NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

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 UK Ltd
   - Roy Castle Lung Cancer Foundation
   - British Thoracic Oncology Group
   - Royal College of Physicians
   - NHS England
   - Bristol Myers Squibb

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

4. **Additional evidence from the company, Merck Sharp and Dohme**
   - Evidence including initial discount
   - Evidence including updated discount

5. **Evidence Review Group critique of additional evidence including initial discount, provided by Aberdeen HTA Group**

The Department of Health provided a 'no comments' response to the ACD.

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SingleTechnology Appraisal

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy

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

Definitions:

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

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

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

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

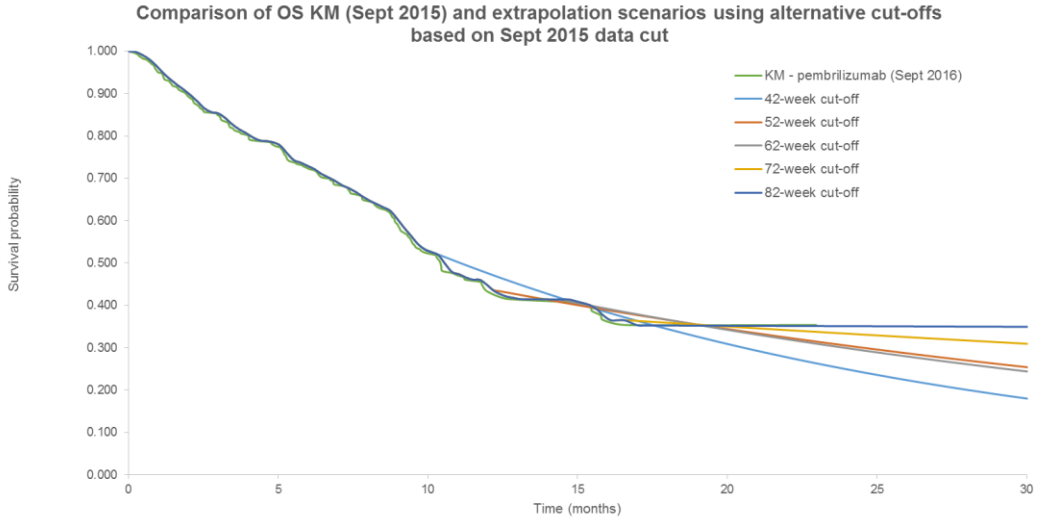
Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not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

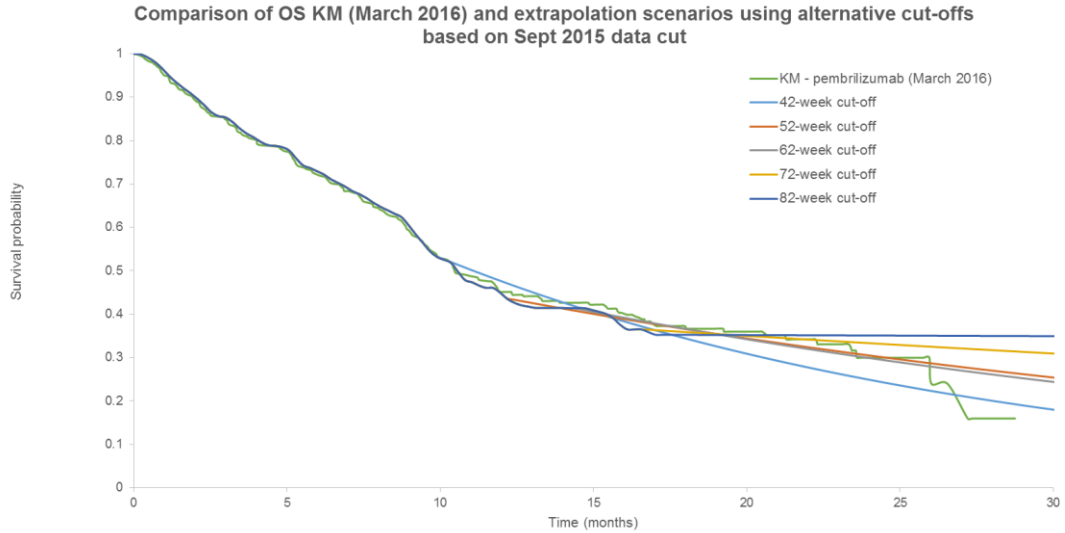
Comments received from consultees

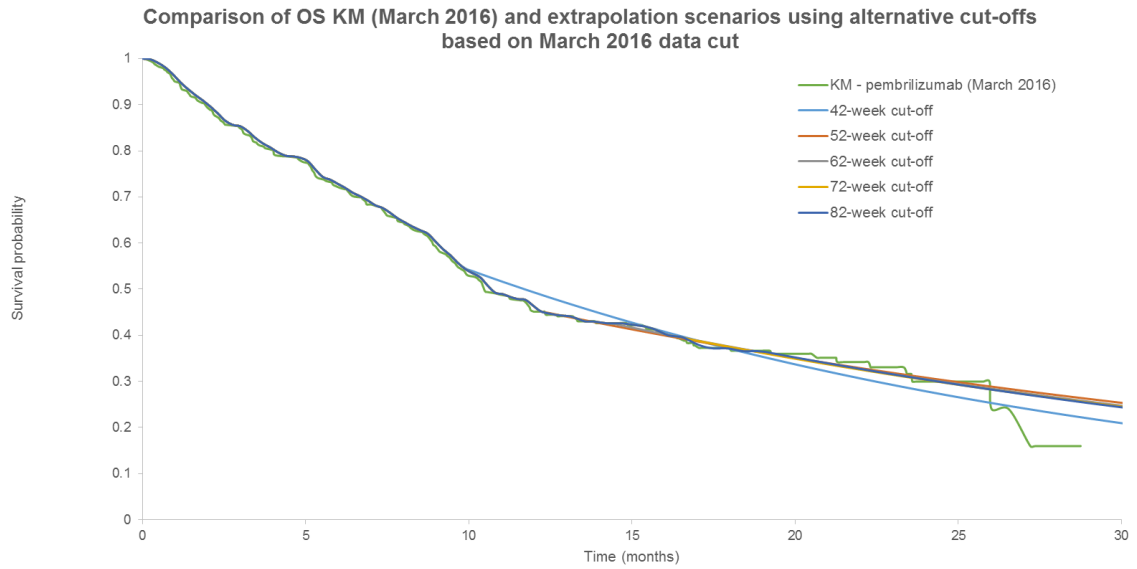
Consultee	Comment [sic]	Response
Merck Sharp & Dohme	We were disappointed after reading the document with the provisional negative recommendation given we are confident that we are cost effective. Our response is provided below and is formulated around what we believe to be the key drivers underpinning the draft recommendation, uncertainty/scepticism around: • Duration of treatment. • Duration of treatment benefit. • Actual treatment benefit. • Selection of extrapolation time point. **Duration of treatment** The ACD states *'…The committee concluded that for the base case, all people having pembrolizumab would continue treatment after 2 years if their disease had not progressed.*' MSD believes that, given the acknowledged uncertainty in the ACD, using one extreme is inappropriate. MSD, acknowledging the uncertainty expressed by one of the clinicians, revised our base case from 0% to 25% to reflect the proportion of patients remaining progression free and on treatment at two years, carrying on treatment with pembrolizumab. We have asked a total of fourteen practicing UK oncologists (including the two clinical experts who had provided evidence at the Committee meeting(s)) treating patients with lung cancer, a number of questions in relation to the ACD (all were aware of the original and the updated KEYNOTE-010 data, KEYNOTE-024 data, as well as data for nivolumab in relation to the treatment of lung cancer). Regarding treatment duration no-one was prepared to provide an answer either way, although a number reflected that in two years' time, when faced with making a decision, they would expect to be	Thank you for your comment. The committee noted the uncertainty around the optimal duration of treatment and concluded that implementation of a 2-year stopping rule and review of the published guidance at 2 years is appropriate. For further information please see sections 4.8 of the final appraisal document (FAD).

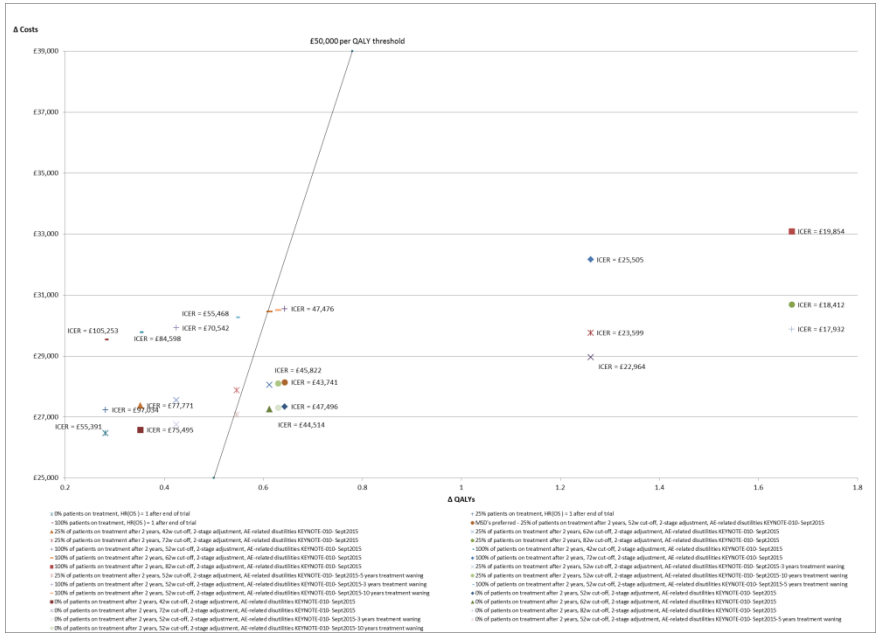
Consultee	Comment [sic]	Response
	in possession of sufficient new information to enable them to be confident about the right duration of therapy. Two of the clinicians who have been involved in KEYNOTE-010 and KEYNOTE-024 expressed the view that the proportion continuing would be lower rather than higher.	
Merck Sharp & Dohme	**Duration of treatment benefit** The ACD states *'…The committee recalled that the modelling projections used by the company suggested that 12% of patients in the pembrolizumab arm would be alive at 5 years and agreed with the experts that this was extremely optimistic, as was the assumption of no waning of treatment effect over 20 years.'* MSD is uncertain about the origin of '12%' (the figure is actually 10.4%). The three, five and ten year estimates from our model, in base case 2, are 21.6%, 10.4% and 1.7% respectively. These estimates demonstrate that we already have a 'waning of treatment effect' reflected in our modelling of overall survival (OS). We are aware that Committee B, evaluating nivolumab for use in patients with metastatic renal cell carcinoma, was presented with an artificially upward manipulated OS curve, based on the belief that a recent analysis of the long term data for the use of ipilimumab in metastatic melanoma provided evidence that check point inhibitors can be expected to provide a long term benefit ('tail'), well after cessation of treatment. Although MSD agrees that there is probably a long term benefit for some patients, this assumption was not incorporated in our analyses; believing that the combination of our Kaplan-Meier data and an exponential parametric extrapolation (in line with virtually every other recent NICE submission for oncology technologies) was the correct approach. Of interest, Committee B dismissed the manufacturer's artificial adjustment and instead accepted their KM data with an exponential extrapolation as the preferred basis for decision making. As noted earlier, we asked a number of clinicians whether they believed the (rounded) 3, 5 and 10 year figures of 20%, 10% and 1.7% were either optimistic, pessimistic or reasonable. 10 answered reasonable, 2 answered pessimistic, and 2 answered optimistic. Of the 2 who answered optimistic, one specified that he believed the 10 year number to be reasonable.	Thank you for your comment. The origin of the '12%' figure was the modelling projections using the KEYNOTE-01 trial data. This has been updated to reflect the modelling projections using both the September 2015 and March 2016 KEYSTONE-010 data. The committee considered that although there is evidence to support a continued benefit of pembrolizumab after stopping treatment and in the progressed state, the size of this effect and its duration is unknown for NSCLC. The committee concluded that the ICERs were sensitive to a continued treatment effect after stopping treatment, and although it considered the company's preferred scenario of a lifetime treatment effect to be implausible, it had not been presented with any evidence on which it could agree a single clinically plausible scenario.

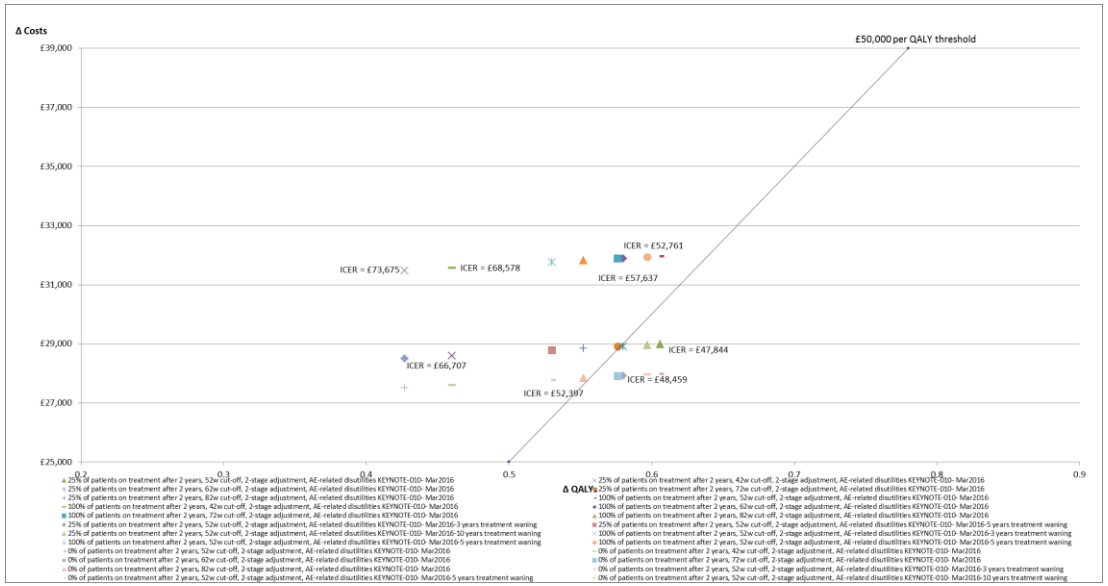
Consultee	Comment [sic]	Response
	MSD therefore believes that both our 5 year survival projection and our longer term estimates of survival (1.7% at 10 years) are credible and reasonable. MSD also believes that artificially manipulating the survival projection downwards is not reasonable, as not reflective of recent approaches by Evidence Review Groups and Appraisal Committees in relation to the evaluation of oncology technologies. In relation to this we also note that the Committee states *'…In contrast, if the analysis is repeated with a hazard ratio of 1, representing no long-term incremental effect on survival, the incremental overall survival would be 0.18 years.'* MSD would note that Professor Hoyle of PenTAG has recently stated that this (changing the Hazard Ratio to 1) would never be done in the presence of survival data from a 'good' RCT. **Actual treatment benefit** Related to the point above, there were concerns expressed at the second Committee meeting that the 10.4% was not credible at five years given that the KEYNOTE-010 analyses showed a worse survival of 5% (possibly due to a misreading of one of the MSD's additional analyses provided between the first and second committee meetings. This has not been reflected in the ACD and we therefore hope that the Committee, given 50% of patients in the pembrolizumab arm of the study were still alive at study end, has recognised that the comments were at odds with the evidence.	For further information please see sections 4.14 of the final appraisal document (FAD).
Merck Sharp & Dohme	**Selection of extrapolation timepoint** The ACD states *'…The committee concluded that there was no evidence that the 52-week cut-off was the most appropriate for extrapolating the Kaplan– Meier data and that the ICER was very sensitive to the cut-off point chosen to model overall survival. The committee concluded that the choice of the 52-week cut-off point was overly optimistic.'* and goes on to rebut all of the supporting arguments used by MSD. MSD is particularly disappointed about this element of the ACD and the discussions it in part reflects. We discussed one comment from the ACD *'…The ERG commented that this inflection is a result of the modelling approach that treats the timing of deaths up to 52 weeks as being unrelated to the timing of deaths beyond 52 weeks.'* We have discussed this today with our head of statistics who is clear that the 'inflection' in the KM curves for both September and March is related to the data and not the model.	Thank you for your comment. The FAD states 'the committee concluded that the 42-week and 82-week cut-offs could be excluded from consideration, however there remained no evidence that the 52-week cut-off chosen by the company and ERG for their base-case analyses is the most appropriate for extrapolating the Kaplan–Meier data. The committee concluded that the choice of the 52-week, 62-week and 72-week cut-off points would all be plausible, but noted that based on the additional evidence submitted by

Consultee	Comment [sic]	Response
	In an attempt to provide clarity regarding the appropriateness of our selection to the 52-week cut-off point, we have superimposed all of the original extrapolations on the K-M data in the figure below. It can be clearly seen that the 42 week and 82 week cut-off points do not fit the data at all (Figure 1). In figure 2 we provide the same analysis using the September cut-off extrapolations superimposed on the March KM data which supports the conclusion above. Figure 3 which applies all of the cut-off points to the new March data supports our assertion that the variability in the original range of cut-offs was generated by the relative paucity of data. **Figure 1. Comparison of OS KM (September 2015) and extrapolation scenarios using alternative cut-off points based on Sept 2015 data cut**  	the company during consultation, the ICER is no longer very sensitive to the choice of these cut-off points chosen to model overall survival.' For further information please see sections 4.13 of the final appraisal document (FAD).

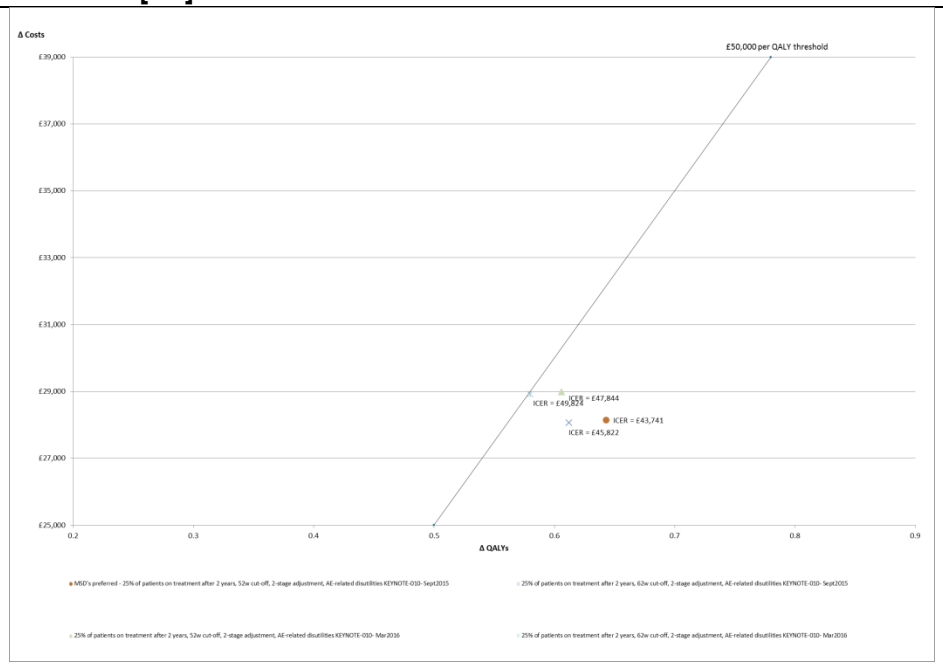
Consultee	Comment [sic]	Response
	Figure 2. Comparison of OS KM (March 2016) and extrapolation scenarios using alternative cut-off points based on Sept 2015 data cut  **Figure 3. Comparison of OS KM (March 2016) and extrapolation scenarios using alternative cut-off points based on March 2016 data cut**	

Consultee	Comment [sic]	Response
		
Merck Sharp & Dohme	The Committee has been presented with a significant number of ICERs over the course of the last two meetings as well as in our most recent submission of evidence. We have become concerned that this 'cloud' of ICERs is masking the small number of ICERs around which we believe any discussion of the value of pembrolizumab for treating patients with advanced NSCLC. We have therefore presented below a summary of the ICERs derived from the September 2015 data cut as originally presented to NICE (see Figure 4). A further summary substituting ICERs derived from the March 2016 data cut for the September equivalent (see Figure 5). In Figure 6 we have removed all ICERs that we argue are implausible, supported in a number of these by the ERG, and for others, on the basis of consultation with clinicians. We have listed between Figures 5 and 6 the rationale for the removal of the various ICERs.	Thank you for your comment. The committee concluded that the key area of uncertainty which remains is the long-term treatment effect. It considered the assumption of a constant treatment effect over 20 years, irrespective of the time spent on treatment or disease progression, was unlikely based on current clinical understanding of disease progression. The ICERs are sensitive to a continued treatment effect after stopping

Consultee	Comment [sic]	Response
	Figure 4. ICERs presented by MSD or discussed at the previous committee meetings using the original data cut from September 2015.  	treatment, but the committee noted that within the uncertainties that exist, there are plausible ICERs that are below the range usually considered to be a cost effective use of NHS resources. For further information please see sections 4.14 and 4.16 of the final appraisal document (FAD).

Consultee	Comment [sic]	Response
	Figure 5. ICERs presented by MSD or discussed at the previous committee meetings using the data cut from March 2016.  The following have been excluded from the figure below: ▪ Scenarios using extreme values for the proportion of patients being treated beyond 2 years (i.e. 0%, as presented in our original submission, and 100%), leaving the analyses that assume 25% of patients would be treated beyond 2 years. ▪ Scenarios where extrapolation based on specific data cut-offs resulted in implausible estimations (including the cut-offs at 42 weeks and 82 weeks). ▪ Scenarios that tested waning of the pembrolizumab treatment effect, including:	

Consultee	Comment [sic]	Response
	○ Analyses where a HR = 1 was assumed for pembrolizumab when compared to docetaxel ○ Those requested by the Committee, assuming the benefit of pembrolizumab would stop at 3, 5 and 10 years. The four remaining ICERs below are those which we believe should form the basis of the third discussion by this Committee around the value of pembrolizumab for patients with advanced NSCLC. **Figure 6. ICERs after the exclusion of selected ICERs**	

Consultee	Comment [sic]	Response
		
British Thoracic Oncology Group	Pembrolizumab is an innovative, novel, targeted compound with very clear clinical data demonstrating superiority over conventional chemotherapy in the second line setting in patients expressing PDL-1. Although outside the remit of this appraisal it is also worthy to note that more recent published data has confirmed the significant superiority of this compound in non-small cell lung cancer (NSCLC) in a first line setting. From the report following the second committee meeting Pembrolizumab was not recommended within its marketing authorisation. From a clinical perspective this is obviously very disappointing. There are a number of specific points I would like to point out and I would be grateful if they could be taken into consideration:	Thank you for your comment. The committee noted the uncertainty around the optimal duration of treatment and concluded that implementation of a 2-year stopping rule and review of the published guidance at 2 years is appropriate. For further information please see sections 4.8 of the final appraisal document (FAD). The committee considered that although there is evidence to support a continued benefit of pembrolizumab after stopping

Consultee	Comment [sic]	Response
	Whilst not expressly mentioned in the document, it is important that direct clinical comparisons between the NSCLC patients and patients with other malignancies in where immunotherapies are used ie. melanoma should not be made. They are distinct clinical entities. The economic modelling system appears to assume that 25% of patients would continue on the treatment at the 2 year period and therefore this would impact the cost effectiveness of the drug. From a clinical perspective whilst it is very difficult to project in the future, through clinical experience it would seem very unlikely and optimistic that this percentage of patients would remain on treatment 2 years on. Furthermore the longer term projections would appear to suggest that an estimated 1-2% of patients being alive at 10 years would clinically seem reasonable, but it would be very difficult to suggest that this would only be the case due to the positive effects of pembrolizumab. From a clinical perspective it would be very reasonable to estimate that in a whole rage of tumour types where long term survival is poor a small number of patients remain alive at both the 5 and 10 year period for a whole variety of reasons even in the absence of novel therapeutic compounds. Nevertheless this percentage represents a small number of patients.	treatment and in the progressed state, the size of this effect and its duration is unknown for NSCLC. The committee concluded that the ICERs were sensitive to a continued treatment effect after stopping treatment, and although it considered the company's preferred scenario of a lifetime treatment effect to be implausible, it had not been presented with any evidence on which it could agree a single clinically plausible scenario. For further information please see sections 4.14 of the final appraisal document (FAD).

Consultee	Comment [sic]	Response
	I would like to reiterate that the population of patients with any PDL-1 expression appears consistently between approximately 50-60% across a number of published clinical trials and those with much higher, i.e. 50% expression is significantly lower than this. Therefore pembrolizumab would not be suitable for every patient in the second line setting. Finally the tolerability and ease of administration of these compounds is a positive and meaningful outcome from a patient perspective.	
NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation. We would like to make the following comments. Although it is very disappointing to see this outcome, we do not have many significant comments on the accuracy of the clinical information within the report. The arrival of immune checkpoint inhibitors is one of the biggest breakthroughs in the management of patients with advanced NSCLC and is revolutionising its management across the world. It is therefore really disappointing that English patients, who have such a poor outcome currently, will not be able to gain the benefits of this important new drug. Patient selection criteria are being further evaluated and more knowledge gained about the best way to use pembrolizumab for patients with lung cancer through ongoing research, but effort has been made within the pembrolizumab development program to select patients most likely to gain benefit, by the parallel evaluation of PD-L1 testing, which is laudable.	Thank you for your comment. The committee noted the uncertainty around the optimal duration of treatment and concluded that implementation of a 2-year stopping rule and review of the published guidance at 2 years is appropriate. For further information please see sections 4.8 of the final appraisal document (FAD). The committee considered that although there is evidence to support a continued benefit of pembrolizumab after stopping treatment and in the progressed state, the size of this effect and its duration is unknown for NSCLC. The committee concluded that the ICERs were sensitive to a continued treatment effect after stopping treatment, and although it considered the company's preferred scenario of a lifetime treatment effect to be implausible, it had not been presented with any

Consultee	Comment [sic]	Response
	Our clinical expert believes that the committee's conclusion that all patients who remain on treatment at 2 years will continue on therapy is inaccurate, and notes that this was voiced at the appraisal committee meeting. A significant proportion of patients whose disease is controlled will stop treatment for other reasons and this proportion will increase over time. It is difficult to accurately estimate the proportion who would continue but the company's estimate of 25% is probably closer to the reality. Our expert notes experience of a number of patients ceasing therapy without progression, citing only 1 patient who had been on for 2 years. This patient stopped therapy at that point (as mandated within the study) without any undue concern and feels better for being off treatment. When considering the long term treatment effects, we highlight again that as data mature from studies with immune checkpoint inhibitors across multiple tumour types there remains a proportion of patients with a maintained effect even out to 5 years, which is expected to be the case in NSCLC too. However, the data for the long term effects of pembrolizumab in NSCLC remain immature and hence require modelling, which is sensitive to even subtle changes in the predictions used, making accurate ICER calculations very difficult. Our experts find the subtleties of the extrapolated survival and associated economic modelling complex and were unable to make any meaningful comments on these. We would strongly encourage that the manufacturers look carefully at their pricing structure to improve pembrolizumab's cost effectiveness in this setting and urge NICE to push for this.	evidence on which it could agree a single clinically plausible scenario. For further information please see sections 4.14 of the final appraisal document (FAD). The Department of Health and Merck Sharp & Dohme have agreed that pembrolizumab will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. For further information please see sections 5.4 of the final appraisal document (FAD).
Roy Castle Lung Cancer Foundation	• We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Pembrolizumab in this indication.	Thank you for your comment. The committee noted the uncertainty around the optimal duration of treatment and concluded that

Consultee	Comment [sic]	Response
	• In our opinion, immunotherapy represents a major new development in the treatment of nsclc patients. Internationally, the discovery of PD-L1 inhibition has altered practice in nsclc management. It is therefore important that a PD-L1 inhibitor be available in the algorithm of lung cancer care in England. • We welcome many of the conclusions reached by the Appraisal Committee in this ACD o Pembrolizumab has an important extension of life benefit, for people with locally advanced or metastatic nsclc, whose tumours express PD-L1, as in the KEYNOTE-010 trial data. (section 4.5) o Pembrolizumab meets the criteria of a life extending, end of life treatment (section 4.17) • We note in section 4.15, the Appraisal Committee's discussion and conclusion, that all patients who continue to benefit would continue Pembrolizumab beyond two years. This would have the effect of increasing the ICER. In the short period since publication of the ACD, we have undertaken some informal discussion, seeking the views of both patients and lung cancer clinical experts. There is no obvious consensus in our anecdotal poll. Some patients say that, should they be benefiting at two years, instinctively, with a disease such as advanced nsclc, they would want to continue. Others have noted that this is a three weekly intra-venous therapy, requiring travel to hospital and at two years, would likely want a break, if no evidence for continuing.	implementation of a 2-year stopping rule and review of the published guidance at 2 years is appropriate. For further information please see sections 4.8 of the final appraisal document (FAD).

Consultee	Comment [sic]	Response
	On discussion with the clinician experts, it appears that there is no consensus, as yet, as to the optimal duration – 6 months, 12 months, 18 months, 24 months…… We appreciate this makes a difference to the cost modelling and as such would encourage the Appraisal Committee to have further discussion with clinical experts, who have experience with using this treatment. Would collection of such information through the Cancer Drugs Fund be appropriate, in reducing the uncertainty?? • We note that the Appraisal Committee has reached this negative decision, based on cost issues. The committee having concluded that the most plausible ICER for Pembrolizumab, in this setting, would exceed £50,000 per QUALY gained and so, not be a cost effective use of NHS resources. (section 4.15). **On behalf of the many lung cancer patients who would derive benefit from this innovative therapy, we strongly urge constructive dialogue between the Manufacturer, NICE and NHS England, to ensure that cost issues and issues of uncertainty, in particular around the optimal duration of treatment, are addressed**. Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.	
NHS England	1. In the protocol-specified final analysis of the main phase 3 trial (KEYNOTE-010), pembrolizumab offered a significant but modest proportion of patients the chance of delaying disease progression, the PFS curves separating at 6 months with the possibility of a degree of plateauing in PFS beyond 12 months. With a median duration of follow-up of 13 months, the PFS hazard ratio (HR) for the intention to treat population (TPS ≥1%) was 0.88	Thank you for your comment. The committee considered that although there is evidence to support a continued benefit of pembrolizumab after stopping treatment and in the progressed state, the size of this effect and its

Consultee	Comment [sic]	Response
	for the pembrolizumab 2mg/kg arm when compared with docetaxel (and the HR was 0.59 for the TPS ≥50% population). NHSE now notes that longer term follow-up of this trial was presented at the ESMO conference in October 2016 with a median duration of follow up of 19 months. The HR is 0.87 for the TPS≥1% ITT population (and the HR for the TPS≥50% is 0.59). The key issue here is that with further follow up, the HRs for PFS are unchanged. 2. In addition, now that the PFS curves with a median 19 mo duration of follow up can be scrutinised and compared with the PFS curves of follow up 13 months in Keynote 010, there is an increased likelihood of a proportion of patients seeming to gain very much greater benefit with pembrolizumab ie plateauing of the PFS curve: a similar phenomenon has been observed in advanced /metastatic melanoma with the use of pembrolizumab and also with nivolumab in melanoma, renal cancer and lung cancer. The fact that the HRs for PFS did not change with further follow up is very encouraging. 3. Pembrolizumab improves median overall survival (OS) but by only 2 months. The overall survival curves separate at about 5 months and the OS curves (as with PFS) then show a significant but larger proportion of patients (than with PFS) appearing to gain a much greater benefit in survival. In the protocol-specified final analysis of the main phase 3 trial (KEYNOTE-010) in which the median duration of follow-up was 13 months, the OS hazard ratio (HR) for the intention to treat population (TPS ≥1%) was 0.71 for the pembrolizumab 2mg/kg arm when compared with docetaxel (and the HR the TPS ≥50% population was 0.54). NHSE now notes that longer term follow-up of this trial was presented at the ESMO conference in October 2016 with a median duration of follow up of 19 months. The HR is 0.72 for the TPS≥1% ITT population (and the HR for the TPS≥50% is 0.54). The very important issue here is that with further follow up, the HRs for OS are unchanged ie benefit from treatment is not lessening with further follow-up. There is therefore no current justification for assigning a HR of 1.0 for treatment effect beyond the end of the trial data.	duration is unknown for NSCLC. The committee concluded that the ICERs were sensitive to a continued treatment effect after stopping treatment, and although it considered the company's preferred scenario of a lifetime treatment effect to be implausible, it had not been presented with any evidence on which it could agree a single clinically plausible scenario. For further information please see sections 4.14 of the final appraisal document (FAD). The committee noted the uncertainty around the optimal duration of treatment and concluded that implementation of a 2-year stopping rule and review of the published guidance at 2 years is appropriate. For further information please see sections 4.8 of the final appraisal document (FAD).

Consultee	Comment [sic]	Response
	4. The other main issue that NHSE wishes to comment on is the treatment duration of pembrolizumab and what would happen at 2 years if patients remain free of disease progression and have continued to tolerate the drug well. The manufacturer's modelled PFS curve for pembrolizumab indicates that about 7-8% of patients are still free of disease progression at 24 months ie this 7-8% would stop treatment with pembrolizumab with a stopping rule in place at 24 months. NHSE previously stated that stopping rules are difficult to implement in practice when primarily instituted for cost reasons alone and also when the only then parallel in oncology is in melanoma when pembrolizumab is continued until disease progression (with significant tails observed in both PFS and OS). In its previous submission, NHSE noted that the EPAR, although recognising the trial design of a maximum treatment duration of pembrolizumab of 2 years, made no comment on treatment duration other than to include wording in the SPC to continue pembolizumab until disease progression. 5. NHSE wishes to inform NICE that current clinical opinion is changing rapidly as to the assessment as to the optimal duration of treatment with checkpoint inhibitors in cancer. Until very recently, treatment with pembrolizumab/nivolumab would have been considered to be optimal when continued to the time of either disease progression or unacceptable toxicity. However, ipilimumab is already given for a fixed duration of treatment only. Recent evidence suggests that (at least in melanoma where use of such drugs has been the greatest and longest – but the parallels with melanoma are reasonable when considering the mode of action of pembrolizumab/nivolumab and the clinical data), patients who discontinue checkpoint inhibitors for reasons other than disease progression (mainly toxicity) derive the same OS benefit as those that continue on treatment until disease progression (eg S Hodi et al, Proc Amer Soc Clin Oncol 2016: abstract 9518). Clinical experience is also pointing to the same conclusion ie that in drugs such as pembrolizumab/nivolumab, when benefits to	

Consultee	Comment [sic]	Response
	patients occur when there is sufficient recruitment of the immune system against the cancer, that recruitment of the immune system and secondary patient benefit may not require continued treatment until disease progression. There are thus trials underway in melanoma and renal cancer which are randomising patients to fixed durations of treatment of checkpoint inhibitors (eg for 1 year) versus treatment to disease progression. However, this type of trial design has already been implemented in the setting of squamous and non-squamous non small cell lung cancer previously treated with chemotherapy in a 1380 patient trial which has randomised patients still on treatment at 1 year to continue on therapy with nivolumab or discontinue treatment at that stage. The trial has completed recruitment and is in its follow up phase. Given that recruitment has been completed, results of the randomisation of treatment duration would be expected to be reported within the next 2 years. 6. Given the increasing questioning as to treatment duration for drugs such as pembrolizumab/nivolumab in cancer and the likelihood that much evidence will merge in the next 2 years as to this issue and especially so in lung cancer, NHSE is much more confident about an implementation of a 2 year stopping rule which would be acceptable to patients and clinicains and thus would be implementable. Since much data will become available as to the optimal duration of treatment of such checkpoint inhibitors within the next 2 years and a NICE recommendation for the use of pembrolizumab in October 2016 which incorporates a 2 year stopping rule would only result in patients who are still on the drug in 2 years having to stop the drug in October 2018, NHSE suggests that the use of pembrolizumab in progressed lung cancer is re-appraised by NICE in 2 years time (ie in the autmn of 2018) in case evidence does emerge that continual and continued treatment beyond 2 years is better for patients.	

Consultee	Comment [sic]	Response
	7. In addition, Keynote 010 had a trial design which allowed patients achieving a complete response to pembrolizumab to discontinue treatment but at further disease progression to re-start pembrolizumab for 12 months. Though the number of such patients eligible for such a treatment policy will be small, in 2 years time there will be lessons to be learned from this group of patients with further follow up as to the consequences of stopping treatment whilst it is still benefitting. 8. Thus, NHSE regards pembrolizumab as being an exciting drug in the 2nd/3rd line treatment of NSCLC as no other drug (bar other checkpoint inhibitors) offers this potentially much longer term survival benefit. The unchanged HRs for PFS but especially for OS that have been recently reported with greater follow up point to the same degree of benefit continuing although there remains uncertainty as to the much longer term benefit. There are no other clinical trials of other checkpoint inhibitors in lung cancer with long enough follow up to help reduce this longer term uncertainty but the parallels from melanoma point to such benefit. 9. NHSE also notes again that the clinical effectiveness of pembrolizumab is only robust when compared with docetaxel though it recognises the need for an indirect comparison with the combination of docetaxel plus nintedanib. There is no comparative data for pembrolizumab vs best supportive care and thus a positive recommendation by NICE for the use of pembrolizumab in 2nd/3rd line systemic therapy of NSCLC should only be in the patients on which the clinical and cost effectiveness rests ie in patients fit for docetaxel-containing chemotherapy as 2nd /3rd line treatment of NSCLC which expresses TPS≥1% and also if the patients are of performance status 0 or 1.	

The Department of Health stated that it had no comments on the appraisal consultation document.

Comments received from clinical experts and patient experts

Comments received from commentators

Commentators	Comment [sic]	Response
Bristol-Myers Squibb	Pembrolizumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have at least 1 chemotherapy regimen. Within this license, both squamous and non-squamous histologies of NSCLC are included. Given that the marketing authorisation has restricted the use of pembrolizumab to those patients that express PD-L1 then the specific threshold should be made clear in the recommendation. Nivolumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. Nivolumab is currently being reviewed by NICE in two separate appraisals – ne for squamous NSCLC [ID811] and another for non-squamous NSCLC [ID900]. As stated in the most recent ACD of the non-squamous appraisal ‘ the committee concluded that for the populations under consideration, the relevant comparators for this appraisal were nintedanib plus docetaxel, docetaxel monotherapy, and BSC. Given that both treatment options relate to similar patient populations, for consistency the comparators in both appraisals should be the same – in particular to the inclusion of nintedanib plus docetaxel in one appraisal and not the other.	Thank you for your comment. The committee noted that the overall population included in the KEYNOTE-010 trial had a tumour proportion score greater or equal to 1%, and heard from the clinical experts that this was likely to be the same as those who have pembrolizumab in clinical practice. The description of the technology has been updated to reflect this specific threshold of PD-L1. For further information please see sections 2 and 4.8 of the final appraisal document (FAD). The committee discussed the network meta-analysis presented by the company, which compared the relative treatment effects of pembrolizumab with nintedanib plus docetaxel in the population with adenocarcinoma. The committee concluded that the network meta-analysis was not robust, and that the trial populations of KEYNOTE-010 and LUME-LUNG-01 were too different. Therefore it was not appropriate for decision-making regarding the relative effectiveness of pembrolizumab compared with nintedanib in the population with adenocarcinoma histology. For further information please see sections 4.6 of the final appraisal document (FAD).

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Patient	General	I am a lung cancer patient diagnosed three and a half years ago, I have had various treatments including drugs trials, chemotherapy etc, some were helpful some were not.I have been given to understand that the drug under discussion could be very helpful for me. I also understand that this drug is available in Scotland but not available to patients in England. To me this is a damned disgrace we are all British citizens paying the same taxes and the same National Insurance contributions, why should they receive preferential treatment over us. This is one very disgusted British lady who is not entitled to the same treatment as other privileged Britons receive.	Thank you for your comment. Following consultation the committee concluded that that within the uncertainties, there are plausible ICERs that are below the range usually considered to be a cost effective use of NHS resources. Therefore pembrolizumab could be recommended with a 2-year stopping rule, but the guidance on this technology should be reviewed 2 years after publication to take in account more mature evidence. For further information please see sections 1.1 and 4.16-4.17 of the final appraisal document (FAD).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

MSD
Hertford Road
Hoddesdon
Hertfordshire
EN11 9BU UK
Telephone +44 (0)1992 452644
Facsimile +44 (0)1992 468175

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

20th October 2016

Dear Kate

Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840] – Appraisal Consultation Document response

We were disappointed after reading the document with the provisional negative recommendation given we are confident that we are cost effective.

Our response is provided below and is formulated around what we believe to be the key drivers underpinning the draft recommendation, uncertainty/scepticism around:

- Duration of treatment.
- Duration of treatment benefit.
- Actual treatment benefit.
- Selection of extrapolation time point.

We have also enclosed an analysis of the various ICERs generated throughout the consultation to date with a view to focusing discussion on the key issues.

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

Kind regards

[redacted]

[redacted]

Duration of treatment

The ACD states *'…The committee concluded that for the base case, all people having pembrolizumab would continue treatment after 2 years if their disease had not progressed.'*

MSD believes that, given the acknowledged uncertainty in the ACD, using one extreme is inappropriate.

MSD, acknowledging the uncertainty expressed by one of the clinicians, revised our base case from 0% to 25% to reflect the proportion of patients remaining progression free and on treatment at two years, carrying on treatment with pembrolizumab.

We have asked a total of fourteen practicing UK oncologists (including the two clinical experts who had provided evidence at the Committee meeting(s)) treating patients with lung cancer, a number of questions in relation to the ACD (all were aware of the original and the updated KEYNOTE-010 data, KEYNOTE-024 data, as well as data for nivolumab in relation to the treatment of lung cancer). Regarding treatment duration no-one was prepared to provide an answer either way, although a number reflected that in two years' time, when faced with making a decision, they would expect to be in possession of sufficient new information to enable them to be confident about the right duration of therapy. Two of the clinicians who have been involved in KEYNOTE-010 and KEYNOTE-024 expressed the view that the proportion continuing would be lower rather than higher.

Duration of treatment benefit

The ACD states *'…The committee recalled that the modelling projections used by the company suggested that 12% of patients in the pembrolizumab arm would be alive at 5 years and agreed with the experts that this was extremely optimistic, as was the assumption of no waning of treatment effect over 20 years.'*

MSD is uncertain about the origin of '12%' (the figure is actually 10.4%). The three, five and ten year estimates from our model, in base case 2, are 21.6%, 10.4% and 1.7% respectively.

These estimates demonstrate that we already have a 'waning of treatment effect' reflected in our modelling of overall survival (OS).

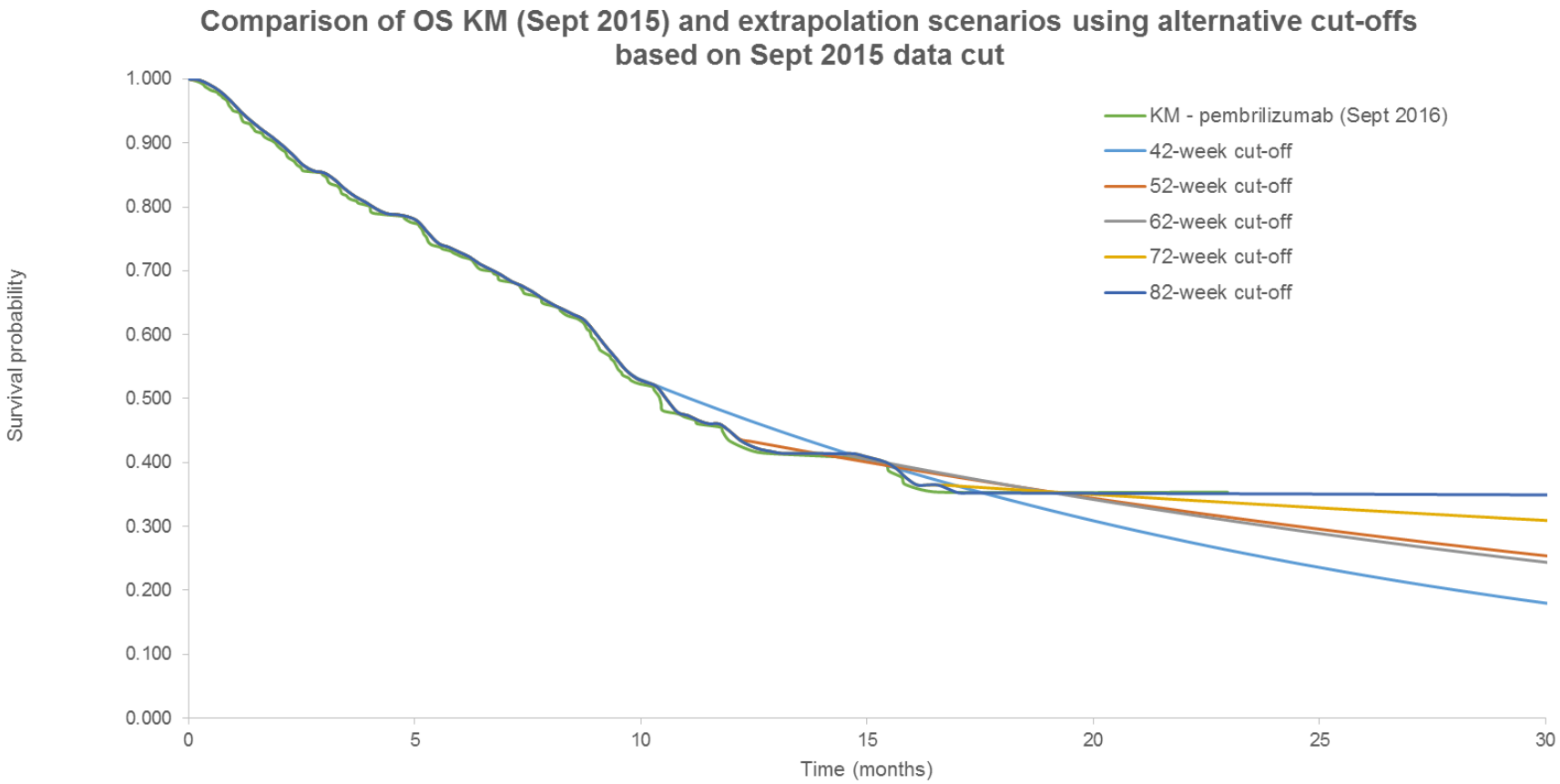
We are aware that Committee B, evaluating nivolumab for use in patients with metastatic renal cell carcinoma, was presented with an artificially upward manipulated OS curve, based on the belief that a recent analysis of the long term data for the use of ipilimumab in metastatic melanoma provided evidence that check point inhibitors can be expected to provide a long term benefit ('tail'), well after cessation of treatment. Although MSD agrees that there is probably a long term benefit for some patients, this assumption was not incorporated in our analyses; believing that the combination of our Kaplan-Meier data and an exponential parametric extrapolation (in line with virtually every other recent NICE submission for oncology technologies) was the correct approach. Of interest, Committee B dismissed the manufacturer's artificial adjustment and instead accepted their KM data with an exponential extrapolation as the preferred basis for decision making.

As noted earlier, we asked a number of clinicians whether they believed the (rounded) 3, 5 and 10 year figures of 20%, 10% and 1.7% were either optimistic, pessimistic or reasonable. 10 answered reasonable, 2 answered pessimistic, and 2 answered optimistic. Of the 2 who answered optimistic, one specified that he believed the 10 year number to be reasonable.
MSD therefore believes that both our 5 year survival projection and our longer term estimates of survival (1.7% at 10 years) are credible and reasonable. MSD also believes that artificially manipulating the survival projection downwards is not reasonable, as not reflective of recent approaches by Evidence Review Groups and Appraisal Committees in relation to the evaluation of oncology technologies.
In relation to this we also note that the Committee states *'…In contrast, if the analysis is repeated with a hazard ratio of 1, representing no long-term incremental effect on survival, the incremental overall survival would be 0.18 years.'* MSD would note that Professor Hoyle of PenTAG has recently stated that this (changing the Hazard Ratio to 1) would never be done in the presence of survival data from a 'good' RCT.

Actual treatment benefit
Related to the point above, there were concerns expressed at the second Committee meeting that the 10.4% was not credible at five years given that the KEYNOTE-010 analyses showed a worse survival of 5% (possibly due to a misreading of one of the MSD's additional analyses provided between the first and second committee meetings. This has not been reflected in the ACD and we therefore hope that the Committee, given 50% of patients in the pembrolizumab arm of the study were still alive at study end, has recognised that the comments were at odds with the evidence.

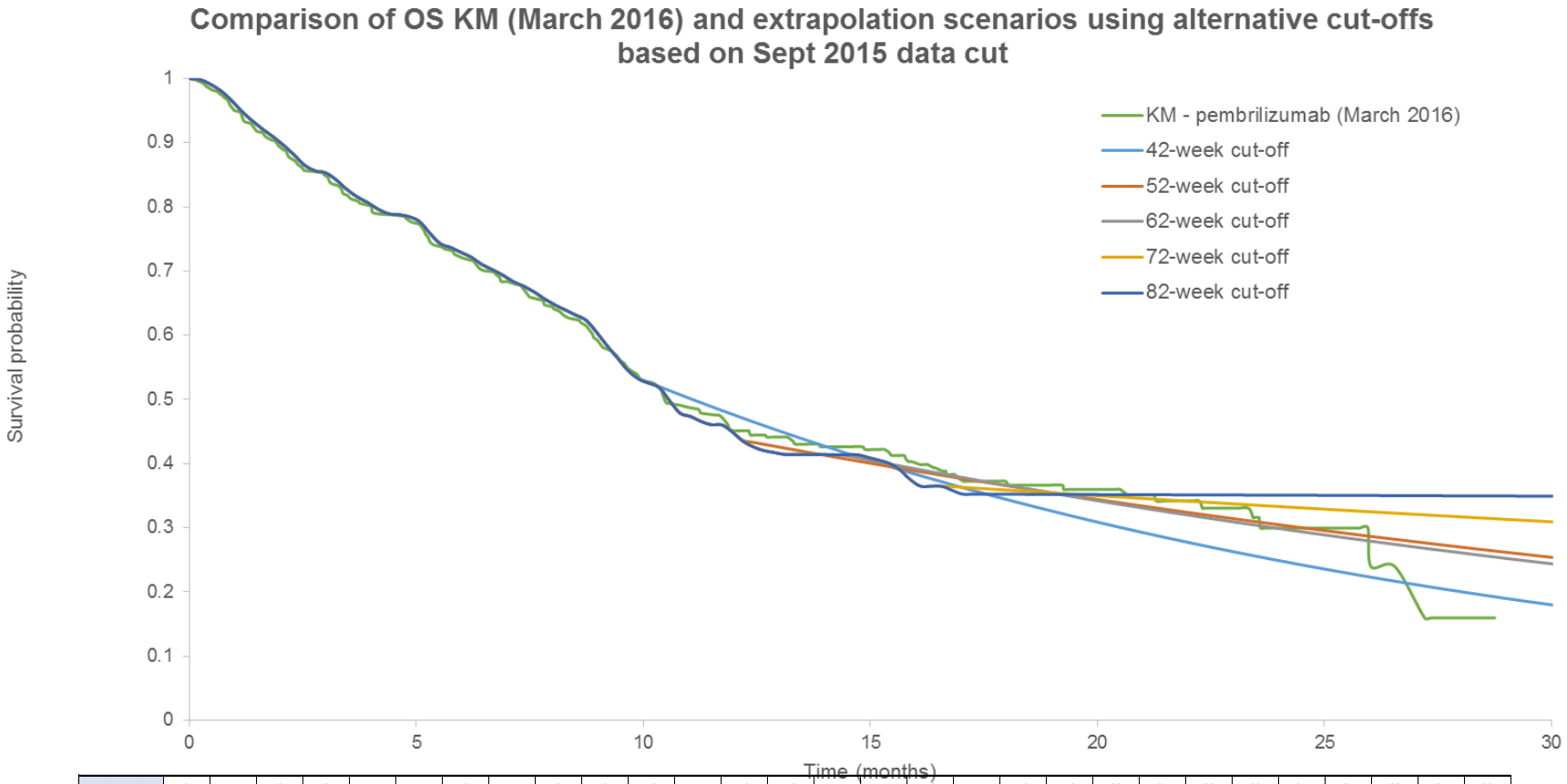
Selection of extrapolation timepoint
The ACD states *'…The committee concluded that there was no evidence that the 52-week cut-off was the most appropriate for extrapolating the Kaplan– Meier data and that the ICER was very sensitive to the cut-off point chosen to model overall survival. The committee concluded that the choice of the 52-week cut-off point was overly optimistic.'* and goes on to rebut all of the supporting arguments used by MSD.
MSD is particularly disappointed about this element of the ACD and the discussions it in part reflects.
We discussed one comment from the ACD *'…The ERG commented that this inflection is a result of the modelling approach that treats the timing of deaths up to 52 weeks as being unrelated to the timing of deaths beyond 52 weeks.'* We have discussed this today with our head of statistics who is clear that the 'inflection' in the KM curves for both September and March is related to the data and not the model.
In an attempt to provide clarity regarding the appropriateness of our selection to the 52-week cut-off point, we have superimposed all of the original extrapolations on the K-M data in the figure below. It can be clearly seen that the 42 week and 82 week cut-off points do not fit the data at all (Figure 1). In figure 2 we provide the same analysis using the September cut-off extrapolations superimposed on the March KM data which supports the conclusion above. Figure 3 which applies all of the cut-off points to the new March data supports our assertion that the variability in the original range of cut-offs was generated by the relative paucity of data.

Figure 1. Comparison of OS KM (September 2015) and extrapolation scenarios using alternative cut-off points based on Sept 2015 data cut



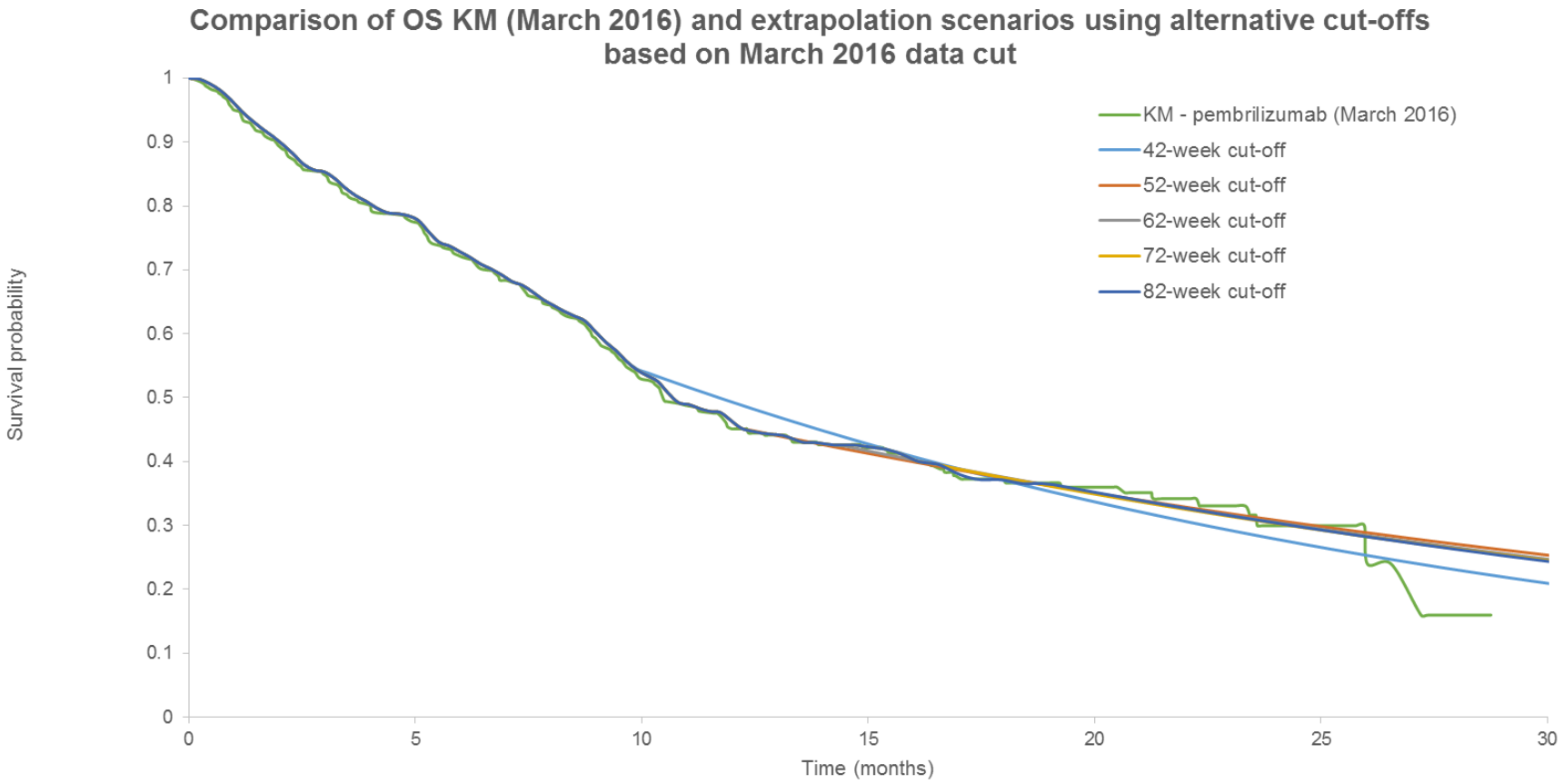
Time in months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Numbers at risk	344	326	304	287	271	259	235	201	174	143	116	93	75	69	69	49	35	29	29	29	29	29	29	0

Figure 2. Comparison of OS KM (March 2016) and extrapolation scenarios using alternative cut-off points based on Sept 2015 data cut



Time in months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Number at risk	344	326	304	287	271	261	242	228	214	197	176	160	146	126	107	96	84	70	62	55	48	40	35	25	16	12	5	3	1

Figure 3. Comparison of OS KM (March 2016) and extrapolation scenarios using alternative cut-off points based on March 2016 data cut



Time in months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Number at risk	344	326	304	287	271	261	242	228	214	197	176	160	146	126	107	96	84	70	62	55	48	40	35	25	16	12	5	3	1

The Committee has been presented with a significant number of ICERs over the course of the last two meetings as well as in our most recent submission of evidence. We have become concerned that this 'cloud' of ICERs is masking the small number of ICERs around which we believe any discussion of the value of pembrolizumab for treating patients with advanced NSCLC. We have therefore presented below a summary of the ICERs derived from the September 2015 data cut as originally presented to NICE (see Figure 4). A further summary substituting ICERs derived from the March 2016 data cut for the September equivalent (see Figure 5).
In Figure 6 we have removed all ICERs that we argue are implausible, supported in a number of these by the ERG, and for others, on the basis of consultation with clinicians. We have listed between Figures 5 and 6 the rationale for the removal of the various ICERs.

Figure 4. ICERs presented by MSD or discussed at the previous committee meetings using the original data cut from September 2015.

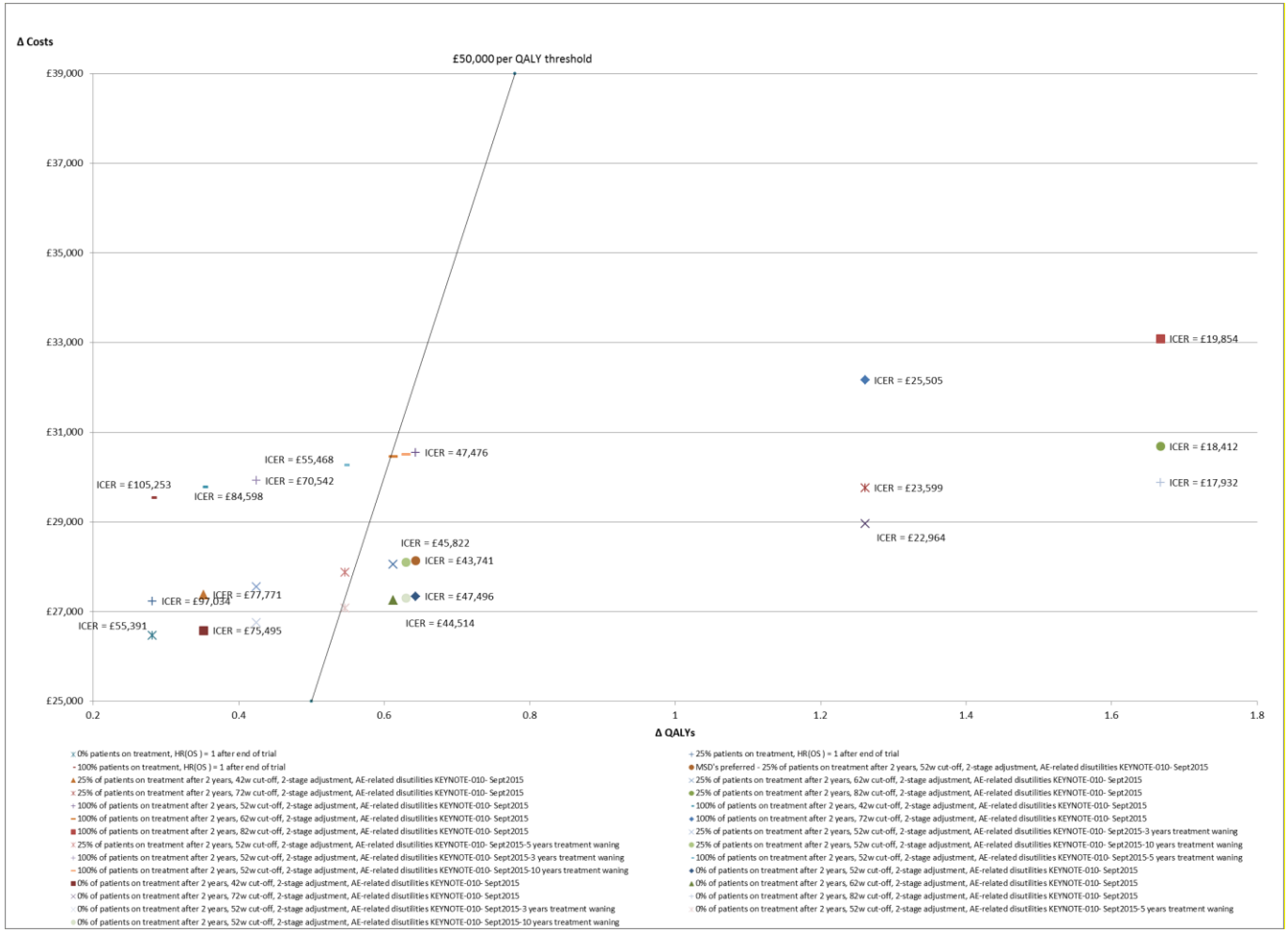
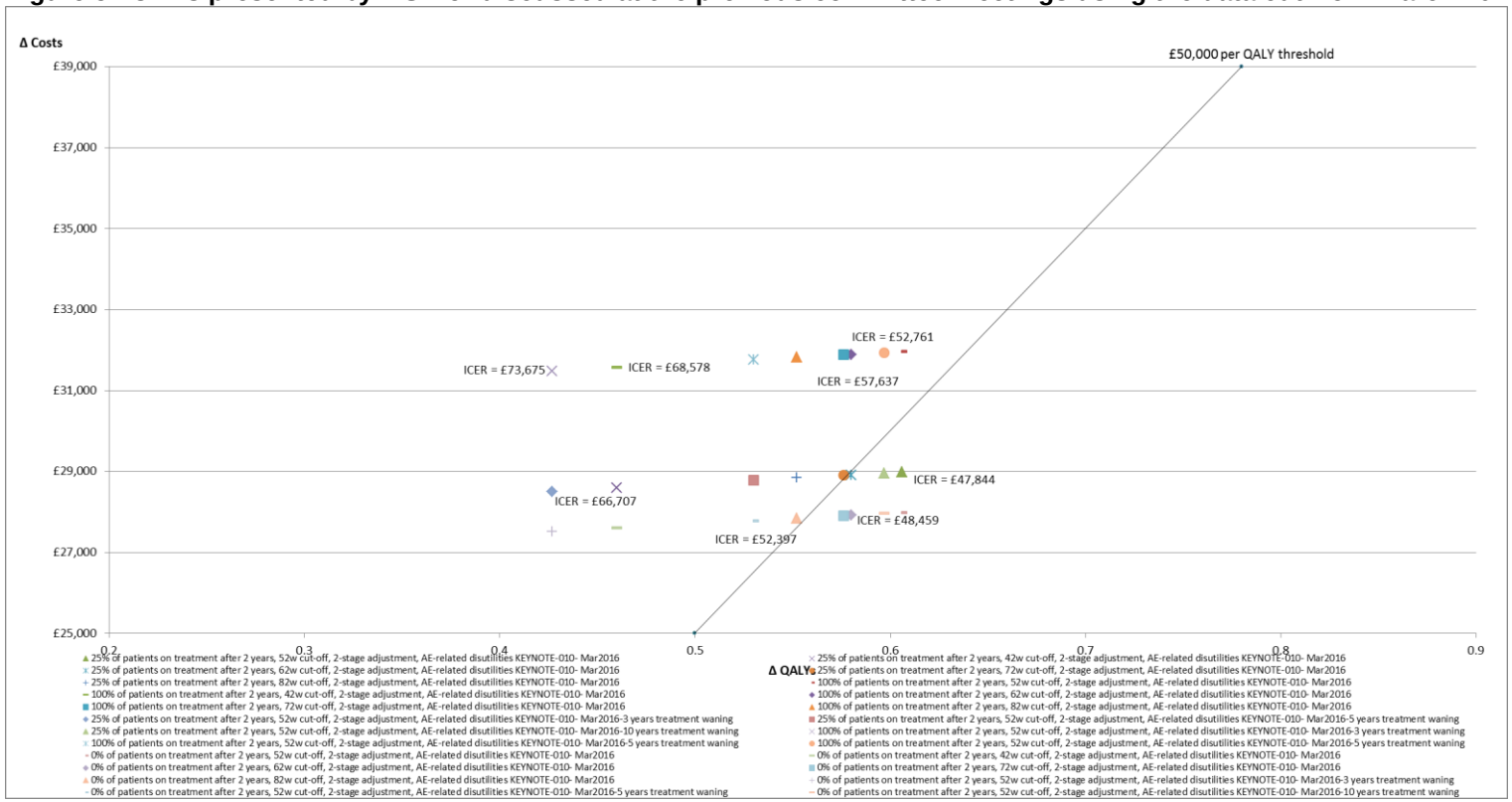


Figure 5. ICERs presented by MSD or discussed at the previous committee meetings using the data cut from March 2016.

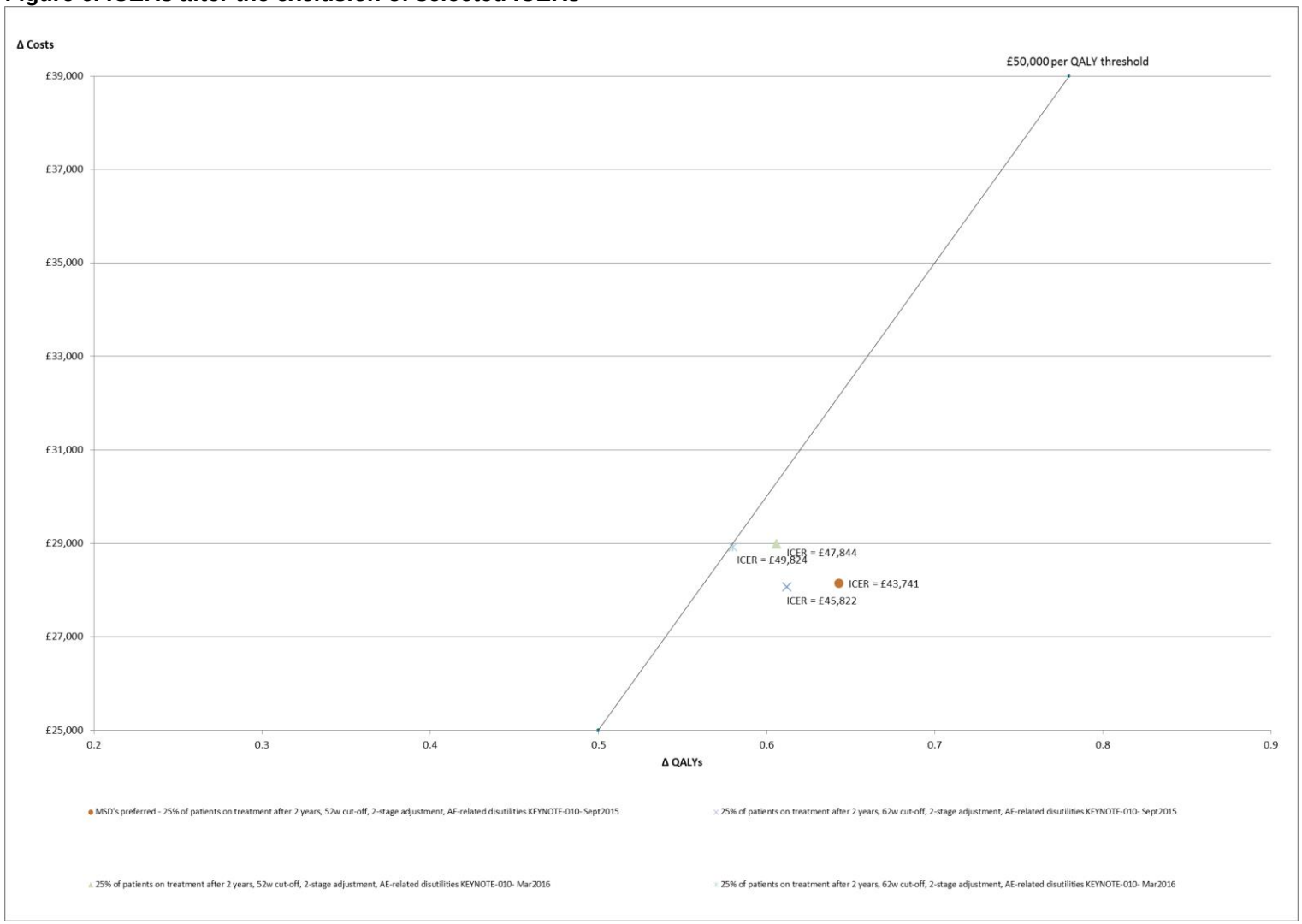


The following have been excluded from the figure below:

- Scenarios using extreme values for the proportion of patients being treated beyond 2 years (i.e. 0%, as presented in our original submission, and 100%), leaving the analyses that assume 25% of patients would be treated beyond 2 years.
- Scenarios where extrapolation based on specific data cut-offs resulted in implausible estimations (including the cut-offs at 42 weeks and 82 weeks).
- Scenarios that tested waning of the pembrolizumab treatment effect, including:
    - Analyses where a HR = 1 was assumed for pembrolizumab when compared to docetaxel
    - Those requested by the Committee, assuming the benefit of pembrolizumab would stop at 3, 5 and 10 years.

The four remaining ICERs below are those which we believe should form the basis of the third discussion by this Committee around the value of pembrolizumab for patients with advanced NSCLC.

Figure 6. ICERs after the exclusion of selected ICERs



Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Pembrolizumab for treating PD-L1 positive non small cell lung cancer after platinum-based chemotherapy [ID840]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are very disappointed that the Appraisal Committee's preliminary decision is not to recommend Pembrolizumab in this indication.

- In our opinion, immunotherapy represents a major new development in the treatment of nsclc patients. Internationally, the discovery of PD-L1 inhibition has altered practice in nsclc management. It is therefore important that a PD-L1 inhibitor be available in the algorithm of lung cancer care in England.

- We welcome many of the conclusions reached by the Appraisal Committee in this ACD

    - Pembrolizumab has an important extension of life benefit, for people with locally advanced or metastatic nsclc, whose tumours express PD-L1, as in the KEYNOTE-010 trial data. (section 4.5)

    - Pembrolizumab meets the criteria of a life extending, end of life treatment (section 4.17)

- We note in section 4.15, the Appraisal Committee's discussion and conclusion, that all patients who continue to benefit would continue Pembrolizumab beyond two years. This would have the effect of increasing the ICER.

  In the short period since publication of the ACD, we have undertaken some informal discussion, seeking the views of both patients and lung cancer clinical experts. There is no obvious consensus in our anecdotal poll. Some patients say that, should they be benefiting at two years, instinctively, with a disease such as advanced nsclc, they would want to continue. Others have noted that this is a three weekly intra-venous therapy, requiring travel to hospital and at two years, would likely want a break, if no evidence for continuing.
  On discussion with the clinician experts, it appears that there is no consensus, as yet, as to the optimal duration – 6 months, 12 months, 18 months, 24 months…… We appreciate this makes a difference to the cost modelling and as such would encourage the Appraisal Committee to have further discussion with clinical experts, who have experience with using this treatment. Would collection of such information through the Cancer Drugs Fund be appropriate, in reducing the uncertainty??

- We note that the Appraisal Committee has reached this negative decision, based on cost issues. The committee having concluded that the most plausible ICER for Pembrolizumab, in this setting, would exceed £50,000 per QUALY gained and so, not be a cost effective use of NHS resources. (section 4.15).

- **On behalf of the many lung cancer patients who would derive benefit from this innovative therapy, we strongly urge constructive dialogue between the**

Manufacturer, NICE and NHS England, to ensure that cost issues and issues of uncertainty, in particular around the optimal duration of treatment, are addressed. Advanced lung cancer remains a devastating disease for many. We hope that compromise and agreement can be reached in advance of further discussion by the Appraisal Committee and that the ultimate Final Appraisal Decision will be a positive recommendation. These patients do not have time to wait.

[redacted]
Roy Castle Lung Cancer Foundation
October 2016

Having been present at two of the appraisal committees I would like to submit the following comments from a personal perspective and also on behalf of the British Thoracic Oncology Group (BTOG)

Pembrolizumab is an innovative, novel, targeted compound with very clear clinical data demonstrating superiority over conventional chemotherapy in the second line setting in patients expressing PDL-1. Although outside the remit of this appraisal it is also worthy to note that more recent published data has confirmed the significant superiority of this compound in non-small cell lung cancer (NSCLC) in a first line setting.

From the report following the second committee meeting Pembrolizumab was not recommended within its marketing authorisation. From a clinical perspective this is obviously very disappointing. There are a number of specific points I would like to point out and I would be grateful if they could be taken into consideration:

Whilst not expressly mentioned in the document, it is important that direct clinical comparisons between the NSCLC patients and patients with other malignancies in where immunotherapies are used ie. melanoma should not be made. They are distinct clinical entities.

The economic modelling system appears to assume that 25% of patients would continue on the treatment at the 2 year period and therefore this would impact the cost effectiveness of the drug.

From a clinical perspective whilst it is very difficult to project in the future, through clinical experience it would seem very unlikely and optimistic that this percentage of patients would remain on treatment 2 years on.

Furthermore the longer term projections would appear to suggest that an estimated 1-2% of patients being alive at 10 years would clinically seem reasonable, but it would be very difficult to suggest that this would only be the case due to the positive effects of pembrolizumab.

From a clinical perspective it would be very reasonable to estimate that in a whole rage of tumour types where long term survival is poor a small number of patients remain alive at both the 5 and 10 year period for a whole variety of reasons even in the absence of novel therapeutic compounds. Nevertheless this percentage represents a small number of patients.

I would like to reiterate that the population of patients with any PDL-1 expression appears consistently between approximately 50-60% across a number of published clinical trials and those with much higher, i.e. 50% expression is significantly lower than this. Therefore pembrolizumab would not be suitable for every patient in the second line setting.

Finally the tolerability and ease of administration of these compounds is a positive and meaningful outcome from a patient perspective.

[redacted]

Royal College of Physicians
11 St Andrews Place
Regent's Park
London NW1 4LE
Tel: +44 (0)20 3075 1560

www.rcplondon.ac.uk

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2B
TACommD@nice.nhs.uk

From [redacted]

28 September 2016

Dear Sir or Madam

Re: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy ID840

The Royal College of Physicians (RCP) plays a leading role in the delivery of high quality patient care by setting standards of medical practice and promoting clinical excellence. We provide physicians in the United Kingdom and overseas with education, training and support throughout their careers. As an independent body representing over 32,000 Fellows and Members worldwide, we advise and work with government, the public, patients and other professions to improve health and healthcare.

The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation. We would like to make the following comments.

Although it is very disappointing to see this outcome, we do not have many significant comments on the accuracy of the clinical information within the report. The arrival of immune checkpoint inhibitors is one of the biggest breakthroughs in the management of patients with advanced NSCLC and is revolutionising its management across the world. It is therefore really disappointing that English patients, who have such a poor outcome currently, will not be able to gain the benefits of this important new drug.

Patient selection criteria are being further evaluated and more knowledge gained about the best way to use pembrolizumab for patients with lung cancer through ongoing research, but effort has been made within the pembrolizumab development program to select patients most likely to gain benefit, by the parallel evaluation of PD-L1 testing, which is laudable.

Our clinical expert believes that the committee's conclusion that all patients who remain on treatment at 2 years will continue on therapy is inaccurate, and notes that this was voiced at the appraisal committee meeting. A significant proportion of patients whose disease is controlled will stop treatment for other reasons and this proportion will increase over time. It is difficult to accurately estimate the proportion who would continue but the company's estimate of 25% is probably closer to the reality. Our expert notes experience of a number of patients ceasing therapy without progression, citing only 1 patient who had been on for 2 years. This patient stopped therapy at that point (as mandated within the study) without any undue concern and feels better for being off treatment.

When considering the long term treatment effects, we highlight again that as data mature from studies with immune checkpoint inhibitors across multiple tumour types there remains a proportion of patients with a maintained effect even out to 5 years, which is expected to be the case in NSCLC too. However, the data for the long term effects of pembrolizumab in NSCLC remain immature and hence require modelling, which is sensitive to even subtle changes in the predictions used, making accurate ICER calculations very difficult.

Our experts find the subtleties of the extrapolated survival and associated economic modelling complex and were unable to make any meaningful comments on these. We would strongly encourage that the manufacturers look carefully at their pricing structure to improve pembrolizumab's cost effectiveness in this setting and urge NICE to push for this.

Yours faithfully

[redacted]

Further NHS England comment in October 2016 on the NICE appraisal of pembrolizumab as 2nd/3rd line treatment of advanced/metastatic non small cell lung cancer (NSCLC)

1. In the protocol-specified final analysis of the main phase 3 trial (KEYNOTE-010), pembrolizumab offered a significant but modest proportion of patients the chance of delaying disease progression, the PFS curves separating at 6 months with the possibility of a degree of plateauing in PFS beyond 12 months. With a median duration of follow-up of 13 months, the PFS hazard ratio (HR) for the intention to treat population (TPS ≥1%) was 0.88 for the pembrolizumab 2mg/kg arm when compared with docetaxel (and the HR was 0.59 for the TPS ≥50% population). NHSE now notes that longer term follow-up of this trial was presented at the ESMO conference in October 2016 with a median duration of follow up of 19 months. The HR is 0.87 for the TPS≥1% ITT population (and the HR for the TPS≥50% is 0.59). The key issue here is that with further follow up, the HRs for PFS are unchanged.
2. In addition, now that the PFS curves with a median 19 mo duration of follow up can be scrutinised and compared with the PFS curves of follow up 13 months in Keynote 010, there is an increased likelihood of a proportion of patients seeming to gain very much greater benefit with pembrolizumab ie plateauing of the PFS curve: a similar phenomenon has been observed in advanced /metastatic melanoma with the use of pembrolizumab and also with nivolumab in melanoma, renal cancer and lung cancer. The fact that the HRs for PFS did not change with further follow up is very encouraging.
3. Pembrolizumab improves median overall survival (OS) but by only 2 months. The overall survival curves separate at about 5 months and the OS curves (as with PFS) then show a significant but larger proportion of patients (than with PFS) appearing to gain a much greater benefit in survival. In the protocol-specified final analysis of the main phase 3 trial (KEYNOTE-010) in which the median duration of follow-up was 13 months, the OS hazard ratio (HR) for the intention to treat population (TPS ≥1%) was 0.71 for the pembrolizumab 2mg/kg arm when compared with docetaxel (and the HR the TPS ≥50% population was 0.54). NHSE now notes that longer term follow-up of this trial was presented at the ESMO conference in October 2016 with a median duration of follow up of 19 months. The HR is 0.72 for the TPS≥1% ITT population (and the HR for the TPS≥50% is 0.54). The very important issue here is that with further follow up, the HRs for OS are unchanged ie benefit from treatment is not lessening with further follow-up. There is therefore no current justification for assigning a HR of 1.0 for treatment effect beyond the end of the trial data.
4. The other main issue that NHSE wishes to comment on is the treatment duration of pembrolizumab and what would happen at 2 years if patients remain free of disease progression and have continued to tolerate the drug well. The manufacturer's modelled PFS curve for pembrolizumab indicates that about 7-8% of patients are still free of disease progression at 24 months ie this 7-8% would stop treatment with pembrolizumab with a stopping rule in place at 24 months. NHSE previously stated that stopping rules are difficult to implement in practice when primarily instituted for cost reasons alone and also when the only then parallel in oncology is in melanoma when pembrolizumab is continued until disease progression (with significant tails observed in both PFS and OS). In its previous submission, NHSE noted that the EPAR, although recognising the trial design of a maximum treatment duration of pembrolizumab of 2 years, made no comment on treatment duration

other than to include wording in the SPC to continue pembolizumab until disease progression.

5. NHSE wishes to inform NICE that current clinical opinion is changing rapidly as to the assessment as to the optimal duration of treatment with checkpoint inhibitors in cancer. Until very recently, treatment with pembrolizumab/nivolumab would have been considered to be optimal when continued to the time of either disease progression or unacceptable toxicity. However, ipilimumab is already given for a fixed duration of treatment only. Recent evidence suggests that (at least in melanoma where use of such drugs has been the greatest and longest – but the parallels with melanoma are reasonable when considering the mode of action of pembrolizumab/nivolumab and the clinical data), patients who discontinue checkpoint inhibitors for reasons other than disease progression (mainly toxicity) derive the same OS benefit as those that continue on treatment until disease progression (eg S Hodi et al, Proc Amer Soc Clin Oncol 2016: abstract 9518). Clinical experience is also pointing to the same conclusion ie that in drugs such as pembrolizumab/nivolumab, when benefits to patients occur when there is sufficient recruitment of the immune system against the cancer, that recruitment of the immune system and secondary patient benefit may not require continued treatment until disease progression. There are thus trials underway in melanoma and renal cancer which are randomising patients to fixed durations of treatment of checkpoint inhibitors (eg for 1 year) versus treatment to disease progression. However, this type of trial design has already been implemented in the setting of squamous and non-squamous non small cell lung cancer previously treated with chemotherapy in a 1380 patient trial which has randomised patients still on treatment at 1 year to continue on therapy with nivolumab or discontinue treatment at that stage. The trial has completed recruitment and is in its follow up phase. Given that recruitment has been completed, results of the randomisation of treatment duration would be expected to be reported within the next 2 years.
6. Given the increasing questioning as to treatment duration for drugs such as pembrolizumab/nivolumab in cancer and the likelihood that much evidence will merge in the next 2 years as to this issue and especially so in lung cancer, NHSE is much more confident about an implementation of a 2 year stopping rule which would be acceptable to patients and clinicains and thus would be implementable. Since much data will become available as to the optimal duration of treatment of such checkpoint inhibitors within the next 2 years and a NICE recommendation for the use of pembrolizumab in October 2016 which incorporates a 2 year stopping rule would only result in patients who are still on the drug in 2 years having to stop the drug in October 2018, NHSE suggests that the use of pembrolizumab in progressed lung cancer is re-appraised by NICE in 2 years time (ie in the autmn of 2018) in case evidence does emerge that continual and continued treatment beyond 2 years is better for patients.
7. In addition, Keynote 010 had a trial design which allowed patients achieving a complete response to pembrolizumab to discontinue treatment but at further disease progression to re-start pembrolizumab for 12 months. Though the number of such patients eligible for such a treatment policy will be small, in 2 years time there will be lessons to be learned from this group of patients with further follow up as to the consequences of stopping treatment whilst it is still benefitting.

8. Thus, NHSE regards pembrolizumab as being an exciting drug in the 2nd/3rd line treatment of NSCLC as no other drug (bar other checkpoint inhibitors) offers this potentially much longer term survival benefit. The unchanged HRs for PFS but especially for OS that have been recently reported with greater follow up point to the same degree of benefit continuing although there remains uncertainty as to the much longer term benefit. There are no other clinical trials of other checkpoint inhibitors in lung cancer with long enough follow up to help reduce this longer term uncertainty but the parallels from melanoma point to such benefit.
9. NHSE also notes again that the clinical effectiveness of pembrolizumab is only robust when compared with docetaxel though it recognises the need for an indirect comparison with the combination of docetaxel plus nintedanib. There is no comparative data for pembrolizumab vs best supportive care and thus a positive recommendation by NICE for the use of pembrolizumab in 2nd/3rd line systemic therapy of NSCLC should only be in the patients on which the clinical and cost effectiveness rests ie in patients fit for docetaxel-containing chemotherapy as 2nd /3rd line treatment of NSCLC which expresses TPS≥1% and also if the patients are of performance status 0 or 1.

[redacted]

[redacted]

October 2016

Bristol-Myers Squibb Pharmaceuticals Limited

Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex UB8 1DH
Tel 01895 523000 Fax 01895 523010

National Institute for Health and Care Excellence
10 Spring Gardens
London
SW1A 2BU

20th October 2016

Dear Sir / Madam,

Re: ACD - Consultees & Commentators: Lung cancer (non-small-cell, PD-L1-positive) - pembrolizumab (after platinum chemotherapy) [840]

Thank you for the opportunity to respond to this ACD [ID840].

Pembrolizumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 and who have at least 1 chemotherapy regimen. Within this license, both squamous and non-squamous histologies of NSCLC are included. Given that the marketing authorisation has restricted the use of pembrolizumab to those patients that express PD-L1, then the specific threshold should be made clear in the recommendation.

Nivolumab has a marketing authorisation for treating locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy in adults. Nivolumab is currently being reviewed by NICE in two separate appraisals – one for squamous NSCLC [ID811] and another for non-squamous NSCLC [ID900]. As stated in the most recent ACD of the non-squamous appraisal, *'the committee concluded that for the populations under consideration, the relevant comparators for this appraisal were nintedanib plus docetaxel, docetaxel monotherapy, and BSC'.*

Given that both treatment options relate to similar patient populations, for consistency, the comparators in both appraisals should be the same – in particular to the inclusion of nintedanib plus docetaxel in one appraisal and not the other.

Yours Sincerely,

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

Name	[redacted]
Role	Patient
Other role	Retired ex Marie Curie Nurse
Organisation	
Location	England
Conflict	
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am a lung cancer patient diagnosed three and a half years ago, I have had various treatments including drugs trials, chemotherapy etc, some were helpful some were not. I have been given to understand that the drug under discussion could be very helpful for me. I also understand that this drug is available in Scotland but not available to patients in England. To me this is a damned disgrace we are all British citizens paying the same taxes and the same National Insurance contributions, why should they receive preferential treatment over us. This is one very disgusted British lady who is not entitled to the same treatment as other privileged Britons receive.

12th October 2016

Dear Helen,

Re. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Please find below updated cost-effectiveness analysis results including the latest available cut-off data from KEYNOTE-010 (March 2016) incorporating [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,

[redacted]

Following on from the additional evidence you provided on Thursday 29 September, NICE would like to request an updated submission with further information and analyses to be included for committee's consideration ahead of the 3rd meeting on Wednesday 26 October.

Please present in your additional evidence submission the underlying clinical trial data from the March 2016 data cut from KEYNOTE-010 (that informs the incremental cost-effectiveness results provided in your additional analyses)

In the ACD released on 27 September, the committee considered that there was considerable uncertainty associated with:

- the different cut-off points used when switching from trial survival data to the exponential survival modelling
- the long term treatment effect of pembrolizumab

To help committee's consideration of these areas of uncertainty, NICE would like you to provide economic analyses incorporating the March 2016 data and also:

- Analyses to explore the sensitivity of the different cut-off points for extrapolation by applying the following assumptions; 100% of patients receiving treatment, assuming no additional drug costs to the NHS beyond 2 years also using the simple discount at:
    - 42 weeks, 62 weeks and 82 weeks (in addition to the 52 weeks cut-off point used in you base case analysis

Base-case 2 deterministic cost-effectiveness analysis of pembrolizumab compared with docetaxel with old and new data cut – OS cut-offs, with PAS

Please find below the deterministic results for MSD's preferred scenario assuming:

- 25% of the patients remain on pembrolizumab after 2 years of treatment in the original base-case 2 (i.e. 1.3% of patients who entered the model)
- a 2-stage cross-over adjustment methodology for the docetaxel arm
- ToT for pembrolizumab is based on HR applied to PFS
- Post progression utilities based on TTD combined with progression-based utilities derived from KEYNOTE-010
- Inclusion of AE disutilities based on KEYNOTE-010
- No fading of treatment effect after the cut-off point

The analysis was also performed for 100% of patients continuing treatment after 2 years. The results presented in Table 1 and 2 were performed using data from KEYNOTE-010 with September 2015 and March 2016 data cuts, respectively.

Table 1. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Originally submitted cut-off data (September, 2015)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
52-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,410	1.213	-	-	-
Docetaxel	£11,267	0.569	£28,143	0.643	£43,741
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,813	1.213	-	-	-
Docetaxel	£11,267	0.569	£30,546	0.643	£47,476
42-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,742	0.96	-	-	-
Docetaxel	£11,366	0.608	£27,376	0.352	£77,771
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,145	0.96	-	-	-
Docetaxel	£11,366	0.608	£29,779	0.352	£84,598
62-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,270	1.16	-	-	-
Docetaxel	£11,210	0.548	£28,059	0.612	£45,822
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,673	1.16	-	-	-
Docetaxel	£11,210	0.548	£30,462	0.612	£49,747
72-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,974	1.81	-	-	-
Docetaxel	£11,214	0.549	£29,760	1.261	£23,599
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,377	1.81	-	-	-
Docetaxel	£11,214	0.549	£32,163	1.261	£25,505
82-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£44,454	3.225	-	-	-
Docetaxel	£13,768	1.559	£30,686	1.667	£18,412
100% of patients receiving treatment after 2 years					
Pembrolizumab	£46,857	3.225	-	-	-
Docetaxel	£13,768	1.559	£33,089	1.667	£19,854

Table 2. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Updated cut-off data (March, 2016)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
52-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,398	1.203	-	-	-
Docetaxel	£11,416	0.597	£28,982	0.606	£47,844
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,376	1.203	-	-	-
Docetaxel	£11,416	0.597	£31,960	0.606	£52,761
42-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,973	1.042	-	-	-
Docetaxel	£11,376	0.581	£28,597	0.46	£62,109
100% of patients receiving treatment after 2 years					
Pembrolizumab	£42,952	1.042	-	-	-
Docetaxel	£11,376	0.581	£31,576	0.46	£68,578
62-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,316	1.171	-	-	-
Docetaxel	£11,401	0.591	£28,914	0.58	£49,825
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,294	1.171	-	-	-
Docetaxel	£11,401	0.591	£31,893	0.58	£54,958
72-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,294	1.163	-	-	-
Docetaxel	£11,392	0.587	£28,903	0.576	£50,183
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,273	1.163	-	-	-
Docetaxel	£11,392	0.587	£31,881	0.576	£55,354
82-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,260	1.15	-	-	-
Docetaxel	£11,420	0.598	£28,840	0.552	£52,241
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,238	1.15	-	-	-
Docetaxel	£11,420	0.598	£31,818	0.552	£57,637

Analyses to explore varying the treatment effect by applying the following assumptions; 100% of patients receiving treatment, and assuming no additional drug costs to the NHS beyond two years of treatment:

- 3 years, 5 years and 10 years

Base-case 2 deterministic cost-effectiveness analysis of pembrolizumab compared with docetaxel with old and new data cut – waning scenarios, with PAS

Please find below the deterministic results for the scenarios requested above, assuming:

- Either 25% (i.e. 1.3% of patients who entered the model; MSD's preferred scenario) or 100% of the patients remain on pembrolizumab after 2 years of treatment in the original base-case 2
- a 2-stage cross-over adjustment methodology for the docetaxel arm
- ToT for pembrolizumab is based on HR applied to PFS
- Post progression utilities based on TTD combined with progression-based utilities derived from KEYNOTE-010
- Inclusion of AE disutilities based on KEYNOTE-010
- Fading of treatment effect after the identified cut-off point

The results presented in Table 3 and
Table **4** were performed using data from KEYNOTE-010 with September 2015 and March 2016 data cuts, respectively. The corresponding OS curves are reported in Figure 1 to Figure 4. The relevance of providing these will be made clear in our answer to the ACD.

Table 3. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Originally submitted cut-off data (September, 2015)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case – No additional treatment waning					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,410	1.213			
Docetaxel	£11,267	0.569	£28,143	0.643	£43,741
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,813	1.213			
Docetaxel	£11,267	0.569	£30,546	0.643	£47,476
Additional treatment waning from year 3 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,817	0.994			
Docetaxel	£11,267	0.569	£27,550	0.424	£64,948
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,190	0.994			
Docetaxel	£11,267	0.569	£29,923	0.424	£70,542

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Additional treatment waning from year 5 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,146	1.115			
Docetaxel	£11,267	0.569	£27,879	0.546	£51,073
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,546	1.115			
Docetaxel	£11,267	0.569	£30,278	0.546	£55,468
Additional treatment waning from year 10 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,374	1.200			
Docetaxel	£11,267	0.569	£28,107	0.630	£44,584
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,776	1.200			
Docetaxel	£11,267	0.569	£30,509	0.630	£48,394

Figure 1. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015) and without implementing additional waning

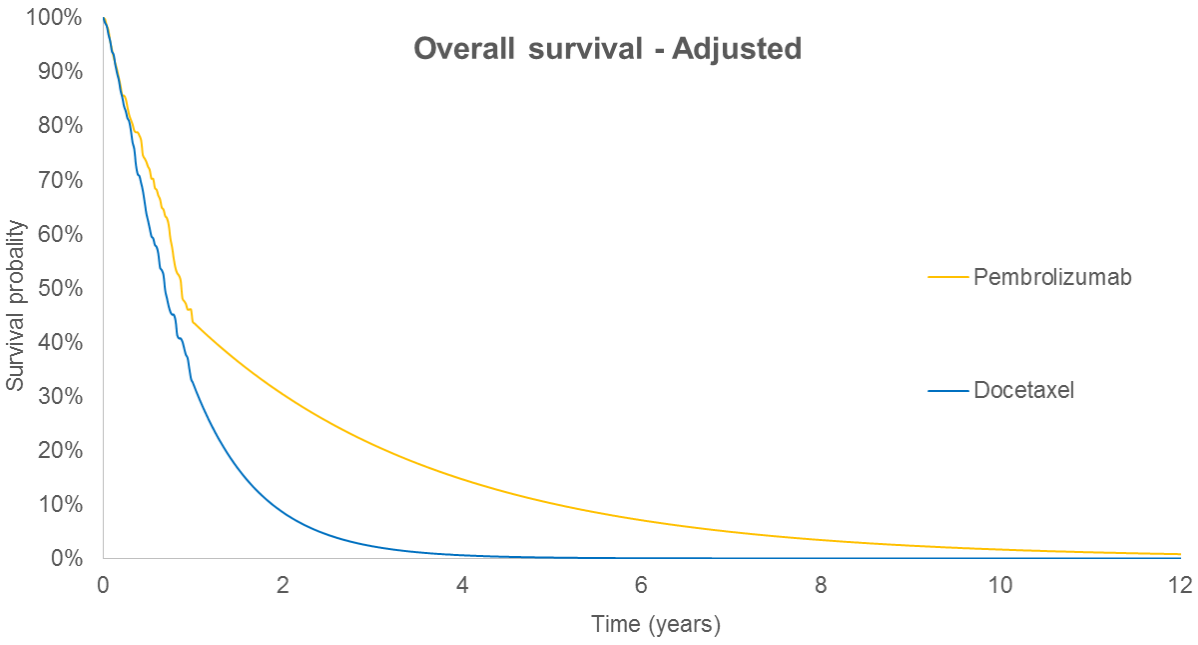


Figure 2. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015), with additional waning beyond year 3

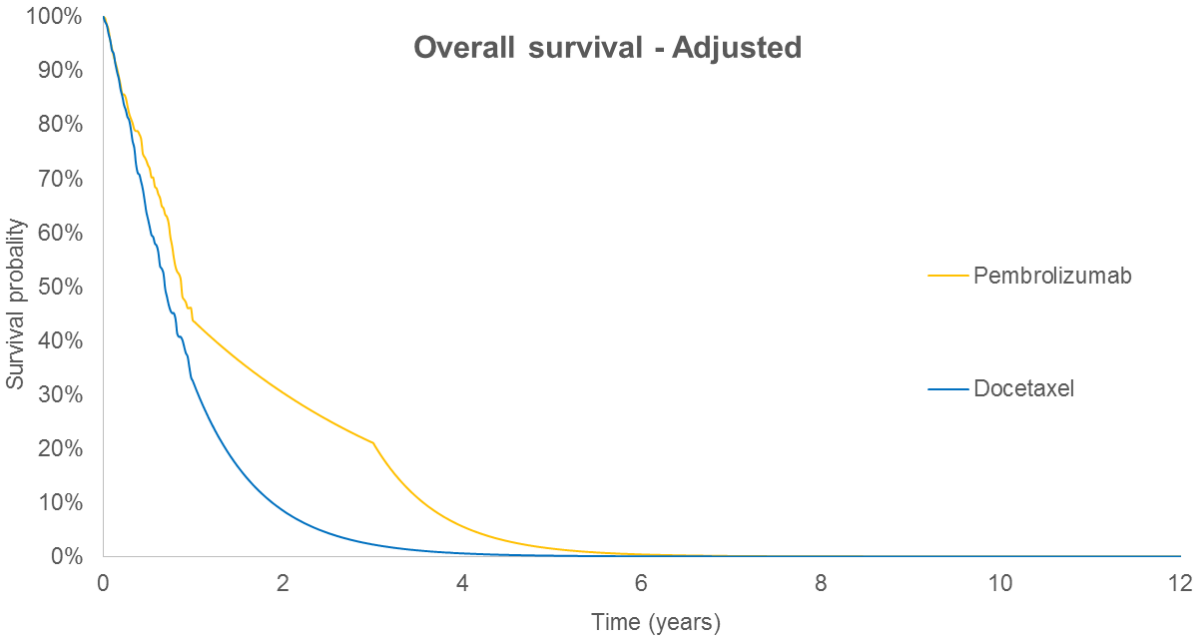


Figure 3. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015), with additional waning beyond year 5

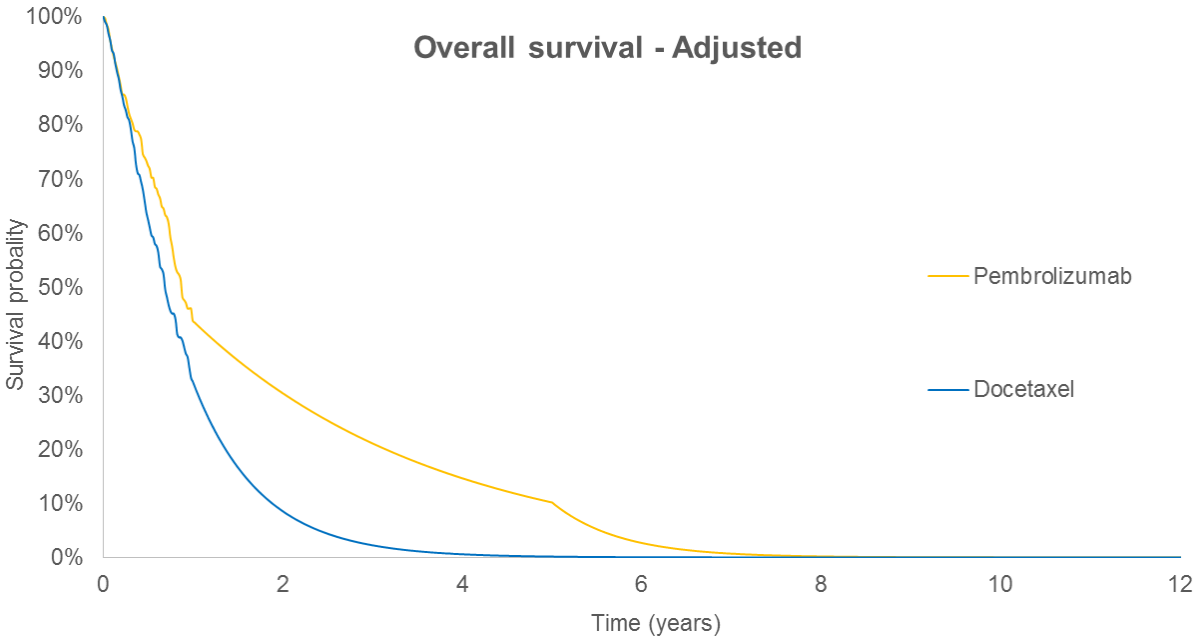


Figure 4. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015), with additional waning beyond year 10

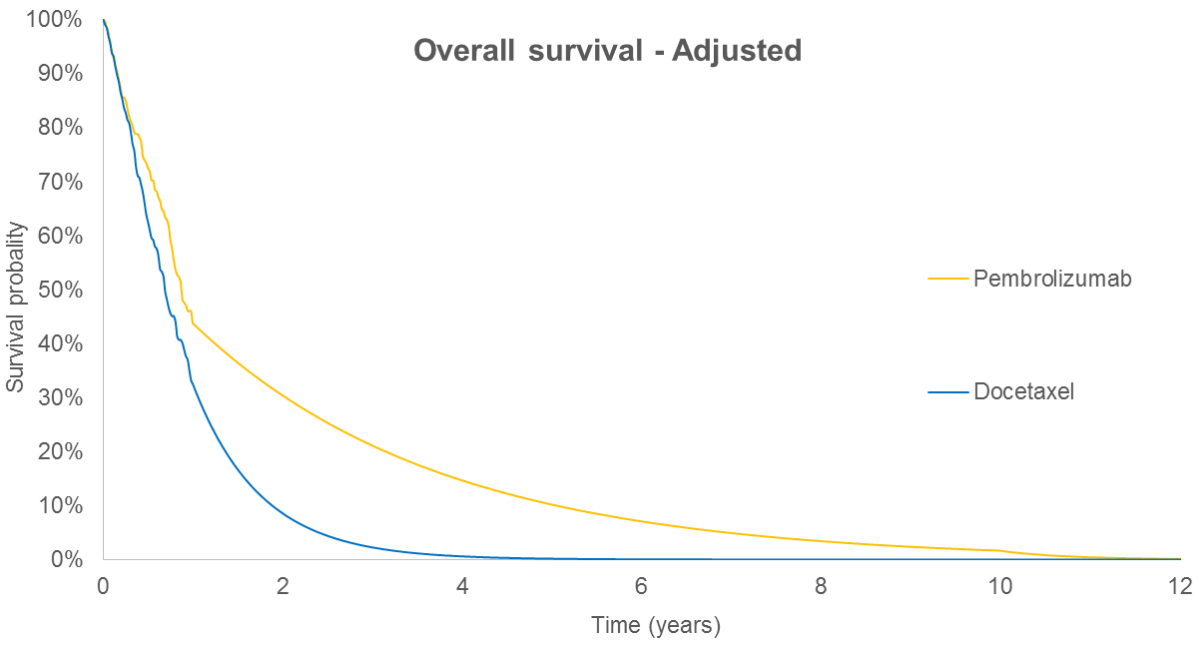


Table 4. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Updated cut-off data (March, 2016)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case – No additional treatment waning					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,398	1.203			
Docetaxel	£11,416	0.597	£28,982	0.606	£47,844
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,376	1.203			
Docetaxel	£11,416	0.597	£31,960	0.606	£52,761
Additional treatment waning from year 3 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,924	1.024			
Docetaxel	£11,416	0.597	£28,508	0.427	£66,707
100% of patients receiving treatment after 2 years					
Pembrolizumab	£42,902	1.024			
Docetaxel	£11,416	0.597	£31,486	0.427	£73,675

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Additional treatment waning from year 5 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,195	1.127			
Docetaxel	£11,416	0.597	£28,779	0.530	£54,269
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,174	1.127			
Docetaxel	£11,416	0.597	£31,758	0.530	£59,885
Additional treatment waning from year 10 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£40,374	1.194			
Docetaxel	£11,416	0.597	£28,958	0.597	£48,503
100% of patients receiving treatment after 2 years					
Pembrolizumab	£43,353	1.194			
Docetaxel	£11,416	0.597	£31,937	0.597	£53,492

Figure 5. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016) and without implementing additional waning

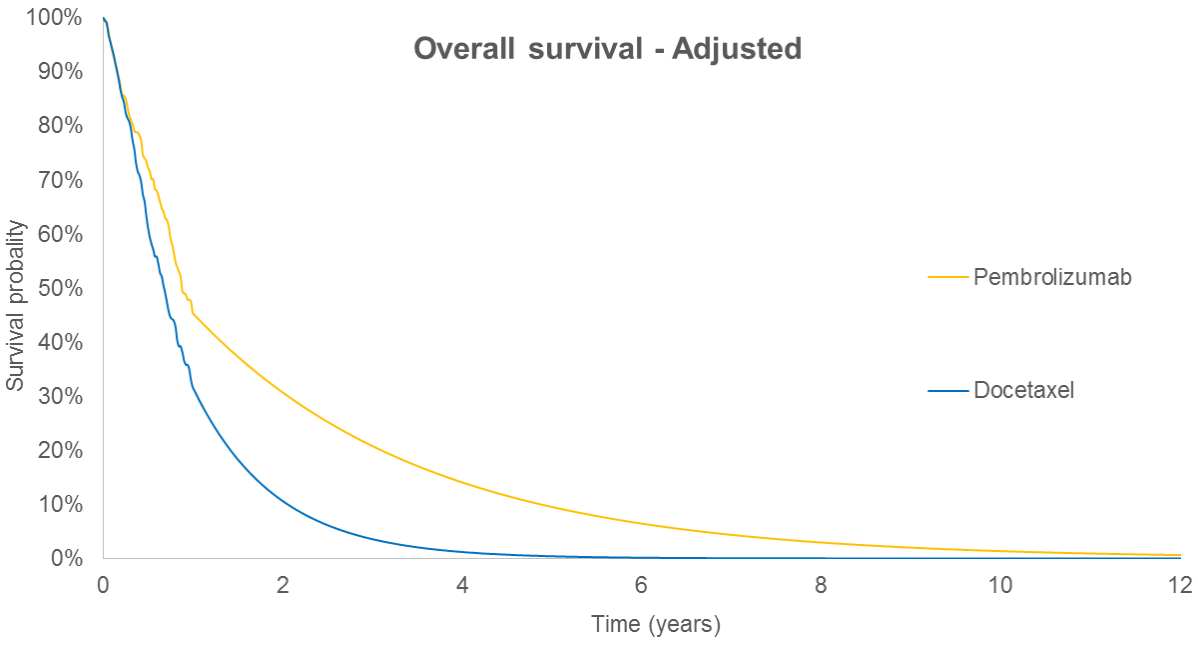


Figure 6. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 3

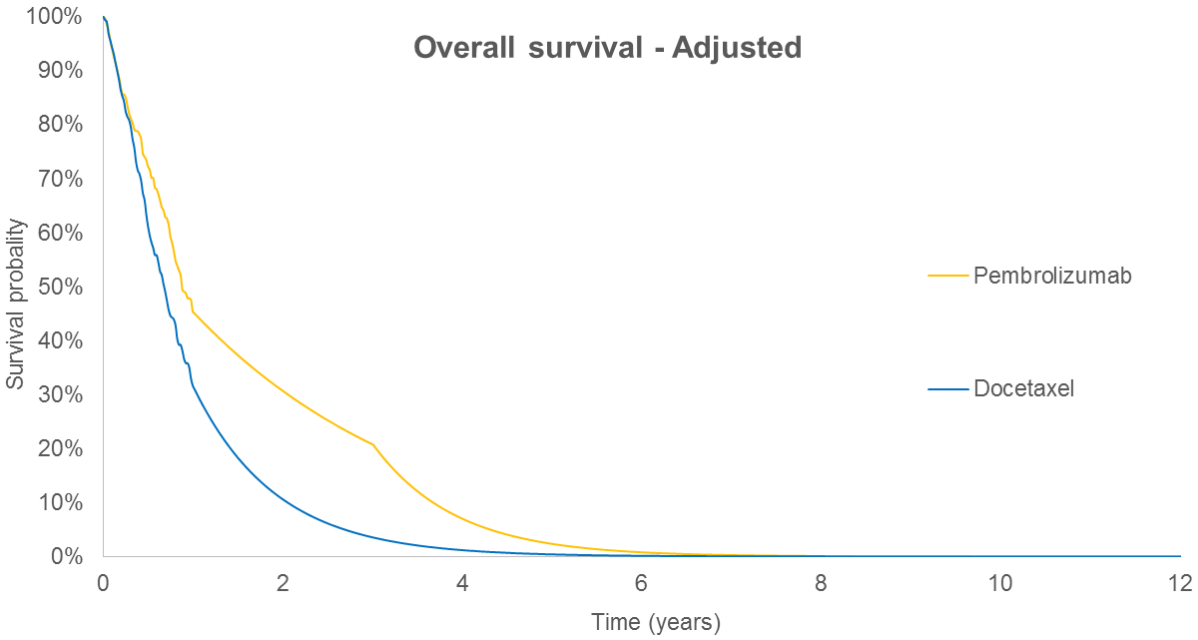


Figure 7. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 5

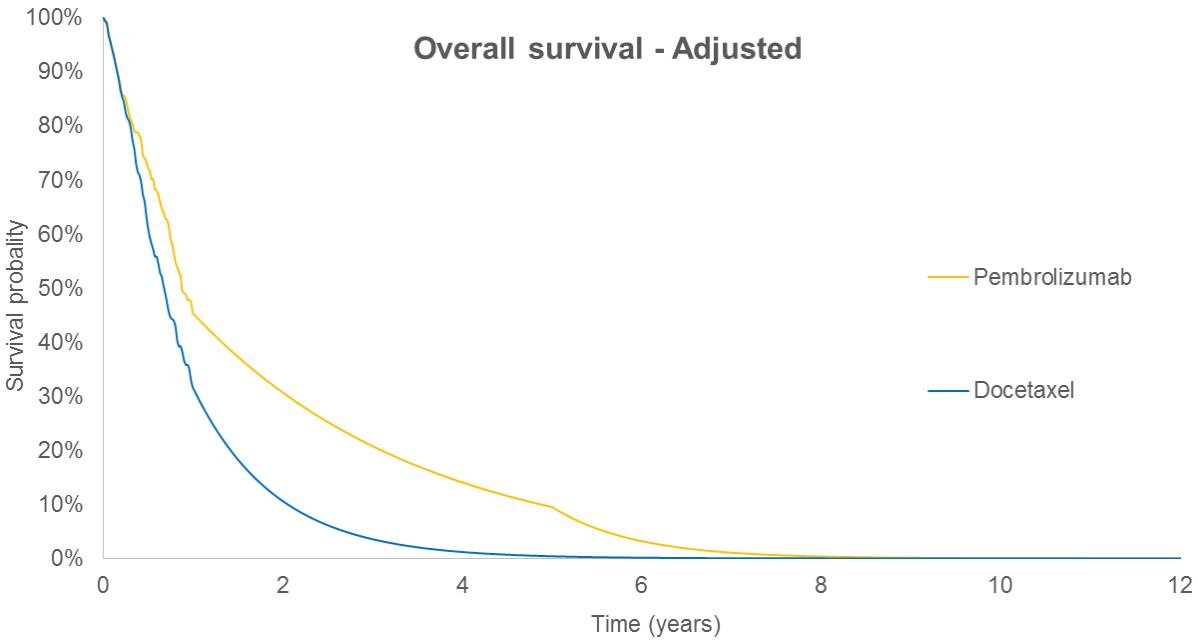
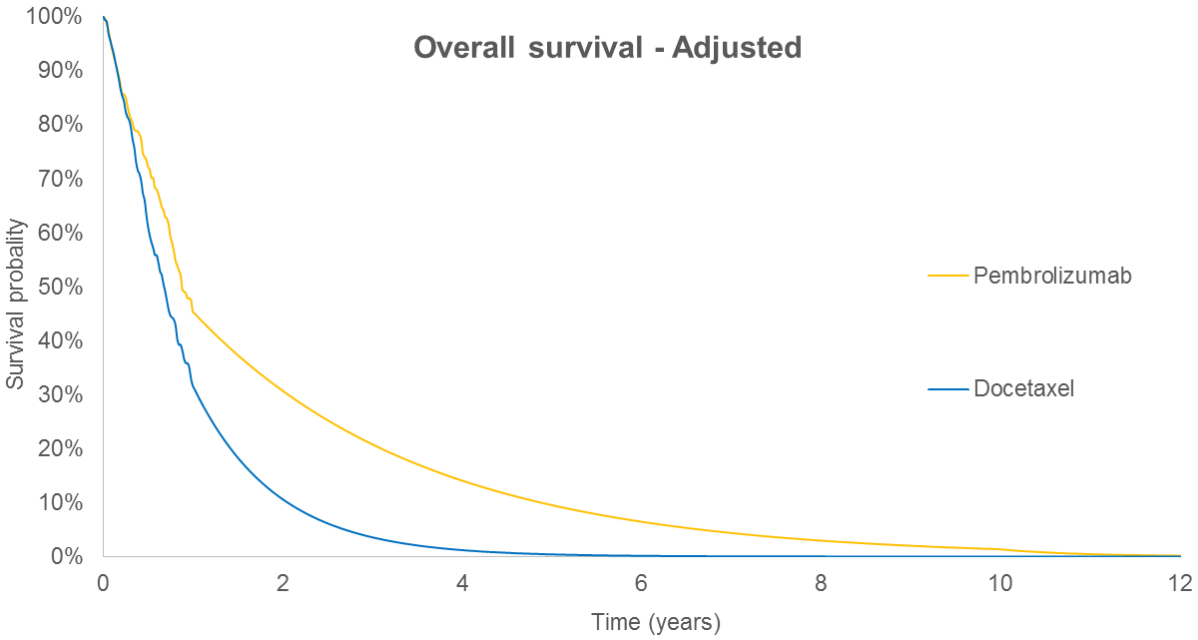


Figure 8. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 10



24th October 2016

Dear Helen,

Re. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after platinum-based chemotherapy [ID840]

Please find below updated cost-effectiveness analysis results including the latest available cut-off data from KEYNOTE-010 (March 2016) incorporating [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,

[redacted]

Following on from the additional evidence you provided on Thursday 29 September, NICE would like to request an updated submission with further information and analyses to be included for committee's consideration ahead of the 3rd meeting on Wednesday 26 October.

Please present in your additional evidence submission the underlying clinical trial data from the March 2016 data cut from KEYNOTE-010 (that informs the incremental cost-effectiveness results provided in your additional analyses)

In the ACD released on 27 September, the committee considered that there was considerable uncertainty associated with:

- the different cut-off points used when switching from trial survival data to the exponential survival modelling
- the long term treatment effect of pembrolizumab

To help committee's consideration of these areas of uncertainty, NICE would like you to provide economic analyses incorporating the March 2016 data and also:

- Analyses to explore the sensitivity of the different cut-off points for extrapolation by applying the following assumptions; 100% of patients receiving treatment, assuming no additional drug costs to the NHS beyond 2 years also using the simple discount at:
    - 42 weeks, 62 weeks and 82 weeks (in addition to the 52 weeks cut-off point used in you base case analysis

Base-case 2 deterministic cost-effectiveness analysis of pembrolizumab compared with docetaxel with old and new data cut – OS cut-offs, with PAS

Please find below the deterministic results for MSD's preferred scenario assuming:

- 25% of the patients remain on pembrolizumab after 2 years of treatment in the original base-case 2 (i.e. 1.3% of patients who entered the model)
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- ToT for pembrolizumab is based on HR applied to PFS
- Post progression utilities based on TTD combined with progression-based utilities derived from KEYNOTE-010
- Inclusion of AE disutilities based on KEYNOTE-010
- No fading of treatment effect after the cut-off point

The analysis was also performed for 100% of patients continuing treatment after 2 years. The results presented in Table 1 and 2 were performed using data from KEYNOTE-010 with September 2015 and March 2016 data cuts, respectively.

Table 1. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Originally submitted cut-off data (September, 2015)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
52-week cut-off point					

25% of patients receiving treatment after 2 years					
Pembrolizumab	£37,444	1.213	-	-	-
Docetaxel	£11,267	0.569	£26,176	0.643	£40,685
100% of patients receiving treatment after 2 years					
Pembrolizumab	£39,678	1.213	-	-	-
Docetaxel	£11,267	0.569	£28,411	0.643	£44,158
42-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£36,776	0.960	-	-	-
Docetaxel	£11,366	0.608	£25,410	0.352	£72,185
100% of patients receiving treatment after 2 years					
Pembrolizumab	£39,011	0.960	-	-	-
Docetaxel	£11,366	0.608	£27,645	0.352	£78,534
62-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£37,304	1.160	-	-	-
Docetaxel	£11,210	0.548	£26,093	0.612	£42,611
100% of patients receiving treatment after 2 years					
Pembrolizumab	£39,538	1.160	-	-	-
Docetaxel	£11,210	0.548	£28,328	0.612	£46,261
72-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£39,008	1.810	-	-	-
Docetaxel	£11,214	0.549	£27,794	1.261	£22,040
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,242	1.810	-	-	-
Docetaxel	£11,214	0.549	£30,028	1.261	£23,812
82-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£42,488	3.225	-	-	-
Docetaxel	£13,768	1.559	£28,720	1.667	£17,232
100% of patients receiving treatment after 2 years					
Pembrolizumab	£44,722	3.225	-	-	-
Docetaxel	£13,768	1.559	£30,955	1.667	£18,573

Table 2. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Updated cut-off data (March, 2016)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
52-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,366	1.203	-	-	-
Docetaxel	£11,416	0.597	£26,950	0.606	£44,490
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,136	1.203	-	-	-
Docetaxel	£11,416	0.597	£29,720	0.606	£49,063
42-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£37,942	1.042	-	-	-
Docetaxel	£11,376	0.581	£26,566	0.460	£57,697
100% of patients receiving treatment after 2 years					
Pembrolizumab	£40,712	1.042	-	-	-
Docetaxel	£11,376	0.581	£29,336	0.460	£63,712
62-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,284	1.171	-	-	-
Docetaxel	£11,401	0.591	£26,883	0.580	£46,324
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,054	1.171	-	-	-
Docetaxel	£11,401	0.591	£29,653	0.580	£51,097
72-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,263	1.163	-	-	-
Docetaxel	£11,392	0.587	£26,871	0.576	£46,655
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,033	1.163	-	-	-
Docetaxel	£11,392	0.587	£29,641	0.576	£51,465
82-week cut-off point					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,228	1.150	-	-	-
Docetaxel	£11,420	0.598	£26,808	0.552	£48,561
100% of patients receiving treatment after 2 years					
Pembrolizumab	£40,998	1.150	-	-	-
Docetaxel	£11,420	0.598	£29,578	0.552	£53,579

Analyses to explore varying the treatment effect by applying the following assumptions; 100% of patients receiving treatment, and assuming no additional drug costs to the NHS beyond two years of treatment:

- 3 years, 5 years and 10 years

Base-case 2 deterministic cost-effectiveness analysis of pembrolizumab compared with docetaxel with old and new data cut – waning scenarios, with PAS

Please find below the deterministic results for the scenarios requested above, assuming:

- Either 25% (i.e. 1.3% of patients who entered the model; MSD's preferred scenario) or 100% of the patients remain on pembrolizumab after 2 years of treatment in the original base-case 2
- a 2-stage cross-over adjustment methodology for the docetaxel arm
- ToT for pembrolizumab is based on HR applied to PFS
- Post progression utilities based on TTD combined with progression-based utilities derived from KEYNOTE-010
- Inclusion of AE disutilities based on KEYNOTE-010
- Fading of treatment effect after the identified cut-off point

The results presented in Table 3 and
Table **4** were performed using data from KEYNOTE-010 with September 2015 and March 2016 data cuts, respectively. The corresponding OS curves are reported in Figure 1 to Figure 4. The relevance of providing these will be made clear in our answer to the ACD.

Table 3. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Originally submitted cut-off data (September, 2015)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case – No additional treatment waning					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£37,444	1.213	-	-	-
Docetaxel	£11,267	0.569	£26,176	0.643	£40,685
100% of patients receiving treatment after 2 years					
Pembrolizumab	£39,678	1.213	-	-	-
Docetaxel	£11,267	0.569	£28,411	0.643	£44,158
Additional treatment waning from year 3 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£36,851	0.994	-	-	-
Docetaxel	£11,267	0.569	£25,584	0.424	£60,315
100% of patients receiving treatment after 2 years					
Pembrolizumab	£39,058	0.994	-	-	-
Docetaxel	£11,267	0.569	£27,791	0.424	£65,517

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Additional treatment waning from year 5 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£37,180	1.115	-	-	-
Docetaxel	£11,267	0.569	£25,913	0.546	£47,471
100% of patients receiving treatment after 2 years					
Pembrolizumab	£39,411	1.115	-	-	-
Docetaxel	£11,267	0.569	£28,144	0.546	£51,558
Additional treatment waning from year 10 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£37,408	1.200	-	-	-
Docetaxel	£11,267	0.569	£26,141	0.630	£41,466
100% of patients receiving treatment after 2 years					
Pembrolizumab	£39,642	1.200	-	-	-
Docetaxel	£11,267	0.569	£28,375	0.630	£45,009

Figure 1. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015) and without implementing additional waning

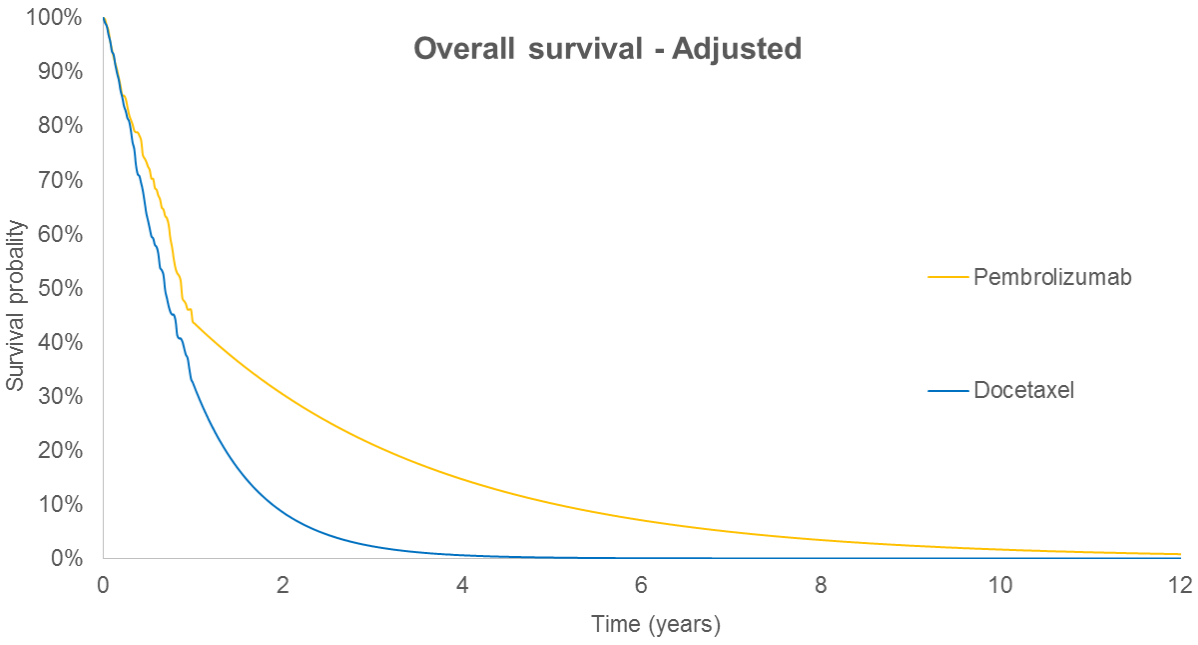


Figure 2. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015), with additional waning beyond year 3

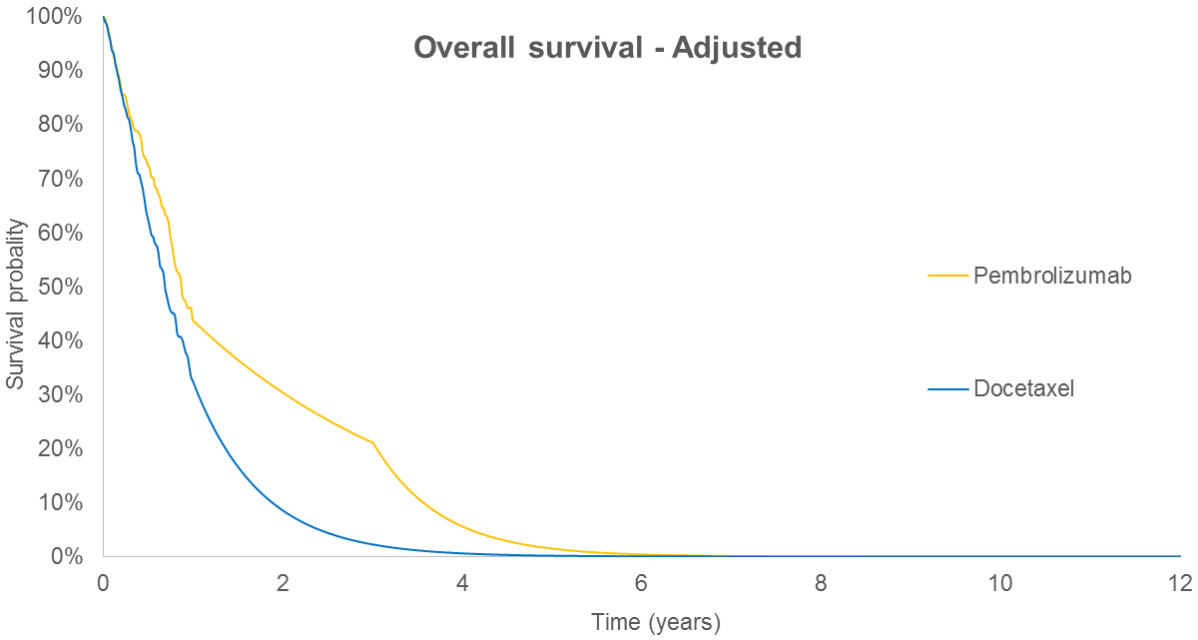


Figure 3. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015), with additional waning beyond year 5

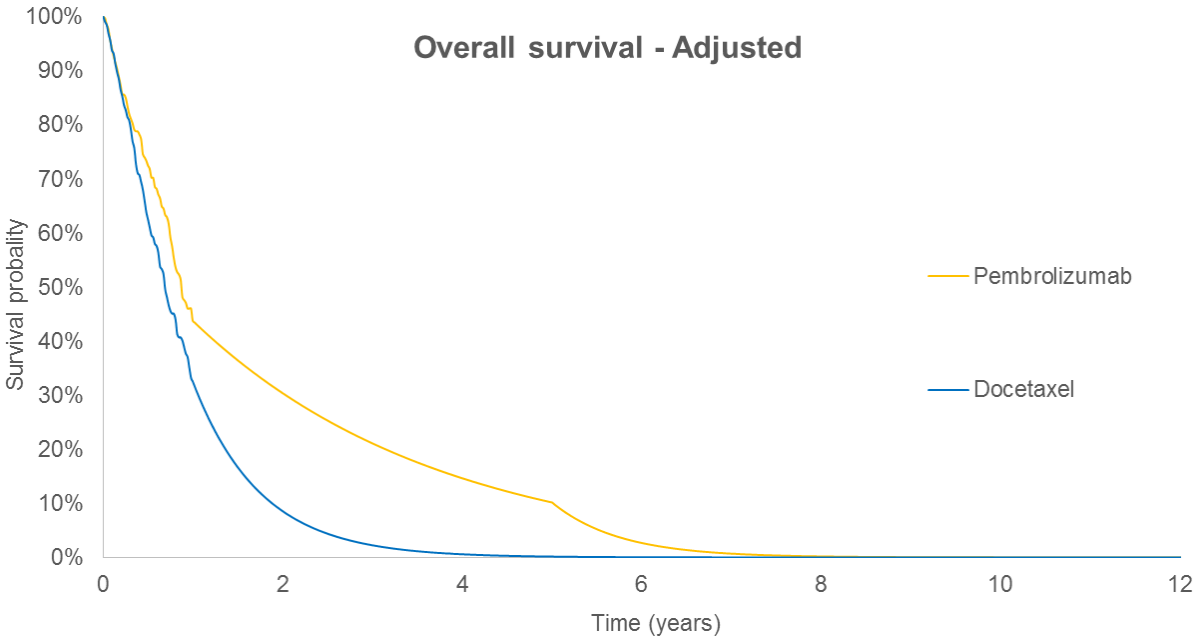


Figure 4. OS for pembrolizumab vs. docetaxel based on originally submitted cut-off data (September, 2015), with additional waning beyond year 10

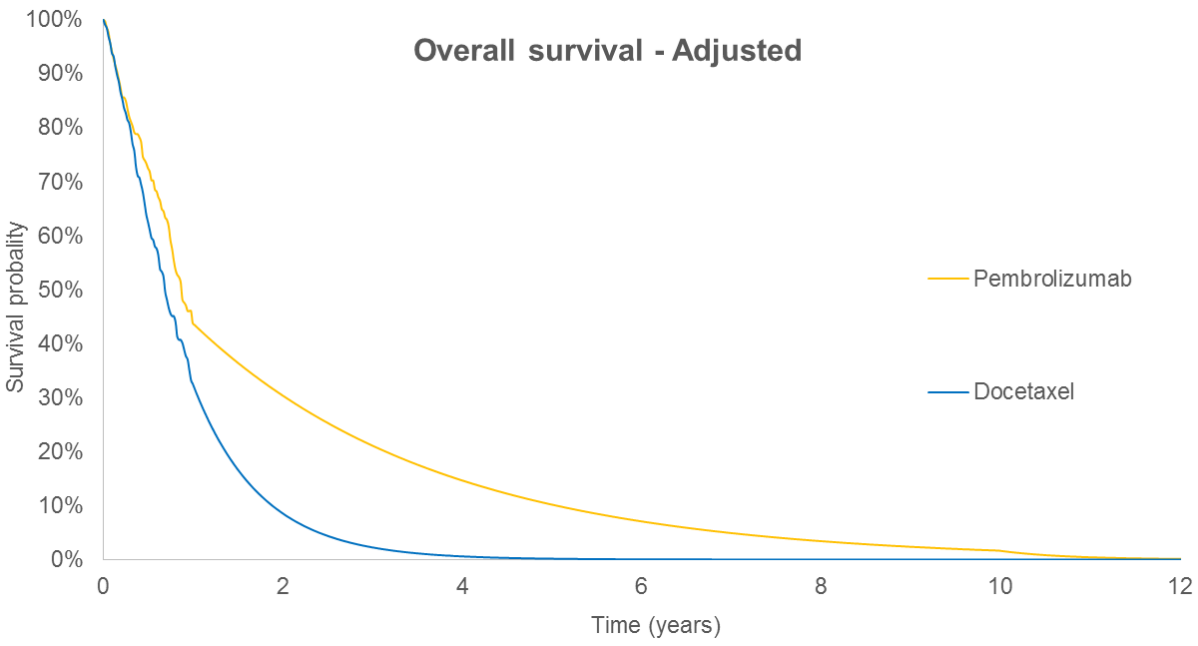


Table 4. Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) – Updated cut-off data (March, 2016)

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Base case – No additional treatment waning					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,366	1.203	-	-	-
Docetaxel	£11,416	0.597	£26,950	0.606	£44,490
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,136	1.203	-	-	-
Docetaxel	£11,416	0.597	£29,720	0.606	£49,063
Additional treatment waning from year 3 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£37,893	1.024	-	-	-
Docetaxel	£11,416	0.597	£26,477	0.427	£61,954
100% of patients receiving treatment after 2 years					
Pembrolizumab	£40,662	1.024	-	-	-
Docetaxel	£11,416	0.597	£29,246	0.427	£68,433

Technologies	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Additional treatment waning from year 5 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,164	1.127	-	-	-
Docetaxel	£11,416	0.597	£26,748	0.530	£50,438
100% of patients receiving treatment after 2 years					
Pembrolizumab	£40,934	1.127	-	-	-
Docetaxel	£11,416	0.597	£29,518	0.530	£55,661
Additional treatment waning from year 10 onwards					
25% of patients receiving treatment after 2 years					
Pembrolizumab	£38,343	1.194	-	-	-
Docetaxel	£11,416	0.597	£26,927	0.597	£45,100
100% of patients receiving treatment after 2 years					
Pembrolizumab	£41,113	1.194	-	-	-
Docetaxel	£11,416	0.597	£29,697	0.597	£49,740

Figure 5. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016) and without implementing additional waning

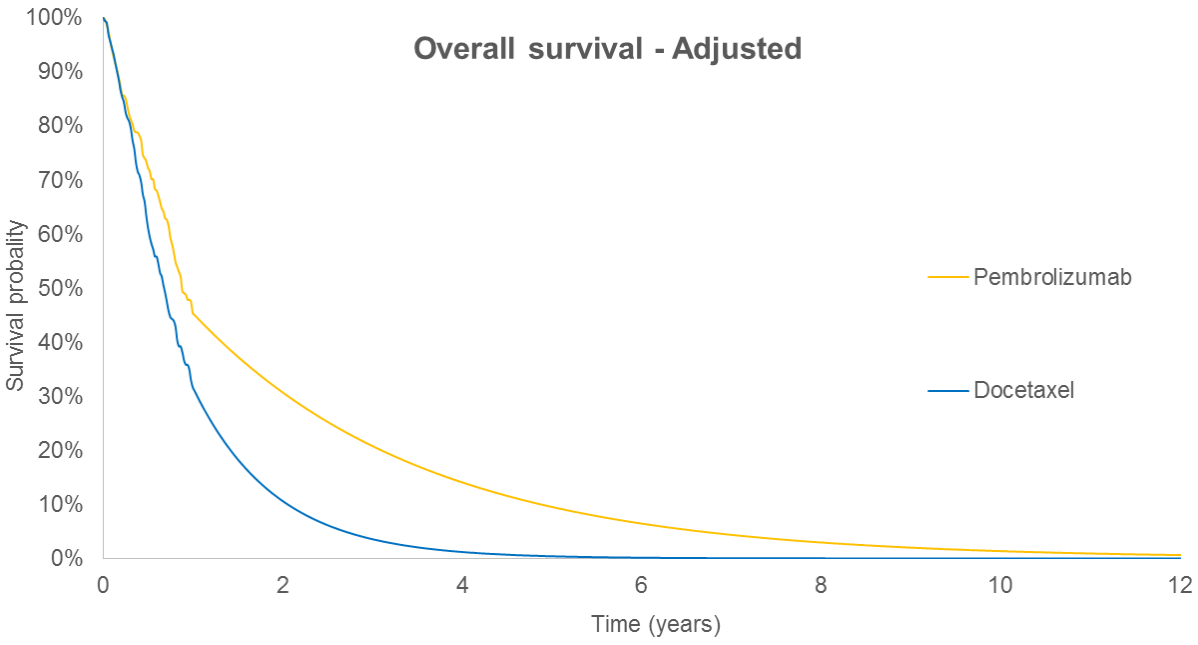


Figure 6. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 3

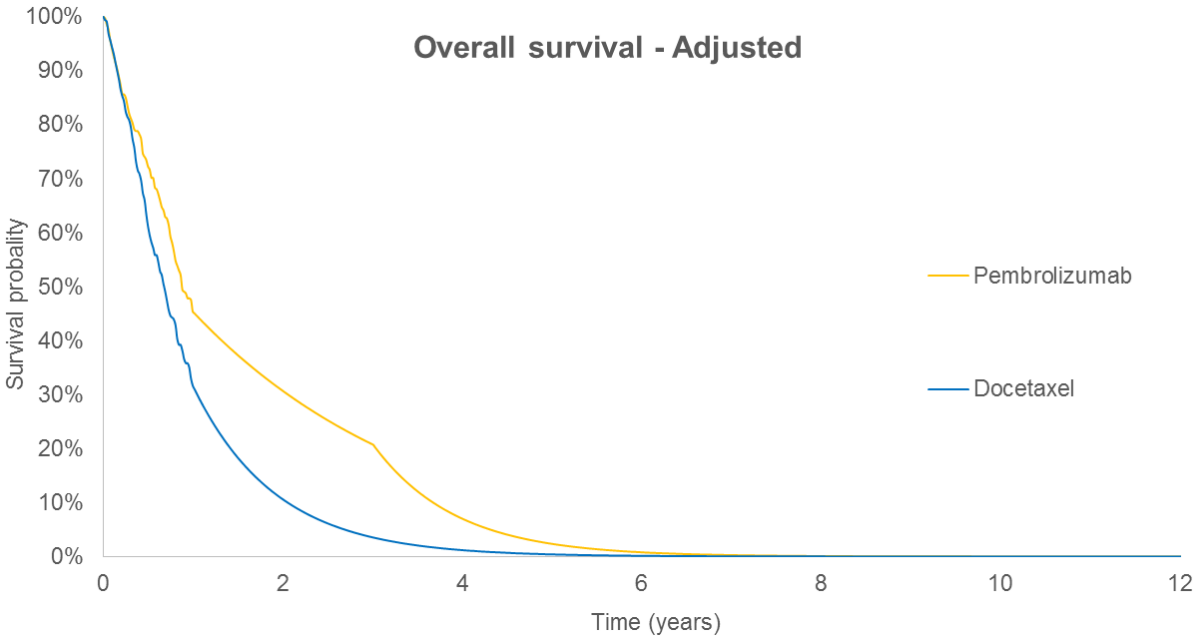


Figure 7. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 5

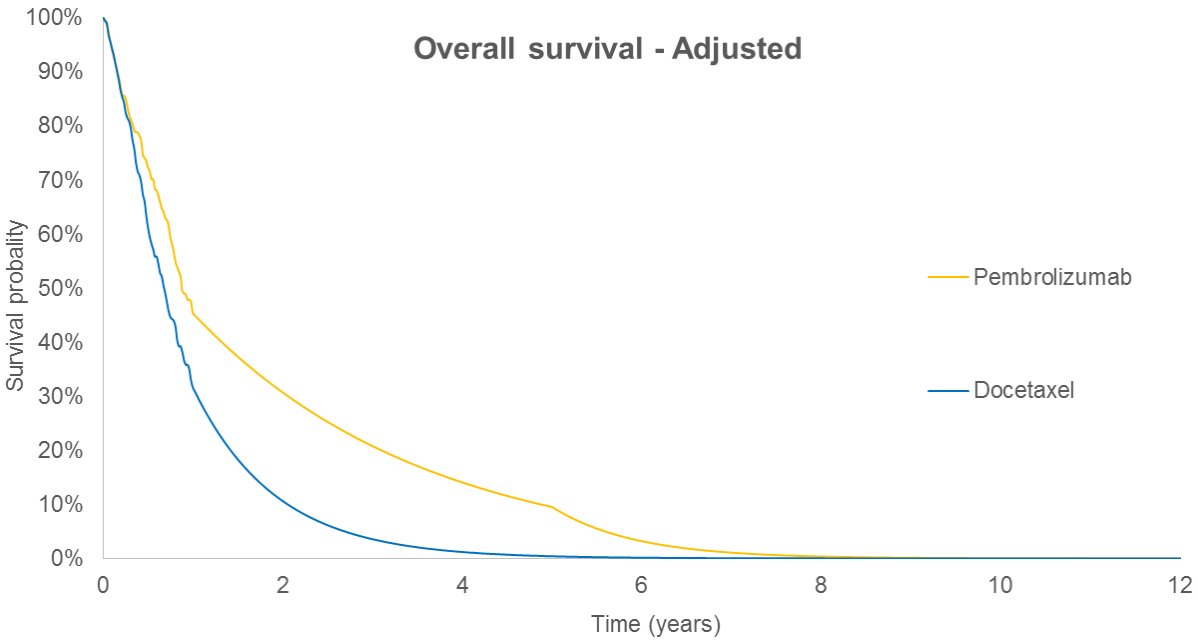
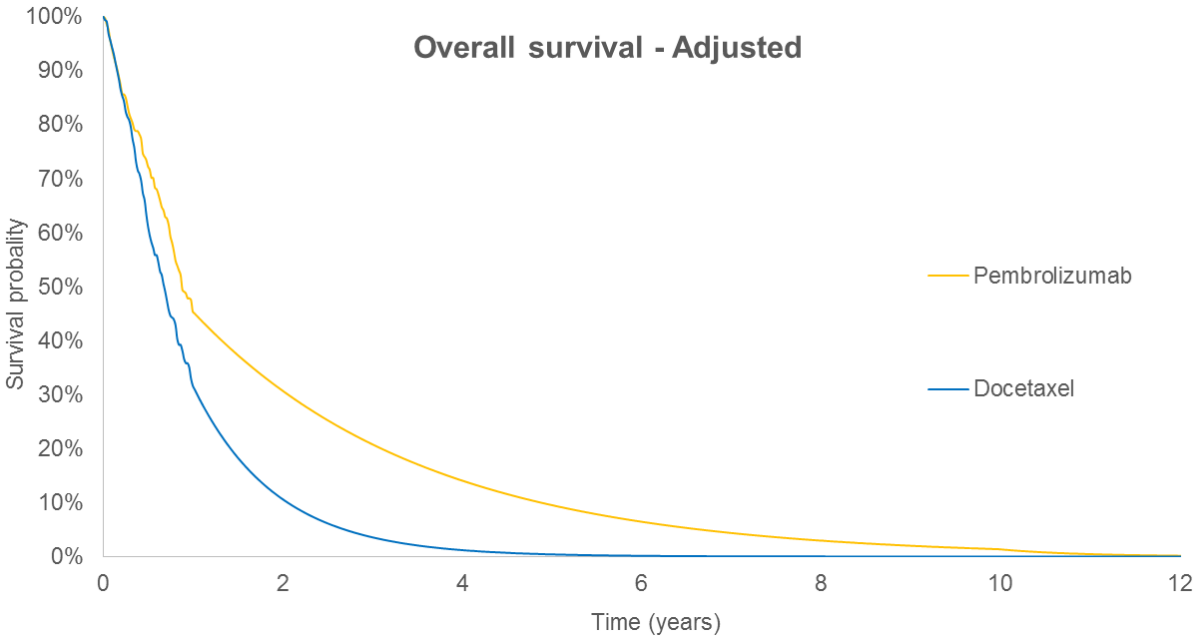


Figure 8. OS for pembrolizumab vs. docetaxel based on updated cut-off data (March, 2016), with additional waning beyond year 10



Single Technology Appraisal

Pembrolizumab for treating advanced or recurrent PD-L1 positive non-small-cell lung cancer after progression with platinum-based chemotherapy

Updated critique of the additional analyses submitted by the company in response to the ACD

Produced by Aberdeen HTA Group

Date completed 20 October 2016

Contains AIC

This report provides the ERG's updated information and critique in response to a request from the NICE technical team dated 18 October 2016.

Following on from the additional ERG report you provided on Monday 17 October, NICE would like to request an updated report with further information and critique on the company's new analyses for committee's consideration ahead of the 3rd meeting on Wednesday 26 October.

- ***A critique of the additional evidence supplied by the company – with a description (with values) for the committee on what within the new clinical data is driving the change in ICER. Please also highlight for the committee any other significant differences from the data they have seen previously.***

The company has supplied additional evidence incorporating an updated data cut at March 2016 compared to the original data cut at September 2015. The March 2016 data-cut adds 26 weeks to the original follow-up period and overall, using the updated data resulted in an increase in the ICERs across all the analyses. The company's preferred scenario is based on the following assumptions:

- 25% of patients remaining on pembrolizumab beyond 2 years of the original base-case 2
- 2-stage cross-over adjustment for the docetaxel arm
- ToT for pembrolizumab based on HR applied to PFS
- Post-progression utilities based on TTD combined with progression-based utilites derived from KEYNOTE-010
- Inclusion of AE disutilites based on KEYNOTE-010
- No fading of treatment effect

The company has presented the results of their base case (based on the assumptions above) and of a scenario of 100% of patients remaining on pembrolizumab beyond 2 years (Table 1).

Table 1 Deterministic incremental cost-effectiveness results of base-case 2 (discounted, with PAS) comparing original and new data cuts

Original data cut –September 2015					
	Total Costs	**Total QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER**
25% of patients remain on treatment after 2 years					
Pembrolizumab	£39,410	1.213			
Docetaxel	£11,267	0.569	£28,143	0.643	£43,741
100% of patients remain on treatment after 2 years					
Pembrolizumab	£41,813	1.213			
Docetaxel	£11,267	0.569	£30,546	0.643	£47,476
New data cut –March 2016					
	Total Costs	**Total QALYs**	**Incremental Costs**	**Incremental QALYs**	**ICER**
25% of patients remain on treatment after 2 years					
Pembrolizumab	£40,398	1.203			
Docetaxel	£11,416	0.597	£28,982	0.606	£47,844
100% of patients remain on treatment after 2 years					
Pembrolizumab	£43,376	1.203			
Docetaxel	£11,416	0.597	£31,960	0.606	£52,761

Incorporating the new data cut increases the ICER from £43,741 to £47,844 when 25% of those patients predicted to remain on treatment stop treatment at 2 years, and from £47,476 to £52,761 when all patients predicted to remain on treatment continue after 2 years. This increase in ICER is driven by a smaller estimated OS gain associated with pembrolizumab in the model with the new data compared with the original data; resulting in a fall in incremental QALYs from 0.643 with the original data cut to 0.606 in the new data cut.

This is further illustrated with the life years gained for each data cut in Table 2 below. Incorporating the new data cut results in lower life-years gained between the pembrolizumab and docetaxel arms – 0.953 using the new data cut compared to 1.028 using the original data cut.

Table 2 Undiscounted life years incorporating original and new data cut

	Progression free life years	Post progression life years	Total life years	Progression free life years gained	Post progression life years gained	Total life years gained
Original data cut September 2015						
Pembrolizumab	0.629	1.289	1.918			
Docetaxel	0.426	0.464	0.890	0.203	0.825	1.028
New data cut March 2016						
Pemrbolizumab	0.697	1.186	1.884			
Docetaxel	0.472	0.458	0.931	0.225	0.728	0.953

- ***An updated critique in light of the new clinical evidence of the company's sensitivity analysis including:***
    - ***A critique on the plausibility of the cut-off points for switching from trial survival data to the exponential model – with a judgement on the most plausible scenario***

The company presented 42, 52 (company's base case assumption), 62, 72 and 82 week cut-offs. Using the March 2016 data cut the 52 week cut-off resulted in the lowest ICER. The new data cut resulted in lower OS than the original data in the model. Based on the assumption that all patients predicted to remain on treatment continue after 2 years, none of the company's ICERs were below £50,000. Using the new data-cut resulted in the ICERs for 72 and 82 week cut-off being higher than the 52 weeks cut-off; whereas the opposite was observed with the original data-cut from March 2015. When the 72 and 82 week cut-offs for the exponential curve were used, this resulted in a smaller marginal difference in survival between pembrolizumab and docetaxel at these cut-off points and therefore higher ICERs. In the original data cut there was a high level of censoring at 72 and 82 weeks leading to high levels of uncertainty at these cut-off points. However, there is more consistency using the new data cut which supports the exponential curve extrapolation. The estimated ICERs are more consistent across the various cut-off points – for all patients predicted to remain on treatment continuing after 2 years, the ICERs at the 52, 62, 72 and 82 week cut-off points were £52,761, £54, 958, £55,354 and £57,637 respectively.

The company's preferred cut-off point was 52 weeks. From 52 weeks onwards the exponential curve gives a reasonable visual fit to the new data cut, suggesting a reasonable basis for extrapolation at this cut-off. The visible 'kink' in the KM data around 52 weeks remains using the later data cut. There is no evidence to support a definitive selection of the cut-off point for switching from trial survival data to exponential model. Therefore, the ERG is unable to select a definitive cut-off point at which the switching from KM data to exponential would be deemed the most appropriate cut-off. However, it is worth noting that based on the committee's preferred scenario of 100% of patients remaining on treatment beyond 2 years, none of the cut-off points in the company's analysis result in an ICER considered to be cost-effective at the £50,000 threshold.

- ***A critique on the plausibility of modifying the treatment effect after a number of years – with a judgement on the most plausible scenario***

The ERG considers the company's preferred assumption of no fading treatment effect, i.e. an incremental treatment effect that continues for a lifetime to be implausible. Due to the limited trial follow-up period, there is no evidential basis for a definitive judgement. The ERG has previously considered that 3 years to be a reasonable estimate of treatment effect duration. We have not been presented with evidence to contradict this assumption.

Table 3 below presents results of varying treatment effect duration using both the original and new data cut with 25% and 100% of patients predicted to remain on treatment continuing beyond 2 years. Incorporating the new data cut results in ICERs that indicate the incremental treatment effect must continue unchanged for 10 years or more for the ICER to be considered cost-effective at a threshold of £50,000 and with 25% of patients remaining on treatment after 2 years. Using the committee's preferred scenario of 100% of patients predicted to remain on treatment continuing beyond 2 years none of the presented treatment effect scenarios would be considered cost-effective at a threshold of £50,000.

Table 3 Deterministic ICERs base-case 2 (discounted, with PAS) original and new data cut

Scenario	**Original data cut (September 2015)**	**New data cut (March 2016)**
No treatment waning	£43,741 (£47,476)	£47,844 (£52,761)
Treatment waning from 3 years	£64,948 (£70,542)	£66,707 (£73,675)
Treatment waning from 5 years	£51,073 (£55,468)	£54,269 (£59,885)
Treatment waning from 10 years	£44,584 (£48,394)	£48,503 (£53,492)

- ***A description and critique of the key drivers of the ICER from the new clinical evidence – including any key uncertainties that have not been addressed by the company in this updated submission, and your opinion on how they would affect the ICER***

Overall the new analysis based on the additional data provided by the company has resulted in smaller OS gain estimates associated with pembrolizumab. Consequently, incremental QALY gain was reduced and ICERs increased. The key uncertainties remain:

- In modelling the long-term OS, there is uncertainty regarding the use of an exponential curve to model long term survival
- In estimating the appropriate long-term treatment effect of pembrolizumab, there is no evidence to conclude on the duration of incremental treatment effect

- ***Finally please provide what you believe to be the most plausible ICER, listing any assumptions you would differ from the company's preferred ICER***

The ERG's previous preferred scenario was:

- 25% of the patients remaining on pembrolizumab after 2 years of treatment in the original base-case 2
- Applying a 2-stage cross-over adjustment for treatment switching
- Using a 52 weeks cut-off for the exponential parametric curves
- ToT based on PFS and hazard ratio adjustment
- Post-progression utilities based on TTD combined with progression-based utilities from KEYNOTE-010

- Inclusion of AE disutilities from KEYNOTE-010
- Treatment effect duration of 3 years

The company has not provided evidence to suggest that these assumptions are not reasonable. Based on the updated data, the ICER based on this preferred scenario is £66,707.