrolizumab with best supportive care*".

Please return to: **NICE DOCS**

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

MSD would like to highlight that the above is yet another misrepresentation of the evidence provided during the original appraisal of TA519 [17], and during the course of this Cancer Drug Fund guidance review.

- During the course of the original appraisal of TA519 [17], MSD clarified, on several occasions, that best supportive care was not a relevant comparator in the population of interest, as alternative active treatments (e.g. docetaxel and paclitaxel) are available; consequently, an indirect comparison of pembrolizumab with best supportive care was **not** provided.
    - Taxanes are offered only in people with a good performance status, which is the population included in KEYNOTE-045. Best supportive care is a valid option for people with a poorer PS (Eastern Cooperative Oncology Group Performance Status >2).
    - Since KEYNOTE-045 only included patients with PS≤2, MSD did not include evidence in our original submission on the clinical effectiveness of pembrolizumab in people who would otherwise be offered best supportive care.
    - Given that the KEYNOTE-045 is the only trial that evaluated pembrolizumab in people with locally advanced or metastatic urothelial cancer after platinum-containing chemotherapy, there is no evidence to compare pembrolizumab to best supportive care in patients with Eastern Cooperative Oncology Group Performance Status >2 either directly or indirectly.

- The value of an indirect comparison of pembrolizumab with best supportive care, if it had been conducted would have been of little value given the heterogeneity in patient populations receiving either pembrolizumab or best supportive care
    - During the original appraisal of TA519 [17], the Evidence Review Group mentioned that there was "*a phase 3 randomised controlled trial (RCT) which compared vinflunine + BSC with BSC alone. This trial could have been used to compare pembrolizumab to BSC indirectly but the relevance is questionable given that the trial only included people with PS 0-1*".
    - The Final Appraisal Document for TA519 [17] states that "*the ERG highlighted that an indirect comparison would be inappropriate because the performance status of people in the trials (KEYNOTE-045) would be much better than in people having best supportive care in clinical practice"* and that *"The committee noted that there was no evidence for people who would be likely to have best supportive care, and therefore concluded that it was unable to make a recommendation for this population".*

In light of the consensus reached at the time of the original appraisal, MSD questions the relevance of now including, within this Appraisal Consultation Document, a statement which highlights that MSD has not submitted any new clinical or cost effectiveness evidence to compare pembrolizumab with best supportive care. We are again concerned that the inclusion of such a statement serves no purpose but to suggest an apparent unwillingness of MSD to provide all necessary evidence to support our Cancer Drug Fund guidance review.

The Terms of Engagement document developed by NICE for this Cancer Drug Fund guidance review outlined all areas of outstanding uncertainty, based on the evidence provided at the time of the original submission. It should be noted that:

- There were no uncertainties highlighted concerning the comparative clinical or cost-effectiveness of pembrolizumab with best supportive care.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	• At no stage of the Cancer Drug Fund guidance review to date has there been any requests made by NICE for MSD to present further clinical or cost-effectiveness analyses for this comparison. It is worth mentioning that the approach taken by MSD in respect to a comparison between pembrolizumab and best supportive care is consistent with that taken during the appraisal of atezolizumab (TA525) [2]. The wording in the atezolizumab Final Appraisal Document [9] confirms that although the Committee would have liked to see a comparison with BSC, "*The comparison with taxanes is sufficient for decision-making"* and also acknowledged that *"a lack of data would have made this [comparison with BSC] difficult".*
11	**<u>Additional inaccuracies in the Appraisal Consultation Document</u>** ***Reference to Nivolumab in in this Appraisal Consultation Document is of no relevance.*** Page 11 (paragraph 3) of the ACD states "*For pembrolizumab for other indications, and for both atezolizumab and nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy, a 2-year stopping rule applied*". MSD considers the inclusion of nivolumab here as of no relevance, since nivolumab for treating locally advanced unresectable or metastatic urothelial cancer is **not** recommended by NICE [20] and it is not established practice in the UK.
12	**<u>Duration of treatment effect</u>** ***MSD considers that a duration of treatment effect of 5 years is a conservative assumption for pembrolizumab and is consistent with precedent accepted by this Committee for atezolizumab in this same patient population. Clinical consensus and KEYNOTE-045 data are also strongly supportive of a long-term treatment effect***. Page 15 of the Appraisal Consultation Document states, "*The committee considered that there was robust evidence to support a 3-year treatment effect after starting pembrolizumab (2 years of treatment plus 1 year of follow up). However, there was no strong evidence to support a 5-year or longer treatment effect, and no more than 5% of people treated with pembrolizumab might be alive after 10 years*." MSD considers a 3-year treatment effect cap both implausible and inappropriate, for the following reasons: <u>*KEYNOTE-045 has median follow-up of 40.9 months [3]*</u> • The follow-up period in KEYNOTE-045 is greater than three years (maximum follow-up was 48.9 months). Time varying hazard ratio data was presented, within the appendices of the company submission, for pembrolizumab versus UK standard of care using both adjusted and unadjusted analysis. The Evidence Review Group claims that the upper confidence limit rising above 1, "*is strong evidence of some degree of waning effect within the observed follow-up*". MSD considers this the only evidence pertaining to a loss of treatment effect, albeit the time varying hazard ratio estimate remaining constant and below 1 post ~60 weeks in both the adjusted and unadjusted analyses, numerically showing a continued treatment effect beyond 3 and even 5 years. • With the upper confidence limit rising above 1, the Technical Report states that the Evidence Review Group has indicated that this "*may have been partially due to the small number of patients remaining at risk, so this wasn't strong evidence of a loss of effect".* To observe a narrower confidence interval at the tail of the hazard ratio curve, it would require a larger trial sample size. Please note that the time varying hazard ratio analysis is a post-

	hoc analysis, and KEYNOTE-045 trial was not designed to significantly detect the long-term hazard ratio for pembrolizumab vs chemotherapy, thus it is plausible the trial lacks power to detect the difference in the hazard level due to an insufficient sample size. • MSD does not consider that there is any robust evidence of a loss of treatment effect. Furthermore, as highlighted during the technical engagement consultation and at the Appraisal Committee Meeting, a 3-year treatment effect cap causes the parametric fitting to visually deviate to below the observed overall survival data. *Clinical opinion suggests a long tail when treated with pembrolizumab* • All clinical input in the company submission and Evidence Review Group report suggested the expectation of a long tail for overall survival when treated with pembrolizumab. The Evidence Review Group report states "*that some sustained long-term benefit could be plausible for patients receiving pembrolizumab"* which supported both the company and Evidence Review Group 's preference for the log-logistic, as the distribution for extrapolation, as the Evidence Review Group report stated *"both of the log models have a sharply decreasing hazard over time, which means a small number of patients will live for a long time".* By introducing a 3-year treatment effect cap, this is a direct contradiction to the Evidence Review Group's rationale for selection of the log-logistic curve. Furthermore, by the nature of the log-logistic curves, fitted to each arm, there is convergence over time; hence there is a reduction in the relative treatment effect over time. This could be considered gradual treatment waning effect. • MSD considers the Appraisal Consultation Document to be contradictory, stating both, "*The clinical expert… found it plausible that 5% to 10% of people having pembrolizumab might survive to 10 years after starting treatment (with a 2-year stopping rule)"*, but later mentions that the Committee concluded "*no more than 5% of people treated with pembrolizumab might be alive after 10 years.*" It is unclear why the committee disagreed with the clinical expert. • As noted in the Appraisal Consultation Document "*The company indicated that with their preferred log-logistic curve for extrapolation of overall survival (see section 3.16), 4.5% of people having pembrolizumab were modelled to still be alive 10 years after starting treatment*." Hence, the use of a 3-year treatment effect cap produces lower estimates for overall survival than the lower bound of the clinical experts' range for 10-year overall survival when treated with pembrolizumab. Using the same extrapolation curve (log-logistic), 10-year overall survival estimates would be 5.48% and 6.92% with a 5-year treatment effect cap and infinite treatment effect, respectively, which is in line, or even conservative, with clinical opinion. *In TA525 [2], atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy, the committee chose a treatment effect cap synonymous to 5 years* • As stated within the Final Appraisal Document of TA525 [9], "*the committee agreed that it should take into account in its decision-making the analysis including a treatment effect cap at 3 years* ***after stopping***". The Evidence Review Group comments on the MSD's response to technical engagement during this Cancer Drug Fund guidance review stated "*TA584 [corrected to TA525] is at least for the same indication so can be considered more relevan*t. The Evidence Review Group was unable to scrutinise the evidence underlying the committee's decision at the time of the atezolizumab appraisal to prefer a 3-year post-stopping-treatment duration effect of atezolizumab." Despite this, the Evidence review Group makes the claim that "*the company's (MSD's) assumption that this is equivalent to a 5-year stopping rule is likely to be incorrect."* MSD strongly dispute this conclusion reached by the Evidence Review Group, based on the following facts: o On page 28 of the 3rd set of committee papers for TA525 [21] (i.e. page 2 of the company submitted additional analyses), it states "*Consistent with the appraisal atezolizumab in second-line non-small cell lung cancer in [ID970/TA520], we*

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	provide additional analyses incorporating a 2-year treatment stopping rule and a range of treatment benefit duration scenarios". Page 552 of the first set of committee papers for TA520 [22], includes the Evidence Review Group report analysis of how the treatment effect cap is implemented, *"If the duration of treatment effect is set to be 'x' months in the model, then the hazard rate for atezolizumab is set to be equal to docetaxel at 'x' months after the start of the model.*" Therefore the 3-year treatment effect cap post maximum treatment duration applied within TA525 is equal to a 5-year treatment effect cap after treatment initiation. ○ The data used to inform the economic model in TA525 [2] had median follow-up data of 17.4 months and maximum follow-up data of 24.5 months, at the time of their submission as opposed to the median follow-up of 40.9 months for pembrolizumab. • Therefore, the decision by the Committee to accept a 5-year treatment effect cap in TA525 [2], in the absence of data suggesting a continued treatment effect of at least 5 years, is entirely inconsistent with the approach of the Evidence Review Group and NICE committee within this Cancer Drug Fund guidance review. • The Appraisal Consultation Document states, "*The committee recalled that in the technology appraisal of atezolizumab, analyses with a treatment effect cap at 3 years after stopping were taken into account in its decision making but there was not enough evidence to support a specific duration of benefit*." Be this the case as it may, the committee did not investigate the impact of a treatment effect cap at 1 year after stopping treatment, regardless of the much less mature overall survival data used to inform the model. Hence the approach, by the same committee (Committee D), to establish a treatment effect duration has been **fundamentally different** between the two appraisals, both of which are assessing an immune-oncology therapy in previously treated urothelial carcinoma patients. *Long-term data availability for pembrolizumab from KEYNOTE-045 and across different tumour types are good evidence to inform decision-making and accept a sustained duration of treatment effect* Section 3.14, page 13 of the Appraisal Consultation Document is entitled "*Evidence of treatment effect duration from other pembrolizumab trials is not appropriate for decision making"* and also reports that (page 14) "*It [the Committee] recognised that the evidence suggests that treatment effect duration varies in different types of cancers. It therefore agreed that the results from those trials were not generalisable to urothelial carcinoma*". MSD considers it inappropriate to entirely disregard longer-term follow-up data from clinical trials investigating the efficacy of pembrolizumab in other tumour types, which provide supportive evidence on the long-term treatment benefit of this therapy. As highlighted previously (see comment 3) NICE has set a precedent of accepting evidence from trials in other tumour types to inform their decision making in the absence of direct evidence; hence we cannot understand why consideration of such evidence in the context of this CDF guidance review is seemingly being disregarded as irrelevant. A clear example can be found in this Cancer Drug Fund review of pembrolizumab whereby the NICE Committee rejected the appropriateness of considering long-term data from KEYNOTE-001 [5, 6], KEYNOTE-006 [7] and KEYNOTE-024 [8], as these were trials in other tumour types. However, in the case of atezolizumab (TA525) [2] where there was a lack of clinical evidence, the Committee decided to use a five-year cap on duration of treatment effect, based on previous immunotherapies appraisals where a stopping rule was applied, even though the evidence did not directly support such choice.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	In contrast, MSD has presented results from KEYNOTE-045 [3] which is the only randomised clinical trial of an immunotherapy for the second-line treatment of urothelial cancer with more than 3 years of follow-up data, which shows a benefit in overall survival when compared to UK standard of care. Given the long-term treatment effect data of pembrolizumab in melanoma (KEYNOTE-006) and lung cancers (KEYNOTE-001) alongside KEYNOTE-045 follow-up, it is not clinically plausible to assume that the effect of pembrolizumab treatment would simply cease 3 years after starting therapy as suggested by the Evidence Review Group. This was already acknowledged by MSD's and the Evidence Review Group's clinical experts who stated that, "*although it is very difficult to ascertain how many patients will be alive after 10 years since no-one has experience of this scenario, it is plausible that for a handful of patients who continue to respond after few years, they would be expected to remain in response and alive when treated with pembrolizumab" (clinical expert statement from MSD technical engagement response).* The longer duration of response (i.e. beyond 3 years) in partial/complete responders and stable disease patients treated with pembrolizumab, was recognised to be "*consistent to other immune-oncology therapies for treating urothelial cancer and across different tumour types" (clinical expert statement from MSD technical engagement response)*. This is supported by KEYNOTE-045 data published by Fradet et al. [23], which shows that overall survival by objective response was prolonged among patients with complete or partial response to pembrolizumab compared with those who responded to standard of care; and that among patients with stable disease as best response, median overall survival was greater with pembrolizumab than with chemotherapy. The sustained and prolonged treatment effect derived from the administration of immune-oncology therapies is also recognised in literature. Several papers [24-26] clearly explain that the mechanism of action of checkpoint inhibitors, such as pembrolizumab, help cytotoxic T-cells avoiding an exhausted state which in turn, enables to maintain the disease in a sort of cancer-immune equilibrium that can be potentially sustained for up to several decades even in the absence of continued therapy. Again, this clinical and biological explanation is translated into reality when take into consideration the results from KEYNOTE-001 [5, 6], KEYNOTE-006 [7], KEYNOTE-024 [8] and KEYNOTE-045 [3]. In light of the above evidence, MSD urges the Committee to recognise the validity of the clinical data from KEYNOTE-045, the long-term duration of treatment effect and a 5-year duration of treatment effect as a conservative assumption which is also consistent with precedent accepted by this Committee for atezolizumab in this same patient population. MSD has provided additional scenario analyses (please refer to Appendix 2) exploring an alternative method of implementing the treatment waning effect to further reduce the uncertainty around the duration of response of pembrolizumab in this indication and also to prove that the results of such scenario analyses generate stable results that further confirm the robustness of the base-case approach use in MSD submission for this Cancer Drug Fund review.

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

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

References

1. Monitor, I.G.O., *Physicians in UK reporting on 124 2nd line mUC patients - Data are projected to represent sample treatment population*. Q4 2018–Q3 2019.
2. NICE. *TA525: Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy*. 2018 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta525.
3. Necchi, A., et al. *Three-year follow-up from the phase III KEYNOTE-045 trial: Pembrolizumab (Pembro) versus investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC)*. in *ANNALS OF ONCOLOGY*. 2019. OXFORD UNIV PRESS GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND.
4. Bellmunt, J., et al., *Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy.* Annals of Oncology, 2013. **24**(6): p. 1466-1472.
5. Garon, E.B., et al., *Five-year long-term overall survival for patients with advanced NSCLC treated with pembrolizumab: Results from KEYNOTE-001*. 2019, American Society of Clinical Oncology.
6. Hamid, O., et al., *Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001.* Annals of Oncology, 2019. **30**(4): p. 582-588.
7. 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.
8. Reck, M., et al., *Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater.* 2019.
9. NICE. *TA525 Final Appraisal Determination: Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinumcontaining chemotherapy*. 2018 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta525/documents/final-appraisal-determination-document.
10. NICE. *TA428 Final Appraisal Determination: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy*. 2017 [cited 2019 3 December]; Available from: https://www.nice.org.uk/guidance/ta428/documents/final-appraisal-determination-document.
11. NICE. *TA519 Final Appraisal Determination: Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy*. 2018 [cited 2019 3 December]; Available from: https://www.nice.org.uk/guidance/ta519/documents/final-appraisal-determination-document.
12. NICE. *TA600 final Appraisal Determination: Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer*. 2019 [cited 2019 3 December]; Available from: https://www.nice.org.uk/guidance/ta600/documents/final-appraisal-determination-document.
13. NICE. *TA484 Final Appraisal Determination: Nivolumab for previously treated non-squamous non-small-cell lung cancer*. 2017 [cited 2019 3 December]; Available from: https://www.nice.org.uk/guidance/ta484/documents/final-appraisal-determination-document.
14. NICE. *TA483 Final Appraisal Determination: Nivolumab for previously treated squamous non-small-cell lung cancer*. 2017 [cited 2019 3 December]; Available from: https://www.nice.org.uk/guidance/ta483/documents/final-appraisal-determination-document.
15. NICE. *TA578 Final Appraisal Determination: Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation*. 2019 [cited 2019 3 December]; Available from: https://www.nice.org.uk/guidance/ta578/documents/final-appraisal-determination-document.

Please return to: **NICE DOCS**

16. NICE. *TA520 Final Appraisal Determination: Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy*. 2018 [cited 2019 3 December]; Available from: https://www.nice.org.uk/guidance/ta520/documents/final-appraisal-determination-document.
17. NICE. *TA519: Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy*. 2018 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta519.
18. NICE. *TA531: Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer*. 2018 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta531.
19. NICE. *TA357: Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab*. 2015 2017 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta357.
20. NICE. *TA530 Final Appraisal Determination: Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy*. 2018 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta530/documents/final-appraisal-determination-document-2.
21. NICE. *TA525 Committee papers: Atezolizumab for treating metastatic urothelial cancer after platinum-based chemotherapy [ID1327]*. 2018 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta525/documents/committee-papers-3.
22. NICE. *TA520 Committee papers: Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy [ID970]*. 2017 [cited 2019 2 December]; Available from: https://www.nice.org.uk/guidance/ta520/documents/committee-papers.
23. Fradet, Y., et al., *Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of> 2 years of follow-up.* Annals of Oncology, 2019. **30**(6): p. 970-976.
24. Mollica, V., V. Di Nunno, and F. Massari, *Pembrolizumab plus axitinib: a new treatment option for patients with metastatic renal cell carcinoma.* Chinese Clinical Oncology, 2019.
25. Mantia, C.M. and D.F. McDermott, *Vascular endothelial growth factor and programmed death-1 pathway inhibitors in renal cell carcinoma.* Cancer, 2019.
26. Ingles Garces, A.H., et al., *Building on the anti-PD1/PD-L1 backbone: combination immunotherapy for cancer.* Expert opinion on investigational drugs, 2019. **28**(8): p. 695-708.

5th December 2019

Dear Kate,

Re. Pembrolizumab for previously treated advanced or metastatic urothelial cancer [TA519], CDF guidance review [ID1536]

Please find below the following:

- Appendix 1: Analysis of Overall Survival - Comparison of Pembrolizumab versus UK Standard of Care (SOC) Adjusting for Treatment Switch to anti-PDL1 treatment in SOC arm using 2-stage analysis - Acceleration Factor Applied to all Subjects Receiving Subsequent Therapy

- Appendix 2: Additional cost-effectiveness analysis results (scenario analyses), provided to assist decision making surrounding the issue of treatment effect duration.

Please note that the AiC/CiC information have been highlighted, respectively.

Should NICE or the ERG require any further clarification around these addition analyses, we would be more than happy to provide an answer to them.

Kind regards,

[redacted]

Appendix 1:

Analysis of Overall Survival | No Recensoring Subjects Pre-Assigned to Paclitaxel or Docetaxel - ITT Population - Comparison Pembrolizumab versus UK Standard of Care (SOC) - Adjusting for Treatment Switch to anti-PDL1 treatment in SOC arm using 2-stage analysis - Acceleration Factor Applied to all Subjects Receiving Subsequent Therapy

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	OS Rate at Month 12 in %[†] (95% CI)	Treatment vs. Control	
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[‖]
Control	182	147 (80.8)	2026.2	7.3	7.0 (5.5, 8.7)	32.2 (25.2, 39.4)	---	---
Control, Adjusted [¶]	182	147 (80.8)	1173.8	12.5	5.5 (4.8, 6.6)	18.6 (12.7, 25.4)	---	---
Pembrolizumab	188	144 (76.6)	2923.5	4.9	10.1 (7.6, 12.9)	43.5 (36.3, 50.6)	0.55 (0.41, 0.69)	0.0139

Stage 1 model[††]	Acceleration factor[‡‡]
[§] Controls eligible to receive subsequent anti-PD-L1/PD1 therapy, patients receiving vs. not receiving subsequent therapy	5.370 (3.231,10.094)

[¶] Survival times shrunk for the patients receiving subsequent anti-PD-L1/PD1 therapy.
[†] From product-limit (Kaplan-Meier) method for censored data.
[‡] Based on Cox regression model with treatment as a covariate, stratified by prior chemotherapy (< 3 months vs. ≥ 3 months), liver metastases (Present vs. Absent) and hemoglobin (<10 g/dL vs. ≥10 g/dL) and ECOG status at baseline (0 vs. 1/2). The 95% CI is based on 1000/1000 bootstrap samples on the ITT population, stratified for treatment arm and SOC arm.
[‖] Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for subsequent therapy treatment.
[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including the following covariates: age, sex, site of primary tumor (upper tract vs. lower tract) and liver metastases at baseline and ECOG performance status (0 vs. ≥1), tumour size and hemoglobin at time of progression (defined as the secondary baseline), time from completion of most recent chemotherapy (<3 months or ≥3 months) and time to disease progression.
[§] Patients were eligible to receive subsequent therapy if they had documented progression.
[‡‡] Acceleration factor used to shrink the survival time of SOC patients eligible for subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy. The 95% CI is based on the same bootstrap samples as for the Cox regression model
(Database Cutoff Date: 30NOV2018).

Appendix 2: Additional Scenario Analyses

Page 14 of the ACD states "*A 3 -year duration of treatment effect from start of pembrolizumab treatment is appropriate*" and concludes on page 16 "*The committee concluded that, although the treatment effect duration was uncertain, based on the available evidence a 3-year duration of treatment effect from start of pembrolizumab treatment was appropriate*"

A member of the ERG indicated during the ACM that it was highly unlikely that all patients would cease benefitting from treatment with pembrolizumab at 3 years.

A key issue of uncertainty for committee was treatment effect duration, choosing a shorter duration of treatment effect than in the MSD base-case, of 3 years (or 1 year post treatment discontinuation). MSD have responded formally to the ACD through the ACD consultation process, however would like to take this opportunity to explore alternative, plausible, treatment waning scenarios to further justify the selection of a 5 year treatment effect duration as base-case.

MSD's base-case

Deterministic analysis results

Table **1** presents our preferred base-case deterministic results based on the November 2018 data cut, this is equivalent to the company submission. Our preferred base-case is based on the following assumptions:

- Two-stage adjust for treatment switching
- 5 year treatment effect cap
- OS cut-off point at 24 weeks with log-logistic distribution for extrapolation
- PFS cut-off point at 21 weeks with log-normal distribution for extrapolation
- Weibull and GenGamma distributions for ToT of pembrolizumab and UK SOC
- Pooled utility values based on health state approach

Table 1. Deterministic results for MSD base-case (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£17,368	1.06	0.72	-	-	-
Pembrolizumab	£52,403	2.14	1.46	£35,035	0.74	£47,123
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Additional scenario analysis

To further justify and validate the base case assumption of a 5-year treatment effect cap, MSD have conducted further scenario analyses exploring the method of implementation of a treatment effect cap within the economic model.

Within MSD's response to the Technical Report Issue 5 surrounding treatment duration, MSD identified the importance of long-term, durable response associated with pembrolizumab therapy.

We report that the median duration of response (DOR) for responders was 29.7 months in the pembrolizumab arm vs 4.4 months in the control arm. The 36-month OS rate is 20.7% in the pembrolizumab arm vs 11.0% in the control arm, and the 36-month DOR rate is 44% in the pembrolizumab arm, all of which are meaningful (based on KM data). A greater proportion of responses lasted ≥24 months (56.8% vs 28.3%, based on KM data); the median survival follow-up for responders was 39.6 months for pembrolizumab and 17.7 months for control. Additionally, the ORR was higher with pembrolizumab vs control (21.1% vs 11.0%) (see Table 2).

Table 2. Summary of Best Overall Response Based on RECIST 1.1 per Central Radiology Assessment - All Subjects (ITT population)

Response Evaluation		Control			Pembrolizumab	
		(N=272)			(N=270)	
	n	%	95% CI[†]	n	%	95% CI[†]
Complete Response (CR)	8	2.9	(1.3, 5.7)	26	9.6	(6.4, 13.8)
Partial Response (PR)	22	8.1	(5.1, 12.0)	31	11.5	(7.9, 15.9)
Objective Response (CR+PR)	**30**	**11.0**	**(7.6, 15.4)**	**57**	**21.1**	**(16.4, 26.5)**
Stable Disease(SD)	92	33.8	(28.2, 39.8)	47	17.4	(13.1, 22.5)
Disease Control (CR+PR+SD)	**122**	**44.9**	**(38.8, 51.0)**	**104**	**38.5**	**(32.7, 44.6)**
Progressive Disease(PD)	90	33.1	(27.5, 39.0)	131	48.5	(42.4, 54.7)
Non-evaluable (NE)	9	3.3	(1.5, 6.2)	4	1.5	(0.4, 3.7)
No Assessment	51	18.8	(14.3, 23.9)	31	11.5	(7.9, 15.9)

Confirmed responses are included.

[†] Based on binomial exact confidence interval method.

Non-evaluable: subject had post-baseline imaging and the BOR was determined to be NE per RECIST 1.1.

No Assessment: subject had no post-baseline imaging.

Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine. Database Cutoff Date: 30NOV2018

Recently, Fradet et al[1], in an updated analysis of KEYNOTE-045, examined OS by best overall response (BOR) (Poster ASCO 2018) and showed that patients who experienced a complete response (CR) or partial response (PR) when treated with pembrolizumab had significantly longer OS (HR = 0.14 (95% CI 0.06-0.33, p<0.00001) and PFS (HR=0.27, 95% CI 0.14-0.51, p<0.0001) compared to chemotherapy, and amongst patients with stable disease (SD) as best response, median OS was greater with pembrolizumab than with chemotherapy[1]. Similar

results were not seen in patients experiencing progressive disease. This suggests that patients who achieve BOR of disease control (comprising patients with CR, PR or SD) with immunotherapy do experience significantly longer survival, as also confirmed by the clinical expert consulted[1].

As seen in Table 2, 38.5% of patients in the pembrolizumab arm achieved a BOR of disease control. These patients are expected to receive a lifetime treatment effect, with the patients who do not achieve disease control having a treatment effect cap implemented at 3 years or 5 years. Please see Table 3 for a summary of the results. The scenario analyses are as follows:

- Lifetime treatment effect for patients achieving disease control, 3-year treatment effect for remainder (Scenario 1)
- Lifetime treatment effect for patients achieving disease control, 5-year treatment effect for remainder (Scenario 2)
- Lifetime treatment effect for patients achieving disease control, 3-year treatment effect for remainder, using a Weibull curve to extrapolate PFS at week 21 (Scenario 3)
- Lifetime treatment effect for patients achieving disease control, 5-year treatment effect for remainder, using a Weibull curve to extrapolate PFS at week 21 (Scenario 4)

Table 3. Additional Scenario Analyses (discounted)

Description	Pembrolizumab		UK SoC		Pembrolizumab vs UK SoC		
	Total costs (£)	Total QALYs	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case: 5 year treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	£35,035	0.74	£47,123
Scenario 1: DC lifetime treatment effect, remainder 3 year treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	£34,833	0.72	£48,089
Scenario 2: DC lifetime treatment effect, remainder 5 year treatment effect	[redacted]	[redacted]	[redacted]	[redacted]	£35,451	0.78	£45,540
Scenario 3: DC lifetime treatment effect, remainder 3 year treatment effect, Weibull PFS extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	£34,552	0.70	£49,573
Scenario 4: DC lifetime treatment effect, remainder 5 year treatment effect Weibull PFS extrapolation	[redacted]	[redacted]	[redacted]	[redacted]	£35,166	0.75	£46,839

Each of these scenarios produce more appropriate and robust results than the use of a clinically implausible 3-year treatment effect cap across the entire pembrolizumab arm. For example, the 10-year overall survival estimate for pembrolizumab is in line with clinical opinion as stated in the ACD of a lower bound of 5% and a higher bound of 10%; these scenarios produce a range from 5.4% to 6.0% and therefore within the specified range.

References

1. Fradet et al, Pembrolizumab versus Investigator's Choice (Paclitaxel, Docetaxel, or Vinflunine) in Advanced Urothelial Cancer: Two-year follow-up from the phase 3 KEYNOTE-045 Trial, Poster presented at the ASCO Annual Meeting, June 1-5, 2018; Chicago, Illinois

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	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):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No
Name of commentator person completing form:	[redacted]

Comment number	Comments

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

	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.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. Please see our comments below.
1	The evidence for this drug in this indication remains the only level one evidence for immunotherapy in urothelial cancer within product label. By contrast, the phase III study supporting the marketing authorisation for atezolizumab in this indication failed to meet its primary objectives (although the data were considered sufficient for the marketing authorisation to remain). The marketing authorisations for both atezolizumab and pembrolizumab in the first line, non-cisplatin-fit populations are currently based on non-randomised phase II data. The Research Group considers level of evidence to be an important consideration in clinical decision making. The NICE appraisal, by its nature, has not adequately considered this factor. However, the Research Group believes that it is undesirable that clinicians may prescribe a drug without level I evidence (atezolizumab, docetaxel, paclitaxel) where there is an alternative where such evidence exists (pembrolizumab). The Research Group urges the Appraisal Committee to consider this factor in weighing up other causes of uncertainty in the economic analysis.
2	Whilst acknowledging the uncertainty regarding the long-term survival benefits of pembrolizumab in this indication, there is insufficient follow up of the pivotal (or any other) data to resolve this one way or the other. Given the transformational effects of pembrolizumab for some patients observed by members of the group in their own practices, the Research Group urges to the Appraisal Committee to permit more 'benefit of doubt' to the optimistic case. The most recent updated analysis of Keynote-045 demonstrates that 20.7% of patients are still alive 36 months after starting pembrolizumab and that the median duration of response is 29.7 months with pembrolizumab (compared to 4.4 months for chemotherapy) (Necchi et al. poster 919P, ESMO meeting ,Barcelona, 30 Sep 2019). The Research Group considers these data to be consistent with more positive long term survival estimates than those assumed by the Appraisal Committee, noting similarities with survival curves seen in other cancers at a similar stage of follow up where long term data supported higher 10 year survival figures than those assumed for urothelial cancer by The Committee.
3	Member of the Research Group are in no doubt that for most patients, immune checkpoint inhibitors such as pembrolizumab, are the technologies which are most likely to meet the needs of patients in this indication. This encompasses patients' expectations around safety and tolerability and also efficacy when compared to the cytotoxic comparators.
4	Paclitaxel and docetaxel, though widely offered in this indication, are of limited efficacy with only low-level evidence. The Research Group is keen to ensure that the standard of evidence in treatment pathways in the UK is aligned to the best available evidence in the world. It would be a backward step if clinicians were to revert to less-evidence based medicine by using these cytotoxic drugs in this indication where previously they were permitted to use pembrolizumab.

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

Please return to: **NICE DOCS**

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer (CDF review TA519) [ID1536]

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 5 December 2019 **email:** NICE DOCS

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.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF review of TA519 [ID1536]: ACD additional evidence

Produced by	Warwick Evidence
Authors	Daniel Gallacher, Research Fellow Mary Jordan, Research Fellow Xavier Armoiry, Honorary Clinical Research Fellow Mubarak Patel, Research Associate Pam Royle, Information Specialist Hema Mistry, Associate Professor
Correspondence to	Dr Hema Mistry Associate Professor in Health Economics Warwick Evidence Division of Health Sciences Warwick Medical School University of Warwick Coventry, CV4 7AL Email: Hema.Mistry@warwick.ac.uk Telephone: 02476 151183
Date completed	9th January 2020

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/108/19

Declared competing interests of the authors

None

Acknowledgements

We would like to thank Dr Sundar Santhanam (Consultant Oncologist, Nottingham University hospitals NHS trust) for providing advice on the survival analysis. Dr Lazaros Andronis read the report and provided advice.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Gallacher D, Jordan M, Armoiry X, Patel M, Royle P, Mistry H. Pembrolizumab for previously treated advanced or metastatic urothelial cancer, CDF review of TA519. Warwick Evidence, 2020.

Contributions of authors

Daniel Gallacher (Research Fellow) conducted, reviewed and critiqued the survival analysis and undertook additional analyses; Mary Jordan (Research Fellow) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Xavier Armoiry (Honorary Clinical Research Fellow) conducted, reviewed and critiqued the clinical effectiveness evidence; Mubarak Patel (Research Associate) conducted, reviewed and critiqued the survival analysis; Pam Royle (Information Specialist) checked the company searches and undertook any additional searching; Hema Mistry (Associate Professor) co-ordinated the project and the report, and provided comments on the report.

ERG Response to Company Comment 1

No ERG response is necessary.

ERG Response to Company Comment 2

No ERG response is necessary.

ERG Response to Company Comment 3

The company state that there are inconsistencies between the current appraisal and the appraisal of atezolizumab for the same indication (TA525).

In general, the ERG are unable to comment on the suitability of the company's comparison to the atezolizumab appraisal, as we have not had the opportunity to scrutinise the information from the appraisal of atezolizumab. However, we advise caution when comparing to TA525 as there are clear differences. Firstly, atezolizumab and pembrolizumab are different interventions and may have different characteristics. Also, using previous appraisals to justify methods in current appraisals may restrict advancement and prevent implementation of best practice.

Treatment effect:

In both of the main trials (IMvigor 210 and IMvigor 211) atezolizumab was not subject to a maximum treatment duration, whereas in KEYNOTE-045, pembrolizumab could only be taken for up to 2 years. Whilst the recommendation by NICE did restrict atezolizumab to a maximum duration of 2 years, this difference in the trial data will likely still confound any comparison.

It is unclear to the ERG how the duration of treatment effect is applied within the economic model of TA525, and whether it is equivalent to only being applied to OS as in this current appraisal. If the two are not equivalent, then it becomes difficult to perform any meaningful comparison.

2-stage adjustment for switching:

The ERG are unable to identify any discussion of adjustment for treatment switching in the TA525 documentation that is available in the public domain. Hence, it is unclear to the ERG what in this appraisal the company believe to be inconsistent with TA525.

Disregard of evidence for treatment effect duration:

The ERG have previously criticised the largely irrelevant sources of external data provided by the company, which did not provide any information on the long-term effect of pembrolizumab on overall survival relative to patients on docetaxel/paclitaxel.

The company states that there was a "dearth" of clinical evidence which contributed to the 2+3 year treatment effect duration of atezolizumab. The ERG are unclear how this evidence compares to that provided within the current appraisal as the company have not highlighted any references, or given any specific detail on which evidence to support their concern for the apparent inconsistency.

ERG Response to Company Comment 4

The company disagrees with the conclusion that the analysis that is unadjusted for treatment switching should be considered within this appraisal. The ERG made this recommendation previously due to a number of concerns with the assumptions and implementation of the 2-stage adjustment.

The company states that the key driver of the concern is the magnitude of the acceleration factor, however from the ERG's perspective there remains many other areas of uncertainty and potential bias. The magnitude of the acceleration factor is not a concern, but the increased magnitude has amplified the influence of this adjustment, which increased the importance of all the other characteristics of the adjustment.

No specific information is provided in this comment in response to the ERG's concerns as these follow in later comments.

Recall that if no patients who switched from UKSOC to receive an anti-PD-1/PD-L1 therapy received any additional benefit from the later therapy, then the unadjusted analysis is likely to be the most representative. In the unlikely scenario that all patients who switched went on to receive benefit from their new therapy, then the 2-stage analysis is likely to be the most representative.

The ERG maintain that it is most plausible that a minority of patients received some benefit, whilst a majority did not, and so neither scenario could be considered accurate in its own right, and both should be considered together.

ERG Response to Company Comment 5

The company reiterate that the 2-stage adjustment is a routine approach, and that the estimate from the most recent data-cut is more reliable than the estimate that originated from the previous data-cut.

The ERG agree with these points, but note that they do not address the concerns raised by the ERG previously. As mentioned in the response to Comment 4, the magnitude of the acceleration factor is not the main concern, but rather the suitability of the 2-stage adjustment and the uncertainty around it. Whilst the wide confidence intervals around the acceleration factor are expected given the small amount of data, it is this lack of data that drives the uncertainty around this influential parameter. The ERG are reluctant to disregard this uncertainty by accepting only the 2-stage analysis.

Additional concerns include an explanation as to why only some patients switched from the UKSOC. As there was no pre-specified rule of treatment switching in KEYNOTE-045 there is the potential for selection bias to be present. Failure to adjust for this bias means that the effect estimated by the acceleration factor is not necessarily attributable to the treatment switching, and may instead be capturing a difference in baseline measurements. The ERG are concerned that this potential selection bias may not be adjusted for in the analysis, especially considering the small number of patients who switched. The ERG would suggest performing a series of sensitivity analyses around the inclusion and exclusion of certain variables to establish the stability of the acceleration parameter, alongside a presentation of the complete output for the model, demonstrating the influence each of the adjusted covariates has on overall survival. The company could also present a table of the baseline characteristics of those who did and did not switch treatments in the UKSOC arm, including

details on their next treatment (e.g. treatment, treatment duration, response). This information could potentially increase the suitability of the 2-stage adjustment.

The ERG also previously recommended only calculating and applying the adjustment to patients who, after switching, achieved a response that is expected to be significant enough to extend their overall survival.

The company present an analysis where the acceleration factor is applied to all 40 patients who switched treatment, and not only to those who switched upon disease progression. Unsurprisingly, reducing the survival time of additional patients in the UKSOC arm makes pembrolizumab slightly better than in the base case analysis. However, the relevance of this analysis is questionable, since the estimation of the acceleration factor is not adjusted in any way.

ERG Response to Company Comment 6

The company state that they believe the 2-stage analysis to be reliable and that the comparison to patients who received vinflunine from the Bellmunt[1] study to be inappropriate.

The ERG acknowledge that there are limitations to naïve comparisons of treatment arms from different trials, however in the absence of alternative sources of evidence, they should still be considered.

The ERG interpret the comparison alongside a consideration of the assumptions and implementation of the 2-stage adjustment. The comparison shows that the median OS, the 12 month OS and 24 month OS from KEYNOTE-045 using the 2-stage adjustment are below that of the Bellmunt[1] study (see Table 1), where the UKSOC patients were expected to have similar or better life-expectancy than the vinflunine patients from Bellmunt[1] according the ERG's clinical advisor.

The 2-stage adjustment applies the same acceleration factor to all patients who switched at disease progression, regardless of whether they were thought to have received benefit from the switch. The ERG finds this implausible given that immunotherapies are typically only effective in some patients. For example, in KEYNOTE-045, the PFS curves only separated when less than 30% of patients remained progression-free. For OS, the curves separated when 65% of patients were still alive, however the patients affected by the 2-stage adjustment have had further disease progression, and on current evidence the ERG believe that it is likely only a minority of switching patients would actually have received any benefit from their next therapy.

When considering this alongside the comparison to the information from Bellmunt[1], the ERG conclude that it is likely that the adjustment to the UKSOC patients is too severe. Whilst the unadjusted ITT UKSOC population may be too optimistic, the ERG maintain the view that the corresponding analysis should still be considered alongside the 2-stage analysis, given the influence on the incremental cost-effectiveness ratios.

Table 1: Comparison of Observed Overall Survival

OS comparison to observed studies	Bellmunt 2013[1]	KEYNOTE-045 UK SoC arm ITT	KEYNOTE-045 UK SoC arm 2-stage adjustment
Median OS	6.9 months	7.0 months	6.2 months
12 month OS	27%	32%	25.0%
24 month OS	11%	16%	10%
30 month OS	5.5%	12%	7.7%

ERG Response to Company Comment 7

The company comment on the wording of how the 2-stage adjustment is described in the Appraisal Consultation Document. The ERG agree that the wording could be clearer, however the implementation of the 2-stage adjustment was clearly understood by the committee at previous committee meeting.

ERG Response to Company Comment 8

The ERG agree with the company that the perceived error in the economic model mentioned in the Appraisal Consultation Document is not an actual error. Hence, the ERG believe that the economic model is correctly implementing the inputs and assumptions.

ERG Response to Company Comment 9

The ERG agree that the company did provide some results for PFS and OS for the two PD-L1 positive subgroups in the clarification response. However the company did not present an analysis showing the interaction between treatment effect and PD-L1 status, and neither did they present results for the PD-L1 negative population. The failure to present these analyses prohibits a greater examination of the effectiveness of pembrolizumab in the PD-L1 positive population.

The company has not provided information that would allow the ERG to present a base-case analysis based on the PD-L1 subgroups.

ERG Response to Company Comment 10

The ERG agree with the company and can confirm that the company did not present a comparison to best supportive care in the previous appraisal for this indication.

ERG Response to Company Comment 11

No ERG response is necessary.

ERG Response to Company Comment 12

The company state that their assumption of a 5 year effect of duration for pembrolizumab is conservative, and that the 3 year assumption preferred by the committee and ERG is implausible and inappropriate.

Follow-up

The company state that since the length of follow-up exceeds 3 years (max 48.9 months) and that the flexible parametric model fitted to the data did not show the hazard ratio crossing within the observed follow-up period, that a 3 year treatment effect is unsuitable. The ERG have previously stated that due to the small number of events in the longer term follow-up, the flexible parametric model only provides clear evidence of a treatment effect for 2 years from the start of treatment. Beyond three years, only one death occurred in the unadjusted UKSOC population and no deaths occurred in the 2-stage adjusted UKSOC population. It would be incorrect to conclude that this demonstrates a sustained effect of pembrolizumab beyond 3 years when there are so few events contributing information. This is reinforced by the fact that the 95% confidence interval for the hazard ratio crosses 1 within the first 2 years of follow-up, highlighting the considerable uncertainty in this parameter.

Given that there is only a maximum follow-up of 4 years, it is unclear to the ERG how this supports a treatment effect duration of 5 years as preferred by the company.

Clinical Opinion

The company state that assuming a 3 year treatment effect duration is contradictory to selecting a log-logistic curve. The ERG disagree with this statement since the log-logistic curve is fitted to both arms, meaning both arms would demonstrate decreasing hazard ratios over time. By assuming equivalence after 3 years, the pembrolizumab hazard rate simply copies that of the UKSOC arm. As can be seen from a comparison of the predictions for the 3 year and 5 year effect durations, any combination of 3 and 5 year extrapolations with and without the 2-stage adjustment result in very similar tails for the pembrolizumab OS curve. Hence, the ERG are unclear exactly what the company's concerns are relative to this point.

Table 2: Long term predictions of OS for Pembrolizumab using log-logistic extrapolation

	Proportion alive with 3 year effect duration, with 2-stage adjustment	Proportion alive with 5 year effect duration, with 2-stage adjustment	Proportion alive with 3 year effect duration, without 2-stage adjustment	Proportion alive with 5 year effect duration, without 2-stage adjustment
10 year	0.0441	0.0545	0.0505	0.0582
20 year	0.0186	0.0230	0.0224	0.0258
30 year	0.0113	0.0139	0.0139	0.0160

Comparison to TA525

This has been discussed in the ERG response to Comment 3. In addition, the ERG are unable to identify what sort of economic model was used in TA525. In order to accurately implement a 3 year post treatment duration of effect, an individual patient level model would be necessary. The treatment effect duration is only applicable to those patients still alive in the pembrolizumab arm. As previously stated in the previous ERG report, from 43 weeks into KEYNOTE-045, a majority of patients alive in the pembrolizumab arm are no longer receiving pembrolizumab. Hence, a 5 year effect duration would be more generous than a correctly implemented 3 year post-treatment effect duration.

Long-term data from KEYNOTE-045 and other pembrolizumab studies

The company presents information that has been presented previously in this appraisal. The ERG maintains the view that the evidence is largely irrelevant to the point in consideration: is there evidence to suggest that the event rate for long-term survivors different between patients who received pembrolizumab and UKSOC? The studies referred to by the company are limited by either: a) being single arm studies, b) having different comparators, c) being for different cancers, or d) having limited follow-up.

The ERG's preference for the 3 year treatment duration is consistent with the observed response data from KEYNOTE-045 which showed that there were long-term responders in both arms, and the ERG have seen no evidence to suggest that these patients would experience different hazard rates based on their trial treatment.

Summary

The ERG interpret the discussed evidence, alongside the observed waning effect observed from 30 weeks of follow-up, and lack of late OS events as support for the assumption of equivalent mortality rates from 36 months between pembrolizumab and UKSOC.

ERG additional responses

The company present additional analyses where they assume lifetime treatment effects for patients with a partial, complete or stable disease response. The ERG have concerns over these analyses presented by the company.

It is unclear how the company models responses to UKSOC, and the ERG are concerned that a failure to account for these in the modelling may be introducing bias. Furthermore, the company appear to assume the same level of response of pembrolizumab between responders and non-responders, for the first 3 or 5 years of the economic model, depending on the scenario. The rationale for this is unclear, as the ERG anticipates that non-responders would potentially have quite different survival outcomes to those who have a response. In the company's accompanying discussion, they appears to overlook the key assumption in question, by considering all UKSOC patients, rather than just those who are still alive at 3 years. All information prior to three years of follow-up is largely irrelevant.

The ERG were able to reproduce each of the ICERs presented by the company, and note that only ICERs with the 2-stage adjustment were shown. For completion, the ERG replicated the analyses without the 2-stage adjustment (Table 3).

Table 3: Scenario analyses provided by the company using company base case, extended by the ERG.

Description	Pembrolizumab vs UKSOC (2-stage adjustment)	Pembrolizumab vs UKSOC (ITT)
	ICER (£/QALY)	ICER (£/QALY)
Company Base Case: 5 year treatment effect	£47,123	£56,422
Scenario 1: DC lifetime treatment effect, remainder 3 year treatment effect	£48,089	£57,566
Scenario 2: DC lifetime treatment effect, remainder 5 year treatment effect	£45,540	£54,398
Scenario 3: DC lifetime treatment effect, remainder 3 year treatment effect, Weibull PFS extrapolation	£49,573	£60,133
Scenario 4: DC lifetime treatment effect, remainder 5 year treatment effect Weibull PFS extrapolation	£46,839	£56,637

Overall the company has presented little new information for the committee and ERG to consider.

The ERG base case analysis is presented in Table 4, which remains unchanged from the previous ERG report. There is also a scenario where the 2-stage adjustment is not applied.

Table 4: ERG Base Case Derivation from Company Base Case, plus scenario analysis

ERG preferred assumption	Scenario detail	Brief rationale and section in ERG report	Impact on base-case ICER
Company base-case			£47,123
1. PFS extrapolation Weibull	PFS extrapolation changed from Log normal curve in new company base-case to Weibull curve	The Weibull curve is best fitting to the control arm of the model, consistent with the ERGs previously accepted PFS and most consistent with the observed data at 2 and 3 years in both arms of the KEYNOTE-045 trial.	£48,518 (+£1,395)
2. 3-year duration of treatment effect	Duration of treatment effect reduced from 5 year cap in company base-case to a	As there is insufficient evidence to conclude whether waning continues, or a treatment effect is sustained beyond 2 years of follow-up. The ERG have chosen	£51,970 (+£4,847)

	maximum 3-year effect	a 3 year duration of treatment effect, this is highlighted in ToE and is preferred alongside 5 year cap.	
3. PFS extrapolation Weibull and 3-year duration of treatment effect (ERG Base Case)	PFS extrapolation and 3-year duration of treatment effect applied to company base-case	Combining change in PFS extrapolation and duration of treatment effect encompass all ERGs preferred assumptions to form new ERG base-case.	£53,678 (+£6,555)
ERG Base Case			£53,678
4.	ERG Base Case without 2-stage adjustment (ITT)	ERG concerns over only considering cost-effectiveness analyses using the 2-stage adjustment	£65,469 (+£11,791)

References

1 Bellmunt, J., et al., Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy. Annals of Oncology, 2013. 24(6): p. 1466-1472