NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

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

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Merck Sharp & Dohme Ltd
   - Fight Bladder Cancer
   - *Joint response from* the British Uro-Oncology Group and the Royal College of Physicians

3. **Comments on the Appraisal Consultation Document from experts:**
   - Dr Rhona McMenemin, Clinical Expert, nominated by the British Uro-Oncology Group and the Royal College of Physicians

4. **Additional evidence** from Merck Sharp & Dohme
   - MSD response to ERG clarification questions regarding additional evidence

5. **Review of additional evidence** by Warwick Evidence

6. **Further additional evidence** from Merck Sharp & Dohme

7. **Further additional evidence (with ERG assumptions)** from Merck Sharp & Dohme

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

Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma

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

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

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

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

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	Company	MSD	MSD is disappointed with the provisional negative recommendation of pembrolizumab given our confidence that it is a cost-effective option for patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy. MSD had communicated to NICE immediately after the Committee meeting [redacted] We believe it is a critical element of any further Committee meeting and we have reiterated below as part of this response. We note that the Committee was presented with 64 different ICERs at the meeting. MSD believes that this creates an unrealistic 'cloud' that militates against determining the most plausible ICER. Based on the content of the ACD, the key drivers underpinning the draft negative recommendation are uncertainty/scepticism around the following defining points, which result in a disparity between our manufacturer's base-case and the ERG's base-case: • Cut-off point and OS extrapolation curves • Utility values • Immune-related adverse events (AEs)	Comment noted.

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
			• Implausible lifetime treatment effect MSD has responded to the Committee's concerns to the best of our ability regarding each of key drivers identified above.	
2	Company	MSD	**Key points supportive of the MSD's approach and assumptions as stated on the released ACD:** • The Committee agreed with MSD that *"the post-hoc subgroup best reflects clinical practice in the UK and is the most appropriate evidence on which to base its decision-making"* • The ACD states that *"The committee concluded that the company's 2-stage method results were appropriate for decision-making."* • The Committee agreed that the trial evidence in patients who have received platinum-containing chemotherapy, "is appropriate for decision-making". • The Committee concluded that incorporating a 2-year stopping rule in its decision-making "was appropriate". • The ACD confirms that the Committee "*concluded that pembrolizumab would extend life by more than 3 months, and therefore met the end-of-life criteria".* • The Committee agreed with the company and the ERG that *"a piecewise model was the most appropriate approach to extrapolation*."	Comment noted.
3	Company	MSD	**MSD UK response to key drivers underpinning the preliminary negative recommendation in the ACD:** • <u>Cut-off point for OS extrapolation and OS extrapolation curves</u> The ACD states "both time points at which to extrapolate the trial data could be plausible and was unable to make a judgement on the most appropriate time	Comment noted. The committee considered both the company and ERG's preferred approach were plausible, and concluded that it would consider both the company and ERG's preferred overall survival extrapolation in its decision-making. Please see sections 3.14 and 3.15 of the Final Appraisal Determination (FAD).

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
			point for decision-making. The committee therefore considered both time points in its decision-making". The selection of the 40-week cut-off point for extrapolation is based on the log-cumulative hazard plot where a more clear change in the slope of the cumulative hazards is observed. Additionally, it utilises the majority of the Kaplan Meier data whilst at the same time there are sufficient remaining patients to fit parametric curves. There are approximately 53% and 40% of patients alive in pembrolizumab and UK SOC arms, respectively. MSD selected the 40 week time point based on recommendations that all of the trial data should be used.[1] Due to a paucity of long-term OS data for UK SOC and the variation observed across UK clinical practice, the Committee *"concluded that the long- term survival was uncertain, and that there are several curves using both the ERG and the company's preferred cut-off which would result in plausible long-term survival estimates".* The ACD also states *"the committee noted that the ICER is very sensitive to the choice of curve and the time point used, with an ICER range of £33,092 to £295,841 per QALY gained using a 24-week time point using the rest of the ERG's preferred assumptions, and a range of £55,118 to £101,593 per QALY gained at the 40-week time point for extrapolation. The committee highlighted that the ERG's preferred log- logistic extrapolation curve, at the 40-week cut-off, would have a plausible 5-year overall survival rate for the UK standard care arm of 7.1% and would result in an ICER of £70,304 per QALY gained*". Those ICERs are based on ERG's assumptions are reported in **Error! Reference source not found.** below, as presented in the ERG's Addendum 1 report. MSD is concerned that the Committee's range of plausible ICERs is based solely on the 5-year OS extrapolated estimates for the UK SOC arm, without taking into account any statistical considerations on how well the parametric curves fit the data. The NICE DSU TSD 14 guidance highlights the importance of goodness of fit as well as clinical plausibility of the extrapolation curves.[2] Therefore, and based on goodness of data fit, some parametric curves should not be considered as credible despite the plausible 5-year OS estimates for UK SOC arm: • At a 24-week time-point for OS extrapolation, the Gompertz and Gen. Gamma parametric curves should be excluded based on the high AIC/BIC for UK SOC and pembrolizumab, respectively.	

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			• At a 40-week time-point for OS extrapolation, the Weibull distribution should be excluded, due to the high AIC/BIC values for pembrolizumab and UK SOC. Similarly, the log-logistic distribution does not fit the OS data for pembrolizumab well, as it is the curve with the second highest AIC/BIC. Therefore, when discussing the ERG's range of plausible ICERs at either a 24-week or 40-week time-point, MSD believes that presenting an ICER range of £41,807 to £51,235 per QALY gained at a 24-week time-point and an ICER of £55,407 per QALY gained at a 40 week time-point is more appropriate and methodologically accurate. MSD is confident that the ICERs are further decreased with the availability of data from the most recent data cut. When applying the discount agreed in the CAA, MSD is confident in having plausible ICERs below the £50,000 threshold.	
4	Company	MSD	• <u>Utility values</u> The Committee agreed with the ERG's rationale for considering the utilities presented based on time-to-death approach as inappropriate for decision making. The time-to-death utility estimates included in MSD's base-case were estimated with the same approach presented in previous TAs for pembrolizumab in melanoma and NSCLC.[3-6] Specifically, in NICE TA447 for pembrolizumab in untreated PD-L1 positive adults with metastatic NSCLC, time-to-death utilities were considered appropriate for decision making by the same Committee. The following issues have been identified by the ERG and accepted by the Committee, despite the precedent set in the appraisal of pembrolizumab in NICE TA447: a) *"The utilities were implausibly high and the values for long term survivors with >360 days from death were similar to the UK population norm." and it is also stated "However the ERG noted that KEYNOTE-045 was open-label, which results in a high risk of bias to the utilities, and therefore also preferred to pool the utilities"* The utility value used in MSD's base case for patients with a survival of 360 days or more before death, was 0.778 which is below the utility	Comment noted. The committee recognised that the company's preferred time to death approach to modelling utilities was capable of describing diminishing quality of life after progression in a way that the progression based utilities could not, however it considered the overall validity of those estimates is questionable when the issues of implausibly high values, small sample sizes and missing data were considered in combination. It agreed with the ERG's approach and concluded that utilities should be based on progression state. Please see section 3.17 of the FAD.

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			estimate for the UK population norm for patients of the same age (i.e. 0.79 as reported in TA447). To understand the wider impact of immunotherapy on patients' quality of life, the charity Lung Cancer Canada conducted a national survey of lung cancer patients and caregivers in August 2015.[7] The survey included 23 patients and 14 caregivers who had experience with pembrolizumab. The majority of respondents interviewed reported no side effects to mild side effects during the period treated with pembrolizumab. Most respondents found that management of adverse events was tolerable and did not interfere with their day-to-day life. Of the 23 patients interviewed, side effects were reported by 6 patients: ▪ One patient reported pneumonitis and stopped treatment ▪ Two patients reported mild fatigue ▪ One patient reported bloody stools at the start of treatment, which was managed with steroids ▪ Three patients reported mild rash, managed with corticosteroids The LCC concluded that pembrolizumab allowed respondents to have a high quality of life in comparison to other available treatments such as chemotherapy. The work conducted by the LCC further supports the utility values collected in KEYNOTE-045 trial. In addition, MSD has successfully incorporated patient reported outcomes, measured with the EQ-5D instrument, into the clinical trial programme. This has been in response to the stated desire of NICE. For the cost-effectiveness analyses, health effects should be expressed in QALYs. For the reference case, the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a	

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			choice-based method. The EQ-5D is the preferred measure of health-related quality of life in adults. (NICE methods guide 2013).[8] It is therefore disappointing to, again, have these rejected by the Committee. MSD was surprised by the concern expressed by the ERG about the influence of an open-label study design on utilities, as this has not been a factor considered by the Committees before.[3-6] We acknowledge that the study was open-label but would challenge that this affects the validity of the results. The European Medicines Agency (EMA) has stated the following in relation to patient reported outcomes in oncology trials: *"Whilst the concern in relation to open label studies remains, it might well be that data of clinical interest a priori can be produced only under open label conditions. One example being an experimental compound assumed to be more efficacious, but also more toxic or less well tolerated. (Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies 2014)."* MSD supports this and would argue that it applies equally to a situation where an experimental compound is assumed to be more efficacious, but also less toxic or better tolerated, as is the case here. Furthermore, a recent appraisal of pembrolizumab in 1L NSCLC by the Canadian Agency For Drugs and Technologies in Health (CADTH), the utility values collected in the KEYNOTE-024 trial were considered appropriate for decision making despite the open label nature of the trial.[7] Guidance from CADTH's clinical panel confirmed that in clinical practice immunotherapy agents are better tolerated than chemotherapy, additionally supported by the information provided by patient groups such as LCC mentioned above. b) *"Small sample sizes, with only 14 responses in the UK SOC arm at <30 days from death."*	

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			The sample size in each time-to-death category of utilities collected in KEYNOTE-045 is consistently higher than the respective sample sizes from KEYNOTE-024 used and accepted in TA447. [6] c) *"MSD's approach for handling missing data."* Missing data have been excluded from utility analyses to minimise uncertainty of estimates. This approach is consistent with the methodology used in the utility analyses for pembrolizumab in previous TAs (i.e.TA366, TA357, TA428, TA447).[3-6]	
5	Company	MSD	Additionally, the ACD states *"the ERG disagreed that there was no statistically significant difference between the arms, because pembrolizumab has significantly higher utilities compared with UK standard care when basing utilities on progression state".* Statistically significant and clinically meaningful differences in utility values are disregarded by the ERG and the Committee. It is unclear how two different approaches of estimating utility values (i.e. by time-to-death- and progression status) can be compared in terms of statistical significance. MSD has tested for statistical significance the utility values per treatment arm by time-to-death and by progression status. When using the time-to death approach, no statistically significant difference between treatment arms has been identified, and therefore, pooled utility estimates should be used. However, when considering utilities based on progression state, the p-values are <0.0001 for both the pre-progressed and progressed state. Even following Bonferroni correction for multiple comparisons, the p-values are still significant under 0.05 confidence level. In addition, clinically meaningful difference is determined by comparing to minimally important difference (MID) in EQ-5D scores for cancers, considered to be 0.08 for UK-based scores.[9] The difference per treatment arm in the progressed disease ranges is 0.12 and 0.13, depending on the inclusion or exclusion of vinflunine data. Therefore, utility values per treatment arm should be used for utilities based on	Comment noted. The ERG considered this rationale inconsistent because any differences in utilities between pembrolizumab and UK standard care should be evident in both approaches. The committee recalled that the utilities using the time to death approach were inconsistent because utility values in the UK standard care arm were often higher than in the pembrolizumab arm, which it considered supported pooling the utilities. Please see section 3.17 of the FAD.

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			progression state, due to the above statistical and clinical considerations.	
6	Company	MSD	• Immune-related adverse events (AEs) In line with previous NICE HTA submissions of pembrolizumab and other immunotherapy agents, only Grade 3+ AEs with an incidence of at least 5% in any of the arms were included in the cost-effectiveness model apart from Grade 2 diarrhoea and febrile neutropaenia. AEs of Special Interest (AEOSI) are immune-mediated events and infusion-related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab.[5] [6] [10] **Error! Reference source not found.** below lists the AEOSI as observed in KEYNOTE-045.[11] Overall, only 4.5% and 1.6% of patients treated in the pembrolizumab and control arm, respectively, of the KEYNOTE-045 trial experienced Grade 3+ AEOSI. MSD has explored the impact of AEOSI in the cost-effectiveness analysis by conservatively including Grade 3+ AEOSI only in the pembrolizumab arm. As one can expect from the low AEOSI rates, the inclusion of AEOSI has a minimal impact on the ICER of MSD's base case increasing the ICER by approximately £66. MSD has also explored the impact of incorporating Grade 3+ AEOSI only into both the pembrolizumab arm and the UK SOC arm; again the inclusion of AEOSI has a minimal impact increasing MSD's base case ICER by approximately £60.	Comment noted. The committee noted that the impact was minimal, and concluded that the company's original approach was appropriate for decision-making. Please see section 3.11 of the FAD.
7	Company	MSD	• Implausible lifetime treatment effect The ACD states *"The Committee was aware that the duration of continued treatment effect is an area of uncertainty for new immunotherapies, but it concluded a lifetime continued treatment effect to be implausible"*. It also states that *"the Committee highlighted that a scenario which assumes no continued treatment effect after 5 years increases the company's base-case ICER by around £6,000 per QALY gained".* Initially, MSD would like to highlight that our deterministic base-case ICER increases by approximately £4,000 per QALY gained when assuming no treatment	Comment noted. The committee was aware that the duration of continued treatment effect after implementation of a stopping rule is an area of uncertainty for new immunotherapies, but it concluded that a lifetime continued treatment effect was implausible. Please see section 3.16 of the FAD.

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			effect after 5 years. MSD understands the concerns of the Committee about the long-term treatment effect of pembrolizumab but the data and the clinical expert opinion suggest that immunotherapies due to their distinct mechanism of action maintain the treatment benefit. Data recently presented at ASCO 2017 demonstrated the long-term efficacy of pembrolizumab following completion of 2-year treatment duration in patients with advanced melanoma enrolled in KEYNOTE-006 trial.[13] The longer-term analysis of KEYNOTE-006 demonstrated the 33 month overall survival rate to be 50% for patients treated with pembrolizumab. During the appraisal of TA366, ERG analysis of the KEYNOTE-006 data estimated at the same 33 month time point, approximately 45% of patients treated with pembrolizumab would remain alive. The follow up of KEYNOTE-006 confirms that the analysis of immature data is underestimating the value of benefit of immunotherapy agents. Furthermore, after a median follow-up of 9 months post treatment completion with pembrolizumab, 98% of patients were still alive. Additional evidence from the KEYNOTE-001 trial demonstrated that among the 64% of patients who stopped treatment after a complete response (median duration of treatment was 23 months) the response duration ranged from 17 to 43 months.[14] It is of note that only 2 of the 61 patients who stopped treatment after complete response experienced disease progression. Similar evidence emerges from other immunotherapy agents. Specifically, a paper from Schadendorf in patients with unresectable or metastatic melanoma treated with ipilimumab revealed the long-term treatment benefit of ipilimumab despite the limited treatment duration.[15] The study observes a plateau in the survival curve beginning at around 3 years, with follow up to 10 years. Of note, and despite the above evidence, the cost-effectiveness analyses presented are based on a combination of Kaplan-Meier data and parametric extrapolation without incorporating a long term plateau of the survival curve. This	

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			approach is in line with other recent NICE submissions for oncology technologies previously accepted by the ERGs and NICE Committees as the preferred basis for decision making. MSD believes that if all of the above are taken into consideration, the uncertainty around the most plausible ICER is decreased; and pembrolizumab for the treatment of locally advanced or metastatic urothelial cancer for adults who received platinum-containing chemotherapy is considered a cost-effective option for NHS resources.	
8	Company	MSD	**Cancer Drugs Fund** Finally, the ACD states regarding Cancer Drugs Fund (CDF) considerations that *"the Committee heard from the company that it preferred pembrolizumab to be made available via routine commissioning".* This statement, although accurate, is misleading in the sense that MSD, as a responsible company that always aims to provide access to patients to the most innovative treatments, would consider the option of a recommendation into the CDF, MSD expects the availability of a final data cut from the KEYNOTE-045 study in [redacted]	Comment noted. Following consultation the committee considered a proposal for the Cancer Drugs Fund rather than routine commissioning and proposed a confidential commercial access agreement for pembrolizumab within the Cancer Drugs Fund. Please see section 3.20 of the FAD.
9	Clinical expert	British Uro-Oncology Group	P3 "Life expectancy for people with locally advanced or metastatic urothelial carcinoma is less than 24 months" – I would agree it is upfront, but in the second line setting where this indication is being appraised overall survival is around 5-7 months.	Comment noted. The committee considered the life expectancy in view of the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods.
10	Clinical expert	British Uro-Oncology Group	P3 "Pembrolizumab is likely to extend people's lives by more than 3 months" – just clarifying this was the improvement in median survival. As in all studies, patients who respond will do better than the median improvement in the trial population and this is what is explained to patients in a real life setting. 44% of patients with pembro were alive at one year, this is often more meaningful in settings where patient survival is only a few months, as stated above (and was often used in lung cancer studies for this reason)	Comment noted. The committee considered the expected life extension in view of the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods.
11	Clinical expert	British Uro-Oncology Group	P4 "Results were not reliable" – it is more that response were reported in all subgroups, and as per KEYNOTE 52, responders and non responders could not be easily separated. It should be stressed that there are similar issues in kidney cancer, while it has been easier to identify subgroups based on PD-L1 testing in lung cancer	Comment noted.
12	Clinical expert	British Uro-Oncology	P5 "The condition and current treatments" – it should also be noted that patients with PS 2 who dominate this group (Payne et al 2012) were eligible for this study	Comment noted. The committee considered the results of the KEYNOTE-045 post-hoc subgroup were

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		Group	and were included, albeit the numbers were low, They are often excluded from clinical trials, so this did reflect a more real life population.	generalisable to UK clinical practice and appropriate for decision-making. Please see section 3.5 of the FAD.
13	Clinical expert	British Uro-Oncology Group	P6 “Comparators” – Reinduction (rechallenge) platin therapy is usually used when there is relapse or progression ideally after 12/12, and therefore maximises potential therapies in these patients keeping other agents in reserve for use thereafter. Vinflunine in Europe has been approved and has been the standard of care for nearly 10 years, based on the only RCT and to date the highest level of evidence in this setting prior to KEYNOTE 45. Vinflunine has been used in the UK, (VICTOR – Hussein et al) but is not funded which is the main reason it is not in current practice.	Comment noted.
14	Clinical expert	British Uro-Oncology Group	P9 “improves overall survival but not PFS” – while this is true, it is not clinically meaningful and I agree with the original paper that this is not a surrogate marker for response in this setting, unlike other treatments e.g. Sunitinib in mRCC which was licensed on this basis.	Comment noted. The committee concluded that, because of the significant improvements in overall survival, pembrolizumab is more clinically effective than docetaxel or paclitaxel. Please see section 3.8 of the FAD.
15	Professional group	BUG-NCRI-RCP-RCR	The BUG-NCRI-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. We are concerned that the committee acknowledged the utility of pembrolizumab in its licensed setting ; that it significantly improves overall survival significantly compared to standard taxane based chemotherapy,, and meets the criteria from NICE to be considered a life extending treatment at the end of life, extending life by more than 3 months yet does not recommend its use. Pembrolizumab was compared in the keynote-045 study with a comparator arm that would reflect current UK practice. In addition to the improvement in overall survival (estimated OS rate at 1 year 39.8% compared with 26.9% for chemotherapy, the one year progression free survival rate was three times greater in the pembrolizumab arm (16.8%) compared to 6.2 % in the chemotherapy arm. Fewer patients deteriorated with a prolonged time to deterioration in the pembrolizumab arm (HR 0.66). Slowing clinical deterioration means reduced cost for primary care input, palliative interventions, such as radiotherapy, ureteric stents with attendant hospital admissions, blood transfusions for haematuria etc. Other trials with this agent have shown global improvements or maintenance in HRQoL measurements compared with chemotherapy, and in particular an improvement in global health status from baseline compared to week 15 (pembrolizumab 6.9 improvement compared with -0.9 for chemotherapy). Whilst these trials with HRQoL domains were in the lung cancer population, there is commonality with urothelial cancer in that these lung cancer patients are usually smokers with the same smoking related comorbidities as urothelial cancer	Comment noted. The committee concluded that, because of the significant improvements in overall survival, pembrolizumab is more clinically effective than docetaxel or paclitaxel. Following consultation the company submitted a proposal for the committee to consider pembrolizumab for the Cancer Drugs Fund rather than routine commissioning and proposed a confidential commercial access agreement for pembrolizumab within the Cancer Drugs Fund. With this agreement pembrolizumab has plausible potential to be cost effective and further data collection would reduce uncertainty. Therefore pembrolizumab can be recommended for use in the Cancer Drugs Fund. Please see sections 3.8, 3.20 and 3.26 of the FAD. The committee noted that, whilst no overall difference was seen for progression-free survival the Kaplan–Meier was skewed, with pembrolizumab being less clinically effective than the investigator's choice of chemotherapy initially, but progression then appears to plateau for people on pembrolizumab. Please see section 3.7 of the FAD.

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			There has been no improvement in survival from metastatic bladder cancer for 20 years. Pembrolizumab improves survival in a group with an unmet need, fulfils end of life criteria, and is the first agent to show such in a phase 3 randomised trial in a tumour where previous survival gains have been lacking. This is reflected in the lack of previous bladder cancer review at NICE with one previous phase 3 drug being reviewed (negatively) in the last 15 years.	
16	Patient group	Fight Bladder Cancer	We are pleased that NICE has concluded that the clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with docetaxel and paclitaxel for people with locally advance or metastatic urothelial carcinoma and that Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. However, we are disappointed that there is no agreement on the cost effectiveness of the treatment between NICE and the Company submission. It appears that this decision is based on the evaluation of the data provided so we would hope that an early reconsideration can be made if/when further data can be provided by the company.	Comment noted. Following consultation the company submitted a proposal for the committee to consider pembrolizumab for the Cancer Drugs Fund rather than routine commissioning and proposed a confidential commercial access agreement for pembrolizumab within the Cancer Drugs Fund. With this agreement pembrolizumab has plausible potential to be cost effective and further data collection would reduce uncertainty. Therefore pembrolizumab can be recommended for use in the Cancer Drugs Fund. Please see sections 3.20 and 3.26 of the FAD.

The following consultees/commentators indicated that they had no comments on the Appraisal Consultation Document

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Technology Appraisals Project Manager - Committee D
National Institute for Health and Care Excellence

23rd August 2017

Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma [ID1019] – Response to Appraisal Consultation Document (ACD)

Dear Kate,

MSD is disappointed with the provisional negative recommendation of pembrolizumab given our confidence that it is a cost-effective option for patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy.

MSD had communicated to NICE immediately after the Committee meeting [redacted]. We believe it is a critical element of any further Committee meeting and we have reiterated below as part of this response.

We note that the Committee was presented with 64 different ICERs at the meeting. MSD believes that this creates an unrealistic 'cloud' that militates against determining the most plausible ICER.

Based on the content of the ACD, the key drivers underpinning the draft negative recommendation are uncertainty/scepticism around the following defining points, which result in a disparity between our manufacturer's base-case and the ERG's base-case:

- Cut-off point and OS extrapolation curves
- Utility values
- Immune-related adverse events (AEs)
- Implausible lifetime treatment effect

MSD has responded to the Committee's concerns to the best of our ability regarding each of key drivers identified above.

Should you have any questions about the content, please do contact me.

Kind regards,

[redacted]

[redacted] , [redacted]

[redacted]

Key points supportive of the MSD's approach and assumptions as stated on the released ACD:

- The Committee agreed with MSD that *"the post-hoc subgroup best reflects clinical practice in the UK and is the most appropriate evidence on which to base its decision-making"*

- The ACD states that *"The committee concluded that the company's 2-stage method results were appropriate for decision-making."*

- The Committee agreed that the trial evidence in patients who have received platinum-containing chemotherapy, "is appropriate for decision-making".

- The Committee concluded that incorporating a 2-year stopping rule in its decision-making "was appropriate".

- The ACD confirms that the Committee "*concluded that pembrolizumab would extend life by more than 3 months, and therefore met the end-of-life criteria".*

- The Committee agreed with the company and the ERG that *"a piecewise model was the most appropriate approach to extrapolation*."

MSD UK response to key drivers underpinning the preliminary negative recommendation in the ACD:

- <u>Cut-off point for OS extrapolation and OS extrapolation curves</u>

The ACD states "both time points at which to extrapolate the trial data could be plausible and was unable to make a judgement on the most appropriate time point for decision-making. The committee therefore considered both time points in its decision-making".

The selection of the 40-week cut-off point for extrapolation is based on the log-cumulative hazard plot where a more clear change in the slope of the cumulative hazards is observed. Additionally, it utilises the majority of the Kaplan Meier data whilst at the same time there are sufficient remaining patients to fit parametric curves. There are approximately 53% and 40% of patients alive in pembrolizumab and UK SOC arms, respectively. MSD selected the 40 week time point based on recommendations that all of the trial data should be used.[1]

Due to a paucity of long-term OS data for UK SOC and the variation observed across UK clinical practice, the Committee *"concluded that the long- term survival was uncertain, and that there are several curves using both the ERG and the company's preferred cut-off which*

would result in plausible long-term survival estimates". The ACD also states *"the committee noted that the ICER is very sensitive to the choice of curve and the time point used, with an ICER range of £33,092 to £295,841 per QALY gained using a 24-week time point using the rest of the ERG's preferred assumptions, and a range of £55,118 to £101,593 per QALY gained at the 40-week time point for extrapolation. The committee highlighted that the ERG's preferred log- logistic extrapolation curve, at the 40-week cut-off, would have a plausible 5-year overall survival rate for the UK standard care arm of 7.1% and would result in an ICER of £70,304 per QALY gained*". Those ICERs are based on ERG's assumptions are reported in **Error! Reference source not found.** below, as presented in the ERG's Addendum 1 report.

Table 1: Verification of NICE ICERs, using the ERG preferred assumptions

Scenario	Pembrolizumab vs UK SOC					
	5-year OS UK SOC	**Incr. costs**	**Incr. LYG**	**Incr. QALYs**	**ICER**	**D ICER**
ERG base case	3.2%	£40,017	1.25	0.78	£51,235	
Model using the ERG preferred assumptions with a 40 week time-point (as in the Company submission)						
Exponential	0.3%	£35,028	0.51	0.35	£100,765	+£49,530
Weibull	2.9%	£35,006	0.51	0.34	£101,593	+£50,358
Gompertz	24.3%	£39,432	1.15	0.72	£55,118	+£3,883
Log-logistic	7.1%	£37,153	0.82	0.53	£70,304	+£19,069
Log-normal	7.8%	£39,239	1.12	0.71	£55,407	+4,172
G. Gamma	17%	£38,116	0.96	0.61	£62,809	+11,574
Model using the ERG preferred assumptions with a 24 week time-point						
Exponential	0.4%	£34,648	0.46	0.31	£110,621	+£59,386
Weibull	0.1%	£35,928	0.64	0.43	£83,381	+£32,146
Gompertz	5.9%	£47,846	2.38	1.45	£33,092	-£18,143
Log-logistic	3.2%	£40,017	1.25	0.78	£51,235	£0
Log-normal	2.9%	£42,816	1.65	1.02	£41,807	-£9,428
G. Gamma	8.9%	£32,242	0.10	0.11	£295,841	£244,606
Source: ERG model						

MSD is concerned that the Committee's range of plausible ICERs is based solely on the 5-year OS extrapolated estimates for the UK SOC arm, without taking into account any statistical considerations on how well the parametric curves fit the data. The NICE DSU TSD 14 guidance highlights the importance of goodness of fit as well as clinical plausibility of the extrapolation curves.[2] Therefore, and based on goodness of data fit, some parametric curves should not be considered as credible despite the plausible 5-year OS estimates for UK SOC arm:

- At a 24-week time-point for OS extrapolation, the Gompertz and Gen. Gamma parametric curves should be excluded based on the high AIC/BIC for UK SOC and pembrolizumab, respectively.
- At a 40-week time-point for OS extrapolation, the Weibull distribution should be excluded, due to the high AIC/BIC values for pembrolizumab and UK SOC. Similarly, the log-logistic distribution does not fit the OS data for pembrolizumab well, as it is the curve with the second highest AIC/BIC.

Therefore, when discussing the ERG's range of plausible ICERs at either a 24-week or 40-week time-point, MSD believes that presenting an ICER range of £41,807 to £51,235 per QALY gained at a 24-week time-point and an ICER of £55,407 per QALY gained at a 40 week time-point is more appropriate and methodologically accurate.

MSD is confident that the ICERs are further decreased with the availability of data from the most recent data cut. When applying the discount agreed in the CAA, MSD is confident in having plausible ICERs below the £50,000 threshold.

Table 2: Goodness of fit data for pembrolizumab and UK SOC, at 24 and 40 weeks point of extrapolation

	Pembrolizumab				UK SOC (2-stage adjustment)			
	24-Week		40-Week		24-Week		40-Week	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	690.1	693.2	339.1	342.1	382.3	384.7	165.1	167.1
Weibull	691	697.4	340.5	346.4	383.7	388.6	165	169.1
Gompertz	689.8	696.1	338.1	344	383.9	388.7	160.4	164.5
Llogistic	690	696.4	339.4	345.3	380.1	385	163.7	167.7
Lnormal	691.7	698.1	337.5	343.4	377.9	382.7	161.8	165.9
GenGamma	692.4	701.8	338.5	347.3	377.8	385.1	160.2	166.3

- Utility values

The Committee agreed with the ERG's rationale for considering the utilities presented based on time-to-death approach as inappropriate for decision making. The time-to-death utility estimates included in MSD's base-case were estimated with the same approach presented in previous TAs for pembrolizumab in melanoma and NSCLC.[3-6] Specifically, in NICE TA447 for pembrolizumab in untreated PD-L1 positive adults with metastatic NSCLC, time-to-death utilities were considered appropriate for decision making by the same Committee. The following issues have been identified by the ERG and accepted by the Committee, despite the precedent set in the appraisal of pembrolizumab in NICE TA447:

a) *"The utilities were implausibly high and the values for long term survivors with >360 days from death were similar to the UK population norm." and it is also stated "However the ERG noted that KEYNOTE-045 was open-label, which results in a high risk of bias to the utilities, and therefore also preferred to pool the utilities"*

   The utility value used in MSD's base case for patients with a survival of 360 days or more before death, was 0.778 which is below the utility estimate for the UK population norm for patients of the same age (i.e. 0.79 as reported in TA447).

   To understand the wider impact of immunotherapy on patients' quality of life, the charity Lung Cancer Canada conducted a national survey of lung cancer patients and caregivers in August 2015.[7] The survey included 23 patients and 14 caregivers who had experience with pembrolizumab. The majority of respondents interviewed reported no side effects to mild side effects during the period treated with pembrolizumab. Most respondents found that management of adverse events was tolerable and did not interfere with their day-to-day life. Of the 23 patients interviewed, side effects were reported by 6 patients:

   - One patient reported pneumonitis and stopped treatment
   - Two patients reported mild fatigue
   - One patient reported bloody stools at the start of treatment, which was managed with steroids
   - Three patients reported mild rash, managed with corticosteroids

   The LCC concluded that pembrolizumab allowed respondents to have a high quality of life in comparison to other available treatments such as chemotherapy. The work conducted by the LCC further supports the utility values collected in KEYNOTE-045 trial.

   In addition, MSD has successfully incorporated patient reported outcomes, measured with the EQ-5D instrument, into the clinical trial programme. This has been in response to the stated desire of NICE.

For the cost-effectiveness analyses, health effects should be expressed in QALYs. For the reference case, the measurement of changes in health-related quality of life should be reported directly from patients and the utility of these changes should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of health-related quality of life in adults. (NICE methods guide 2013).[8]

It is therefore disappointing to, again, have these rejected by the Committee. MSD was surprised by the concern expressed by the ERG about the influence of an open-label study design on utilities, as this has not been a factor considered by the Committees before.[3-6] We acknowledge that the study was open-label but would challenge that this affects the validity of the results. The European Medicines Agency (EMA) has stated the following in relation to patient reported outcomes in oncology trials:

"Whilst the concern in relation to open label studies remains, it might well be that data of clinical interest a priori can be produced only under open label conditions. One example being an experimental compound assumed to be more efficacious, but also more toxic or less well tolerated. (Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies 2014)."

MSD supports this and would argue that it applies equally to a situation where an experimental compound is assumed to be more efficacious, but also less toxic or better tolerated, as is the case here.

Furthermore, a recent appraisal of pembrolizumab in 1L NSCLC by the Canadian Agency For Drugs and Technologies in Health (CADTH), the utility values collected in the KEYNOTE-024 trial were considered appropriate for decision making despite the open label nature of the trial.[7] Guidance from CADTH's clinical panel confirmed that in clinical practice immunotherapy agents are better tolerated than chemotherapy, additionally supported by the information provided by patient groups such as LCC mentioned above.

b) *"Small sample sizes, with only 14 responses in the UK SOC arm at <30 days from death."*

The sample size in each time-to-death category of utilities collected in KEYNOTE-045 is consistently higher than the respective sample sizes from KEYNOTE-024 used and accepted in TA447. [6]

c) *"MSD's approach for handling missing data."*

Missing data have been excluded from utility analyses to minimise uncertainty of estimates. This approach is consistent with the methodology used in the utility analyses for pembrolizumab in previous TAs (i.e.TA366, TA357, TA428, TA447).[3-6]

Additionally, the ACD states *"the ERG disagreed that there was no statistically significant difference between the arms, because pembrolizumab has significantly higher utilities*

compared with UK standard care when basing utilities on progression state". Statistically significant and clinically meaningful differences in utility values are disregarded by the ERG and the Committee. It is unclear how two different approaches of estimating utility values (i.e. by time-to-death- and progression status) can be compared in terms of statistical significance.

MSD has tested for statistical significance the utility values per treatment arm by time-to-death and by progression status. When using the time-to death approach, no statistically significant difference between treatment arms has been identified, and therefore, pooled utility estimates should be used. However, when considering utilities based on progression state, the p-values are <0.0001 for both the pre-progressed and progressed state. Even following Bonferroni correction for multiple comparisons, the p-values are still significant under 0.05 confidence level. In addition, clinically meaningful difference is determined by comparing to minimally important difference (MID) in EQ-5D scores for cancers, considered to be 0.08 for UK-based scores.[9] The difference per treatment arm in the progressed disease ranges is 0.12 and 0.13, depending on the inclusion or exclusion of vinflunine data. Therefore, utility values per treatment arm should be used for utilities based on progression state, due to the above statistical and clinical considerations.

- <u>Immune-related adverse events (AEs)</u>

In line with previous NICE HTA submissions of pembrolizumab and other immunotherapy agents, only Grade 3+ AEs with an incidence of at least 5% in any of the arms were included in the cost-effectiveness model apart from Grade 2 diarrhoea and febrile neutropaenia. AEs of Special Interest (AEOSI) are immune-mediated events and infusion-related reactions considered to be identified risks (adverse drug reactions) or potential risks for pembrolizumab.[5 6 10]

Table 3 below lists the AEOSI as observed in KEYNOTE-045.[11] Overall, only 4.5% and 1.6% of patients treated in the pembrolizumab and control arm, respectively, of the KEYNOTE-045 trial experienced Grade 3+ AEOSI.

MSD has explored the impact of AEOSI in the cost-effectiveness analysis by conservatively including Grade 3+ AEOSI only in the pembrolizumab arm. As one can expect from the low AEOSI rates, the inclusion of AEOSI has a minimal impact on the ICER of MSD's base case increasing the ICER by approximately £66. MSD has also explored the impact of incorporating Grade 3+ AEOSI only into both the pembrolizumab arm and the UK SOC arm; again the inclusion of AEOSI has a minimal impact increasing MSD's base case ICER by approximately £60.

Table 3: AEOSI's in the As-Treated Population* [12]

Event	Pembrolizumab Group (N = 266)		Chemotherapy Group (N = 255)		UK SOC Group [redacted]	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4 or 5
	Number of patients (percent)					
AEOSI's §						
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)	[redacted]	[redacted]
Hypothyroidism	17 (6.4)	0	3 (1.2)	0	[redacted]	[redacted]
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0	[redacted]	[redacted]
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0	[redacted]	[redacted]
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0	[redacted]	[redacted]
Infusion reaction	2 (0.8)	0	10 (3.9)	0	[redacted]	[redacted]
Nephritis	2 (0.8)	2 (0.8)	0	0	[redacted]	[redacted]
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)	[redacted]	[redacted]
Thyroiditis	2 (0.8)	0	0	0	[redacted]	[redacted]
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0	[redacted]	[redacted]
Myositis	0	0	1 (0.4)	1 (0.4)	[redacted]	[redacted]

** The as-treated population included all the patients who received at least one dose of study treatment.*
§ The events of interest are those with an immune-mediated and infusion related reactions and are considered regardless of attribution to study treatment by the investigator. They are listed in descending order of frequency in the pembrolizumab group. In addition to the specific preferred terms listed, related terms were also included.

- Implausible lifetime treatment effect

The ACD states *"The Committee was aware that the duration of continued treatment effect is an area of uncertainty for new immunotherapies, but it concluded a lifetime continued treatment effect to be implausible"*. It also states that *"the Committee highlighted that a scenario which assumes no continued treatment effect after 5 years increases the company's base-case ICER by around £6,000 per QALY gained".*

Initially, MSD would like to highlight that our deterministic base-case ICER increases by approximately £4,000 per QALY gained when assuming no treatment effect after 5 years. MSD understands the concerns of the Committee about the long-term treatment effect of pembrolizumab but the data and the clinical expert opinion suggest that immunotherapies due to their distinct mechanism of action maintain the treatment benefit.
Data recently presented at ASCO 2017 demonstrated the long-term efficacy of pembrolizumab following completion of 2-year treatment duration in patients with advanced melanoma enrolled in KEYNOTE-006 trial.[13] The longer-term analysis of KEYNOTE-006 demonstrated the 33 month overall survival rate to be 50% for patients treated with pembrolizumab. During the appraisal of TA366, ERG analysis of the KEYNOTE-006 data estimated at the same 33 month time point, approximately 45% of patients treated with pembrolizumab would remain alive. The follow up of KEYNOTE-006 confirms that the analysis of immature data is underestimating the value of benefit of immunotherapy agents. Furthermore, after a median follow-up of 9 months post treatment completion with pembrolizumab, 98% of patients were still alive. Additional evidence from the KEYNOTE-001 trial demonstrated that among the 64% of patients who stopped treatment after a complete response (median duration of treatment was 23 months) the response duration ranged from 17 to 43 months.[14] It is of note that only 2 of the 61 patients who stopped treatment after complete response experienced disease progression.

Similar evidence emerges from other immunotherapy agents. Specifically, a paper from Schadendorf in patients with unresectable or metastatic melanoma treated with ipilimumab revealed the long-term treatment benefit of ipilimumab despite the limited treatment duration.[15] The study observes a plateau in the survival curve beginning at around 3 years, with follow up to 10 years.

Of note, and despite the above evidence, the cost-effectiveness analyses presented are based on a combination of Kaplan-Meier data and parametric extrapolation without incorporating a

long term plateau of the survival curve. This approach is in line with other recent NICE submissions for oncology technologies previously accepted by the ERGs and NICE Committees as the preferred basis for decision making.

MSD believes that if all of the above are taken into consideration, the uncertainty around the most plausible ICER is decreased; and pembrolizumab for the treatment of locally advanced or metastatic urothelial cancer for adults who received platinum-containing chemotherapy is considered a cost-effective option for NHS resources.

Cancer Drugs Fund

Finally, the ACD states regarding Cancer Drugs Fund (CDF) considerations that *"the Committee heard from the company that it preferred pembrolizumab to be made available via routine commissioning".* This statement, although accurate, is misleading in the sense that MSD, as a responsible company that always aims to provide access to patients to the most innovative treatments, would consider the option of a recommendation into the CDF, MSD expects the availability of a final data cut from the KEYNOTE-045 study in [redacted].

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9. Pickard AS, Jiang R, Lin HW, et al. Using Patient-reported Outcomes to Compare Relative Burden of Cancer: EQ-5D and Functional Assessment of Cancer Therapy-General in Eleven Types of Cancer. Clin Ther 2016;**38**(4):769-77.
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Pembrolizumab for previously treated advanced or metastatic urothelial cancer

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments: 5pm on Thursday 24 August 2017
Email: TACommD@nice.org.uk/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	Fight Bladder Cancer
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

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.

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1	We are pleased that NICE has concluded that the clinical trial evidence shows that pembrolizumab significantly improves overall survival compared with docetaxel and paclitaxel for people with locally advance or metastatic urothelial carcinoma and that Pembrolizumab meets NICE's criteria to be considered a life-extending treatment at the end of life. However, we are disappointed that there is no agreement on the cost effectiveness of the treatment between NICE and the Company submission. It appears that this decision is based on the evaluation of the data provided so we would hope that an early reconsideration can be made if/when further data can be provided by the company.

Insert extra rows as needed

Checklist for submitting comments

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

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

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

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	BUG-NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]

Pembrolizumab for previously treated advanced or metastatic urothelial cancer

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Name of commentator person completing form:	[redacted]
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	The BUG-NCRI-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. We are concerned that the committee acknowledged the utility of pembrolizumab in its licensed setting ; that it significantly improves overall survival significantly compared to standard taxane based chemotherapy,, and meets the criteria from NICE to be considered a life extending treatment at the end of life, extending life by more than 3 months yet does not recommend its use. Pembrolizumab was compared in the keynote-045 study with a comparator arm that would reflect current UK practice. In addition to the improvement in overall survival (estimated OS rate at 1 year 39.8% compared with 26.9% for chemotherapy, the one year progression free survival rate was three times greater in the pembrolizumab arm (16.8%) compared to 6.2 % in the chemotherapy arm. Fewer patients deteriorated with a prolonged time to deterioration in the pembrolizumab arm (HR 0.66). Slowing clinical deterioration means reduced cost for primary care input, palliative interventions, such as radiotherapy, ureteric stents with attendant hospital admissions, blood transfusions for haematuria etc. Other trials with this agent have shown global improvements or maintenance in HRQoL measurements compared with chemotherapy, and in particular an improvement in global health status from baseline compared to week 15 (pembrolizumab 6.9 improvement compared with -0.9 for chemotherapy). Whilst these trials with HRQoL domains were in the lung cancer population, there is commonality with urothelial cancer in that these lung cancer patients are usually smokers with the same smoking related comorbidities as urothelial cancer There has been no improvement in survival from metastatic bladder cancer for 20 years. Pembrolizumab improves survival in a group with an unmet need, fulfils end of life criteria, and is the first agent to show such in a phase 3 randomised trial in a tumour where previous survival gains have been lacking. This is reflected in the lack of previous bladder cancer review at NICE with one previous phase 3 drug being reviewed (negatively) in the last 15 years.

Insert extra rows as needed

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Consultation on the appraisal consultation document – deadline for comments: 5pm on Thursday 24 August 2017
Email: TACommD@nice.org.uk/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):	[**Rhona McMenemin/British Uro-Oncology Group**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**none**]

Pembrolizumab for previously treated advanced or metastatic urothelial cancer

NICE National Institute for Health and Care Excellence

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Name of commentator person completing form:	[Rhona McMenemin]
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.
Example 1	We are concerned that this recommendation may imply that ……..
1	P3 “Life expectancy for people with locally advanced or metastatic urothelial carcinoma is less than 24 months” – I would agree it is upfront, but in the second line setting where this indication is being appraised overall survival is around 5-7 months.
2	P3 “Pembrolizumab is likely to extend people’s lives by more than 3 months” – just clarifying this was the improvement in median survival. As in all studies, patients who respond will do better than the median improvement in the trial population and this is what is explained to patients in a real life setting. 44% of patients with pembro were alive at one year, this is often more meaningful in settings where patient survival is only a few months, as stated above (and was often used in lung cancer studies for this reason)
3	P4 ”Results were not reliable” – it is more that response were reported in all subgroups, and as per KEYNOTE 52, responders and non responders could not be easily separated. It should be stressed that there are similar issues in kidney cancer, while it has been easier to identify subgroups based on PD-L1 testing in lung cancer
4	P5 “The condition and current treatments” – it should also be noted that patients with PS 2 who dominate this group (Payne et al 2012) were eligible for this study and were included, albeit the numbers were low, They are often excluded from clinical trials, so this did reflect a more real life population.
5	P6 “Comparators” – Reinduction (rechallenge) platin therapy is usually used when there is relapse or progression ideally after 12/12, and therefore maximises potential therapies in these patients keeping other agents in reserve for use thereafter. Vinflunine in Europe has been approved and has been the standard of care for nearly 10 years, based on the only RCT and to date the highest level of evidence in this setting prior to KEYNOTE 45. Vinflunine has been used in the UK, (VICTOR – Hussein et al) but is not funded which is the main reason it is not in current practice.
6	P9 “improves overall survival but not PFS” – while this is true, it is not clinically meaningful and I agree with the original paper that this is not a surrogate marker for response in this setting, unlike other treatments e.g. Sunitinib in mRCC which was licensed on this basis.

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

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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.

Dear Kate,

Re. Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Please find below requested cost-effectiveness analysis results including the latest available cut-off data from KEYNOTE-045 (18 January 2017) incorporating [redacted] simple discount as per the signed CAA.

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

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

Kind regards,

[redacted]

"The technical team noted that the additional trial evidence submitted prior to the ACD publication did not incorporate the committee's preferred assumptions. NICE would expect the following assumptions to be incorporated:

- excluding the vinflunine data from utilities (see section 3.17)
- pooling utilities across treatment arms by progression state (see sections 3.16 to 3.17)
- using an updated algorithm to calculate age-related disutility (see section 3.16)
- changing the proportion of people having docetaxel and paclitaxel to UK market share.

A key uncertainty for committee was the assumptions around the extrapolation modelling. NICE would expect to see full sensitivity analyses around the following:

- The choice of cut-off point at which to extrapolate the overall survival trial data (see section 3.13) – please note that the ERG stated that a cut-off at week 16 (the point at which the cumulative hazards cross) would be their choice, but were unable to explore this in the economic model.
- Choice of parametric curve to extrapolate overall survival (see section 3.14).

In addition the committee noted that the economic model excludes rare but potentially serious adverse events that are specific to immunotherapy (see section 3.11) and assume an implausible lifetime continued treatment effect (see section 3.15). NICE would prefer to see scenario analyses which explore these assumptions around the new company base case."

MSD's base-case

- **Deterministic analysis results**

Table **1** presents our preferred base-case deterministic results based on the 18 Jan 2017 data cut. Our preferred base-case is based on the following assumptions:

- Two-stage for treatment switching
- OS cut-off point at 40 weeks with log-normal distribution for extrapolation
- PFS cut-off point at 21 weeks with Gompertz distribution for extrapolation
- Weibull and GenGamma distributions for ToT of pembrolizumab and UK SOC
- Pooled (pembrolizumab and control group) utility values based on time-to-death 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	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£64,867	2.81	2.02	£43,620	0.90	£48,601

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

- **Probabilistic analysis results**

Probabilistic sensitivity analysis was undertaken using 1,000 samples. The results are presented in Table **2. Probabilistic results for MSD base-case (discounted)**, below.

Table 2. Probabilistic results for MSD base-case (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,644	1.15	1.65			
Pembrolizumab	£65,351	2.04	2.84	43,706	0.90	£48,731
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

"The technical team noted that the additional trial evidence submitted prior to the ACD publication did not incorporate the committee's preferred assumptions. NICE would expect the following assumptions to be incorporated:

- excluding the vinflunine data from utilities (see section 3.17)
- pooling utilities across treatment arms by progression state (see sections 3.16 to 3.17)
- using an updated algorithm to calculate age-related disutility (see section 3.16)
- changing the proportion of people having docetaxel and paclitaxel to UK market share.

Committee's preferred assumptions

- **Deterministic analysis results**

Table 3 presents the deterministic results based on 18 Jan 2017 data cut incorporating the Committees preferred assumptions to the MSD base-case:

- Excluding the vinflunine data from utilities
- Pooling utilities across treatment arms by progression state
- Using an updated algorithm to calculate age-related disutility
- Changing the proportion of people having docetaxel and paclitaxel to UK market share
    - Please note that the most current UK market share proportions (re-adjusted by the exclusion of platinum-containing chemotherapy) have changed since the CS and are currently as follows:
        - Paclitaxel – 39%

        - Docetaxel – 61%
    - This has been incorporated into the Committees preferred assumptions

Table 3. Deterministic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,193	1.62	1.05			
Pembrolizumab	£64,867	2.81	1.93	£43,674	0.88	£49,644
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

- **Probabilistic analysis results**

Probabilistic sensitivity analysis was undertaken using 1,000 samples. The results are presented in Table 4. **Probabilistic results** below.

Table 4. Probabilistic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,591	1.65	1.08			
Pembrolizumab	£65,351	2.84	1.95	£43,760	0.87	£50,478
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

A key uncertainty for committee was the assumptions around the extrapolation modelling. NICE would expect to see full sensitivity analyses around the following:

- The choice of cut-off point at which to extrapolate the overall survival trial data (see section 3.13) – please note that the ERG stated that a cut-off at week 16 (the point at which the cumulative hazards cross) would be their choice, but were unable to explore this in the economic model.
- Choice of parametric curve to extrapolate overall survival (see section 3.14)

16-week time point for extrapolation

The goodness of fit data presented below in Table 5. **Goodness-of-fit statistics based on the extrapolations using data beyond the 16-week cut-off, for pembrolizumab and UK SOC** is based on analysis using a 16-week time point for extrapolation.

For both the pembrolizumab and the UK SOC treatment arms, the curves presenting the closest statistical fit to the trial data are the Gompertz, the Llogistic and the Lnormal, in order of best fit. In the ACD, the Committee concluded that they would expect the 5 year overall survival in the UK SOC arm to be within the range of estimates used by the ERG (2-3%) and the company (9-11%). Based on this range, extrapolation using Gompertz is not appropriate as it estimates a 5-year OS of 11.6% (Table **6**) which is outside the range considered plausible by the Committee. Furthermore, using the Exponential and Weibull curves underestimates 5-year OS estimates of 0.2% and 1.3% respectively. The GenGamma is the curve with the second highest AIC/BIC values indicating its poor fit to the trial data, and so despite a clinically plausible 5 year OS of 3.8%, it is not appropriate for extrapolation. Therefore, based on both the goodness of fit and the clinical plausibility of the 5-year OS estimates, the most plausible curve for extrapolation at 16 weeks is the Llogistic. The Lnormal may also be considered appropriate; however its statistical fit to the trial data is second to that of the Llogistic curve.

Table 5. Goodness-of-fit statistics based on the extrapolations using data beyond the 16-week cut-off, for pembrolizumab and UK SOC

Fitted Function	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	730.2	733.1	734.3	737.1
Weibull	726.7	732.6	731.7	737.2

Gompertz	724.6	730.4	729.2	734.8
Llogistic	725.2	731	729.4	735
Lnormal	725.8	731.6	731	736.5
GenGamma	727.2	736	731.7	740

Table 6. Overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
UK SOC						
1-year	31.8%	31.5%	30.8%	30.4%	30.0%	30.8%
3-year	9.4%	12.6%	17.0%	15.8%	16.5%	14.8%
5-year	0.2%	1.3%	6.6%	6.2%	11.6%	3.8%
10-year	0.0%	0.0%	2.8%	3.0%	10.5%	0.9%
Pembrolizumab						
1-year	49.9%	48.3%	46.9%	47.3%	46.5%	47.3%
3-year	26.9%	30.3%	33.1%	31.8%	33.7%	32.0%
5-year	4.2%	9.8%	18.7%	16.6%	28.0%	15.6%
10-year	0.2%	2.1%	11.1%	9.5%	25.3%	7.5%

Table**TABLE** 7 compares the outcomes of the pembrolizumab and UK SOC arms of the KEYNOTE-045 trials with the outcomes from the model. Both the 16-week and the 40-week time points for extrapolation produce model estimates which are similar to the results of the trial.

Table 7. Comparison of model and trial outcomes

	Pembrolizumab			**UK SOC**		
Outcome	**MSD-base case (40 week, Lnormal)**	**ERG request (16 week, Llogistic)**	**KEYNOTE-045**	**MSD-base case (40 week, Lnormal)**	**ERG request (16 week, Llogistic)**	**KEYNOTE-045**
Median PFS (months)	2.3	2.3	2.1	3.4	3.4	3.2
6-month PFS	28.6%	27.9%	28.8%	22.8%	24.7%	22.7%
Median OS (months)	10.3	10.8	10.3	7.1	6.7	6.9

6-month OS	64.1%	64.4%	63.9%	54.8%	54.0%	54.5%
1-year OS	45.5%	47.3%	43.9%	29.6%	30.4%	30.2%
2-year OS	30.0%	31.8%	-	16.4%	15.8%	-
5-year OS	16.7%	16.6%	-	7.8%	6.2%	-
10-year OS	9.9%	9.5%	-	4.2%	3.0%	-

Cost-effectiveness analysis results incorporating the Committees preferred assumptions at a 16 week time point for extrapolation

- **Deterministic analysis results**

Table Table 8 presents the deterministic results based on a 16-week time point for extrapolation using the Llogistic curve and incorporating the Committees preferred assumptions:

- Excluding the vinflunine data from utilities
- Pooling utilities across treatment arms by progression state
- Using an updated algorithm to calculate age-related disutility
- Changing the proportion of people having docetaxel and paclitaxel to UK market share
    - As above, please note this has been updated in line with the most recent market shares.

Table 8. Deterministic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£19,814	1.42	0.94	-	-	-
Pembrolizumab	£64,185	2.72	1.88	£44,370	0.94	£47,040
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

- **Probabilistic analysis results**

Probabilistic sensitivity analysis was undertaken using 1,000 samples. The results are presented on Table 9 below.

Table 9. Probabilistic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	20,133	1.44	0.96	-	-	-
Pembrolizumab	64,768	2.77	1.90	£44,636	0.94	£47,270
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

In Table 10, MSD have also explored the impact of the 16 week cut off on the ICER when using MSDs preferred assumptions (excepting the 40 week time point for extrapolation) and including the Committees preferred assumptions using all plausible parametric curves for extrapolation.

Table 10. Comparison of impact of assumptions on the incremental cost-effectiveness ratio at a 16-week time point

Parametric curve	Basecase	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Llogistic	MSDs assumptions	UK SOC	£19,868	1.42	0.97	-	-	-
		Pembrolizumab	£64,185	2.72	1.96	£44,317	0.99	£44,908
	Including the Committees preferred assumptions	UK SOC	£19,814	1.42	0.94	-	-	-
		Pembrolizumab	£64,185	2.72	1.88	£44,370	0.94	£47,040
Lnormal	MSDs assumptions	UK SOC	£19,821	1.42	0.97	-	-	-
		Pembrolizumab	£65,799	2.94	2.12	£45,978	1.15	£39,884
	Including the Committees preferred assumptions	UK SOC	£19,767	1.42	0.93	-	-	-
		Pembrolizumab	£65,799	2.94	2.02	£46,032	1.09	£42,352
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In addition the committee noted that the economic model excludes rare but potentially serious adverse events that are specific to immunotherapy (see section 3.11) and assume an implausible lifetime continued treatment effect (see section 3.15). NICE would prefer to see scenario analyses which explore these assumptions around the new company base case.

MSD base-case

- Two-stage for treatment switching
- OS cut-off point at 40 weeks with log-normal distribution for extrapolation
- PFS cut-off point at 21 weeks with Gompertz distribution for extrapolation
- Weibull and GenGamma distributions for ToT of pembrolizumab and UK SOC
- Pooled (pembrolizumab and control group) utility values based on time-to-death approach

Adverse events of special interest (AEOSI)

In line with previous NICE HTA submissions of pembrolizumab and other immunotherapy agents, only Grade 3+ AEs with an incidence of at least 5% in any of the arms were included in the cost-effectiveness model (Table 11).

In line with this approach, MSD has included only Grade 3+ AEOSIs in the requested analysis. MSD has explored the impact of AEOSI's in the cost-effectiveness analysis by conservatively incorporating Grade 3+ AEOSI's only in the pembrolizumab arm (

Table **12**), and also by incorporating Grade 3+ AEOSI's into both the pembrolizumab and the UK SOC arms (Table 13).

Table 11. AEOSI's in the As-Treated Population (KEYNOTE-045)

Event	Pembrolizumab Group (N = 266)		Chemotherapy Group (N = 255)		UK SOC Group [redacted]	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4 or 5
	Number of patients (percent)					
AEOSI's						
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)	[redacted]	[redacted]
Hypothyroidism	17 (6.4)	0	3 (1.2)	0	[redacted]	[redacted]
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0	[redacted]	[redacted]
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0	[redacted]	[redacted]
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0	[redacted]	[redacted]
Infusion reaction	2 (0.8)	0	10 (3.9)	0	[redacted]	[redacted]
Nephritis	2 (0.8)	2 (0.8)	0	0	[redacted]	[redacted]
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)	[redacted]	[redacted]
Thyroiditis	2 (0.8)	0	0	0	[redacted]	[redacted]
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0	[redacted]	[redacted]

Myositis	0	0	1 (0.4)	1 (0.4)	[redacted]	[redacted]

Table 12. Deterministic results including Grade 3+ AEOSIs in pembrolizumab arm only

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,247	1.62	1.12			
Pembrolizumab	£64,926	2.81	2.02	£43,679	0.90	£48,667
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 13. Deterministic results including Grade 3+ AEOSIs in both treatment arms

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,251	1.62	1.12			
Pembrolizumab	£64,926	2.81	2.02	£43,675	0.90	£48,661
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Long term treatment effect

Table 14. Impact of lifetime treatment effect on ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Lifetime treatment effect						
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£64,867	2.81	2.02	£43,620	0.90	£48,601
Continued treatment effect over 10 years						
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£64,655	2.78	2.00	£43,408	0.88	£49,478

Continued treatment effect over 5 years						
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£64,066	2.70	1.94	£42,819	0.82	£52,156
Continued treatment effect over 3 years						
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£63,397	2.62	1.88	£42,150	0.75	£55,833

The Evidence Review Group, Warwick Evidence, would like further clarification on the clinical and cost effectiveness data submitted as part of the MSD's response to consultation.

1. Please provide an update (as of data-cut off January 2017) on the number of people still ongoing treatment in both the control (docetaxel, paclitaxel, or vinflunine group) and pembrolizumab arms of the KEYNOTE trial.

   Based on the updated data cut-off Jan 2017, 33 patients are still ongoing in the pembrolizumab arm while no patients are still on treatment in the control arm.

2. Please provide the individual patient data (IPD) for both progression-free survival and overall survival for pembrolizumab and UK standard of care. We would like to know when both censoring and treatment switching occurred in the analysis. This will help the ERG to re-construct the Kaplan-Meier plots.

   Please refer to Appendix for the requested individual patient level data.

3. Please include updated plots of the log cumulative hazards of pembrolizumab and UK SOC for overall survival (OS) and progression-free survival (PFS), e.g. updated versions of Figures 36 and 38 of the original submission. This will help us to evaluate alternative data cut-offs and thus inform which parametric model is the most appropriate.

   Please find below the updated OS and PFS cumulative hazard plots in Figure 1 and Figure 2, respectively.

   Figure 1. Updated cumulative hazard plot of OS for pembrolizumab and UK SOC arm

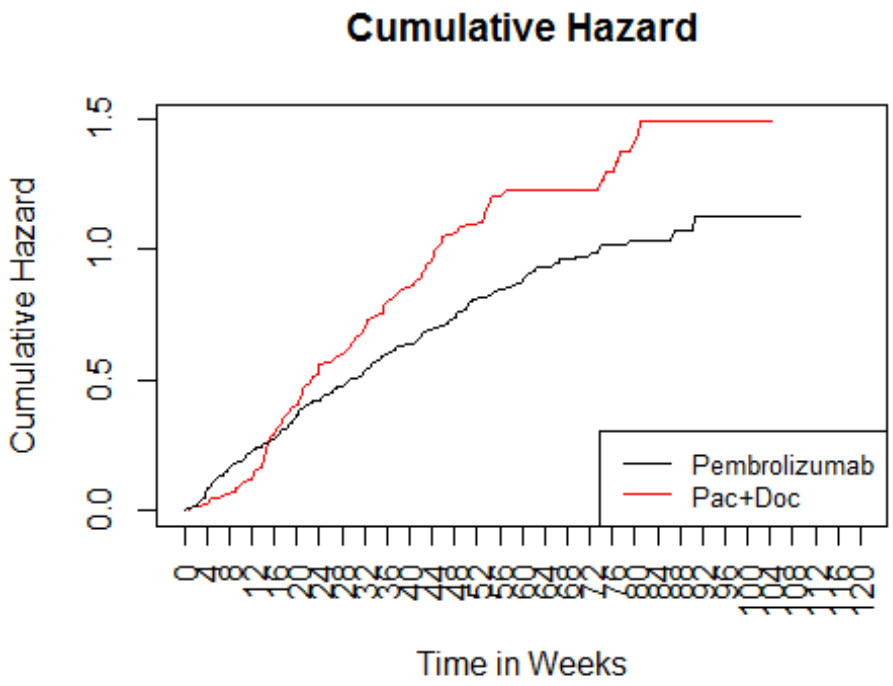
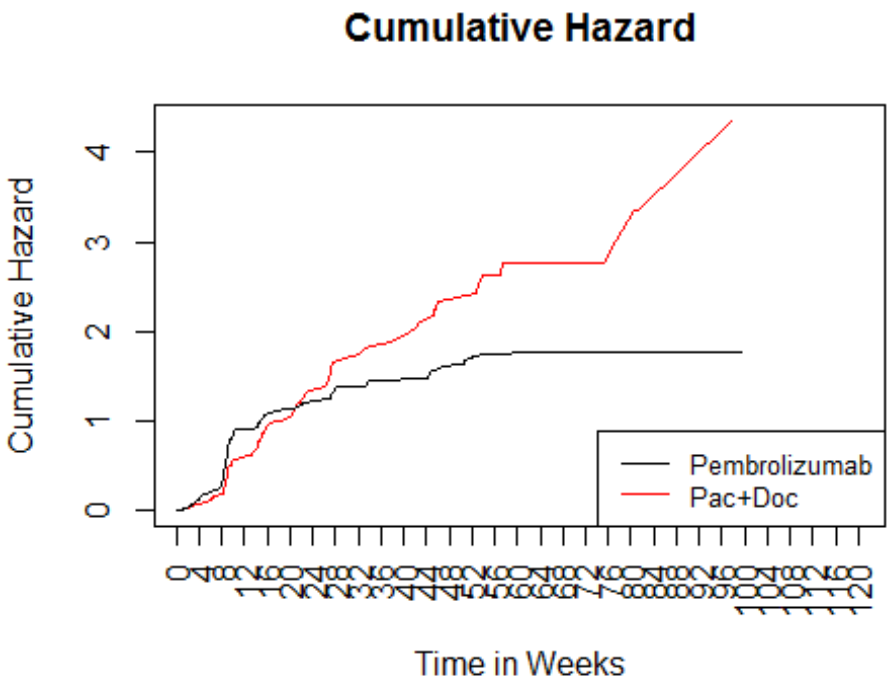


Figure 2. Updated cumulative hazard plot of PFS for pembrolizumab and UK SOC arm



4. In addition, please provide a separate plot for each 9wk-40wk time-point of both PFS and OS of the log cumulative hazard overlaid with the predicted cumulative hazard from each parametric fit. (8 plots in total, see for example: https://www.dovepress.com/cr_data/article_fulltext/s107000/107498/img/CEOR_107498_S002.jpg) [this will provide more information for model selection]

   Please find below the requested plots for PFS and OS for the cut-off points that were updated based on the Jan 2017 cut-off date. Please refer to Figure 3 for the PFS plots based on a 21-week cut-off point for extrapolation. Regarding the OS plots, please refer to Figure 4, Figure 5 and Figure 6 for the OS plots at 16, 24 and 40 weeks cut-off points, respectively.

Figure 3. PFS log cumulative hazard plot overlaid with the predicted cumulative hazard from each parametric fit at 21-week cut-off point

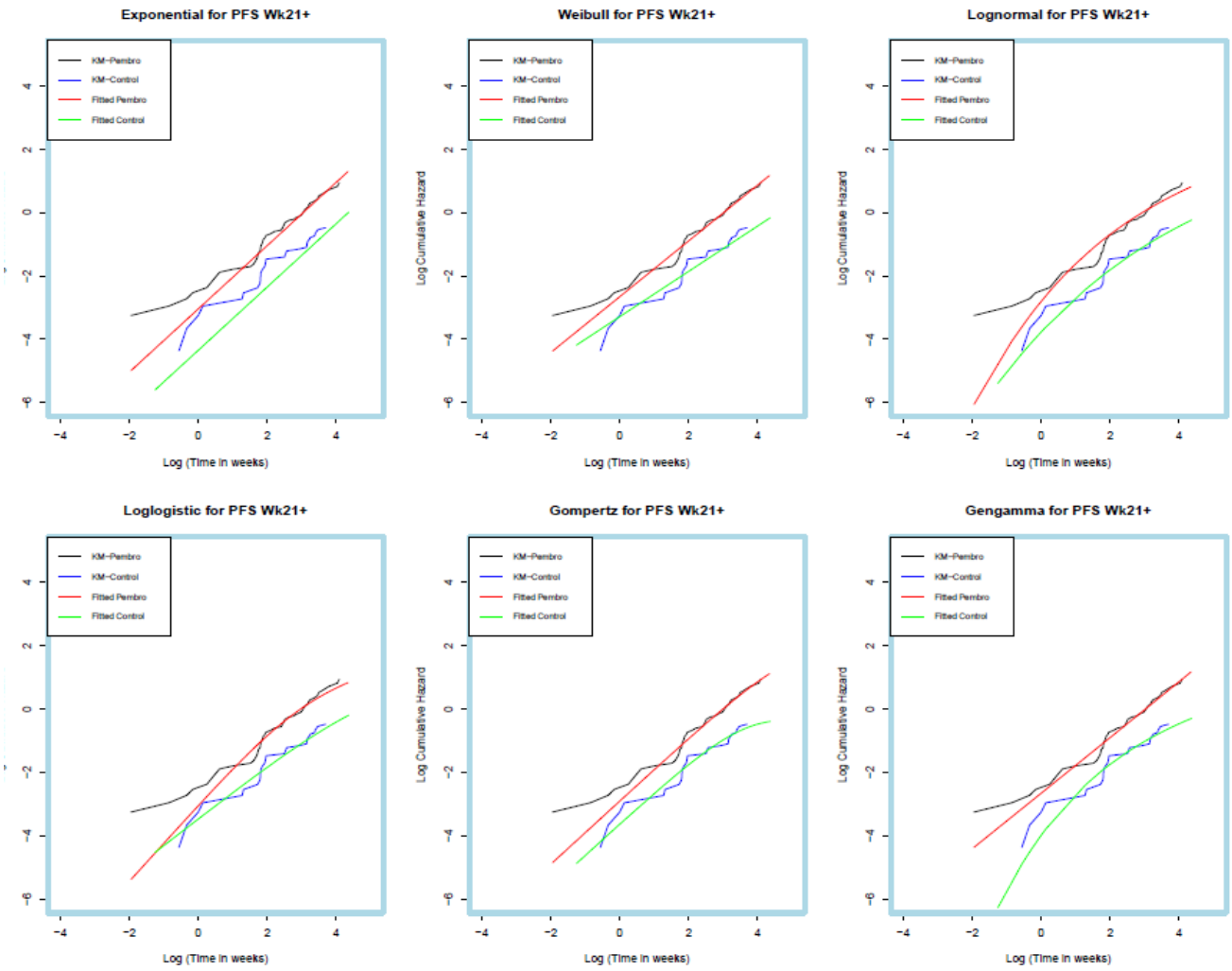


Figure 4. OS log cumulative hazard plot overlaid with the predicted cumulative hazard from each parametric fit at 16-week cut-off point

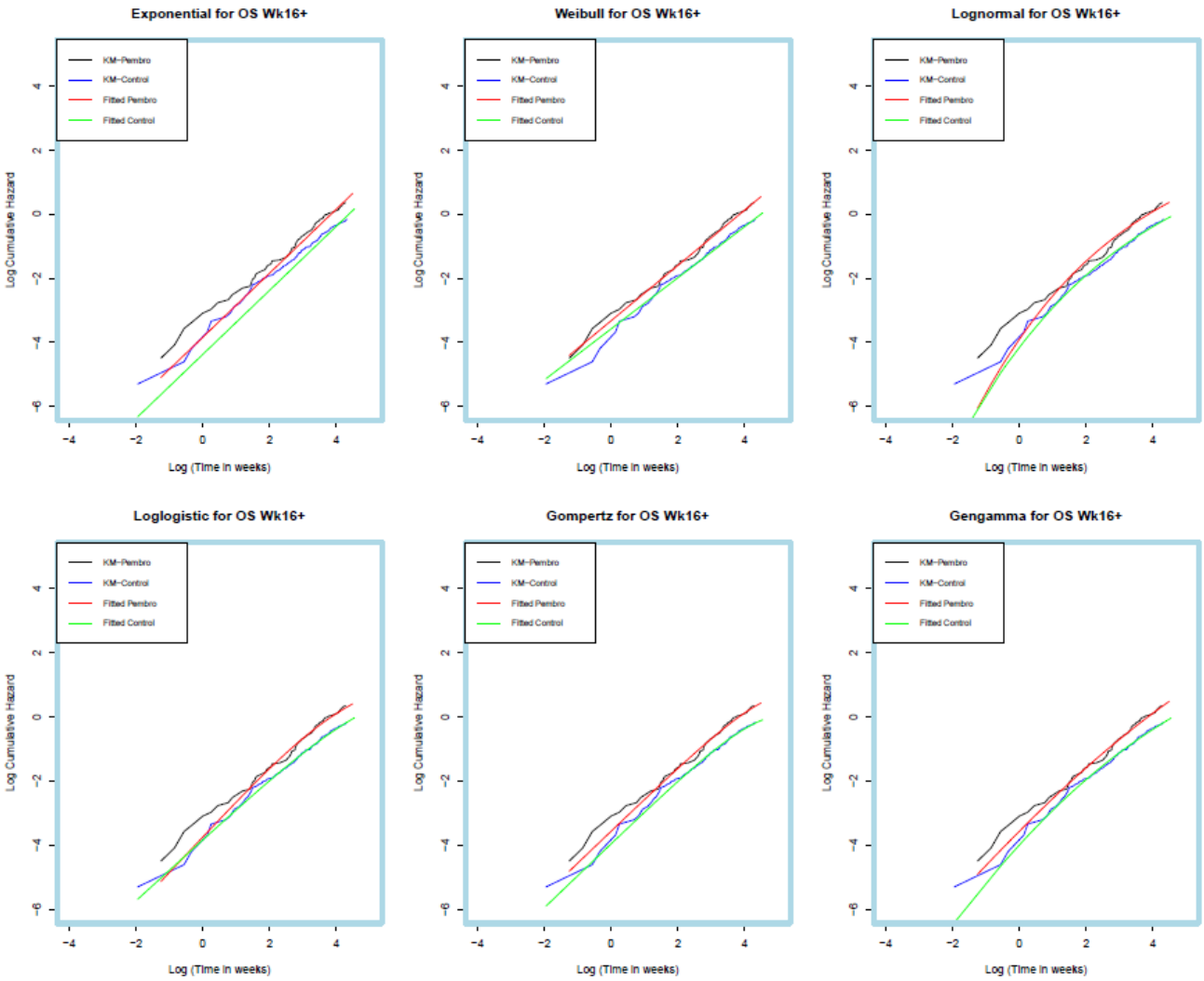


Figure 5. OS log cumulative hazard plot overlaid with the predicted cumulative hazard from each parametric fit at 24-week cut-off point

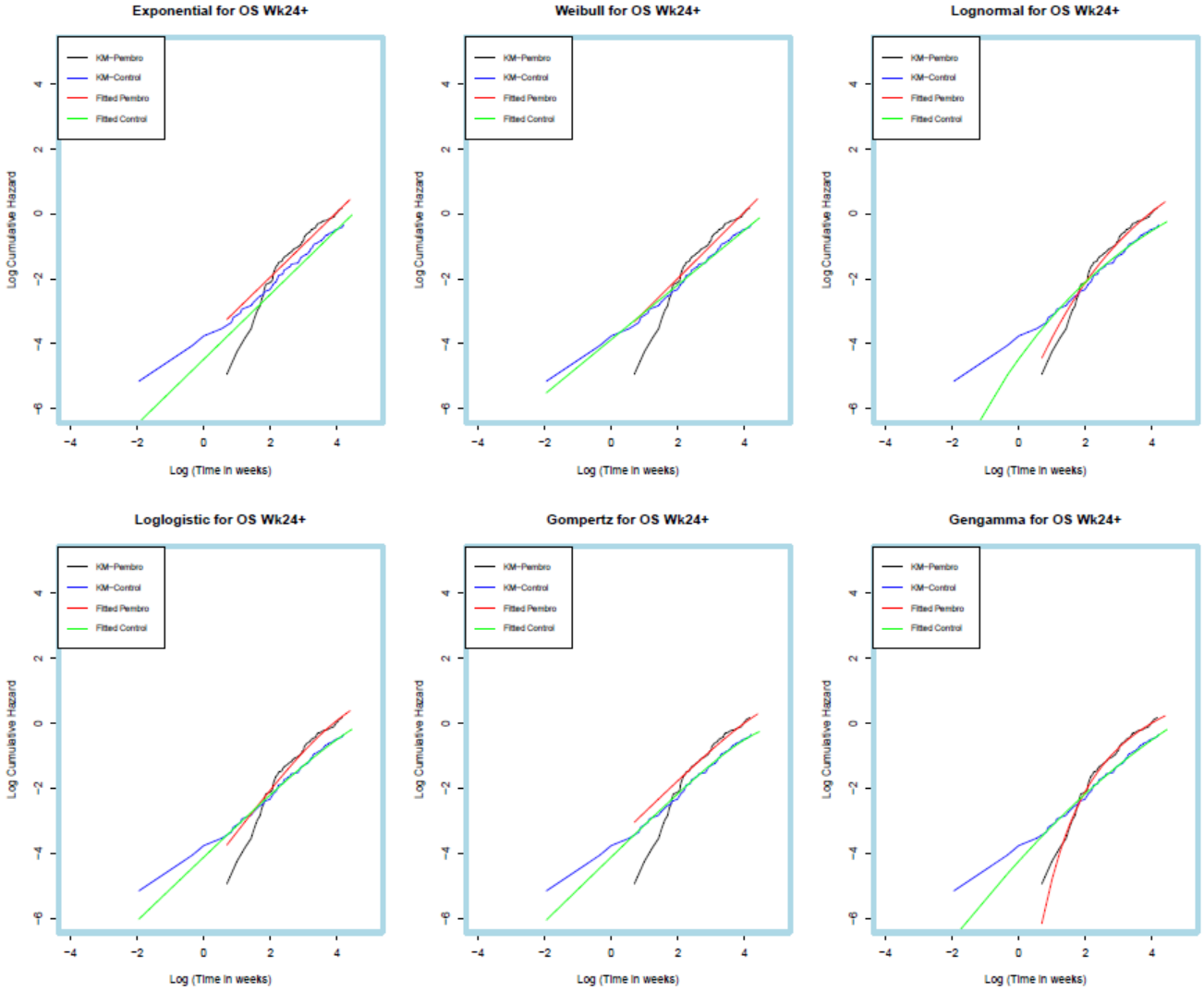
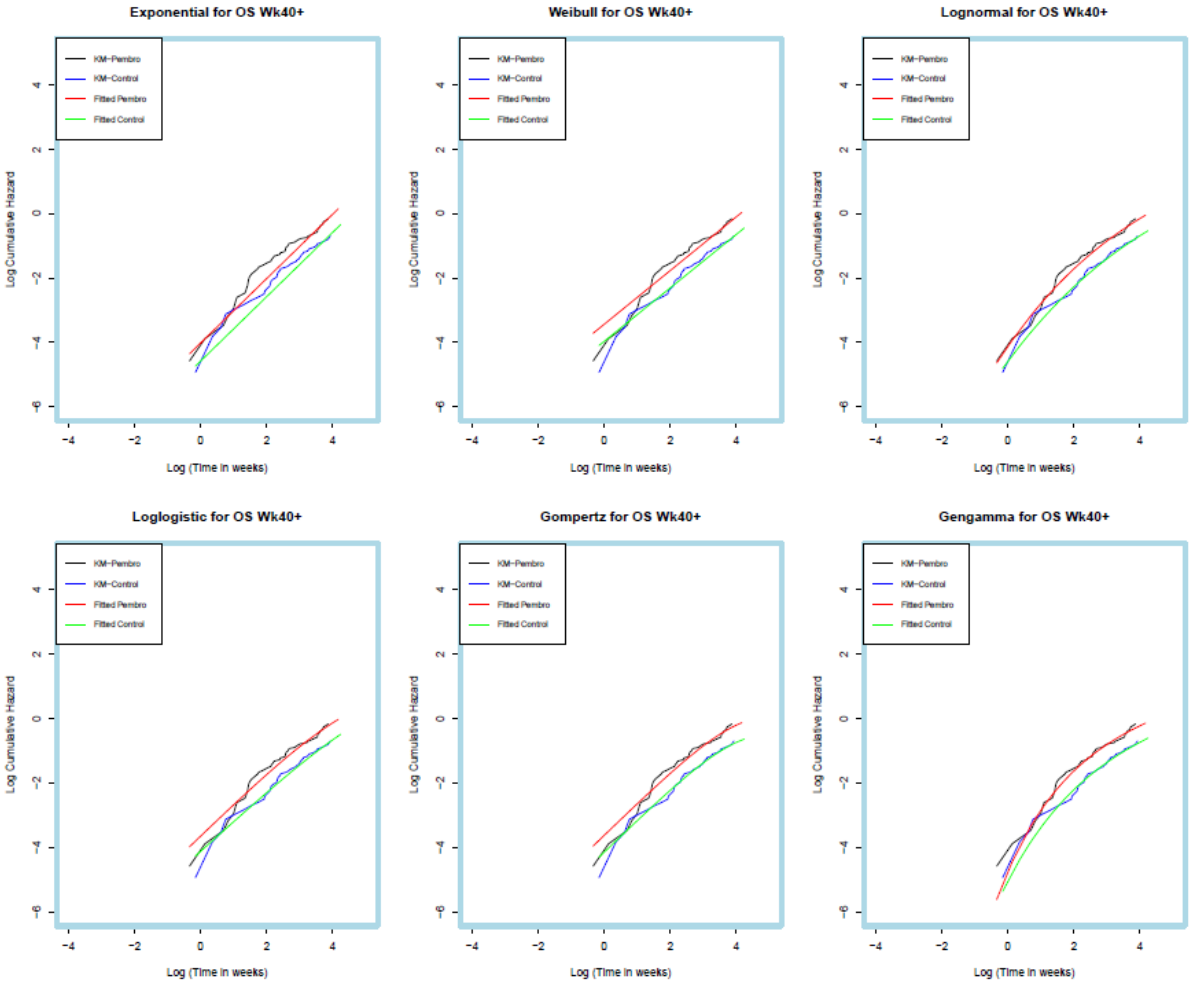


Figure 6. OS log cumulative hazard plot overlaid with the predicted cumulative hazard from each parametric fit at 40-week cut-off point



5. Please provide updated AIC/BIC for OS, PFS and Time on treatment (ToT) for Scenarios 1 (pembrolizumab [Overall]) and 8 (Paclitaxel+Docetaxel [Overall, with 2 stage adjustment]) for every parametric model and at every time-point (16-week, 24-week etc) (i.e. row 352 and below of the KN045_2 Tab of the economic model). It is currently unclear to the ERG which scenarios have been updated.

   Please find below the AIC/BIC tables for OS, PFS and ToT for the cut-off points that have been updated based on the new data cut-off date (Jan 2017).

Table 1. Goodness-of-fit measures of OS for pembrolizumab and UK SOC

	Pembrolizumab						UK SOC (two-stage adjustment)					
	16-Week		24-Week		40-Week		16-Week		24-Week		40-Week	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	730.2	733.1	867.6	870.7	515.6	518.5	734.3	737.1	476	478.5	243.2	245.2
Weibull	726.7	732.6	866.6	873	515.6	521.4	731.7	737.2	478	482.9	241.8	245.8
Gompertz	724.6	730.4	863.9	870.2	512.6	518.5	729.2	734.8	475.8	480.8	241.5	245.6
Llogistic	725.2	731	864.7	871	514.1	519.9	729.4	735	473.3	478.2	240.9	245
Lnormal	725.8	731.6	866	872.4	512	517.8	731	736.5	470.1	475.1	239.1	243.2
GenGamma	727.2	736	867	876.5	513.2	522	731.7	740	468.4	475.8	239.3	245.4

Table 2. Goodness-of-fit measures of PFS defined per RECIST v1.1 as assessed by BICR for pembrolizumab and UK SOC at 21-week

	Pembrolizumab		UK SOC	
	21-Week		21-Week	
	AIC	BIC	AIC	BIC
Exponential	376.6	379	308.4	310.3
Weibull	373.1	377.9	308.9	312.5
Gompertz	367.6	372.3	309.7	313.3
Llogistic	371	375.8	310.8	314.5
Lnormal	369.6	374.4	311.2	314.9
GenGamma	371.1	378.2	310.8	316.2

Table 3. Goodness-of-fit measures of ToT for pembrolizumab and UK SOC

	Pembrolizumab		UK SOC	
	21-Week		21-Week	
	AIC	BIC	AIC	BIC
Exponential	2068.8	2072.4	1145.4	1148.5
Weibull	2011	2018.2	1139.8	1146
Gompertz	2037.8	2045	1147	1153.2
Llogistic	2031	2038.2	1184	1190.2
Lnormal	2046.4	2053.6	1193.6	1199.8
GenGamma	2012.4	2023.1	1134.2	1143.6

6. Please provide evidence for the change in the UK market share of Paclitaxel and Docetaxel from the original submission.

   Please find in the uploaded Excel document the UK market shares for urothelial cancer following treatment with platinum-based chemotherapy as provided by IPSOS. Please note that the market shares are based on small sample size.

7. Please confirm that the values of total LYG and total QALYs have been erroneously reported in table 2? The NICE technical team believe the two columns are the wrong way round.

   As observed by the NICE technical team, MSD confirms that the values of total LYGs and QALYs were not reported in the respective columns.

Appendix

1.1.1 Overall Survival

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Overall Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

1.1.2 Progression-Free Survival

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Individual Patient Data for Progression Free Survival
Patients Pre-assigned to Paclitaxel or Docetaxel
KN045

Patient ID number	Treatment Arm	Comparator	Time of event or censoring (days)	Event or Censoring	Study Day of First Receipt of Subsequent Therapy
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019] – Addendum 2 following new analyses submitted by the Company after ACD

Produced by: Warwick Evidence

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Declared competing interests of the authors

Dr Maria De Santis received consultancy fees within the last 5 years from MSD, Merck, Pfizer, Roche, AstraZeneca, Pierre Fabre, Sanofi, BMS**,** Amgen, Astellas, Bayer, Celgene, Eisai, ESSA, Ferring, GSK, Ipsen, Janssen, Novartis, Dendreon, Seattle Genetics, Shionogi, Synthon, Teva and

OncoGenex. She also received reimbursement for attending a symposium and/or speaker fees from Bayer, MSD, Janssen, Astellas, Sanofi, Pierre Fabre, GSK and funds for research from Pierre Fabre.

Dr Jo Cresswell is employed by South Tees NHS Trust Hospital. South Tees is part of the Imvigor clinical trial which is a commercially funded RCT. The research costs are met by Roche. Dr Cresswell has not received any personal funding from Roche.

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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

Pembrolizumab for previously treated advanced or metastatic urothelial cancer: A Single Technology Appraisal. Warwick Evidence, 2017.

Contributions of authors

Xavier Armoiry (Senior Research Fellow) helped co-ordinate the project and the report, and conducted, reviewed and critiqued the clinical effectiveness evidence; Theodoros Mantopoulos (Research Associate) conducted, reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Daniel Gallacher (Research Associate) conducted, reviewed and critiqued the survival analysis and cost-effectiveness evidence; Peter Auguste (Research Fellow) conducted, reviewed and critiqued the survival analysis and undertook additional analyses; Jacoby Patterson (Independent Research Consultant) conducted, reviewed and critiqued the clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional analyses; Karoline Munro (Research Project Administrator) conducted, reviewed and critiqued the background section; Maria De Santis (Associate Clinical Professor) provided expert clinical advice; Joanne Cresswell (Consultant Urological Surgeon) provided expert clinical advice; Hema Mistry (Assistant Professor) co-ordinated the project and the report, and reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses.

Word count: 10,369

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

AE	Adverse Event
AEOSI	AEs of Special Interest
AIC	Akaike Information Criterion
ALK	Anaplastic Lymphoma Kinase
APaT	All Patients as Treated
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BOR	Best Overall Response
BSA	Body Surface Area
BSC	Best Supportive Care
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIS	Carcinoma In Situ
CPS	Combined Positive Score
CRD	Centre for Review and Dissemination
CR	Complete Response
CS	Company Submission
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DoR	Duration of Response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMit	Electronic Market information tool
EORTC	*European Organisation for Research and Treatment of Cancer*
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	European Union

FDA	Food and Drug Administration
FAS	Full Analysis Set
GFR	Glomerular Filtration Rate
Hb	Haemoglobin
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IPCW	Inverse Probability of Censoring Weighting
ITT	Intention-To-Treat
IVRS/IWRS	Interactive Voice Response System/ Interactive Voice and Web Response System
KM	Kaplan Meier
LS	Least Squares
LTUC	Lower Tract Urinary Cancers
LYG	Life Year Gained
MIBC	Muscle Invasive Bladder Cancer
MHRA	Medicines & Healthcare Products Regulatory Agency
mRECIST	Modified RECIST
MSD	Merck Sharp and Dohme
MVAC	Methotrexate, Vinblastine, Doxorubicin and Cisplatin
NMA	Network Meta-Analysis
NCCN	National Comprehensive Cancer Network
NMB	Net Monetary Benefit
NMIBC	Non-Muscle Invasive Bladder Cancer
NSCLC	Non-Small Cell Lung Cancer
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive Disease
PD-1	Programmed Death 1 protein
PD-L1	Programmed cell Death 1 ligand 1
PD-L2	Programmed cell Death 1 ligand 2

PFS	Progression-Free Survival
PH	Proportional Hazards
PICOS	Population Intervention Comparator Outcome Study design
PIM	Promising Innovative Medicines
PR	Partial Response
PS	Performance Score
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality Assessment
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria In Solid Tumours
RoB	Risk of Bias
RPSFT	Rank Preserving Structural Failure Time
RR	Response Rate
SD	Standard Deviation
SOC	Standard of Care
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
StD	Stable Disease
TA	Technology Appraisal
ToT	Time on Treatment
TPS	Tumour Proportion Score
TTP	Time To Progression
TTR	Time To Response
TNM	Tumour, Node and Metastases
UK	United Kingdom
US	United States
UTUC	Upper Tract Urinary Cancers
VAS	Visual Analogue Score
WTP	Willingness To Pay

Introduction

This addendum focuses primarily on the new economic analysis submitted by MSD and additional information received in response to the Evidence Review Group's (ERG) clarification questions regarding the additional data. The ERG has critically appraised the evidence used in the analysis and examined the company's economic model.

The addendum starts with a re-cap/summary of the key methods and results (base-case, sensitivity analyses, patient access scheme and ERG base-case analyses) as reported in the original submission and in our ERG report, followed by a summary of changes in the methods and results in the current submission.

The ERG then provides a critique of the two main submission documents, using the NICE reference case to assess the overall quality and validity of these new analyses.

Finally, the ERG presents their new preferred base case analysis, alongside justification for the various decisions made.

The ERG received new documentation that included:

- Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma [ID1019] – Company Response to Appraisal Consultation Document (ACD)
- Re: Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019] which was sent from the Company which included the additional data and analyses.

Other documents submitted and considered in the model selection process:

- Pembrolizumab versus Paclitaxel, Docetaxel, or Vinflunine for recurrent, advanced urothelial cancer: mature results from the phase 3 KEYNOTE-045 trial[1]
- ID1019 Pembrolizumab MSD post ACD clarification response 19092017AS [CIC]
- ID1019 Pembrolizumab MSD UK urothelial cancer market shares 19092017AS [CIC]
- Electronic version of the most recent *de novo* survival Markov model built in Microsoft Excel by MSD

1. New economic analyses submitted by MSD

1.1. Summary of the original Company submission and ERG's original exploratory analyses

Original Company submission

The company submitted a *de novo* partitioned survival model comparing pembrolizumab with UK SOC i.e. investigator's choice of paclitaxel or docetaxel. A weekly cycle length and a lifetime horizon were used. The model had three defined health states: progression-free, progressed disease and death. All patients in the pembrolizumab and UK SOC arms started in the progression-free health state.

The population modelled in this submission were patients with metastatic or locally advanced/unresectable urothelial cancer which has recurred or progressed following platinum containing chemotherapy. Data for pembrolizumab and UK SOC arms came from the KEYNOTE-045 trial.[2] For the UK SOC, overall survival (OS) was estimated by adjusting for treatment switching using a two-stage adjustment method. OS and progression-free survival (PFS) for pembrolizumab and UK SOC were both derived using a piecewise modelling approach:

- For OS, KEYNOTE-045 Kaplan-Meier data was used for the initial period of 40 weeks with a log-normal distribution fitted to data beyond 40 weeks.
- For progression-free survival, KEYNOTE-045 Kaplan-Meier data was used for the first 21 weeks, with an exponential distribution fitted to data beyond 21 weeks.

Quality of life values were obtained using EQ-5D-3L from the KEYNOTE-045 trial. For the base-case analysis, utility values were estimated based on time-to-death. Time-to-death was categorised in the following groups: 360 or more days to death, 180 to 360 days to death, 90 to 180 days to death, 30 to 90 days to death, and under 30 days to death. The company included data for patients receiving vinflunine in the estimation of utility values, however, vinflunine is not currently recommended by NICE.[3] Quality of life losses associated with adverse events and ageing were included in the base-case analysis.

A National Health Service (NHS) and Personal Social Services (PSS) perspective was adopted for the costs. An annual discount rate of 3.5% was used for both costs and outcomes. Costs of treatment with pembrolizumab were provided by the company. Pembrolizumab treatment was assumed to continue until disease progression, unacceptable toxicity or a maximum of 24 months of uninterrupted

treatment (approximately 35 cycles). The treatment effect was assumed to persist for the lifetime of the model. For UK SOC, patients received treatment for a maximum of six cycles to reflect UK clinical practice. To estimate the duration of treatment in the pembrolizumab and UK SOC arms, time on treatment data from KEYNOTE-045 was used. UK SOC treatment costs were obtained from the latest electronic market information tool (eMit). The model also included costs for adverse events, routine care and terminal care.

In Table 1 we present MSD's original base-case and probabilistic results. Base-case results show that pembrolizumab is expected to cost approximately an additional £39,100 and expected to generate an additional 0.85 QALYs with an incremental cost-effectiveness ratio (ICER) of approximately £45,800 per QALY. Probabilistic results in terms of cost per QALY gained were similar to the base-case deterministic results.

Table 1: Original submission base-case results (discounted with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Deterministic results					
UK SOC	£20,938	1.10	-	-	-
Pembrolizumab	£60,053	1.95	£39,115	0.85	£45,833
Probabilistic results					
UK SOC	£21,367	1.13	-	-	-
Pembrolizumab	£60,634	1.98	£39,267	0.85	£46,194

ERG's preferred exploratory analyses

In the exploratory analyses presented in our report, the ERG made a number of modifications to the model assumptions made by the company.

Overall changes:

- Excluding vinflunine patients from the estimation of utility values.
- Using utility values based on progression status rather than time to death.
- Using adverse event disutility values and pooled utility values
- Changing source of estimating age-related utility decrements.
- Estimating the cost of UK SOC based on the UK market share of docetaxel and paclitaxel.
- Use a cut-off point of 24 weeks for the OS modelling approach.
- Use a log-logistic distribution for OS modelling for pembrolizumab and UK SOC.

The ERG presented a scenario with a preferred base-case analysis for pembrolizumab versus UK SOC. The ICER increased slightly compared with the CS submission, resulting in a deterministic ICER of £51,235 per QALY including a patient access scheme (PAS).

The ERG also carried out some exploratory analyses using the ERG preferred base-case, and noted that the vast majority (84% to 97%) of benefits in terms of life years gained was from the extrapolated data rather than the observed data.

1.2. Summary of the current submission and results

In response to ACD, the company submitted new economic analyses. These are based on the same partitioned survival model that was presented in the original submission. The choice of survival models relies on more mature results (cut-off date January 2017 vs September 2016 i.e four months of additional data than in the original submission).

As in the original submission, OS and PFS for pembrolizumab and UK SOC were both derived using a piecewise modelling approach, and for OS, the company used the KEYNOTE-045 Kaplan-Meier data for the initial period of 40 weeks with a log-normal distribution fitted to data beyond 40 weeks. However, for PFS, KEYNOTE-045 Kaplan-Meier data was used for the first 21 weeks, with a Gompertz distribution fitted to data beyond 21 weeks, whereas in the original submission an exponential distribution was fitted to data beyond 21 weeks.

As in the original submission, utility values were estimated based on time-to-death and data for patients receiving vinflunine were included in the estimation of utility values.

In response to the ERG's critique, AC meeting and in light of slightly more mature overall and progression-free survival data, the company made some changes to key model input parameters and assumptions. In Table 2, these changes are outlined.

Table 2: Key changes to the economic model

Parameters	Original submission	Current submission
Observed data	Kaplan-Meier data is based on observed data until September 2017 cut-off (14 months).	Model was updated to include OS and PFS data up until January 2017 cut-off (18.5 months).
Overall survival (OS)	0, 24, 32 and 40 week cut-offs were available to be used for the partitioned survival model	An option for a 16 week cut-off was added to the model as suggested by the ERG who expressed an interest in exploring this cut-off
Age-related disutilites	Economic model implements age related disutility with no further disutility past the age of 75 years.	A feature now exists in the model, which allows the option to consider age-related disutility values by Ara (et al 2010) as suggested by the ERG.
Patient access scheme (PAS)	The economic analyses undertaken included a PAS discount of the cost of pembrolizumab.	The economic analyses undertaken included a new PAS discount of the cost of pembrolizumab.
Costs associated with adverse events		A feature now exists in the model, which allows the option to add additional costs (and prevalence) of adverse events of special interest (AEOSI). However adverse event (AE) disutility and duration were not affected by this option.
Market share	Distribution of people according to UK market share for Docetaxel (74%) and Paclitaxel (26%).	The company provided new UK market share data for Docetaxel (61%) and Paclitaxel (39%).

Table 3: Key features of the company's base case model

Parameters	Original submission	Current submission
Overall survival (OS)	Two-phase piecewise approach to extrapolate beyond trial time horizon. Original model used Kaplan-Meier OS data up to 40 weeks, then chose the lognormal parametric curve to fit the remaining observed data and to extrapolate to the model time horizon.	No change
Progression-free survival (PFS)	Two-phase piecewise approach to extrapolate beyond trial time horizon. Original model used Kaplan-Meier PFS data up to 21 weeks, then chose the exponential curve to fit the remaining observed data and to	Used the same two-phase approach to extrapolate beyond trial time horizon with 21 week cut-off. However, a Gompertz parametric curve to fit to the remaining PFS observed data as opposed to an exponential

	extrapolate beyond the trial time horizon.	curve. No justification was provided by the company for this change.

Table 4 presents MSD's base-case results using the discounted PAS for the cost of pembrolizumab. Based on the changes made to the original model (see Table 2), pembrolizumab compared to UK standard of care was approximately £43,600 more expensive and yielded 0.90 additional QALYs; this equated to an ICER of approximately £48,600 per QALY gained. Probabilistic sensitivity analysis results based on the outcome cost per QALY were in line with those results for the base-case analysis.

Table 4: Current submission base-case results (discounted with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Deterministic results					
UK SOC	£21,247	1.12	-	-	-
Pembrolizumab	£64,867	2.02	£43,620	0.90	£48,601
Probabilistic results					
UK SOC	£21,644	1.15	-	-	-
Pembrolizumab	£65,351	2.04	£43,706	0.90	£48,731

1.3. Summary of changes undertaken according to the committee's preferred assumptions and company's exploratory analysis results

MSD undertook an exploratory analysis which included some of the committee's preferred assumptions (obtained from MSD document):

- *Excluding the vinflunine data from utilities*
- *Pooling utilities across treatment arms by progression state*
- *Using an updated algorithm to calculate age-related disutility*
- *Changing the proportion of people having docetaxel and paclitaxel to UK market share*

Please note that the most current UK market share proportions (re-adjusted by the exclusion of platinum-containing chemotherapy) have changed since the CS and are currently as follows: Paclitaxel – 39% and Docetaxel – 61%.

Table 5 shows the company's exploratory results based on some of the committee's preferred assumptions. Results show that pembrolizumab is approximately £43,700 more expensive than UK standard of care and yielded 0.88 more QALYs; this equated to an ICER of approximately £49,600

per QALY gained. Probabilistic sensitivity analysis results were in line with those results for the deterministic analysis.

Table 5: Exploratory results based on the committee's preferred assumptions (discounted with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Deterministic results					
UK SOC	£21,193	1.05	-	-	-
Pembrolizumab	£64,867	1.93	£43,674	0.88	£49,644
Probabilistic results					
UK SOC	£21,591	1.08	-	-	-
Pembrolizumab	£65,351	1.95	£43,760	0.87	£50,478

2. ERG Response/critique of the main documents

2.1. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma [ID1019] – Company Response to Appraisal Consultation Document (ACD)

- **Key points supportive of the MSD's approach and assumptions as stated on the released ACD:**

The ERG accepts the points presented in this section.

- **MSD's UK response to key drivers underpinning the preliminary negative recommendation in the ACD:**

Cut-off point for OS extrapolation and OS extrapolation curves

The company begins with some justification of their choice for the 40 week cut off. The reference[4] provided by the company which apparently suggests "that all of the trial data should be used" in fact does not discuss partitioned survival models like those used in this STA. The reference suggests that all trial data should be used when fitting explanatory models, hence supporting the ERG decision to choose an earlier time point for the fitting of parametric models to OS, thus increasing the data used in the parametric fit.

The company then references NICE DSU Document 14[5] to support their model selection over that of the ERGs, mentioning the importance of the "goodness of fit" in addition to clinical plausibility of extrapolated curves. However, the ERG finds that DSU 14[5] also states that AIC/BIC are only

measures of goodness of fit to the observed data, and does not inform "how suitable a parametric model is for the time period beyond the final trial follow-up". Hence the AIC/BIC scores should be interpreted with caution, and not solely relied upon. As the long-term effects of pembrolizumab are still unknown, it is possible that the model that is the worst fit to the data in the short follow up, may be the best predictor of long term behaviour.

The company initially presented a table of AIC and BIC scores which did not match the scores presented in the economic model. An updated table was provided in the clarification response (see Table 7). AIC has a lesser penalty than BIC for additional model parameters, hence is a better indicator of overall fit. Based on the AIC scores, the ERG believes there is justification for excluding Weibull, exponential and Gompertz models for the 24-week cut-off based on the fit to the UK SOC, however, there is very little to separate the models for the 40-week cut-off.

Utility values

The company follows with some justification for using time-to-death based utilities over progression based utilities as favoured by the ERG and the committee. However, the supporting examples are all for differing disease areas and severities and so their support and relevance to this STA is limited. The company accepts that the utility value for the ≥360 day survival was surprisingly high, 0.778 compare to a UK population norm of 0.79 reported in TA447, considering patients had stage IV bladder cancer and were on second line treatment. The company presents evidence supporting the high value from a small sample of lung cancer patients on pembrolizumab. However, these patients have a different disease type, the sample is small, and it does not explain the high utility score observed in the UK SOC arm (0.82).

The company then argues that should progression based utilities be used, then the utility values for each arm should not be pooled. However this was previously recommended by the ERG and accepted by the committee, with the decision made based on concerns over the open label nature of the trial. The ERG feels that any major difference in patient experience would be captured, at least in part, by the adverse event disutility, which is not pooled by treatment, and therefore has confidence in using the pooled utilities.

Implausible lifetime treatment effect

The company provides examples supporting its view that it is right to assume a lifetime treatment effect for pembrolizumab, which for this model would be 35 years. In summary, these examples are from different disease areas (lung cancer and melanoma) with different severities, which have different survival rates to patients in KEYNOTE-045 trial and have up to 4-years' worth of follow-up data.

The company also draws attention to ipilimumab, an immunotherapy with a different mechanism of action, and its application to unresectable or metastatic melanoma. Whilst a plateau appears to begin from between 3 and 4 years, at 4 years there are only 10% of the original population left at risk. Only five patients make it into the tenth year of follow-up, whereas the company suggests this data might be available for all patients. After examining these examples, the ERG considers there to be no certainty of the duration of treatment effect, especially a lifetime treatment effect, for patients in the KEYNOTE-045 trial.

Overall, this advocates for scenario analyses to be conducted exploring the impact of a waning effect on the ICER (see section 3).

2.2. Re: Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

The company begins this document with the presentation of their base case analysis.

Summary of the concerns identified by the Evidence Review Group (ERG)

Below we list the ERG's main concerns relating to the company's base case economic analysis submitted on 24 August 2017. These include:

1. Using a 21-week cut-off and fitting Gompertz curves to the remaining progression-free survival data for pembrolizumab and UK standard of care
2. Failure to adjust appropriately for people in the progressive health state
3. Omission of some of the committee's preferred assumptions

Using a 21-week cut-off then fitting Gompertz curves to the remaining progression-free data for pembrolizumab and UK standard of care

The company undertook a two-phase piecewise approach and fitted parametric models to the PFS survival data using a 21-week cut-off. Statistical goodness-of-fit of these curves to the data was assessed using the AICs and BICs. In the previous submission, the AICs and BICs were lowest for the exponential model for both pembrolizumab and UK SOC, resulting in the company selecting it for use in the extrapolation.

However, the ERG noted that in the model submitted on 24 August 2017, which is based on 18 January 2017 data cut-off, the company chose the Gompertz parametric model for progression-free survival and log-logistic for OS for both the pembrolizumab and UK standard of care. It should be noted that the company drew little attention to this change (i.e. change from exponential to Gompertz for PFS) and provided no justification to support it.

Upon investigation, the ERG believes this decision appears to be based entirely on the AIC/BIC scores with little consideration of the consequences of the model choice in terms of clinical plausibility. Figure 1 shows the OS and PFS based on the log-logistic and the Gompertz parametric curves for pembrolizumab, respectively. It can be seen that the progression-free survival and OS curves cross at approximately 350 week time-point.

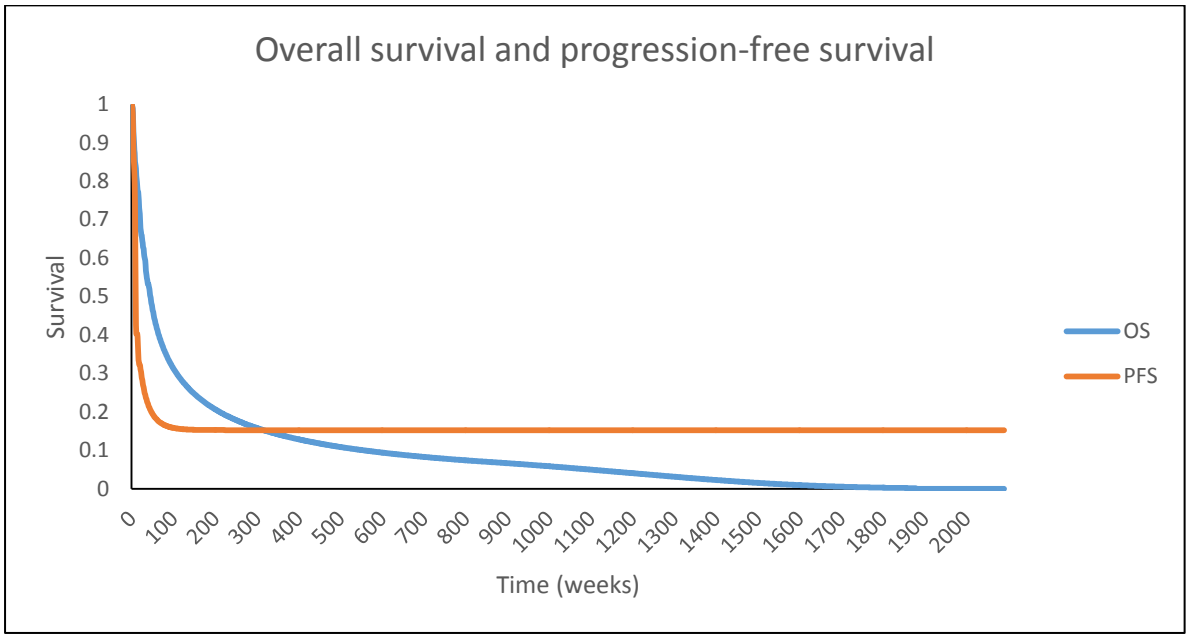

Figure 1: Overall and progression-free survival for pembrolizumab

This suggests that beyond this time horizon, more patients are predicted to be alive and not progressed, than the total predicted alive patients. From the definition of OS and PFS, we consider this to be a logical inconsistency.

Failure to adjust appropriately for people in the progressive health state

The ERG noted that the company made an adjustment for the logical inconsistency stated in the previous point. The fact that this adjustment is necessary suggests that this combinations of parametric distributions for OS and PFS is clinically implausible and flawed.

Though not explicitly stated by the company, it is assumed that people who progressed whilst being treated with pembrolizumab, all die before the end of the 6-year time horizon. This can be seen in Figure 2, which shows the Markov trace plot for pembrolizumab. Using these model options assumes that there is a sudden restriction of the size of this group from the one year time point, suggesting both an increased mortality rate among the group, and a vastly reduced rate of patients entering this health state. After the 6-year time horizon, all progressed patients died, and no new patients transitioned to

the progressive state. This means that according to the illustrative structure, people in the progression-free state either remained in this health state or transitioned to the dead state but none could transition to the progressive disease state. The ERG agrees that it is plausible for people to transition from the progressive-free state to death, as suggested by the definition of PFS, but it is clinically implausible that from 6 years, PFS events are exclusively represented by events that relate to death.

Using this PFS model, compared to other models, the ERG was surprised to see that the Gompertz PFS model led to similar life years gained, but with a higher amount of QALYs gained. This results from the assumption described above which favours pembrolizumab. Indeed, people who transition to the progressive health state incur higher costs and lower utilities compared to people who are in the progression-free health state, thus improving the cost-effectiveness when using progression based utilities as recommended by both the ERG and the NICE committee.

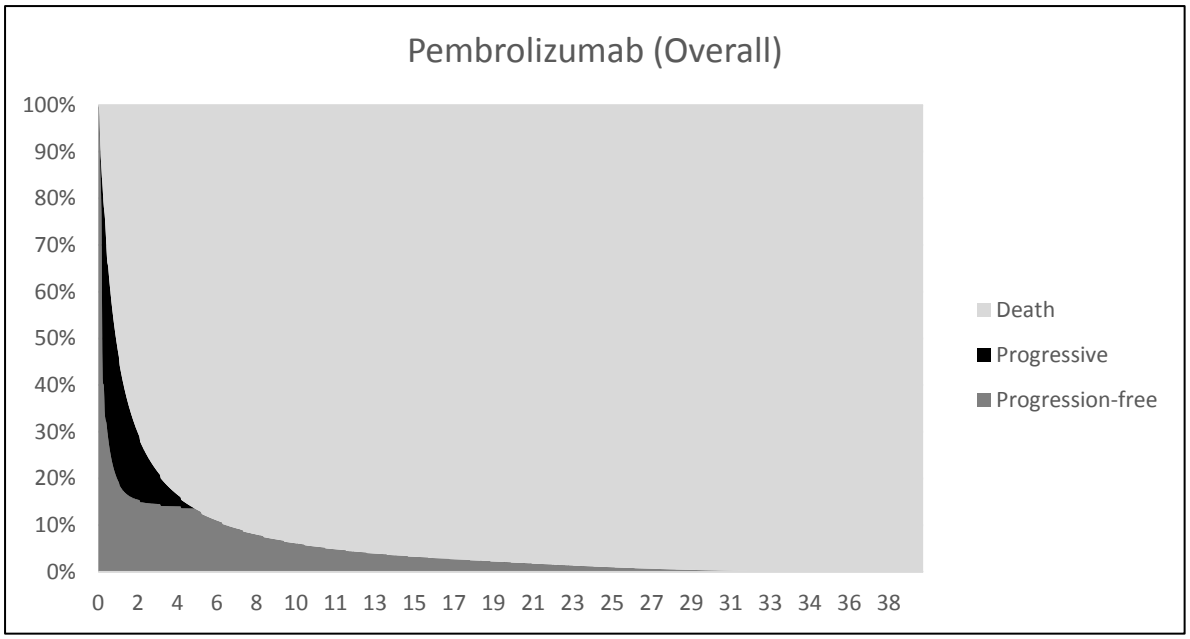

Figure 2: Trace plot for pembrolizumab (obtained from the company's electronic model)

Figure 3 shows the trace plots for UK standard of care. Here people remain in the progressive health state longer than people treated with pembrolizumab. The ERG does not believe there is evidence to support such a contrast between the Markov plots of the two treatment arms.

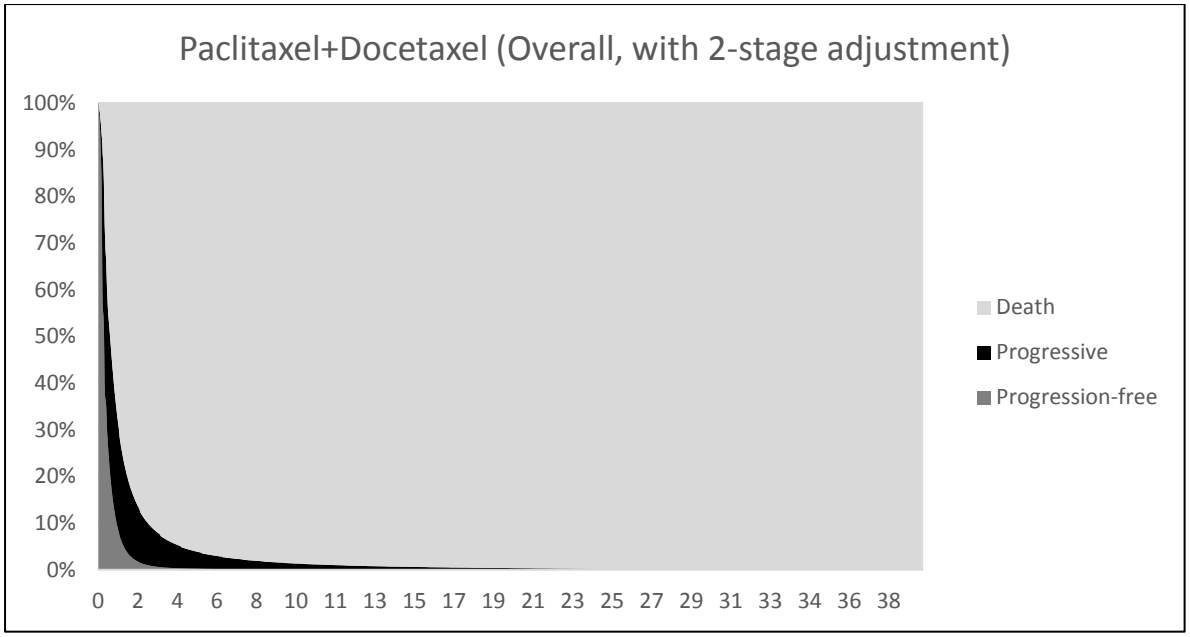

Figure 3: Trace plot for UK standard of care (obtained from the company's electronic model)

Cut-off point for overall survival extrapolation and the choice of parametric curves to model overall survival

'MSD is concerned that the Committee's range of plausible ICERs is based solely on the 5-year OS extrapolated estimates for the UK SOC arm, without taking into account any statistical considerations on how well the parametric curves fit the data. The NICE DSU TSD 14 guidance highlights the importance of goodness of fit as well as clinical plausibility of the extrapolation curves. Therefore, and based on goodness of data fit, some parametric curves should not be considered as credible despite the plausible 5-year OS estimates for UK SOC arm:'

Table 6: Goodness-of-fit for OS data for pembrolizumab and UK SOC, at 24 and 40 weeks point extrapolation (obtained from re-submission by MSD on August 2017)

	Pembrolizumab				UK SOC (2-stage adjustment)			
	24-Week		40-Week		24-Week		40-Week	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	690.1	693.2	339.1	342.1	382.3	384.7	165.1	167.1
Weibull	691	697.4	340.5	346.4	383.7	388.6	165	169.1
Gompertz	689.8	696.1	338.1	344	383.9	388.7	160.4	164.5
Llogistic	690	696.4	339.4	345.3	380.1	385	163.7	167.7
Lnormal	691.7	698.1	337.5	343.4	377.9	382.7	161.8	165.9
GenGamma	692.4	701.8	338.5	347.3	377.8	385.1	160.2	166.3

Table 6, shows the goodness-of-fit measures for fitting various parametric curves to OS data cut-off at 24-weeks and 40-weeks for pembrolizumab and UK standard of care. It should be noted that these AICs/BICs presented were not the same as those in the electronic model. On clarification, MSD

provided AICs/BICs which are based on the new data (cut-off date January 2017) (please see Table 7). The ERG now consider these values to reflect those in the electronic model.

Table 7: Goodness-of-fit for OS data for pembrolizumab and UK SOC, at 16, 24 and 40 weeks point of extrapolation (obtained from clarification document submitted by MSD on September 2017)

	Pembrolizumab						UK SOC (two-stage adjustment)					
	16-Week		24-Week		40-Week		16-Week		24-Week		40-Week	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	730.2	733.1	867.6	870.7	515.6	518.5	734.3	737.1	476	478.5	243.2	245.2
Weibull	726.7	732.6	866.6	873	515.6	521.4	731.7	737.2	478	482.9	241.8	245.8
Gompertz	724.6	730.4	863.9	870.2	512.6	518.5	729.2	734.8	475.8	480.8	241.5	245.6
Llogistic	725.2	731	864.7	871	514.1	519.9	729.4	735	473.3	478.2	240.9	245
Lnormal	725.8	731.6	866	872.4	512	517.8	731	736.5	470.1	475.1	239.1	243.2
GenGamma	727.2	736	867	876.5	513.2	522	731.7	740	468.4	475.8	239.3	245.4

MSD provided justification for the choice of parametric function to model OS. As stated earlier, the ERG's preferred choice of OS estimates for UK standard of care is guided by the goodness-of-fit measures, and clinical plausibility. It should be noted that there is little differences between the AICs/BICs. This suggests that all parametric functions are plausible because they offer good fits to the observed data. However, these measures do not consider the extrapolations; hence choice of parametric curve should be also guided by clinical plausibility.

Committee Preferred Assumptions

The company presented exploratory results that were based on the committee's preferred assumptions. The ERG can confirm that we are able to reproduce both the deterministic and probabilistic results.

However, the ERG noted that the company did not implement all of the committee's recommendations. The company has not considered including the uncertainty about the time-point at which to implement the partition in the survival modelling and also the uncertainty over the choice of parametric curve.

More significantly, the committee also concluded that they did not agree with the plausibility of a lifetime treatment effect. In the table below, the ERG shows the corresponding ICERs for the range of duration of treatment effects permitted in the model using the committees preferred assumptions. It is clear that in the non-lifetime effect cases, the ICER is above the £50,000. The company presents results investigating the varying duration of treatment, but for their base-case analysis (see Table 14 in document 2.2), with the ICERs being roughly £1,000 less than those shown in Table 8.

Table 8: Showing the incremental differences and ICERs by treatment effect duration using the company's "Committee's preferred assumptions" model

	Incremental Costs	Incremental QALY	ICER
Lifetime	£ 43,674	0.88	£ 49,644
10 year	£ 43,462	0.86	£ 50,410
5 year	£ 42,872	0.81	£ 52,837
3 year	£ 42,203	0.75	£ 56,074

The ERG have taken these assumptions into consideration and included the majority in their preferred base-case analysis. However, given the paucity of evidence about the lifetime treatment effect, we explored in scenario analyses the impact of assuming the hazard ratio of OS between pembrolizumab and UK SOC were the same starting at year 3, 5 and 10. These results are presented in the ERG exploratory results section (see section 3).

16-week cut-off then fitting parametric curves to the remaining OS data

In the base-case, MSD used a 40-week cut-off then fitted various parametric curves to the remaining data.

At the appraisal stage, the ERG considered using a 24-week cut-off as this provided plausible estimates for 5-year OS for people randomised to UK standard of care. The ERG also stated that a 16-week cut-off may be plausible because at this time-point, the Kaplan-Meier curves for pembrolizumab and UK standard of care diverged. Based on the original model, the ERG was unable to explore this cut-off point because this was not an option within the economic model.

In the new analyses submitted, the company states that a cut-off at week 16 would be the ERG's choice. However, the ERG would like to clarify that although this cut-off was considered to be theoretically plausible, this would have to be examined and confirmed once it became possible in the economic model. So based on the current submission, the ERG welcomes the opportunity to explore using the 16-week cut-off and choice of parametric curves to extrapolate OS.

In **Error! Reference source not found.** and Table 10, we have presented the OS estimates for UK standard of care and pembrolizumab, respectively.

Table 9: UK SOC overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
Using a 16-week cut-off						
1-year	0.4962	0.4801	0.4672	0.4706	0.4631	0.4709
3-year	0.1445	0.2021	0.2616	0.2416	0.2982	0.2404
5-year	0.0421	0.0986	0.1876	0.1661	0.2802	0.1565
10-year	0.0019	0.0206	0.1105	0.0950	0.2774	0.0745
Using a 24-week cut-off						
1-year	0.4736	0.4613	0.4481	0.4534	0.4482	0.4534
3-year	0.1454	0.1823	0.2396	0.2177	0.2614	0.2154
5-year	0.0447	0.0815	0.1681	0.1439	0.2350	0.1320
10-year	0.0023	0.0132	0.0957	0.0782	0.2291	0.0556
Using a 40-week cut-off						
1-year	0.4661	0.4542	0.4485	0.4517	0.4455	0.4431
3-year	0.1608	0.1989	0.2397	0.2234	0.2894	0.2640
5-year	0.0555	0.1003	0.1734	0.1520	0.2802	0.2135
10-year	0.0038	0.0219	0.1048	0.0863	0.2795	0.1597

Table 10: Pembrolizumab overall survival estimates by parametric distribution Error! Reference ource not found.

The ERG believes that the 24-week cut-off for OS should be used as it is from this point that the hazard has stabilised and demonstrates behaviour that is representative of the hazard moving forward in time, as seen from the cumulative hazard plot provided by the company in Figure 1 of their clarification response. This follows the advice of the NICE DSU Technical Support Document 19[6] which suggests focusing the model fit to data "where transient effects are expected to have dissipated". Whilst the behaviour from 16 weeks is comparable and worth investigating, there is a noticeable change in the gradient prior to 24 weeks. The ERG also believes the 24-week cut-off is preferable to the 40 week, as the 24-week shares almost identical trends in the cumulative hazard plot, whilst maximising the amount of data the parametric curves are fitted to.

Adverse events of special interest (AEOSI)

In their revised model, the company has added grade 3+ adverse events (AEs) of Special Interest (AEOSI) on top of grade 3+ AEs with an incidence of at least 5% which were initially included in the model. Although the impact of adding AEOSI in the model was minimal as suggested by the company, the ERG believes the addition of AEOSI was not relevant because these were not reported consistently compared to other types of AE. Indeed, only grade 3+ AE that were attributed to treatment by the investigator (treatment-related event) were included in the model while AEOSI were included regardless of attribution to study treatment by the investigator. The ERG considers that AEOSI should have been included but only for those judged to be treatment-related as for other types of AE.

The company presents ICERs where data from grade 3+ AEOSI are included. They allowed the AEOSI to be included in both arms or just the pembrolizumab arm options in the economic model, or alternatively no AEOSI as in the original submission. The ERG was able to reproduce the ICERs presented by the company in Table 12 and 13 of their re-submission. It is worth noting that only the prevalence and associated costs of the AEOSIs are included in the model, and their inclusion does not influence the effectiveness of either treatment arm. They have no influence on the calculation of the AE disutility or AE duration.

Whilst the adverse events currently have minimal impact on the ICER, it is possible that this impact could increase should the disutility extend to include the AEOSI or if lower graded events were also included, as these still have associated treatment costs and can affect a patient's quality of life. This could even be extended to include all drug related AEs, such as the list found in Appendix 16 of the original company submission.

Long term treatment effect

The ERG includes comments on this section in the 'Committee Preferred Assumptions' response. It is worth recalling that the results presented by the company here are on their base case, and not the committee preferred assumptions model.

Additional comments on company's base case regarding pre-progression survival and post-progression survival gain

Based on the model structure, the transition to death state can occur either from the progression-free state or from the progressive disease state. The transition to the death state from one of these states translates into a life expectancy originating from pre-progression, for patients in the progression-free state, or from post-progression for those in the progressive disease state.

Depending on the initial state prior to the death state, the company's model enables to generate a pre-progression life years (PFS for progression-free survival) and a post-progression life years (PPS for post-progression survival). From the PFS and PPS generated for pembrolizumab and UK SOC separately, we can calculate the PFS gain and the PPS gain. The ERG tried to validate the plausibility of survival models by looking at the relative importance of PFS and PPS gains.

With conventional cytotoxic chemotherapies:

- PFS is usually a valid surrogate outcome of OS because a beneficial effect of a new drug on PFS often translates into a beneficial effect on OS.

- Treatments are discontinued at the time of progression and mechanism of actions are such that the beneficial effect is likely to be reduced at progression state compared to the progression-free state.
- Therefore, one would expect the PFS gain to be much higher compared to the PPS gain.

In contrast, the effectiveness profile of pembrolizumab is characterised as following:

- Pembrolizumab does not reduce the median time-to-progression or death compared to chemotherapy, though PFS rate at 12 months appears to be higher with pembrolizumab
- Like for UK SOC, progressions occur rapidly with pembrolizumab because median PFS time was only 2.1 months (3.3 months with chemotherapy)
- Pembrolizumab reduces the time to death compared to chemotherapy as illustrated by more favourable median OS time and OS rates at 6, 12, and 18.5 months.

Translating this using the Markov structure gives the following:

- Pembrolizumab reduces the time for people to transition to the dead state compared to UK SOC.
- Because overall pembrolizumab does not reduce the flow of people going from progression-free to progressive disease state, and because progressions occur rapidly with both strategies, it makes more sense that the life-years gained associated with pembrolizumab originate more from post-progression state compared to pre-progression state.
- Therefore, this implies that PPS gain should be higher compared to PFS gain.

The ERG validated these statements with their clinical expert.

Using the company's survival model (Gompertz for PFS and Log-normal for OS), life–years gained (LYG) is 1.18 years and the split between PFS gain and PPS gain is 1.66 and -0.48 years, respectively. This suggests that pembrolizumab increases life-expectancy compared to UK SOC from pre-progression while UK SOC does better compared to pembrolizumab at post-progression. The main clinical outcomes from KEYNOTE-045 disagree with these statements and this further demonstrates the implausibility of the model results using the company's preferred survival models.

Verification of MSD's results

It should be noted that the ERG has not re-built MSDs economic model. For model validation, the ERG double-checked the results presented in the new documents against the results in the most recent electronic model. The ERG were able to replicate MSDs results.

The company provided the ERG with individual patient data (IPD) for OS and PFS for pembrolizumab and UK SOC, however no information was provided on patients who were randomised and received pembrolizumab but were allocated to vinflunine prior to randomization. This meant the ERG was unable to completely reproduce the company's base case Kaplan-Meier plots. The ERG was able to produce Kaplan-Meier plots for the UK SOC and analyse the data on an intention-to-treat (ITT) (scenario 7) basis, and noted that they appeared similar to those presented by the company within the economic model. However, when comparing the occurrences of events in both PFS and OS between scenario seven of the economic model and the IPD provided, the ERG noted some discrepancies. For PFS there were eight events where the two datasets did not agree on a time of occurrence, and seven differences in the number of patients at risk. For OS there were 12 events that did not match and eight differences in the number at risk. In general, there were less people at risk in the UK SOC arm in the economic model than observed in the IPD, suggesting each later event having a stronger impact on any models fitted. Generally, more events occurred in the IPD, than in the economic model, suggesting that UK SOC may perform less well than it appears in the economic model. The ERG were unable to identify the cause of these discrepancies; but together they increased the ERG's uncertainty in the company's survival models and the resulting cost-effectiveness analyses.

3. ERG's exploratory and sensitivity analyses

The ERG raised some concerns regarding MSD's most up-to-date economic analyses. In this section, where possible, we addressed these concerns and undertook scenario analyses. Our analyses uses the MSDs electronic model with our assumptions to compare pembrolizumab with UK SOC for people previously treated for advanced or metastatic urothelial cancer. Below we outline the changes made to the economic model and the results. It should be noted that MSD's current results are based on a new PAS discount on the cost of pembrolizumab. The ERG therefore used this new PAS in our analyses.

3.1. Changes made to the MSDs model

- Distribution of people receiving paclitaxel and docetaxel is based on the UK market share
- Choice of parametric function for PFS; we used the 21-week cut-off time-point and fitted a Weibull parametric function to the remaining data
- Choice of parametric function for OS; used the 24-week cut-off time-point and fitted a log logistic parametric function to the remaining data
- Pooling utilities across treatment arms by progression status
- Excluded utilities based on people who were treated with vinflunine
- Used the update algorithm (Ara et al., 2010)[7] to derive age-related disutilities

The justifications on the changes undertaken by the ERG are provided in Table 11.

Table 11 : Changes undertaken by the ERG and justification

Change	Company's new base-case	ERG's new base-case	Justification
OS cut-off	40-week	24-week	The behaviour of the hazard from 24 weeks appears to match the behaviour from 40 weeks whereas the behaviour prior to 24 weeks is slightly different. 24 weeks maximises the data fitted to the parametric model. The ERG chose the same setting in the previous submission, which was accepted by the committee.
OS parametric fit	Log Normal	Log Logistic	The 5 year OS rate was considered most plausible by ERG. Of the distributions with plausible long term survival estimates, log logistic had the lowest AIC for pembrolizumab arm. The ERG chose the same setting in the previous submission, which was accepted by the committee.
PFS parametric fit	Gompertz	Weibull	No justification was provided by the company for their selection of the Gompertz distribution. The ERG found that the Gompertz resulted in a larger post-progression survival for UK SOC and pembrolizumab; whereas Weibull distribution produced the most plausible balance of pre- and post-progression survival benefit of pembrolizumab, with acceptable AIC scores for both arms. Other PFS models using the log normal and the log logistic distributions were excluded because these led to less plausible split between PFS and PPS gain.
Distribution of patients in UK SOC	Source: Distribution from Keynote 045	Source: UK market share	This better reflects current UK practice. The ERG chose the same setting in the previous submission, which was accepted by the committee.
Approach to utility measure	Time-to-Death based utilities	Progression based utilities	Low sample sizes and high utility values observed in the time-to-death based values lead the ERG to prefer progression based utilities, which are more widely used in technology appraisals. The ERG chose the same setting in the previous submission, which was accepted by the committee.
Pooled utility values	Pooled (time-to-death based)	Pooled (progression based)	The open label nature of the KEYNOTE-045 trial means that there is a high risk of bias in reported utility values. Any major difference between the arms should be at least partially captured by the adverse event disutility, hence pooling is the preference of the ERG. The ERG chose the same setting in the previous submission, which was accepted by the committee.
Utility UK SOC	Vinflunine, Docetaxel and Paclitaxel patients combined	Docetaxel and Paclitaxel patients only.	Vinflunine is not recommended for use in the UK market, and so patient information from this group should not be used in this economic model. The ERG chose the same setting in the previous submission, which was accepted by the committee.
Age-adjusted disutility	Kind et al 1999	Ara et al 2010	Ara et al is a more up-to-date disutility which continues to have effect past the age of 75. The ERG chose the same setting in the previous submission, which was accepted by the committee.

The base-case analysis was undertaken from an NHS and PSS perspective and the outcome reported as an ICER, expressed in terms of cost per QALY gained. We undertook probabilistic sensitivity analysis and scenario analyses to assess the impact of the uncertainty of the model input parameters. Table 12 shows the scenario analyses undertaken.

Table 12: Scenario analyses undertaken by the ERG

Scenario analyses	
1	Waning effect: Changing the starting year (3, 5 and 10 years) of the same hazard assumption, using the 21-week cut-off and Weibull parametric fit to PFS data
2	21-week cut-off and using an exponential parametric fit to PFS data
3	Waning effect: Changing the starting year (3, 5 and 10 years) of the same hazard assumption, using the 21-week cut-off and exponential parametric fit to PFS data
4	24-week cut-off and using log normal parametric fit to OS data
5	Waning effect: Changing the starting year (3,5 and10 years) of the same hazard assumption, and using the 24-week cut-off and log normal parametric fit to OS data

3.2. Results

3.2.1. ERG's base-case results

Table 13 shows the results of the ERG's base-case. Results showed that pembrolizumab compared to UK standard of care was approximately £43,000 more expensive and yielded 0.81 additional QALYs; this equated to an ICER of approximately £52,900 per QALY gained. The results from the probabilistic analyses were similar (see Figure 6 and Figure 7 for the scatter plot and the CEAC).

Table 13: ERG's base-case and probabilistic sensitivity analysis results (discounted with PAS)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Deterministic results					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	61,265	1.61	42,994	0.81	52,892
Probabilistic results					
UK SOC	18,503	0.81	-	-	-
Pembrolizumab	61,764	1.63	43,261	0.82	52,757

It should be noted that as a result of these changes, the ERG's ICER is greater than MSDs base-case ICER, and this is a due to a reduction in the QALYs gained. The choice of parametric fit for PFS underpinned the reduction in QALYs gained. The ERG considered it to be more plausible to use the 21-week cut-off and fitting Weibull curves to the remaining progression-free data for pembrolizumab and UK standard of care. Our choice of model fit for PFS is based on AICs/BICs and clinical plausibility. In terms of clinical plausibility we considered the pre-progression survival and post-progression gain *in tandem*. Table 14 shows the expected total life years gained (LYG) of 2.45 and 1.20 for pembrolizumab and UK SOC, respectively at the 35-year time-horizon. Based on clinical input, it is expected that the LYG associated with post-progression to be higher than the contribution of the LYG from pre-progression. Here, pre-progression and post-progression gain accounted for approximately 40% and 60% of the expected LYG, respectively, which is consistent as suggested in the section on PPS and PFS gain (see section 2.2).

Table 14: Incremental pre-progression and post-progression gain

Technologies	Life-years gained (LYG)			Incremental		
	Pre-progression	Post-progression	Total LYG	Pre-progression gain	Post-progression gain	LYG
UK SOC	0.42	0.78	1.20	-	-	-
Pembrolizumab	0.91	1.54	2.45	0.49	0.77	1.25

Figure 4 and Figure 5 show the trace plots which are based on using 21-week cut-off with Weibull fits to the PFS data and 24-week cut-off with log logistic fits to the OS data. These trace plots show a more consistent disease pathway compared to that resulting from the company's preferred survival model for pembrolizumab.

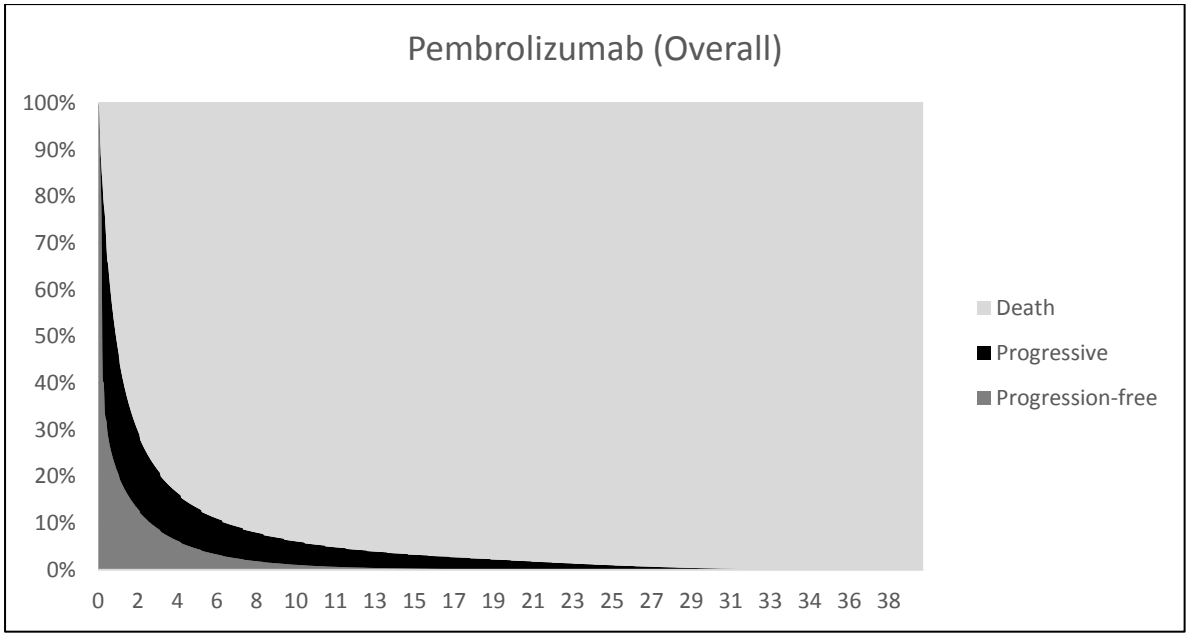

Figure 4: Trace plots based on a Weibull parametric model for progression-free survival for pembrolizumab

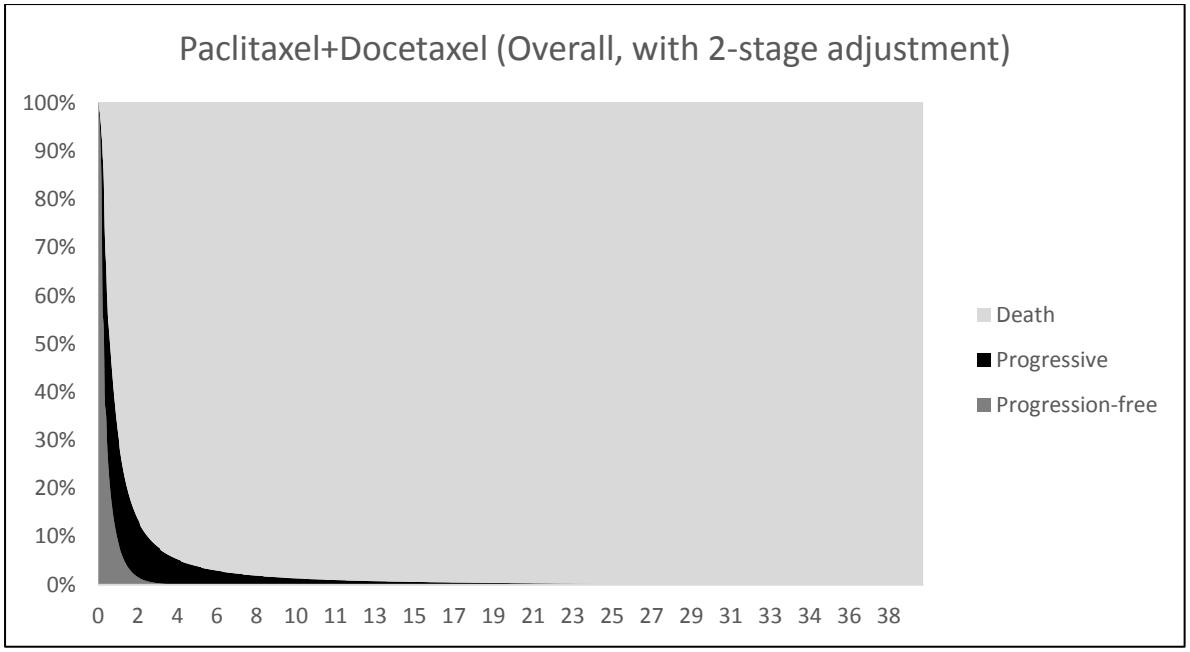

Figure 5: Trace plots based on a Weibull parametric model for progression-free survival for UK standard of care

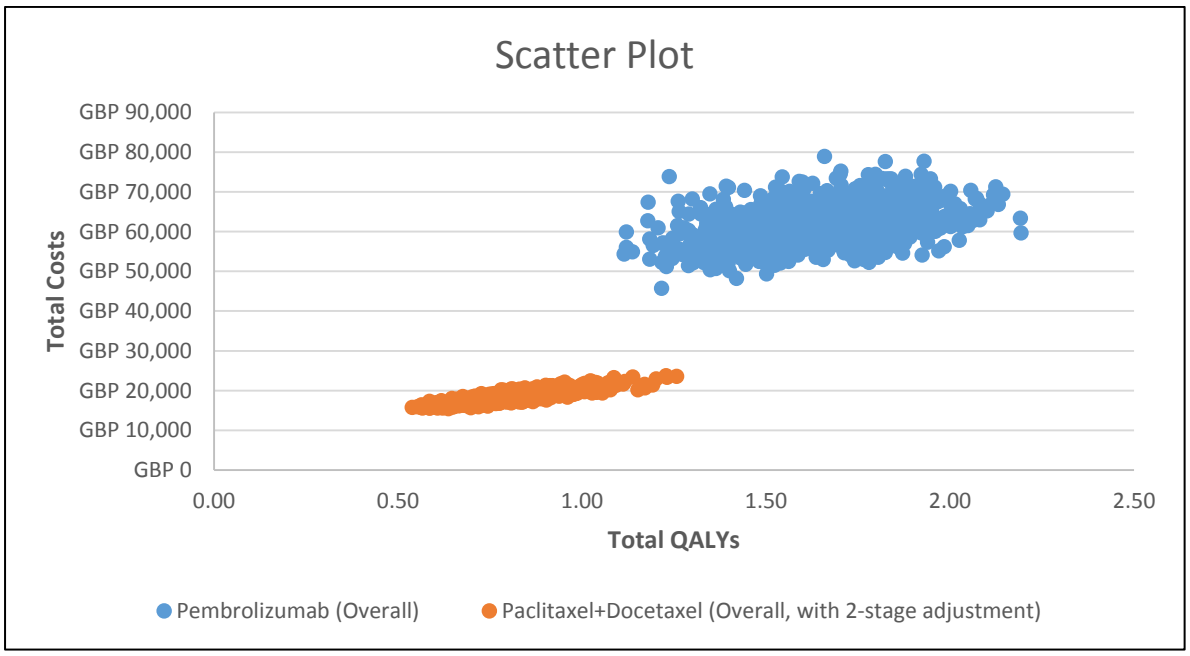

Figure 6: Scatterplot using distributions around model input parameters

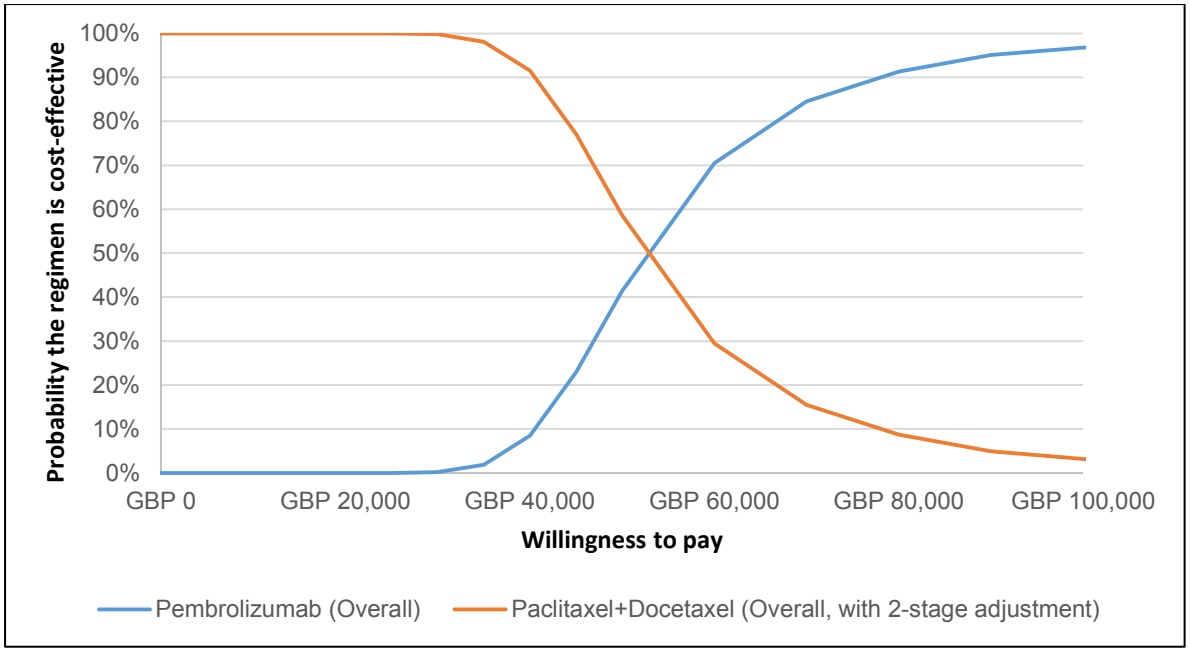

Figure 7: Cost-effectiveness acceptability curves for pembrolizumab versus UK SOC at different willingness-to-pay thresholds

3.2.2. Scenario analyses results

→ Scenario analysis 1: Waning effect: Changing the starting year (3, 5 and 10 years) of the same hazard assumption, and using the 21-week cut-off with Weibull parametric fits to PFS data

Results from scenario analysis 1 show that including treatment waning effects leads to an increase in the ICERs. It can be seen that the earlier a waning effect is implemented in the model, the greater the impact on the ICER. This is expected because from this point onwards pembrolizumab is assumed to have the same benefit/effect as UK standard of care. Results for scenarios 3 and 5 follow similar patterns; see Table 17 and Table 19, respectively.

Table 15: Results for scenario analysis 1 (deterministic results)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG's base-case results					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	61,265	1.61	42,994	0.81	52,892
Waning at 3 years					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	58,690	1.39	40,419	0.59	68,225
Waning at 5 years					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	59,879	1.50	41,607	0.70	59,729
Waning at 10 years					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	60,891	1.58	42,620	0.78	54,455

→ Scenario analysis 2: 21-week cut-off and using an exponential parametric fit to PFS data

Changing the 21-week cut-off and using exponential model fits for PFS data for pembrolizumab and UK SOC resulted in a decrease in the incremental QALYs gain when compared to the ERG's base-case. As a result, there was an increase in the ICER by approximately £1000.

Table 16: Results for scenario analysis 2 (deterministic results)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG's base-case results					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	61,265	1.61	42,994	0.81	52,892
Using 21-week cut-off and exponential fit to the PFS data					
UK SOC	18,266	0.80	-	-	-
Pembrolizumab	61,058	1.59	42,793	0.79	53,941

→ Scenario analysis 3: Waning effect: Changing the starting year (3, 5 and 10 years) of the same hazard assumption, and using the 21-week cut-off with exponential parametric fits to PFS data

Table 17: Results for scenario analysis 3 (deterministic results)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG's base-case results					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	61,265	1.61	42,994	0.81	52,892
Waning at 3 years					
UK SOC	18,266	0.80	-	-	-
Pembrolizumab	58,483	1.37	40,217	0.57	70,200
Waning at 5 years					
UK SOC	18,266	0.80	-	-	-
Pembrolizumab	59,672	1.48	41,406	0.68	61,156
Waning at 10 years					
UK SOC	18,266	0.80	-	-	-
Pembrolizumab	60,684	1.56	42,419	0.76	55,585

→ Scenario analysis 4: Using the 24-week cut-off with log normal parametric fit to OS data

In scenario 4, we explored the impact to the ERG's base-case results by using the 24-week cut-off with log normal parametric fits to the remaining OS data. Extrapolations based on the log normal fits resulted in greater OS estimates, and these results were shown in the cost-effectiveness analysis. Table 18 shows that there is an increase in the estimated mean costs from approximately £61,300 to £62,900 and an increase in the expected QALYs from 1.61 to 1.76, resulting in an ICER of approximately £45,300 per QALY gained.

Table 18: Results for scenario analysis 4 (deterministic results)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
ERG's base-case results					
UK SOC	18,271	0.80	-	-	-
Pembrolizumab	61,265	1.61	42,994	0.81	52,892
24-week cut-off with log normal parametric fit to OS data					
UK SOC	17,832	0.76	-	-	-
Pembrolizumab	62,936	1.76	45,104	1.00	45,303

→ Scenario analysis 5: Waning effect: Changing the starting year (3, 5 and 10 years) of the same hazard assumption, and using the 24-week cut-off and log normal parametric fit to OS data

Table 19: Results for scenario analysis 5 (deterministic results)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Results for scenario analysis 4					
UK SOC	17,832	0.76	-	-	-
Pembrolizumab	62,936	1.76	45,104	1.00	45,303
Waning at 3 years					
UK SOC	17,832	0.76	-	-	-
Pembrolizumab	57,852	1.32	40,021	0.56	71,349
Waning at 5 years					
UK SOC	17,832	0.76	-	-	-

Pembrolizumab	59,570	1.48	41,739	0.71	58,508
Waning at 10 years					
UK SOC	17,832	0.76	-	-	-
Pembrolizumab	61,651	1.65	43,819	0.89	49,124

In Table 20, we show that majority of the benefits are based on the extrapolated difference and not based on the observed difference. At a 35-year time horizon, the model yielded a 1.25 LYG (2.34 life years with pembrolizumab vs. 1.09 life years for UK SOC – see Table 14). Using the 22-month time-point (median follow-up duration), the LYG with observed data could be estimated at 0.20 suggesting that the benefit from observed data contributed to 16% of the total benefit (1.25 LYG) while 84% of the incremental life-expectancy comes from extrapolation.

Table 20: Proportion of LYG based on the observed and extrapolated data

Time-point	LYG		Incremental LYG	Proportion of LYG from observed data	Proportion of LYG from extrapolated survival
	UK SOC	Pembrolizumab			
22 months	0.79	0.99	0.20	16%	84%

4. Summary

MSD re-submitted a *de novo* partitioned survival health economic model which contained four months additional follow-up and assessed the cost-effectiveness of pembrolizumab compared to UK SOC for people previously treated for advanced or metastatic urothelial cancer. The model simulated the disease progression for a hypothetical cohort of people aged 65 years being treated, and the cost-effectiveness was estimated over a 35-year time horizon. The model defined health states of progression-free, progressive and dead. The model used weekly cycles to show transitions between health states. In each cycle, people incurred costs and accrue benefits (QALYs) depending on the health state occupied.

Information relating to overall survival and progression-free survival was derived from parametric survival curves fitted to Kaplan-Meier plots of the observed data from the KEYNOTE-045 trial. The analysis was undertaken from the NHS and PSS perspective, and the outcomes are reported in terms of life-years gained (LYG) and quality-adjusted life years (QALYs) gained, and results are reported in terms of an incremental costs-effectiveness ratio (ICER), expressed as cost per QALY. Both costs and benefits were discounted at 3.5% per annum. The company undertook probabilistic and scenario analyses based on the outcome cost per QALY gained. All results are based on a patient access scheme (PAS) on the list price for pembrolizumab.

The company's base-case results showed that the estimated ICER was approximately £48,600 per QALY gained. Results for the PSA showed that at a willingness-to-pay of £50,000 per QALY, pembrolizumab had a 0.51 probability of being cost-effective.

In the current submission, the ERG highlighted concerns relating to the company's model, in particular: 1) the fitted Gompertz curve to the remaining progression-free survival data, 2) failure to adjust appropriately for people in the progressive health state and 3) omission of some of the committee's preferred assumptions. The ERG considers that in light of these concerns that the ICER is likely to be higher than the company's base-case.

With regards to the concerns identified about the MSD's economic analysis, the ERG modified the company's economic model and assessed the cost-effectiveness of pembrolizumab compared to UK SOC. In our analyses, we utilised the updated overall and progression-free survival data, and the committee's preferred assumptions. In addition to our base-case analysis, we conducted five scenario analyses, which mainly included implementing a waning effect at different time-horizons. Our base-case deterministic results showed that the ICER is expected to be approximately £52,900 per QALY gained. Results for the probabilistic sensitivity analysis showed that a willingness-to-pay of £50,000

per QALY, pembrolizumab had a 0.41 probability of being cost-effective. In general, across the scenario analyses, the effect of these changes led to an increase in the ICER.

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Dear Kate,

Re. Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Please find below requested cost-effectiveness analysis results including the latest available cut-off data from KEYNOTE-045 (18 January 2017) incorporating a [redacted]

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

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

Kind regards,

Chris O'Regan, Head of HTA and OR

The text below is taken from the request or additional information communicated to MSD by email on 18th August 2017. In response to this MSD submitted revised analysis in our response to the ACD.

"The technical team noted that the additional trial evidence submitted prior to the ACD publication did not incorporate the committee's preferred assumptions. NICE would expect the following assumptions to be incorporated:

- excluding the vinflunine data from utilities (see section 3.17)
- pooling utilities across treatment arms by progression state (see sections 3.16 to 3.17)
- using an updated algorithm to calculate age-related disutility (see section 3.16)
- changing the proportion of people having docetaxel and paclitaxel to UK market share.

A key uncertainty for committee was the assumptions around the extrapolation modelling. NICE would expect to see full sensitivity analyses around the following:

- The choice of cut-off point at which to extrapolate the overall survival trial data (see section 3.13) – please note that the ERG stated that a cut-off at week 16 (the point at which the cumulative hazards cross) would be their choice, but were unable to explore this in the economic model.
- Choice of parametric curve to extrapolate overall survival (see section 3.14).

In addition the committee noted that the economic model excludes rare but potentially serious adverse events that are specific to immunotherapy (see section 3.11) and assume an implausible lifetime continued treatment effect (see section 3.15). NICE would prefer to see scenario analyses which explore these assumptions around the new company base case."

What follows is our response to these points updated to reflect the discount proposed to enter the CDF.

MSD's base-case

- **Deterministic analysis results**

Table 1 presents our preferred base-case deterministic results based on the 18 Jan 2017 data cut. Our preferred base-case is based on the following assumptions:

- Two-stage for treatment switching
- OS cut-off point at 40 weeks with log-normal distribution for extrapolation
- PFS cut-off point at 21 weeks with Gompertz distribution for extrapolation
- Weibull and GenGamma distributions for ToT of pembrolizumab and UK SOC

- Pooled (pembrolizumab and control group) utility values based on time-to-death 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	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£58,049	2.81	2.02	£36,802	0.90	£41,004
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

- **Probabilistic analysis results**

Probabilistic sensitivity analysis was undertaken using 1,000 samples. The results are presented in Table **2. Probabilistic results for MSD base-case (discounted)**, below.

Table 2. Probabilistic results for MSD base-case (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,246	1.62	1.12	-	-	-
Pembrolizumab	£58,049	2.81	2.02	£36,864	0.90	£41,103
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

"The technical team noted that the additional trial evidence submitted prior to the ACD publication did not incorporate the committee's preferred assumptions. NICE would expect the following assumptions to be incorporated:

- excluding the vinflunine data from utilities (see section 3.17)
- pooling utilities across treatment arms by progression state (see sections 3.16 to 3.17)
- using an updated algorithm to calculate age-related disutility (see section 3.16)
- changing the proportion of people having docetaxel and paclitaxel to UK market share.

Committee's preferred assumptions

- **Deterministic analysis results**

Table 3 presents the deterministic results based on 18 Jan 2017 data cut incorporating the Committees preferred assumptions to the MSD base-case:

- Excluding the vinflunine data from utilities
- Pooling utilities across treatment arms by progression state
- Using an updated algorithm to calculate age-related disutility
- Changing the proportion of people having docetaxel and paclitaxel to UK market share
    - Please note that the most current UK market share proportions (re-adjusted by the exclusion of platinum-containing chemotherapy) have changed since the CS and are currently as follows:
        - Paclitaxel – 39%
        - Docetaxel – 61%
    - This has been incorporated into the Committees preferred assumptions

Table 3. Deterministic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,193	1.62	1.05	-	-	-
Pembrolizumab	£58,049	2.81	1.93	£36,856	0.88	£41,894
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

- **Probabilistic analysis results**

Probabilistic sensitivity analysis was undertaken using 1,000 samples. The results are presented in Table 4. **Probabilistic results** below.

Table 4. Probabilistic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,591	1.65	1.08			

Pembrolizumab	£58,508	2.84	1.95	£36,918	0.87	£42,585
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

A key uncertainty for committee was the assumptions around the extrapolation modelling. NICE would expect to see full sensitivity analyses around the following:

- The choice of cut-off point at which to extrapolate the overall survival trial data (see section 3.13) – please note that the ERG stated that a cut-off at week 16 (the point at which the cumulative hazards cross) would be their choice, but were unable to explore this in the economic model.
- Choice of parametric curve to extrapolate overall survival (see section 3.14)

16-week time point for extrapolation

The goodness of fit data presented below in Table 5. **Goodness-of-fit statistics based on the extrapolations using data beyond the 16-week cut-off, for pembrolizumab and UK SOC** is based on analysis using a 16-week time point for extrapolation.

For both the pembrolizumab and the UK SOC treatment arms, the curves presenting the closest statistical fit to the trial data are the Gompertz, the Llogistic and the Lnormal, in order of best fit. In the ACD, the Committee concluded that they would expect the 5 year overall survival in the UK SOC arm to be within the range of estimates used by the ERG (2-3%) and the company (9-11%). Based on this range, extrapolation using Gompertz is not appropriate as it estimates a 5-year OS of 11.6% (Table **6**) which is outside the range considered plausible by the Committee. Furthermore, using the Exponential and Weibull curves underestimates 5-year OS estimates of 0.2% and 1.3% respectively. The GenGamma is the curve with the second highest AIC/BIC values indicating its poor fit to the trial data, and so despite a clinically plausible 5 year OS of 3.8%, it is not appropriate for extrapolation. Therefore, based on both the goodness of fit and the clinical plausibility of the 5-year OS estimates, the most plausible curve for extrapolation at 16 weeks is the Llogistic. The Lnormal may also be considered appropriate; however its statistical fit to the trial data is second to that of the Llogistic curve.

Table 5. Goodness-of-fit statistics based on the extrapolations using data beyond the 16-week cut-off, for pembrolizumab and UK SOC

Fitted Function	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	730.2	733.1	734.3	737.1
Weibull	726.7	732.6	731.7	737.2
Gompertz	724.6	730.4	729.2	734.8
Llogistic	725.2	731	729.4	735
Lnormal	725.8	731.6	731	736.5
GenGamma	727.2	736	731.7	740

Table 6. Overall survival estimates by parametric distribution

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
UK SOC						
1-year	31.8%	31.5%	30.8%	30.4%	30.0%	30.8%
3-year	9.4%	12.6%	17.0%	15.8%	16.5%	14.8%
5-year	0.2%	1.3%	6.6%	6.2%	11.6%	3.8%
10-year	0.0%	0.0%	2.8%	3.0%	10.5%	0.9%
Pembrolizumab						
1-year	49.9%	48.3%	46.9%	47.3%	46.5%	47.3%
3-year	26.9%	30.3%	33.1%	31.8%	33.7%	32.0%
5-year	4.2%	9.8%	18.7%	16.6%	28.0%	15.6%
10-year	0.2%	2.1%	11.1%	9.5%	25.3%	7.5%

Table**TABLE** 7 compares the outcomes of the pembrolizumab and UK SOC arms of the KEYNOTE-045 trials with the outcomes from the model. Both the 16-week and the 40-week time points for extrapolation produce model estimates which are similar to the results of the trial.

Table 7. Comparison of model and trial outcomes

	Pembrolizumab			UK SOC		
Outcome	**MSD-base case (40 week, Lnormal)**	**ERG request (16 week, Llogistic)**	**KEYNOTE-045**	**MSD-base case (40 week, Lnormal)**	**ERG request (16 week, Llogistic)**	**KEYNOTE-045**

Median PFS (months)	2.3	2.3	2.1	3.4	3.4	3.2
6-month PFS	28.6%	27.9%	28.8%	22.8%	24.7%	22.7%
Median OS (months)	10.3	10.8	10.3	7.1	6.7	6.9
6-month OS	64.1%	64.4%	63.9%	54.8%	54.0%	54.5%
1-year OS	45.5%	47.3%	43.9%	29.6%	30.4%	30.2%
2-year OS	30.0%	31.8%	-	16.4%	15.8%	-
5-year OS	16.7%	16.6%	-	7.8%	6.2%	-
10-year OS	9.9%	9.5%	-	4.2%	3.0%	-

Cost-effectiveness analysis results incorporating the Committees preferred assumptions at a 16 week time point for extrapolation

- **Deterministic analysis results**

Table Table 8 presents the deterministic results based on a 16-week time point for extrapolation using the Llogistic curve and incorporating the Committees preferred assumptions:

- Excluding the vinflunine data from utilities
- Pooling utilities across treatment arms by progression state
- Using an updated algorithm to calculate age-related disutility
- Changing the proportion of people having docetaxel and paclitaxel to UK market share
    - As above, please note this has been updated in line with the most recent market shares.

Table 8. Deterministic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£19,814	1.42	0.94	-	-	-
Pembrolizumab	£57,367	2.72	1.88	£37,552	0.94	£39,812
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

- **Probabilistic analysis results**

Probabilistic sensitivity analysis was undertaken using 1,000 samples. The results are presented on Table 9 below.

Table 9. Probabilistic results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£19,814	1.42	0.94	-	-	-
Pembrolizumab	£57,366	2.72	1.88	£37,793	0.94	£40,024
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

In Table 10, MSD have also explored the impact of the 16 week cut off on the ICER when using MSDs preferred assumptions (excepting the 40 week time point for extrapolation) and including the Committees preferred assumptions using all plausible parametric curves for extrapolation.

Table 10. Comparison of impact of assumptions on the incremental cost-effectiveness ratio at a 16-week time point

Parametric curve	Basecase	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Llogistic	MSDs assumptions	UK SOC	£19,868	1.42	0.97	-	-	-
		Pembrolizumab	£57,367	2.72	1.96	£37,499	0.99	£37,999
	Including the Committees preferred assumptions	UK SOC	£19,814	1.42	0.94	-	-	-
		Pembrolizumab	£57,367	2.72	1.88	£37,552	0.94	£39,812
Lnormal	MSDs assumptions	UK SOC	£19,821	1.42	0.97	-	-	-
		Pembrolizumab	£58,981	2.94	2.12	£39,160	1.15	£33,969
	Including the Committees preferred assumptions	UK SOC	£19,767	1.42	0.93	-	-	-
		Pembrolizumab	£58,981	2.94	2.02	£39,214	1.09	£36,079
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

In addition the committee noted that the economic model excludes rare but potentially serious adverse events that are specific to immunotherapy (see section 3.11) and assume an implausible lifetime continued treatment effect (see section 3.15). NICE would prefer to see scenario analyses which explore these assumptions around the new company base case.

MSD base-case

- Two-stage for treatment switching
- OS cut-off point at 40 weeks with log-normal distribution for extrapolation
- PFS cut-off point at 21 weeks with Gompertz distribution for extrapolation
- Weibull and GenGamma distributions for ToT of pembrolizumab and UK SOC
- Pooled (pembrolizumab and control group) utility values based on time-to-death approach

Adverse events of special interest (AEOSI)

In line with previous NICE HTA submissions of pembrolizumab and other immunotherapy agents, only Grade 3+ AEs with an incidence of at least 5% in any of the arms were included in the cost-effectiveness model (Table 11).

In line with this approach, MSD has included only Grade 3+ AEOSIs in the requested analysis. MSD has explored the impact of AEOSI's in the cost-effectiveness analysis by conservatively incorporating Grade 3+ AEOSI's only in the pembrolizumab arm (

Table **12**), and also by incorporating Grade 3+ AEOSI's into both the pembrolizumab and the UK SOC arms (Table 13).

Table 11. AEOSI's in the As-Treated Population (KEYNOTE-045)

Event	Pembrolizumab Group (N = 266)		Chemotherapy Group (N = 255)		UK SOC Group [redacted]	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4 or 5
	Number of patients (percent)					
AEOSI's						
Any event	45 (16.9)	12 (4.5)	19 (7.5)	4 (1.6)	[redacted]	[redacted]
Hypothyroidism	17 (6.4)	0	3 (1.2)	0	[redacted]	[redacted]
Hyperthyroidism	10 (3.8)	0	1 (0.4)	0	[redacted]	[redacted]
Pneumonitis	11 (4.1)	6 (2.3)	1 (0.4)	0	[redacted]	[redacted]
Colitis	6 (2.3)	3 (1.1)	1 (0.4)	0	[redacted]	[redacted]
Infusion reaction	2 (0.8)	0	10 (3.9)	0	[redacted]	[redacted]
Nephritis	2 (0.8)	2 (0.8)	0	0	[redacted]	[redacted]
Severe skin reaction	2 (0.8)	1 (0.4)	3 (1.2)	3 (1.2)	[redacted]	[redacted]
Thyroiditis	2 (0.8)	0	0	0	[redacted]	[redacted]
Adrenal insufficiency	1 (0.4)	1 (0.4)	0	0	[redacted]	[redacted]

Myositis	0	0	1 (0.4)	1 (0.4)	[redacted]	[redacted]

Table 12. Deterministic results including Grade 3+ AEOSIs in pembrolizumab arm only

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,251	1.62	1.12	-	-	-
Pembrolizumab	£58,108	2.81	2.02	£36,857	0.90	£41,065
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Table 13. Deterministic results including Grade 3+ AEOSIs in both treatment arms

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£58,108	2.81	2.02	£36,861	0.90	£41,070
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

Long term treatment effect

Table 14. Impact of lifetime treatment effect on ICER

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER (£) versus baseline (QALYs)
Lifetime treatment effect						
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£58,049	2.81	2.02	£36,802	0.90	£41,004
Continued treatment effect over 10 years						

UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£57,837	2.78	2.00	£35,590	0.88	£41,706
Continued treatment effect over 5 years						
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£57,247	2.70	1.94	£36,001	0.82	£43,851
Continued treatment effect over 3 years						
UK SOC	£21,247	1.62	1.12	-	-	-
Pembrolizumab	£56,579	2.62	1.88	£34,727	0.75	£46,801

Dear Thomas,

Re. Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1019]

Following your email, please find below the requested cost-effectiveness analysis results.

Please note that there is no confidential information in this document.

Kind regards,

Chris O'Regan,
Head of HTA and OR

Could we please request that you submit an additional document which includes the new value proposition for the following key analyses:

- Deterministic ICER using the ERG's preferred assumptions (i.e. using the assumptions listed in table 11 of the ERG addendum)

Please find in Table 1 below the deterministic results based on the following ERG's preferred assumptions:

- OS cut-off at 24 weeks
- OS parametric distribution: Log-logistic
- PFS parametric distribution: Weibull
- Distribution of patients in the UK based on UK market shares
- Pooled progression-based utilities of only paclitaxel and docetaxel patients
- Age-adjusted utility decrements based on Ara et al 2010

Table 1: Deterministic results based on ERG's preferred assumptions

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£18,271	0.80	-	-	-
Pembrolizumab	£54,447	1.61	£36,176	0.81	£44,504

- As above, but using the company's preferred overall survival extrapolation assumptions (i.e. a log-normal curve at the week 40 cut-off)

Please find in Table 1 below the deterministic results based on the following assumptions:

- OS cut-off at 40 weeks
- OS parametric distribution: Log-normal
- PFS parametric distribution: Weibull
- Distribution of patients in the UK based on UK market shares
- Pooled progression-based utilities of only paclitaxel and docetaxel patients
- Age-adjusted utility decrements based on Ara et al 2010

Table 2: Deterministic results based on MSD's preferred overall survival extrapolation assumptions

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
UK SOC	£21,165	1.05	-	-	-
Pembrolizumab	£56,881	1.82	£35,715	0.77	£46,447

- Scenario analyses on continued treatment effect (3, 5 and 10 years) for both of the above.

Please find in Table 3 below scenario analyses based on the above ERG's preferred assumptions with continued treatment effect at 3, 5 and 10 years.

Table 3: Scenario analyses based on ERG's preferred assumptions

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
					Base case
UK SOC	£18,271	0.80	-	-	-
Pembrolizumab	£54,447	1.61	£36,176	0.81	£44,504
					3 years
UK SOC	£18,271	0.80	-	-	-
Pembrolizumab	£51,872	1.39	£33,600	0.59	£56,716
					5 years
UK SOC	£18,271	0.80	-	-	-
Pembrolizumab	£53,061	1.50	£34,789	0.70	£49,942
					10 years
UK SOC	£18,271	0.80	-	-	-
Pembrolizumab	£54,073	1.58	£35,802	0.78	£45,743

Please find in Table 4 below scenario analyses based on the ERG's preferred assumptions and MSD's preferred approach to parametric extrapolation with continued treatment effect at 3, 5 and 10 years.

Table 4: Scenario analyses based on ERG's preferred assumptions and MSD's approach to OS extrapolation

Technologies	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
					Base case
UK SOC	£21,165	1.05	-	-	-
Pembrolizumab	£56,881	1.82	£35,715	0.77	£46,447
					3 years
UK SOC	£21,165	1.05	-	-	-
Pembrolizumab	£55,574	1.71	£34,409	0.66	£52,310
					5 years
UK SOC	£21,165	1.05	-	-	-
Pembrolizumab	£56,177	1.76	£35,012	0.71	£49,303

					10 years
UK SOC	£21,165	1.05	-	-	-
Pembrolizumab	£56,695	1.81	£35,529	0.75	£47,126