NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer [ID3798]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer [ID3798]

Contents:

The following documents are made available to consultees and commentators:

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

Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee (company)	MSD	MSD is grateful for the opportunity to respond to the Appraisal Consultation Document (ACD) for the above Technology Appraisal. We are pleased that the committee recognised the substantial unmet need for innovative treatment for this cancer and acknowledged the strength of the KEYNOTE-826 clinical data in supporting pembrolizumab as a highly clinically effective treatment option. Confirmation that pembrolizumab meets the End of Life criteria in this indication is critically important. In this response we address uncertainties raised in the ACD and present plausible ICERs between, £34,000 - £55,000/QALY gained, the substantial majority below the decision making threshold for End of Life products and indications. Both the progression free survival (PFS) estimates and the overall survival (OS) estimates generated by the economic model are plausible, particularly in the context of the high complete (CR) and partial response (PR) rates reported in the KEYNOTE-826 study. The CR and PR rates on the pembrolizumab treated arm are some of the highest for any immunotherapy trial to date (1). Given the encouraging outcomes observed in the trial, for example that ~90% of the complete responders were still alive at 2 years in this highly aggressive cancer, the committee should be reassured that model's predictions are a realistic prediction of outcomes in the population. Focusing on the themes highlighted in the ACD our response addresses the following:- 1) Different modelling approaches for PFS and TTP result in consistent curves resulting in similar ICERs (ACD section 3.7), with a range of ICERs below the decision-making threshold. 2) Demonstration of the relationship between PFS and OS and therefore the appropriateness of the state transition model structure (ACD Section 3.6). 3) All available evidence indicates that PFS and OS extrapolations produced by the model are plausible (ACD section 3.7). 4) Implementing a treatment effect waning assumption of 5-7 years, not the highly conservative 3-5 years, results in plausible ICER estimates below the decision making threshold, and mitigates longer term uncertainty (ACD section 3.9). 5) Correction of a programming error for PD utility (ACD section 3.10) 6) Areas of uncaptured value not yet considered by the committee are described, including the ability of pembrolizumab to address inequalities in cervical cancer outcomes experienced by certain vulnerable groups (ACD section 3.16). We note in the ACD that while End of Life criteria are met the committee consider the decision making threshold to be lower than £50,000 due to uncertainty. MSD considers this to be unreasonable in any scenario that includes an assumption of treatment effect waning and given that three different modelling approaches converge on similar estimated ICERs, the majority of which are below the decision making threshold. We discuss this in theme 7 below.	Comments noted. The committee considered the consultation response from the company. Please see responses to individual issues below.

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			MSD is grateful for the opportunity to present additional modelling approaches within our ACD response. These multiple modelling approaches have confirmed a range of ICER estimates from the model, that are below the threshold. These model estimates are similar to estimates previously validated by clinical experts, as such we hope this reassures the committee that there is minimal uncertainty in this appraisal. In the light of this reduced uncertainty and applying the decision-making threshold of £50,000/QALY gained, we kindly request the committee reviews it initial decision and positively recommends pembrolizumab for these cervical cancer patients. This group have extremely limited options and no new NICE-assessed treatments for 13 years.	
2	Consultee (company)	MSD	In response to the ACD the company looked at two alternative modelling approaches as well as revisiting the previous modelling options. Two-piece, spline and responder based models for PFS and TTP converged on estimated ICERs in the range ~£34,000 - £55,000/QALY gained when treatment waning from 5-7 years is applied. <u>KEYNOTE-826 Outcomes by Response Group</u> In KEYNOTE-826, outcomes vary by a patient's level of response to treatment, as illustrated by Figure 1, originally presented in the company's response to clarification questions and here updated with PFS data.	Thank you for your comments. At the first committee meeting, the committee discussed the company's justification for a 3-state Markov state transition model to estimate the cost effectiveness of pembrolizumab plus chemotherapy with or without bevacizumab. The committee concluded the company's model may be adequate for decision making but the most appropriate modelling approach may change when further data becomes available from KEYNOTE-826. Please see FAD section 3.5. At the second committee meeting, the committee considered the company's

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			 *Figure 1: PFS and OS by responder status for both arms (CR=Complete Response, PR=Partial Response,SD=Stable Disease,PD=Progressed Disease,NE/NA=No Assessment* In these above Kaplan Meier curves by responder status, it should be noted that: • There are a high proportion of PR and CR responders in the PFS curves in advanced cervical cancer (both arms) compared with other advanced cancers	additional analyses using spline-based extrapolation methods and a response-based model to analyse the time to progression and progression-free survival data. The committee concluded that the company's updated analyses were helpful for decision making, but the results are still highly uncertain. Please see FAD section 3.7.

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CR PR is 18% higher on the pembrolizumab arm than the SoC arm (Error! Reference source not found.)
There are notably fewer PD patients on the pembrolizumab arm than on the SoC arm, though absolute numbers are small

Table 1: CS Document B Table 11 Confirmed objective response based on investigator assessment per RECIST 1.1 (CPS ≥ 1 population)
<table>
<tr><th></th><th colspan="2">CPS ≥ 1 population (n = 548)</th></tr>
<tr><th></th><th>Pembrolizumab + chemotherapy ± bevacizumab (n = 273)</th><th>Placebo + chemotherapy ± bevacizumab (n = 275)</th></tr>
<tr><td>Number of confirmed OR</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ORR, % (95% CI)</td><td>68.1 (62.2, 73.6)</td><td>50.2 (44.1, 56.2)</td></tr>
<tr><td>CR, n (%)</td><td>62 (22.7)</td><td>36 (13.1)</td></tr>
<tr><td>PR, n (%)</td><td>124 (45.4)</td><td>102 (37.1)</td></tr>
<tr><td>SD, n (%)</td><td>58 (21.2)</td><td>88 (32.0)</td></tr>
<tr><td>PD, n (%)</td><td>9 (3.3)</td><td>29 (10.5)</td></tr>
<tr><td>Difference in percentage pembrolizumab group versus placebo group</td><td colspan="2">[redacted]</td></tr>
<tr><td>p-value</td><td colspan="2">[redacted]</td></tr>
<tr><td colspan="3">Key: CI, confidence interval; CPS, combined positive score; OR, objective response; ORR, objective response rate; RECIST 1.1, response evaluation criteria in solid tumours version 1.1.</td></tr>
</table>
It can be seen from Figure 1 that almost all people with a best response of Stable or Progressed Disease had died by the end of the trial period. Whereas, OS was ~90% among Complete Responders in the pembrolizumab arm. The patients alive at the end of the trial period therefore comprise a cohort of responders who had much slower rates of progression and death. Because of this pattern of response, the hazard functions for both PFS and OS are likely to be complex.
As outlined in our submission, directly projecting OS from the available data would therefore have underestimated survival among responders. A State Transition Model (STM) where OS is linked to progression of disease was therefore built. The model has three states: pre-progression, post-progression and death. Movement between the three health states is determined by transition probabilities calculated from the individual patient data in KEYNOTE-826; time-to-progression (TTP), progression-free survival (PFS) and post-progression survival (PPS).
</td><td></td></tr>
<tr><td>3</td><td>Consultee (company)</td><td>MSD</td><td>
<u>Theme 1: PFS / TTP modelling approaches (ACD sections 3.7)</u>

In this section we will briefly present the three modelling approaches we have incorporated. We then discuss the impact on the modelled results and validation of the modelled estimates. The modelling approaches discussed are spline based, response based and the original piecewise modelling. We discuss spline models in this comment section, response based in comment section 4 and piecewise modelling and results from all three approaches in comment section 5.
</td><td>Thank you for your comments. At the second committee meeting, the committee considered the company's additional analyses</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			Spline based approach In response to the ACD, MSD evaluated alternate approaches to modelling time to progression (TTP) and progression free survival (PFS). Taking into account NICE TSD21, we explored spline models using the package *flexsurvspline* (R statistical software; methodology from Royston and Parmar (2002))(2, 3). We modelled the spline function on the "odds", "hazard" and "normal" scales. Without knots, these spline models would correspond to single piece Weibull, log-logistic and lognormal models. For each of these scales we fitted spline models based on one, two or three knots (k=1, k=2, k=3). We did not pre-specify the location of the knots. If location is unspecified, the software automatically assigns knots to quantiles of the observed event times. For k=1 the knot is at the median, for k=2 the knots are at the 33rd and 66th percentile and for k=3 the knots are at the 25th, 50th and 75th percentile. We felt that this approach had the strength of being independent of any previous assessment we had made about inflection points in the data and therefore would help to validate, or not, previous approaches. We therefore had 9 spline models to consider. *Spline model selection criteria* Our selection criteria were:- 1) best statistical fit measured by lowest AIC 2) visual fit to the smooth spline hazard curve 3) same model type for TTP as PFS 4) long term OS plausible 5) priority given to same model type (number of knots, scale) between the arms (TSD14 advice) The PFS and TTP datasets are comprised of mostly the same data. In line with our original submission, it is reasonable to use the same type of model for both. Priority was given to PFS as this was a primary trial outcome, includes more events and has less censoring than TTP. All models with 1 knot were rejected from both arms for having significantly higher AICs and for being a poor visual fit to the data, particularly in the pembrolizumab arm. It is less easy to outright reject any of the other six models, which all have similar properties. The hazard scale model with 2 knots ("hazard, 2") had the lowest AIC for PFS for both arms. It also provided a good visual fit to the smooth spline curves. The "hazard, 2" model had the second-lowest AIC and a good visual fit for TTP. The AIC was very slightly higher for the "hazard, 2" model than the "odds, 2" model for TTP but not meaningfully so (1 point higher for pembrolizumab and 0.1 for Standard of Care [SoC). Long term PFS for pembrolizumab was relatively high using any of the 2 and 3 knot models (range 13%-21% at 20 years (if unadjusted by treatment waning), 14.7% for the "hazard, 2" model). For the SoC less variation was observed. Estimates ranged between 4.9%-7.3% at 5 years and 1%-3.5% at 10 years. The "hazard, 2" model had 5 and 10 year PFS of 5.5% and 1.4%, which was slightly higher than the estimates produced by the one-piece curve at these milestones (3.5% and 1.1%).	using spline-based extrapolation methods and a response-based model to analyse the time to progression and progression-free survival data. The committee concluded that the company's updated analyses were helpful for decision making, but the results are still highly uncertain. Please see FAD section 3.7.

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			 *Figure 2: Long term PFS for different Spline models also showing how the treatment waning assumption controls long term PFS* All models produce higher mean OS on pembrolizumab and similar mean OS on SoC than estimated by our original piecewise approach. Life year gain is therefore increased using any of the 2 and 3 knot spline approaches. Regardless of the choice of knots and scale, implementation of spline modelling would therefore reduce the ICER considerably vs. the MSD base case. We therefore considered all the 2 and 3 knot spline models to be qualitatively similar and did not need to implement them all in the economic model. We implemented the “hazard, 2” model into the economic model and reviewed the resulting 4-year OS in the SoC arm against GOG240 and concluded it was plausible at 13% (vs. 15% in GOG240). We reviewed the 5-year OS for pembrolizumab and concluded that the magnitude and incremental benefit and the absolute level was within the range that has been observed in published 5-year trials of pembrolizumab in metastatic solid tumours (e.g. OS was 28.5% vs. 31.9% in KEYNOTE-024). We also noted that “hazard, 2” was in the middle of the available spline models	

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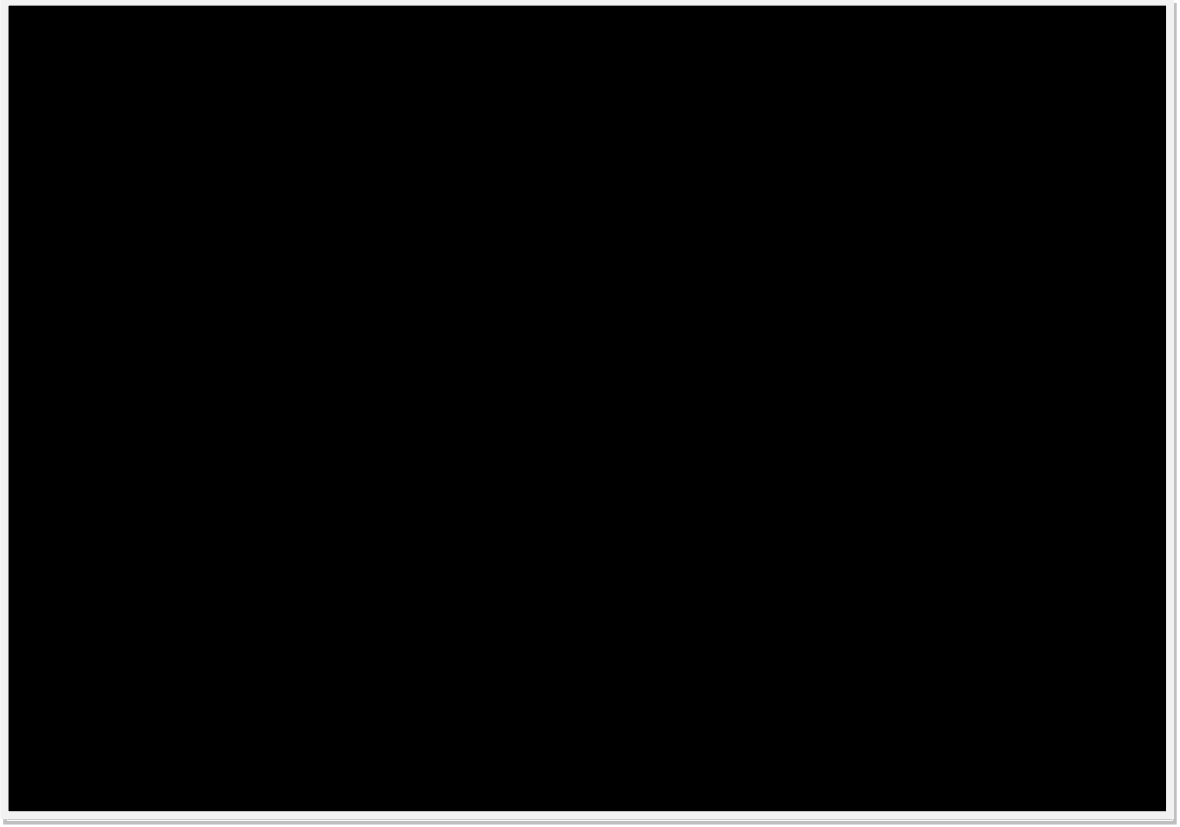
			rather than the most optimistic or pessimistic. The “hazard, 2” spline model was a very good fit to the short term PFS and TTP data for both arms.  *Figure 3: "Hazard, 2" spline models fit to PFS KM data*	

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			 *Figure 4: "Hazard, 2" spline models fit to TTP KM data* Taking these considerations together, we believe the “hazard, 2” model to be the best fitting spline model for both PFS and TTP for both arms. The “hazard, 3” model was tested in sensitivity analysis and produced similar conclusions. Our approach to model fitting and selection for spline models is consistent with guidance in NICE TSD21. We note that long term PFS and OS produced by the 2 and 3 knot spine models might be considered optimistic. Importantly, this is tightly constrained in practice by the treatment waning assumption in the economic model, as can be seen in Figure 4 above, the blue and the grey curves that move rapidly towards 0% PFS are those with the treatment effect waning assumption included. Overall progression-free life year gains on treatment-waned spline models are similar to, but slightly higher than the base-case two-piece curves. The visual fits of all 1, 2 and 3 knot models to the smooth spline hazards are shown in an appendix comment.	

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			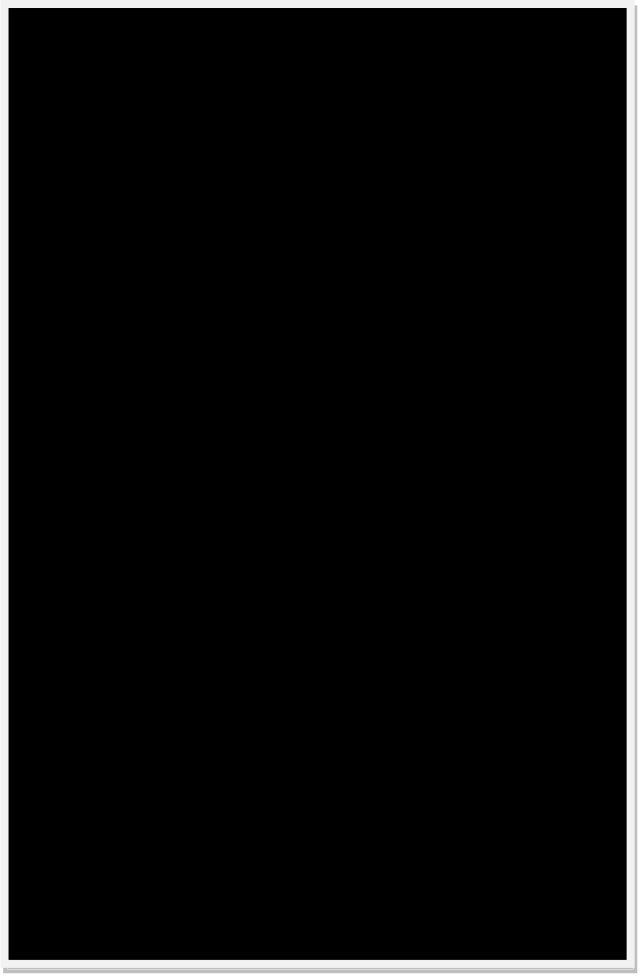 *Figure 5: AIC for PFS and TTP spline models*	
4	Consultee (company)	MSD	As already mentioned, rates for partial responders (PR) and complete responders (CR) in KEYNOTE-826 are amongst the highest reported in any advanced cancer immunotherapy RCT. Rates of CR are nearly twice as high in the pembrolizumab + SoC arm than the SoC arm and responses are more durable. Detailed examination and extrapolation of these responder data support the plausibility of the existing OS and PFS estimates.	Thank you for your comments. At the second committee meeting, the

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			The response based model (RBM) explicitly recognises responder status. We presented this approach in the "weighted survival analysis" previously submitted as validation of the economic model's predicted OS. We consider this model to be helpful in understanding why the hazard functions for PFS, TTP and OS are likely to be complex (i.e. not suitably modelled using single-piece parametric fits) and to provide information on the survival of distinct groups of patients within the PFS health state. Initially the PFS hazard function in the whole cohort in each arm is dominated by events among Progressed Disease (PD) and Stable Disease (SD) patients but gradually, as these patients progress, the cohort becomes more comprised of CR and PR patients who have slower event rates. This provides some explanation as to why one-piece parametric curves may not be appropriate, particularly in the pembrolizumab + SoC arm where difference in event rate between CR patients and the other groups appears even more marked.	committee considered the company's additional analyses using spline-based extrapolation methods and a response-based model to analyse the time to progression and progression-free survival data. The committee concluded that the company's updated analyses were helpful for decision making, but the results are still highly uncertain. Please see FAD section 3.7.

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			 *Figure 6: OS and PFS KM curves by responder status and arm* The RBM splits patients out into their responder categories and fits separate PFS parametric survival curves for each of Complete Responders, Partial Responders, Stable Disease, Progressed Disease (in the case of PD, progression happens at the first assessment for all patients) and Not Evaluable/No Assessment. [redacted] in each arm belong to this last group and all recorded events were deaths rather than progressions. It is difficult to know with certainty to which group they biologically belong, although the patients with an event are likely to be SD.	

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			We selected parametric survival curves for each group based on the criteria in Table 2. “Plausible compared to other response models” means that mean survival should follow the biologically sensible order CR > PR > SD > PD. Survival being longer in the pembrolizumab + SoC arm within any of the groups was also considered plausible in light of the DoR data from the trial. The standard suite of single-piece fits were examined for each cohort of patients and in all cases, there was strong evidence to select one particular model. The justifications are listed below:-	

Table 2: PFS parametric model selection and justification for each responder cohort in each arm

Model Selection Justification		
	Best Model	**Reason**
Pembrolizumab		
[redacted]	[redacted]	[redacted]

AIC and BIC statistics are available in the “ACM2 – PFS Responder” sheet of the updated version of the economic model.

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			We examined fitting the [redacted] model to SoC CR patients in a sensitivity analysis based on it having better mean OS that is perhaps more in-keeping with a CR patient, despite the long plateau. As with other analyses, the same type of model was adopted for TTP as for PFS due to the datasets being comprised of almost the same data but with PFS having more events/less censoring. This caused a slight issue with TTP for the NE/NA group because there are no TTP events in this group (every patient is either censored or died pre-progression). This leads to a slight overestimation of the ongoing PFS->Death transition probability for both arms, which is conservative for Pem+SoC because patients spend longer in the PFS health state in this arm. We handled this with one sensitivity analysis where we assumed the TTP curves were equal to the PR group (because this group had heavy censoring followed by a rapid drop). This improved the visual fit of the RBM for TTP to the TTP KM data. We named this model RBM2. An alternate sensitivity analysis where TTP was equal to a weighted average of the TTP across the other groups was also used and labelled RBM3. It should be noted that over and underestimation of TTP has a relatively modest effect on the model's results. The RBM is calculated by multiplying the proportion of patients in each group in each arm by their survival probability and summing the total to create a single survival curve weighted by response. The resulting curves produce extremely similar results in the SoC arm and slightly more conservative results in the Pem+SoC arm.	

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			 *Figure 7: Comparison of PFS curves between RBM and CEM (original piecewise model)*	

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			 *Figure 8: Comparison of Base case, RBM and Spline PFS curves and effect of Treatment Waning*	

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			 *Figure 9: Comparison of PFS - RBM and Trial Data*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Figure 10: Comparison of TTP RBM vs Trial Data (some overestimation caused by NE/NA patients)*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Figure 11: RBM2 (overestimation corrected) vs Trial Data*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *Figure 12: Composition of PFS Curve Over time by response status – Pem+SoC arm*	

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			 *Figure 13: Composition of PFS Curve Over time by response status – SoC arm* The RBM illustrates how the hazard function changes over time, from initially being dominated by patients who had progressed or stable disease before being dominated by those who achieved Complete Response. It is helpful validation of the company's original approach: TTP, PFS and OS curves are all similar to those used in/predicted by the original piecewise approach despite an entirely different modelling approach having been used. Although OS is not used directly in the economic model, it is possible to construct an OS curve using the RBM method to directly extrapolate OS by response group. This method was outlined in the company's submission in the "Weighted survival analysis report" and can capture the complexities of the hazard function in the same way as it did for PFS.	

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			 *Figure 14: OS over time by response status Pem+SoC*	

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			 *Figure 15: OS over time by response status SoC*	

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			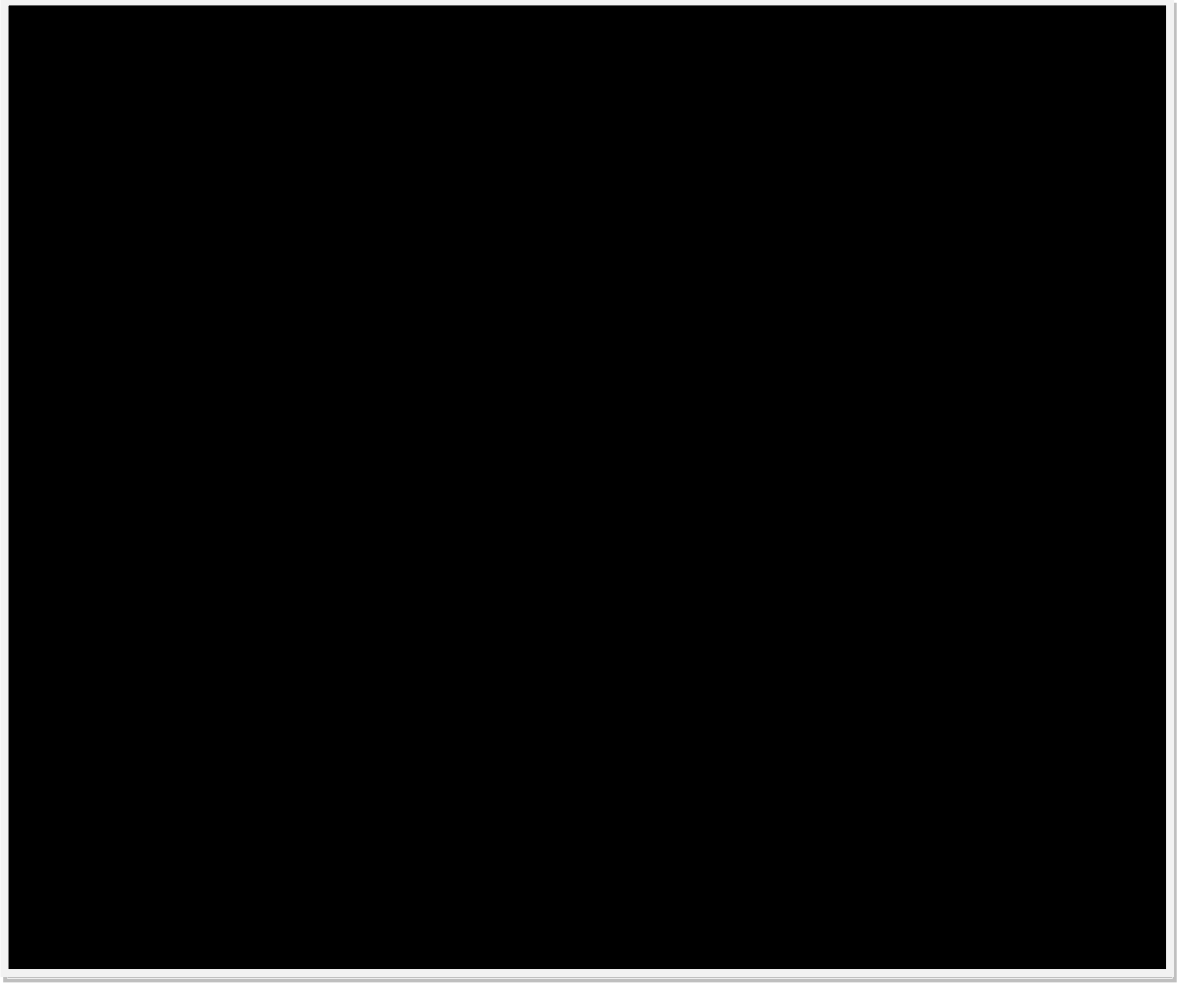 *Figure 16: Comparison of RBM for direct extrapolation of OS and Curves from economic model* Although they are not used in the economic model, the OS the curves in Figure 16 are useful in illustrating the concept of the RBM. A different modelling method for OS can produce similar results to the economic model. The RBM constructed from OS data by response group is almost the same as the one-piece curve used in the economic model while the Pem+SoC data are a little more pessimistic, being equal to those produced by the RBM-based economic model. We can infer from this data that, had a partitioned survival model based on the RBM method been built, it would likely have produced similar results to those we see in the RBM based state transition	

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			model. It should be noted that the RBM's results are inherently potentially more variable due to the number of underpinning survival curves; the usual range of options are available for all five groups in both arms and there are therefore a lot of curve combinations that could be chosen. We note that there are very few events among CR patients, particularly in the pembrolizumab arm and the tail of the RBM will obviously be sensitive to curve selection for this group. We have not attempted to explore these myriad alternatives, although there are no obvious statistical or plausibility related reasons to deviate from the curves we selected. The RBM is not intended as a more robust replacement for the piecewise model; we have presented it as reassuring validation that the piecewise model's results are explainable and plausible in the context of survival by response status.	
5	Consultee (company)	MSD	*Piecewise approach – original base case* Having explored two alternative approaches with splines and RBMs, we consider it helpful to re-present the company's previous preferred modelling approach: the 37-week piecewise model. We initially examined one-piece models for PFS but rejected them as inappropriate due to very poor visual fit to the pembrolizumab + SoC arm and OS that was inconsistent with 4-year data from GOG240 in the SoC arm. We also note that fitting a one-piece model for Pem+SoC implies a drop in OS between year 2 and 5 ([redacted] that would be much greater than anything observed in five-year pembrolizumab trials to date. Given the relatively high levels of CR and PR in KEYNOTE-826, there is no reason to believe this would be the case for this indication. We re-iterate that we do not believe single piece models should be among the plausible sets of analyses used for decision-making. After rejecting one-piece models we examined a series of potential cut-offs for a piecewise approach. Of these, 37-weeks was chosen because the resulting model included a good number of events upon which to base a parametric curve, the hazard estimates fitted well with the smooth spline estimates over time, it was close to the observed inflection point and produced survival estimates close to GOG240 at 2 years in the SoC arm (~15%) and ones that appeared plausible in the pembrolizumab + SoC arm, given other long term data from 5-year trials of pembrolizumab. The resulting predictions were validated as clinically plausible at an advisory board of eight UK clinicians from across the UK who treat advanced cervical cancer in their day to day practice. Since that advisory board, the estimates have been revised downwards be the use of a one-piece curve in the SoC arm and the imposition of a treatment waning assumption in the pembrolizumab + SoC arm. The experts at the Appraisal Committee Meeting (ACM) confirmed these newer, more conservative data were plausible (slide 20). In section 3.7 of the ACD, it is stated that the company believe separate models might be justified based on pembrolizumab having a different mechanism of action to SoC. This is true, and it is well known that I/O survival curves have long tails compared to more traditional treatments, but we would also stress that the design of KEYNOTE-826 is not immunotherapy vs. another type of treatment. Pembrolizumab is used in addition to SoC and therefore provides not only a different mechanism of action but an additional mechanism of action by which patients can respond to treatment. *Results:* For the SoC arm the different approaches produced fairly consistent results, especially in the long term. The RBM tended to underestimate OS to begin with but this is largely accounted for when correcting for the probable	Thank you for your comments. At the second committee meeting, the committee considered the company's additional analyses using spline-based extrapolation methods and a response-based model to analyse the time to progression and progression-free survival data. The committee recognised that the company's additional analyses may address some of the concerns around the company's two-piece extrapolation approach but uncertainties around the long-term survival projections remained. The

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Please insert each new comment in a new row</th><th>NICE Response
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<tr><td></td><td></td><td></td><td>overestimation of TTP in the NE/NA group (this sensitivity analysis is labelled “RBM2”). The long-term OS on all SoC models is consistent with the base case and therefore with clinical expectation.
In the Pem+SoC arm, the spline model estimates higher OS than the base case and the RBM lower. The treatment waning assumption controls the curves to the extent that 15y+ OS is very similar for all models. All models produce a reduction in OS from year 2 to year 5 that is conservative compared to observed data in other five-year pembrolizumab trials.
Table 3: Overall survival scenarios
<table>
<tr><td></td><td></td><td colspan="6">Overall Survival</td></tr>
<tr><td>Scenario</td><td>Waning</td><td>2y</td><td>3y</td><td>5y</td><td>10y</td><td>15y</td><td>20y</td></tr>
<tr><td>Piecewise Pem+SoC</td><td>None</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>RBM Pem+SoC</td><td>None</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Spline Pem+SoC</td><td>None</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Piecewise Pem+SoC (basecase)</td><td>5-7</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>RBM Pem+SoC</td><td>5-7</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>RBM2 Pem+SoC</td><td>5-7</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Spline Pem+SoC</td><td>5-7</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Piecewise Pem+SoC</td><td>3-5</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>RBM Pem+SoC</td><td>3-5</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>RBM2 Pem+SoC</td><td>3-5</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Spline Pem+SoC</td><td>3-5</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SoC - Piecewise</td><td>-</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>SoC - One Piece</td><td>-</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>RBM SoC</td><td>-</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>RBM2 SoC</td><td>-</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Spline SoC</td><td>-</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table></td><td>committee concluded that the company’s updated analyses were helpful for decision making, but the results are still highly uncertain. Please see FAD section 3.7.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

*NB waning is vs. the corresponding SoC model e.g. spline vs. spline

We conclude that all of these approaches produce curves that have clinically plausible long-term OS for both Pembrolizumab + SoC and SoC. The data for SoC are consistent with clinical expectation that there are a small number of patients who respond well to treatment and get durable response. The estimates for Pembrolizumab + SoC are well within a plausible range given data from five-year trials, UK clinical experience and the discussion at the NICE ACM. It is reassuring that different modelling approaches arrive at similar conclusions in terms of OS for both arms.

Cost-effectiveness Results

The company's base case model includes the following assumptions:-

- Pembrolizumab + SoC modelled piecewise from 37 weeks
- One piece model for SoC
- Treatment waning from 5-7 years post cessation
- Health state utility values with programming error corrected
- Other settings are the same as agreed prior to ACM

Table 4: ICER

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
SOC	[redacted]	2.060	[redacted]	-	-	-	
PEM+SOC	[redacted]	4.247	[redacted]	[redacted]	[redacted]	[redacted]	**£40,203**

The results of the model are reassuringly below the cost-effectiveness threshold for End of Life medicines. Having undertaken different modelling approaches, the company considers the above to be the most appropriate scenario for decision making. We present below results from numerous other approaches to demonstrate the consistency in estimated ICERs regardless of the modelling.

Table 5: Sensitivity/scenario analyses results

Scenario	Waning years	Mean LYs SoC	Mean LYs Pem+SoC	Inc. Costs	Inc. LYs	Inc QALYs	ICER
Piecewise (loglog) vs. One piece (basecase)	5-7	2.06	4.25	[redacted]	2.19	[redacted]	£40,203
Piecewise (lognorm) vs. One piece	5-7	2.06	4.45	[redacted]	2.39	[redacted]	£36,881
Piecewise (av. Loglog/weibull) vs. One piece	5-7	2.06	3.91	[redacted]	1.86	[redacted]	£46,081
Piecewise (loglog) vs. Piecewise	5-7	2.51	4.76	[redacted]	2.25	[redacted]	£41,821

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

RBM	5-7	2.00	3.74	[redacted]	1.74	[redacted]	£50,207
RBM2	5-7	2.13	3.92	[redacted]	1.79	[redacted]	£49,156
RBM3	5-7	2.15	3.92	[redacted]	1.77	[redacted]	£49,839
Spline (2 knot)	5-7	2.21	4.63	[redacted]	2.41	[redacted]	£34,773
Spline (3 knot)	5-7	2.15	4.59	[redacted]	2.44	[redacted]	£33,798
Piecewise (loglog) vs. One piece	3-5	2.06	3.95	[redacted]	1.89	[redacted]	£44,893
Piecewise (lognorm) vs. One piece	3-5	2.06	4.10	[redacted]	2.04	[redacted]	£41,605
Piecewise (av. Loglog/weibull) vs. One piece	3-5	2.06	3.75	[redacted]	1.69	[redacted]	£49,418
Piecewise (loglog) vs. Piecewise	3-5	2.51	4.56	[redacted]	2.05	[redacted]	£44,825
RBM	3-5	2.00	3.61	[redacted]	1.61	[redacted]	£53,213
RBM2	3-5	2.13	3.80	[redacted]	1.67	[redacted]	£51,686
RBM3	3-5	2.15	3.81	[redacted]	1.66	[redacted]	£52,414
Spline (2 knot)	3-5	2.21	4.19	[redacted]	1.97	[redacted]	£41,014
Spline (3 knot)	3-5	2.15	4.12	[redacted]	1.97	[redacted]	£40,332
RBM (GenGamma SoC CR)	3-5	2.40	4.01	[redacted]	1.60	[redacted]	£55,633
Piecewise (loglog) vs. One piece (basecase)	None	2.06	5.31	[redacted]	3.25	[redacted]	£31,675

The scenario analyses tables shows the cost-effectiveness results using a wide array of different plausible approaches for extrapolating PFS and TTP. The results are reassuring in that they produce ICER estimates that are either close to or substantially below the cost-effectiveness threshold. Given there are several areas of value for patients, carers and dependents that are not captured in the model (see Theme 6), we are confident that pembrolizumab is a cost-effective addition to SoC in this indication.
Critically, the RBM validates the assumptions in the piecewise model which the company suggests is the most appropriate for decision making.

6	Consultee (company)	MSD	<u>Theme 2: Relationship between PFS and OS (ACD Section 3.6)</u> The committee state in the ACD that one of the two key areas of uncertainty is “the level of benefit pembrolizumab will have on overall survival”. We suggest this is only uncertain to the extent that gains in PFS are uncertain. To summarise why mean gains in PFS should be expected to translate into similar mean gains OS in this indication:-	Thank you for your comments. The committee considered the company’s

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			1) For mean PFS gain not to lead to at least the same mean OS gain, post progression survival would have to be shorter in the pembrolizumab + SoC arm. The committee have confirmed the opposite; that their preferred assumption is that PPS is slightly longer in the pembrolizumab + SoC arm. 2) Clinical experts at ACM1 commented that the benefits of pembrolizumab might persist beyond progression. This fits with response data from the clinical trial that shows that the depth of response is greater in the pembrolizumab + SoC arm. Progression in the trial was assessed from the greatest extent of response and therefore patients entering the PD health state have less extensive disease on average after responding to pembrolizumab + SoC than SoC alone. 3) The observed PPS data in KEYNOTE-826 is relatively mature and is in line with data observed in GOG240. 4) The same PFS-OS phenomenon has been observed in this disease area before in GOG240. Clinicians at ACM1 confirmed this is in line with their experience using bevacizumab and that OS gains may be even greater than PFS gains (slide 17) 5) There are no effective second line treatments and second line treatments do not differ by arm, either in the study or in proposed clinical practice, therefore there is no confounding off efficacy due to subsequent treatment 6) The patient population is relatively young and non-cancer mortality does not influence survival 7) PFS and OS HRs are the same within the trial (~0.6) These arguments also support the appropriateness of the state-transition model structure, where OS depends to a great extent on PFS rather than being modelling entirely independently of it as in a partitioned survival model.	evidence for the relationship between progression-free survival and overall survival alongside comments from other stakeholders. The committee concluded that it was likely that pembrolizumab also improved overall survival. However, the level of this benefit is uncertain. Please see FAD section 3.6.
7	Consultee (company)	MSD	<u>Theme 3: Plausibility of PFS and OS (ACD section 3.7)</u> The ACD states "…the company's 2-piece approach led to an optimistic projection of people achieving long-term survival on pembrolizumab" (4). It is unclear the origin of this statement. The survival estimates predicted by the model are plausible and realistic based on all the information and insight the company has. To reiterate why we believe the PFS and OS estimates are plausible:- 1) They are validated by the Response Based Model, which, despite taking an different approach to extrapolation and model structure produces similar estimates for PFS and OS as the economic model and illustrates the changing nature of the hazard function over time as it transitions from being dominated by non-responders to responders. 2) MSD conducted an advisory board with 8 clinicians treating cervical cancer from across the UK who confirmed that the model's estimates are plausible. 3) The clinical experts at the NICE committee meeting confirmed that the model's results are plausible and in line with published data (slide 17, slide 20 of ACM slides). 4) The SoC model is validated by published longer term data from GOG240 and supported by the published description of patients with long term PFS on bevacizumab. 5) Both the absolute OS and magnitude of OS gain are within the range that has been seen in other 5-year trials of pembrolizumab in metastatic solid tumours (data were supplied in the company's TE response). 6) The Complete and Partial response data are some of the highest ever observed in an immunotherapy trial and a great cause for optimism about long term survival in patients who respond well to treatment. 7) Non-cancer mortality is not a factor in this relatively young population. 8) Uncertainty beyond 5 years is controlled by the imposition of the treatment waning assumption. 9) There is a consistent morphology for PFS curves across long term pembrolizumab trials. 10) The one piece model considered as part of the analyses for decision-making at ACM1 does not produce	Thank you for your comments. The committee considered the company's evidence and additional analysis of the time to progression and progression-free survival data. The committee recognised that the company's additional analyses may address some of the concerns around the company's extrapolation approach but uncertainties around the long-term survival

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>plausible results for the following reasons:-
a. Poor visual fit to the KM data, especially in the pembrolizumab arm
b. Estimated 4-year OS is [redacted]. This is only [redacted] higher than the 4-year OS observed in GOG240. An incremental benefit this small has never been observed in a long term study of pembrolizumab (see KM data from KEYNOTE-024, KEYNOTE-010 and KEYNOTE-006 submitted by the company at Technical Engagement).
c. The one-piece curve leads to OS and PFS decreasing at a rate much greater than that observed in long term trials of pembrolizumab. Below are data from the advanced solid tumour trials the company presented at Technical Engagement and those published since. It can be seen that the company's base case piecewise model is within the range of other trials for PFS and conservative for OS. By contrast, the company considers the one-piece model to produce extraordinarily pessimistic results with OS and PFS being roughly one quarter of their two-year value by five years. Given the response data in KEYNOTE-826, it would be very surprising if PFS and OS declined faster than in other comparable pembrolizumab trial.

Table 6: 2 year and 5 year PFS and OS in pembrolizumab arms of advanced solid tumour trials
<table>
<tr><th></th><th colspan="3">PFS</th><th colspan="3">OS</th><th>Ref</th></tr>
<tr><td></td><td>2 years</td><td>5 years</td><td>Ratio</td><td>2 years</td><td>5 years</td><td>Ratio</td><td>(5)</td></tr>
<tr><td>KEYNOTE-024</td><td>29%</td><td>12.8%</td><td>0.44</td><td>50.0%</td><td>31.9%</td><td>0.64</td><td>(5)</td></tr>
<tr><td>KEYNOTE-010 TPS ≥50%</td><td>30%</td><td>18.2%</td><td>0.61</td><td>34.5%</td><td>25.0%</td><td>0.72</td><td>(5)</td></tr>
<tr><td>KEYNOTE-010 TPS ≥1%</td><td>19%</td><td>9.4%</td><td>0.49</td><td>22.9%</td><td>15.6%</td><td>0.68</td><td>(5)</td></tr>
<tr><td>KEYNOTE-006+</td><td>35%</td><td>21.5%</td><td>0.61</td><td>60.0%</td><td>45.0%</td><td>0.75</td><td>(5)</td></tr>
<tr><td>KEYNOTE-189*</td><td>23.1%</td><td>7.5%</td><td>0.32</td><td>45.7%</td><td>19.4%</td><td>0.42</td><td>(6)</td></tr>
<tr><td>KEYNOTE-407*</td><td>20.7%</td><td>10.8%</td><td>0.52</td><td>36.0%</td><td>18.4%</td><td>0.51</td><td>(7)</td></tr>
<tr><td>Company - KN826</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td></tr>
<tr><td>One-piece model - KN826</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td></td></tr>
</table>
+ projected from 26% at 4 years to 21.5% at 5
*included approximately 1/3 PDL1 negative patients</td><td>projections remained. Please see FAD section 3.7.</td></tr>
<tr><td>8</td><td>Consultee (company)</td><td>MSD</td><td><u>Theme 4: Treatment effect waning assumption (ACD section 3.9)</u>

It is important to re-emphasise that treatment effect waning is an uncertain assumption. Although we understand the logic that at some point progression free patients may become qualitatively similar in each arm and exhibit the same hazards of progression, no empirical evidence exists on if and when that time point exists.</td><td>Comments noted. The committee took into consideration evidence presented by the company</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			1) Although we understand that the committee consider 3-5 years post treatment to be their preferred assumption, it is important to keep in mind that there is no more empirical evidence for this than the 5-7 year assumption and indeed, no waning at all. 2) We emphasise that, given the data we showed on multiple 5-year trials of pembrolizumab showing no evidence of waning, 3-5 years post treatment cessation is the most conservative this assumption could be. 3) We have therefore continued to submit alternate waning scenarios for the committee's consideration and propose that waning at 5-7 years could be considered a 'middle ground'. 4) We note that the treatment waning assumption controls model uncertainty and variability to a great degree. We further note that all the models we have submitted are at or below the decision-making threshold when this assumption is imposed.	and the ERG relating to this issue. It concluded that a treatment waning effect from 3 years to 5 years after stopping treatment with a 2-year stopping rule was reasonable for pembrolizumab. Please see FAD section 3.10.
9	Consultee (company)	MSD	Theme 5: PD utility value corrected (ACD section 3.10) MSD understand that the committee's preference is that the model uses health state utility values (HSUV) based on the Progression Free (PF) and Progressed Disease (PD) health states. We initially presented HSUVs only as a sensitivity analysis and have revisited our calculations in light of the committee's preferences. In the version of the model that was used to generate results for ACM1, this value was set to the beta coefficient for PD rather than the combination of the PF value and the coefficient i.e. the actual PD utility. We apologise for this error. Correcting this error reduces the ICER by a small amount.	Thank you for your comments. No action required.
10	Consultee (company)	MSD	Theme 6: Uncaptured Value (ACD section 3.16) The ACD states that 'all relevant benefits are captured in the QALY calculations' but these calculations only reflect data from the EQ-5D forms filled in by patients within the trial period (4). 1) We urge the committee to reconsider the evidence from Jo's Cervical Cancer Trust and BGCS that was discussed at the meeting (slide 7), 'This cancer mostly affects young women of working age. Many have families and dependents. Treatment can enable women to return to their daily lives, including work and their caring responsibilities' (8). The health related quality of life of patients' carers and those that they may care for, such as young children has not been included in the economic model. We consider that the benefit of prolonged response (particularly Complete Response) would add QALYs to both the patients' carers and children/dependents (9, 10) 2) Many of the QALYs in the model are accrued by patients who have remained progression free after the 2-year time point in KEYNOTE-826. There are no data on the utility of these patients from KEYNOTE-826 but it is likely that the ability to be free from treatment, to have long term progression free status and to "return to their daily lives" would lead to a significant increase in quality of life and therefore incremental QALYs. It is also likely that the cohort of progression free patients will become steadily more comprised of patients who achieved a Complete Response. It is logical that this "enriching" of the progression free population would increase incremental QALYs above what has been captured in the model. 3) Section 6.2.3 of NICE health technology evaluations: the manual states that non-health factors can be taken into account by the committee when contained within the NICE Principles . NICE Principle 9: Aim to reduce health inequalities would seem to be applicable (11) . For a variety of socio-economic reasons, metastatic cervical	Thank you for your comments. The committee took into consideration evidence presented by the company and the ERG relating to uncaptured value, alongside comments from other stakeholders. The committee concluded that all relevant benefits of the technology were captured in the QALY calculations. Please see FAD section 3.17.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			cancer is more common among the most deprived communities in society as well as ethnic minority groups and migrants who have low engagement with vaccination and screening programmes (12-16). A recommendation that generates QALYs for these groups will work towards reducing health inequalities.	The committee also recognised that metastatic cervical cancer was more common among people with low socioeconomic status as well as ethnic minority groups and migrants who have low engagement with vaccination and screening programmes. However, issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. Please see FAD section 3.16.
11	Consultee (company)	MSD	<u>Theme 7: Decision Threshold</u> MSD considers the decision threshold should be £50,000/QALY gained for the following reasons (specific reference to the decision-making considerations outlined in the NICE Methods Guide issued in 2013 6.3.3) (11): 1. Certainty about the appropriateness of the model structure. a. The economic model structure captures the natural history of the disease well because mean PFS and OS have a strong relationship in advanced cervical cancer (see Theme 2) b. The two-piece model is validated by the Response Based Model, a totally different modelling approach that explicitly accounts for response status and produces similar PFS and OS (Theme 1) 2. A relatively tightly defined range of plausible ICERs, all close to or below the threshold mean there is a low risk of decision error 3. Certain clinical benefit a. The data from the trial show separate and separating PFS and OS curves b. The CR and PR rates are some of the highest ever observed in an immunotherapy trial c. Close to 90% of CR patients are alive at two years 4. Uncaptured benefit, which would move the base case ICER downwards a. Carer QoL uncaptured	Thank you for your comments. The committee considered the totality of the evidence including the consultation comments from stakeholders. It also noted that the final analysis data from the KEYNOTE-826 trial were not yet available and this increased the uncertainty in the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			b. Dependent QoL uncaptured c. Long term ability to return to daily activities uncaptured d. Enrichment of PFS health state by CR patients uncaptured 5. Pembrolizumab represents a badly needed innovation in advanced cervical cancer. There has been no new NICE approved treatment for 13 years. Potential to reduce health inequalities by generating QALYs in a disease area that most affects certain vulnerable and disadvantaged groups.	long-term results. The committee recognised the high unmet need for people with recurrent, persistent or metastatic cervical cancer and that there would be substantive clinical benefits associated with a positive recommendation for the pembrolizumab group but considered these benefits to already be captured by the model. Given the level of uncertainty, the committee concluded that the maximum acceptable ICER for routine commissioning would be substantially less than £50,000 per QALY gained. Please see FAD section 3.13.
12	Consultee (company)	MSD	**References:** 1. Chang E, Pelosof L, Lemery S, Gong Y, Goldberg KB, Farrell AT, et al. Systematic Review of PD-1/PD-L1 Inhibitors in Oncology: From Personalized Medicine to Public Health. Oncologist. 2021;26(10):e1786-e99. 2. Rutherford M, Lambert,PC., Sweeting, MJ., Pennington, R., Crowther, MJ., Abrams,, KR. L, NR. NICE DSU technical support document 21. Flexible methods for survival analysis. 2020. 3. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med. 2002;21(15):2175-97. 4. NICE. Appraisal Consultant Document - Pembrolizumab with platinum-based chemotherapy for recurrent,	Comment noted. No action required

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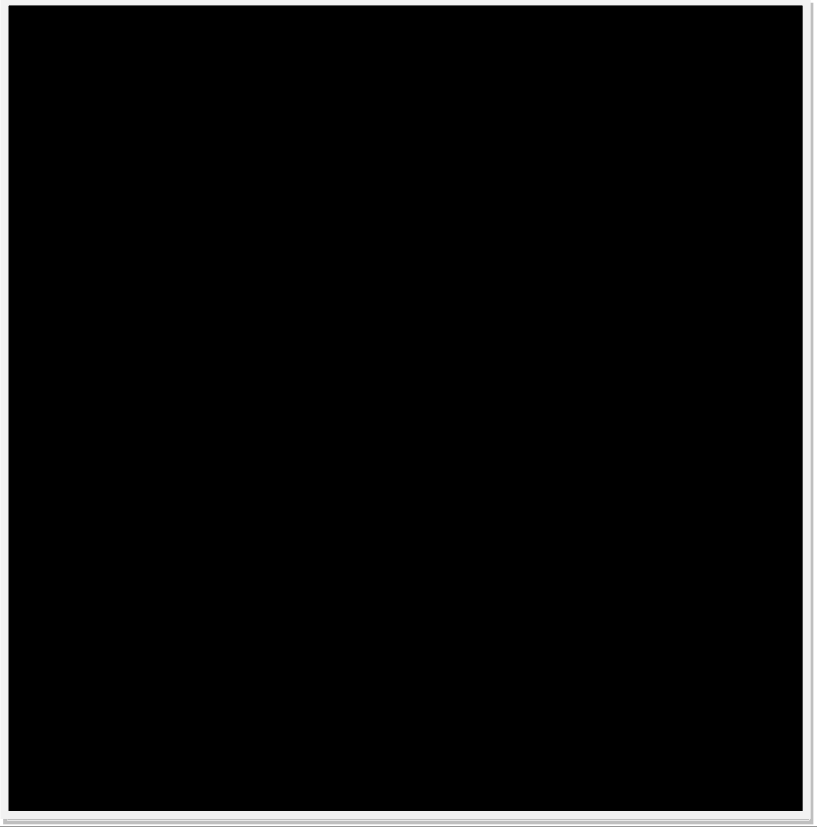
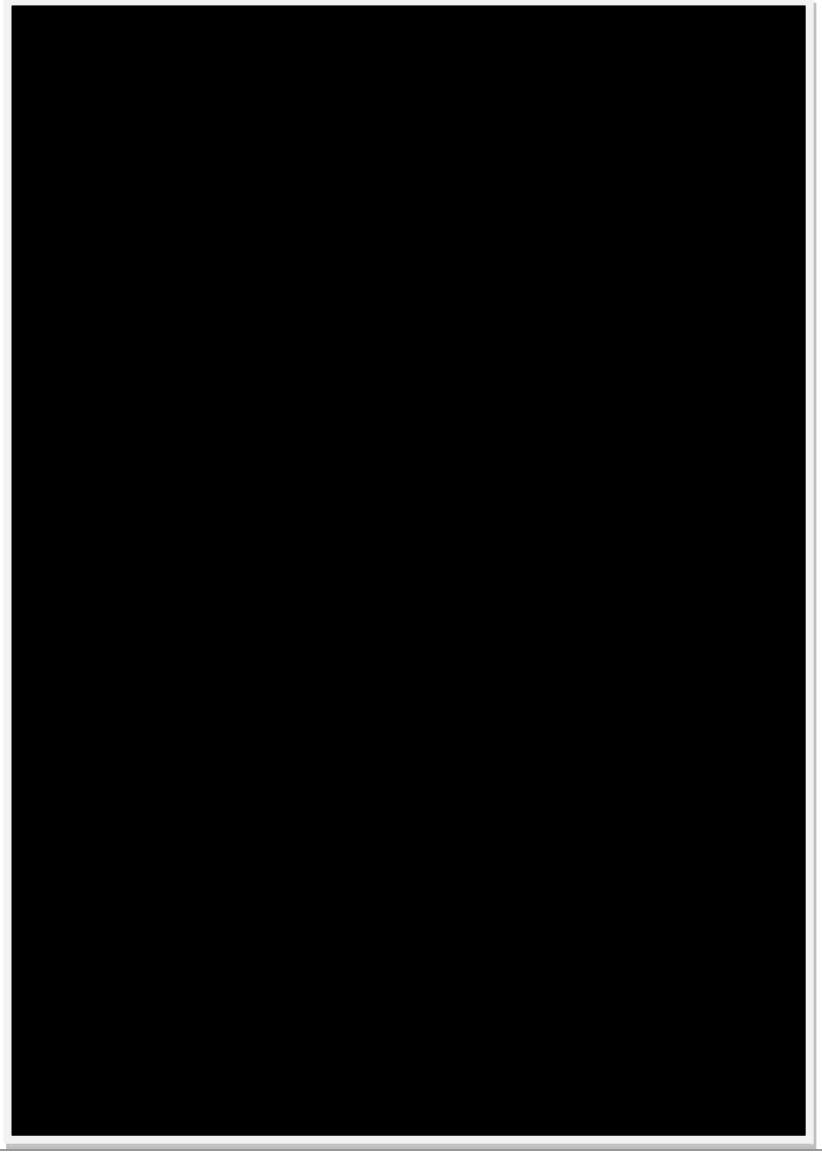
			persistent or metastatic cervical cancer, 2022. Available from: https://www.nice.org.uk/guidance/gid-ta10669/documents/129. [Accessed 8th November 2022] 5. MSD. Supportive analysis - submitted at technical engagement stage. 2022. 6. Garassino Mea. KEYNOTE-189 5-Year Update: First Line Pembrolizumab + Pemetrexed and Platinum vs Placebo + Pemetrexed and Platinum for Metastatic Nonsquamous NSCLC - ESMO2022. 2022. 7. Novello Aea. 5-Year update from KEYNOTE-407: Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer - ESMO2022. 2022. 8. NICE. Public Committee Slides - Pembrolizumab in combination with platinumbased chemotherapy for treating recurrent, persistent or metastatic cervical cancer 2022. Available from: https://www.nice.org.uk/guidance/gid-ta10669/documents/1. [Accessed 8th November 2022] 9. Bobinac A, van Exel NJA, Rutten FFH, Brouwer WBF. Caring for and caring about: Disentangling the caregiver effect and the family effect. Journal of Health Economics. 2010;29(4):549-56. 10. Salter J. "Revealing the true cost of cervical cancer…" - Behind the Screen, 2014. Available from: https://www.demos.co.uk/files/Behind_the_screen_-_web.pdf?1402772155. 11. NICE. Guide to the methods of technology appraisal 2013 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. [Accessed 8th November 2022] 12. Massat NJ, Douglas E, Waller J, Wardle J, Duffy SW. Variation in cervical and breast cancer screening coverage in England: a cross-sectional analysis to characterise districts with atypical behaviour. BMJ Open. 2015;5(7):e007735. 13. Patel H, Sherman SM, Tincello D, Moss EL. Awareness of and attitudes towards cervical cancer prevention among migrant Eastern European women in England. Journal of Medical Screening. 2019;27(1):40-7. 14. Cancer Research UK. Cervical cancer incidence by deprivation. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence#ref-5. [Accessed 25th October 2022] 15. The King's Fund. The health of people from ethnic minority groups in England, 2021. Available from: https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england#cancer. 16. Jo's Cervical cancer trust. The differing understanding of cervical screening among white women and women from a Black, Asian and Minority Ethnic (BAME) community 2011.	
13	Consultee (company)	MSD	**Appendix**	Comment noted. No action required.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				
14	Web	(Web	**Comments on the ACD:**	Thank you for your

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	comment (public)	commenter 1)	All relevant evidence has been taken into account but i strongly disagree with the outcome of this and think that this treatment will make a huge impact on our patients. The KEYNOTE 826 paper is a seminal paper with massive significant improvements in outcomes in a patient cohort who have very limited treatment options and therefore is a huge area of unmet need. These patients are often young and fit with dependants/young families and therefore they tolerate treatment well and any disease control and survival improvements lead to significant QoL improvements. There are very limited treatment options despite fitness often with enrollment in phase 1 trials etc. In view of the lack of second line treatment options in this patient cohort I do agree that the PFS benefit is very likely to be reflected in OS benefit and the not yet reached median OS of estimated 2 years in my view is groundbreaking for this patient cohort. Even if that is an overestimate it is the most dramatic impact and step forward since the addition of bevacizumab which has now been available for 8 years. I am very disheartened and am concerned that the treatment i am able to deliver to this patient cohort is suboptimal if access to pembrolizumab is not possible despite the solid evidence.	comment. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.
15	Web comment (public)	(Web commenter 1)	**Has all of the relevant evidence been taken into account?** yes it has **Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** i disagree that the PFS is not likely to translate into OS benefit as these patients have no good second line treatment options and even if the calculations are an overestimate the improvements in survival still represent a massive step change for our treatment outcomes. **Are the recommendations sound and a suitable basis for guidance to the NHS?** NO. I strongly believe that this drug should be available for this patient cohort who have a massive unmet need as this paper demonstrates seminal step change improvements in outcomes. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** no.	Thank you for your comment. The committee concluded it was likely that improvements in progression-free survival are associated with an overall survival benefit. Please see FAD section 3.6. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.
16	Web	(Web	**Comments on the ACD:**	Thank you for your

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	comment (public)	commenter 2)	I think that this decision is incorrect and doesn't take into account that this is an aggressive cancer with limited options. This patient group needs more options and this trial represents the biggest improvement in progression free survival.	comment. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.
17	Web comment (public)	(Web commenter 2)	**Has all of the relevant evidence been taken into account?** Yes	Comment noted. No action required.
18	Web comment (public)	Colchester General Hospital	**Comments on the ACD:** I understand its an early result but at least it is showing some improvement in the progression free survival and it is significant. This is an area of unmet need and we don't have any strong alternatives or treatment options for this group of patients where mostly the population is very young. This is showing the way forward . Please consider it.	Thank you for your comment. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.
19	Consultee (patient/carer groups)	Jo's Cervical Cancer Trust	• We want to bring the faces and stories behind the models to the forefront of this consultation. Trial evidence shows pembrolizumab plus chemotherapy can slower progression, thus extending life. • The fact evidence regarding how long this extension is should not be the factor that prohibits its approval • The only advance in treatment options for this cohort of patients in many years has been the addition of bevacizumab. This has been shown to extend by a shorter amount of time than pembrolizumab at just over 3 months • Patients are often young. Becky, below, is in her 30s and has a 4-year-old child. Pembrolizumab has given her a chance to have more time with her son. The other stories show the anguish and inequity faced by others with an	Thank you for your comments. The committee acknowledged the unmet need of people with recurrent, persistent or metastatic cervical

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			advanced cancer diagnosis around accessing treatments	cancer when formulating its recommendations. Please see FAD section 3.13. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund. Please see responses to individual issues and patients' comments below.
20	Consultee (patient/carer groups)	Jo's Cervical Cancer Trust	**Sima*:** I'd read some information online about a study showing that Pembro alongside the chemo showed an increase in response rate for advanced CC and through some social media networks that I'm part of, I was aware this was a standard first line treatment offered in the US and some other countries. After finding out that I was PD-L1 positive and therefore a candidate for immunotherapy then I knew that this was something I wanted to get access to, to give me the best chance of more time with my loved ones and most importantly, time with my 4-year-old son. It was very stressful in trying to gain access to the immunotherapy treatment option. I felt like I had to fight for a treatment that is currently a postcode lottery as I was aware of some ladies from Jo's being offered Pembro, depending on their cancer centre location. This felt very unfair and adding this on top of dealing with an incurable cancer diagnosis is an unnecessary mental pressure when we are already going through a lot. I'd been offered the standard chemo to start at my local hospital in Newcastle but was told they were unable to offer immunotherapy as they had never offered this before as a first line option. I then had a private consultation with the Royal Marsden thanks to a private healthcare policy I had already - I went to the Royal Marsden as the North East where I live doesn't have a private cancer hospital anymore. I'd made the decision that getting the treatment was the best thing for me so was very close to travelling from Newcastle to London to have this at the Royal Marsden. Logistically this would have been expensive for stays in London every 3 weeks but would also mean time away from my son and a big upheaval	Thank you for your comments. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			on our lives. Fortunately, after some searching, I was recommended a private consultant in the North East that offers treatment at home so was able to get access to the immunotherapy alongside chemotherapy. It was a big relief and my family, and I celebrated that I was getting access to this. I do feel it's incredibly unfair that I have this option when so many women aren't getting the chance of immunotherapy on the NHS when they may benefit from it. As a cancer with only one line of standardised treatment for metastasis, we need more options and more of a focus on potential 'maintenance' treatments like they have with many other cancers. I know I'm not alone in finding it terrifying how little there is available to advanced CC women so it's great that Pembro is potentially coming available across the NHS in the future.	
21	Consultee (patient/carer groups)	Jo's Cervical Cancer Trust	**Catherine*** I'm 57 and living with advanced cervical cancer. I am currently going through carbo/paclitaxel and Avastin and am responding well, I'm tolerating it and after three cycles the tumour has shrunk by a third. I'm hoping for an NED but will be thinking about what to do next when the cancer inevitably comes back. Other women I have spoken to have wanted to access Keytruda when it was in trial state but couldn't get funding or couldn't get it at their usual cancer treatment hospitals and missed out due to being unable to travel hundreds of miles. I live in a very rural area so my options are already limited in where I can access treatments. The fact that drugs which have shown such positive results may be refused to patients in the England is awful. Very few new drugs become available which work for cervical cancer, and this means women are left without options and hope. This drug being made widely available on the NHS would save the heartbreak and devastation suffered by their families. "	Thank you for your comments. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.
22	Consultee (patient/carer groups)	Jo's Cervical Cancer Trust	**Ava*** The day I was diagnosed with stage 4 cervical cancer, my oncologist spoke to me about a new-to-cervical cancer drug, pembrolizumab, that was being administered to patients at the Marsden for the first time on compassionate basis, as agreed with the NHS. If I qualified, I would be one of a very, very small number of women receiving this novel treatment for cervical cancer in the UK. I agreed to waiting an extra week to have my tumour tested for PDL-1 to see if I qualified (which I did) and began treatment on 7 July. After three infusions, including carboplatin, taxol and bevacizumab alongside pembrolizumab, I was given a midpoint PET scan which showed a "complete metabolic response" – the very best possible outcome. There was no cancer activity visible, and my oncologist is fairly confident that the "chemo cocktail" including pembrolizumab is helping deliver good results. I went from an initial diagnosis that included extensive lymphadenopathy, to having zero hotspots visible on my midway PET. As I near the finish line of this round of treatment, I am cautiously optimistic and beginning to think about the future again after so many months of worry, fear and utter despair. Pembrolizumab gives me hope that I can reclaim my life. When I tell other women with advanced cervical cancer about being on pembrolizumab, all have said it was not made available to them, but they wished it were. I sometimes feel guilty for having been "at the right place, at the right time" because I certainly did nothing else to set me apart from these women to get access. Most of them wondered if I had gone the private route, which I hadn't, and no one should not have to. I am very grateful to the Royal Marsden and the NHS for allowing me to receive this treatment, but why can't my friends? To say we live in an unequal world is putting it mildly.	Thank you for your comments. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.

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23	Consultee (patient/carer groups)	Jo's Cervical Cancer Trust	**Sarah*** I was diagnosed with adenocarcinoma in December 2019 stage 2B followed by recurrent cervical cancer with multiple lung mets in June 2021. After my first line of treatment with carbo/taxol/avastin, I had to fight to get suitable follow up treatment and even paid for some private treatment at one point. For those living with advanced cancer, we often find we have to advocate loudly and forcefully ourselves within our own hospitals for treatment. At our most vulnerable, a huge amount of time and energy is used this way and on top of everything else, the financial burden can sometimes be crippling. There is a huge discrepancy as to what is already available across different parts of the UK. The addition of pembromizulab has been a very long time coming but it worries me that it may not be considered for use wherever, and at whatever stage, needed and that lack of funding might remain a barrier. There is so much inequality in access to treatments. Many on our side have ended up on trial after trial desperately in search of something that works. Some are left so ill, it is hard to tell where the treatment ends and the cancer begins. We are a much under-funded minority in the world of cancer and woefully behind in research. There just aren't the numbers of us to make it interesting or worthwhile, and it sometimes feels that as a 'woman's illness' further stigmatised by the mention of HPV, things just have not moved on for decades. We feel written off. Many of us are young; some have young children. It is heartbreaking to see. The idea that those lucky enough to have private health insurance have so much more available to them is never something I would have dreamt possible in this country. I had assumed that when we were at our most sick and vulnerable, the NHS would step up and give us the very best of care that was available anywhere. It has been a huge eye-opener. Little did we know that this would be the time when so little would be on offer, and we would feel written off as statistics. We are people, not numbers. The situation is desperate.	Thank you for your comments. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.
24	Consultee (patient/carer groups)	Jo's Cervical Cancer Trust	*Pseudonyms used for anonymity	Comment noted. No action required.
25	Clinical expert	Dr Susan Lalondrelle	In considering the draft consultation I would like to add the following comments.	Comments noted. Please see responses to individual issues below.
26	Clinical expert	Dr Susan Lalondrelle	The evidence provided by Keynote 826 demonstrates the benefit of pembrolizumab in this setting. Whilst the OS data may not be considered mature, the significant improvement in PFS is highly indicative of a similar OS benefit. In other trials of the same technology where a DFS benefit is seen, there is also an OS benefit. It is not logical to think that this would be different for this group of patients. It should also be highlighted that a proportion of patients are able to achieve a complete response - this is unprecedented in advanced cervical cancer. Data in the company submission highlights that in this cohort of responders the OS rate at 2 years is 90% - this figure is more in keeping with the responses expected with radically treated, earlier stage disease.	Thank you for your comments. The committee considered the company's evidence for the relationship between progression-free survival and overall survival alongside comments from other stakeholders. The committee concluded that it was likely that

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				pembrolizumab also improved overall survival. However, the level of this benefit is uncertain. Please see FAD section 3.6.
27	Clinical expert	Dr Susan Lalondrelle	Extrapolations of OS for the SOC arm are in line with those observed in GOG240. This would support the model used by the company and are in line with clinically observed outcomes from my experience.	Thank you for your comments. The committee recognised that the company's additional analyses may address some of the concerns around the company's two-piece extrapolation approach but uncertainties around the long-term survival projections remained. The committee concluded that the company's updated analyses were helpful for decision making, but the results are still highly uncertain. Please see FAD section 3.7.
28	Clinical expert	Dr Susan Lalondrelle	With regard to the waning effect; in my experience of use of this and similar technologies in other cancers, I have not observed a waning effect to the extent being considered here. i.e. patients who respond and are long term responders do not relapse subsequently.	Comments noted. The committee took into consideration evidence presented by the company and the ERG relating to this issue. It concluded

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				that a treatment waning effect from 3 years to 5 years after stopping treatment with a 2-year stopping rule was reasonable for pembrolizumab. Please see FAD section 3.10.
29	Clinical expert	Dr Susan Lalondrelle	I would like to emphasise the lack of therapeutic treatment options for this group of patients and therefore the significant impact that this technology could have on outcomes for them. Most eligible patients are young women, often with young families, facing a terminal diagnosis and progressive symptoms. When GOG240 reported an OS benefit for bevacizumab , this was a landmark of hope for these patients. There is now evidence of further PFS and OS gains with this new technology which should be granted to patients with cervical cancer, as it has been with many other tumour types, sometimes with less clinical benefit and wider treatment options. It should be remembered that this technology is not available as second line therapy in the UK and therefore approval in this first line setting would represent the only chance for these patients to access immunotherapy.	Thank you for your comments. The committee acknowledged the unmet need of people with recurrent, persistent or metastatic cervical cancer when formulating its recommendations. Please see FAD section 3.13. The committee concluded that pembrolizumab plus chemotherapy with or without bevacizumab met the criteria for inclusion in the Cancer Drugs Fund and recommended it for use within the Cancer Drugs Fund.

NICE National Institute for Health and Care Excellence

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 26 October 2022. Please submit via NICE Docs.

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

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NICE National Institute for Health and Care Excellence

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	MSD is grateful for the opportunity to respond to the Appraisal Consultation Document (ACD) for the above Technology Appraisal. We are pleased that the committee recognised the substantial unmet need for innovative treatment for this cancer and acknowledged the strength of the KEYNOTE-826 clinical data in supporting pembrolizumab as a highly clinically effective treatment option. Confirmation that pembrolizumab meets the End of Life criteria in this indication is critically important. In this response we address uncertainties raised in the ACD and present plausible ICERs between, £34,000 - £55,000/QALY gained, the substantial majority below the decision making threshold for End of Life products and indications. Both the progression free survival (PFS) estimates and the overall survival (OS) estimates generated by the economic model are plausible, particularly in the context of the high complete (CR) and partial response (PR) rates reported in the KEYNOTE-826 study. The CR and PR rates on the pembrolizumab treated arm are some of the highest for any immunotherapy trial to date (1). Given the encouraging outcomes observed in the trial, for example that ~90% of the complete responders were still alive at 2 years in this highly aggressive cancer, the committee should be reassured that model's predictions are a realistic prediction of outcomes in the population. Focusing on the themes highlighted in the ACD our response addresses the following:- 1) Different modelling approaches for PFS and TTP result in consistent curves resulting in similar ICERs (ACD section 3.7), with a range of ICERs below the decision-making threshold. ~~2)~~ Demonstration of the relationship between PFS and OS and therefore the appropriateness of the state transition model structure (ACD Section 3.6). 3) All available evidence indicates that PFS and OS extrapolations produced by the model are plausible (ACD section 3.7). 4) Implementing a treatment effect waning assumption of 5-7 years, not the highly conservative 3-5 years, results in plausible ICER estimates below the decision making threshold, and mitigates longer term uncertainty (ACD section 3.9). 5) Correction of a programming error for PD utility (ACD section 3.10) 6) Areas of uncaptured value not yet considered by the committee are described, including the ability of pembrolizumab to address inequalities in cervical cancer outcomes experienced by certain vulnerable groups (ACD section 3.16). We note in the ACD that while End of Life criteria are met the committee consider the decision making threshold to be lower than £50,000 due to uncertainty. MSD considers this to be unreasonable in any scenario that includes an assumption of treatment effect waning and given that three different modelling approaches converge on similar estimated ICERs, the majority of which are below the decision making threshold. We discuss this in theme 7 below.

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

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	MSD is grateful for the opportunity to present additional modelling approaches within our ACD response. These multiple modelling approaches have confirmed a range of ICER estimates from the model, that are below the threshold. These model estimates are similar to estimates previously validated by clinical experts, as such we hope this reassures the committee that there is minimal uncertainty in this appraisal. In the light of this reduced uncertainty and applying the decision-making threshold of £50,000/QALY gained, we kindly request the committee reviews it initial decision and positively recommends pembrolizumab for these cervical cancer patients. This group have extremely limited options and no new NICE-assessed treatments for 13 years.
2	In response to the ACD the company looked at two alternative modelling approaches as well as revisiting the previous modelling options. Two-piece, spline and responder based models for PFS and TTP converged on estimated ICERs in the range ~£34,000 - £55,000/QALY gained when treatment waning from 5-7 years is applied. <u>KEYNOTE-826 Outcomes by Response Group</u> In KEYNOTE-826, outcomes vary by a patient's level of response to treatment, as illustrated by Figure 1, originally presented in the company's response to clarification questions and here updated with PFS data. [redacted] *Figure 1: PFS and OS by responder status for both arms (CR=Complete Response, PR=Partial Response,SD=Stable Disease,PD=Progressed Disease,NE/NA=No Assessment* In these above Kaplan Meier curves by responder status, it should be noted that: • There are a high proportion of PR and CR responders in the PFS curves in advanced cervical cancer (both arms) compared with other advanced cancers • CR PR is 18% higher on the pembrolizumab arm than the SoC arm (**Error! Reference source not found.**) • There are notably fewer PD patients on the pembrolizumab arm than on the SoC arm, though absolute numbers are small *Table 1: CS Document B Table 11 Confirmed objective response based on investigator assessment per RECIST 1.1 (CPS ≥ 1 population)*

	CPS ≥ 1 population (n = 548)	
	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	**Placebo + chemotherapy ± bevacizumab (n = 275)**
Number of confirmed OR	[redacted]	[redacted]
ORR, % (95% CI)	68.1 (62.2, 73.6)	50.2 (44.1, 56.2)
CR, n (%)	62 (22.7)	36 (13.1)

PR, n (%)	124 (45.4)	102 (37.1)
SD, n (%)	58 (21.2)	88 (32.0)
PD, n (%)	9 (3.3)	29 (10.5)
Difference in percentage pembrolizumab group versus placebo group	[redacted]	
p-value	[redacted]	
Key: CI, confidence interval; CPS, combined positive score; OR, objective response; ORR, objective response rate; RECIST 1.1, response evaluation criteria in solid tumours version 1.1.		

It can be seen from Figure 1 that almost all people with a best response of Stable or Progressed Disease had died by the end of the trial period. Whereas, OS was ~90% among Complete Responders in the pembrolizumab arm. The patients alive at the end of the trial period therefore comprise a cohort of responders who had much slower rates of progression and death. Because of this pattern of response, the hazard functions for both PFS and OS are likely to be complex.

As outlined in our submission, directly projecting OS from the available data would therefore have underestimated survival among responders. A State Transition Model (STM) where OS is linked to progression of disease was therefore built. The model has three states: pre-progression, post-progression and death. Movement between the three health states is determined by transition probabilities calculated from the individual patient data in KEYNOTE-826; time-to-progression (TTP), progression-free survival (PFS) and post-progression survival (PPS).

3

Theme 1: PFS / TTP modelling approaches (ACD sections 3.7)

In this section we will briefly present the three modelling approaches we have incorporated. We then discuss the impact on the modelled results and validation of the modelled estimates. The modelling approaches discussed are spline based, response based and the original piecewise modelling. We discuss spline models in this comment section, response based in comment section 4 and piecewise modelling and results from all three approaches in comment section 5.

Spline based approach

In response to the ACD, MSD evaluated alternate approaches to modelling time to progression (TTP) and progression free survival (PFS). Taking into account NICE TSD21, we explored spline models using the package *flexsurvspline* (R statistical software; methodology from Royston and Parmar (2002))(2, 3). We modelled the spline function on the "odds", "hazard" and "normal" scales. Without knots, these spline models would correspond to single piece Weibull, log-logistic and lognormal models. For each of these scales we fitted spline models based on one, two or three knots (k=1, k=2, k=3). We did not pre-specify the location of the knots. If location is unspecified, the software automatically assigns knots to quantiles of the observed event times. For k=1 the knot is at the median, for k=2 the knots are at the 33rd and 66th percentile and for k=3 the knots are at the 25th,

50th and 75th percentile. We felt that this approach had the strength of being independent of any previous assessment we had made about inflection points in the data and therefore would help to validate, or not, previous approaches. We therefore had 9 spline models to consider.

Spline model selection criteria

Our selection criteria were:-

1) best statistical fit measured by lowest AIC

2) visual fit to the smooth spline hazard curve

3) same model type for TTP as PFS

4) long term OS plausible

5) priority given to same model type (number of knots, scale) between the arms (TSD14 advice)

The PFS and TTP datasets are comprised of mostly the same data. In line with our original submission, it is reasonable to use the same type of model for both. Priority was given to PFS as this was a primary trial outcome, includes more events and has less censoring than TTP.

All models with 1 knot were rejected from both arms for having significantly higher AICs and for being a poor visual fit to the data, particularly in the pembrolizumab arm. It is less easy to outright reject any of the other six models, which all have similar properties.

The hazard scale model with 2 knots (“hazard, 2”) had the lowest AIC for PFS for both arms. It also provided a good visual fit to the smooth spline curves. The “hazard, 2” model had the second-lowest AIC and a good visual fit for TTP. The AIC was very slightly higher for the “hazard, 2” model than the “odds, 2” model for TTP but not meaningfully so (1 point higher for pembrolizumab and 0.1 for Standard of Care [SoC).

Long term PFS for pembrolizumab was relatively high using any of the 2 and 3 knot models (range 13%-21% at 20 years (if unadjusted by treatment waning), 14.7% for the “hazard, 2” model). For the SoC less variation was observed. Estimates ranged between 4.9%-7.3% at 5 years and 1%-3.5% at 10 years. The “hazard, 2” model had 5 and 10 year PFS of 5.5% and 1.4%, which was slightly higher than the estimates produced by the one-piece curve at these milestones (3.5% and 1.1%).

Figure 2: Long term PFS for different Spline models also showing how the treatment waning

assumption controls long term PFS

All models produce higher mean OS on pembrolizumab and similar mean OS on SoC than estimated by our original piecewise approach. Life year gain is therefore increased using any of the 2 and 3 knot spline approaches. Regardless of the choice of knots and scale, implementation of spline modelling would therefore reduce the ICER considerably vs. the MSD base case. We therefore considered all the 2 and 3 knot spline models to be qualitatively similar and did not need to implement them all in the economic model.

We implemented the “hazard, 2” model into the economic model and reviewed the resulting 4-year OS in the SoC arm against GOG240 and concluded it was plausible at 13% (vs. 15% in GOG240). We reviewed the 5-year OS for pembrolizumab and concluded that the magnitude and incremental benefit and the absolute level was within the range that has been observed in published 5-year trials of pembrolizumab in metastatic solid tumours (e.g. OS was 28.5% vs. 31.9% in KEYNOTE-024). We also noted that “hazard, 2” was in the middle of the available spline models rather than the most optimistic or pessimistic. The “hazard, 2” spline model was a very good fit to the short term PFS and TTP data for both arms.

[redacted]

Figure 3: "Hazard, 2" spline models fit to PFS KM data

[redacted]

Figure 4: "Hazard, 2" spline models fit to TTP KM data

Taking these considerations together, we believe the “hazard, 2” model to be the best fitting spline model for both PFS and TTP for both arms. The “hazard, 3” model was tested in sensitivity analysis and produced similar conclusions. Our approach to model fitting and selection for spline models is consistent with guidance in NICE TSD21.

We note that long term PFS and OS produced by the 2 and 3 knot spine models might be considered optimistic. Importantly, this is tightly constrained in practice by the treatment waning assumption in the economic model, as can be seen in Figure 4 above, the blue and the grey curves that move rapidly towards 0% PFS are those with the treatment effect waning assumption included. Overall progression-free life year gains on treatment-waned spline models are similar to, but slightly higher than the base-case two-piece curves.

The visual fits of all 1, 2 and 3 knot models to the smooth spline hazards are shown in an appendix comment.

[redacted]

	Figure 5: AIC for PFS and TTP spline models
4	As already mentioned, rates for partial responders (PR) and complete responders (CR) in KEYNOTE-826 are amongst the highest reported in any advanced cancer immunotherapy RCT. Rates of CR are nearly twice as high in the pembrolizumab + SoC arm than the SoC arm and responses are more durable. Detailed examination and extrapolation of these responder data support the plausibility of the existing OS and PFS estimates. The response based model (RBM) explicitly recognises responder status. We presented this approach in the "weighted survival analysis" previously submitted as validation of the economic model's predicted OS. We consider this model to be helpful in understanding why the hazard functions for PFS, TTP and OS are likely to be complex (i.e. not suitably modelled using single-piece parametric fits) and to provide information on the survival of distinct groups of patients within the PFS health state. Initially the PFS hazard function in the whole cohort in each arm is dominated by events among Progressed Disease (PD) and Stable Disease (SD) patients but gradually, as these patients progress, the cohort becomes more comprised of CR and PR patients who have slower event rates. This provides some explanation as to why one-piece parametric curves may not be appropriate, particularly in the pembrolizumab + SoC arm where difference in event rate between CR patients and the other groups appears even more marked. [redacted] *Figure 6: OS and PFS KM curves by responder status and arm* The RBM splits patients out into their responder categories and fits separate PFS parametric survival curves for each of Complete Responders, Partial Responders, Stable Disease, Progressed Disease (in the case of PD, progression happens at the first assessment for all patients) and Not Evaluable/No Assessment. [redacted] in each arm belong to this last group and all recorded events were deaths rather than progressions. It is difficult to know with certainty to which group they biologically belong, although the patients with an event are likely to be SD. We selected parametric survival curves for each group based on the criteria in Table 2. "Plausible compared to other response models" means that mean survival should follow the biologically sensible order CR > PR > SD > PD. Survival being longer in the pembrolizumab + SoC arm within any of the groups was also considered plausible in light of the DoR data from the trial. The standard suite of single-piece fits were examined for each cohort of patients and in all cases, there was strong evidence to select one particular model. The justifications are listed below:-

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

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Table 2: PFS parametric model selection and justification for each responder cohort in each arm

Model Selection Justification		
	Best Model	**Reason**
Pembrolizumab		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

AIC and BIC statistics are available in the “ACM2 – PFS Responder” sheet of the updated version of the economic model.

We examined fitting the [redacted] model to SoC CR patients in a sensitivity analysis based on it having better mean OS that is perhaps more in-keeping with a CR patient, despite the long plateau.

As with other analyses, the same type of model was adopted for TTP as for PFS due to the datasets being comprised of almost the same data but with PFS having more events/less censoring. This caused a slight issue with TTP for the NE/NA group because there are no TTP events in this group (every patient is either censored or died pre-progression). This leads to a slight overestimation of the ongoing PFS->Death transition probability for both arms, which is conservative for Pem+SoC because patients spend longer in the PFS health state in this arm. We handled this with one sensitivity analysis where we assumed the TTP curves were equal to the PR group (because this group had heavy censoring followed by a rapid drop). This improved the visual fit of the RBM for TTP to the TTP KM data. We named this model RBM2. An alternate sensitivity analysis where TTP was equal to a weighted average of the TTP across the other groups was also used and labelled RBM3. It should be noted that over and underestimation of TTP has a relatively modest effect on the model’s results.

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The RBM is calculated by multiplying the proportion of patients in each group in each arm by their survival probability and summing the total to create a single survival curve weighted by response. The resulting curves produce extremely similar results in the SoC arm and slightly more conservative results in the Pem+SoC arm.

Figure 7: Comparison of PFS curves between RBM and CEM (original piecewise model)

Figure 8: Comparison of Base case, RBM and Spline PFS curves and effect of Treatment Waning

Figure 9: Comparison of PFS - RBM and Trial Data

Figure 10: Comparison of TTP RBM vs Trial Data (some overestimation caused by NE/NA patients)

Figure 11: RBM2 (overestimation corrected) vs Trial Data

Figure 12: Composition of PFS Curve Over time by response status – Pem+SoC arm

Figure 13: Composition of PFS Curve Over time by response status – SoC arm

The RBM illustrates how the hazard function changes over time, from initially being dominated by patients who had progressed or stable disease before being dominated by those who achieved Complete Response. It is helpful validation of the company's original approach: TTP, PFS and OS curves are all similar to those used in/predicted by the original piecewise approach despite an entirely different modelling approach having been used.

Although OS is not used directly in the economic model, it is possible to construct an OS

	curve using the RBM method to directly extrapolate OS by response group. This method was outlined in the company's submission in the "Weighted survival analysis report" and can capture the complexities of the hazard function in the same way as it did for PFS. [redacted] *Figure 14: OS over time by response status Pem+SoC* [redacted] *Figure 15: OS over time by response status SoC* [redacted] *Figure 16: Comparison of RBM for direct extrapolation of OS and Curves from economic model* Although they are not used in the economic model, the OS the curves in Figure 16 are useful in illustrating the concept of the RBM. A different modelling method for OS can produce similar results to the economic model. The RBM constructed from OS data by response group is almost the same as the one-piece curve used in the economic model while the Pem+SoC data are a little more pessimistic, being equal to those produced by the RBM-based economic model. We can infer from this data that, had a partitioned survival model based on the RBM method been built, it would likely have produced similar results to those we see in the RBM based state transition model. It should be noted that the RBM's results are inherently potentially more variable due to the number of underpinning survival curves; the usual range of options are available for all five groups in both arms and there are therefore a lot of curve combinations that could be chosen. We note that there are very few events among CR patients, particularly in the pembrolizumab arm and the tail of the RBM will obviously be sensitive to curve selection for this group. We have not attempted to explore these myriad alternatives, although there are no obvious statistical or plausibility related reasons to deviate from the curves we selected. The RBM is not intended as a more robust replacement for the piecewise model; we have presented it as reassuring validation that the piecewise model's results are explainable and plausible in the context of survival by response status.
5	*Piecewise approach – original base case* Having explored two alternative approaches with splines and RBMs, we consider it helpful to re-present the company's previous preferred modelling approach: the 37-week piecewise

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model. We initially examined one-piece models for PFS but rejected them as inappropriate due to very poor visual fit to the pembrolizumab + SoC arm and OS that was inconsistent with 4-year data from GOG240 in the SoC arm. We also note that fitting a one-piece model for Pem+SoC implies a drop in OS between year 2 and 5 ([redacted]) that would be much greater than anything observed in five-year pembrolizumab trials to date. Given the relatively high levels of CR and PR in KEYNOTE-826, there is no reason to believe this would be the case for this indication. We re-iterate that we do not believe single piece models should be among the plausible sets of analyses used for decision-making.

After rejecting one-piece models we examined a series of potential cut-offs for a piecewise approach. Of these, 37-weeks was chosen because the resulting model included a good number of events upon which to base a parametric curve, the hazard estimates fitted well with the smooth spline estimates over time, it was close to the observed inflection point and produced survival estimates close to GOG240 at 2 years in the SoC arm (~15%) and ones that appeared plausible in the pembrolizumab + SoC arm, given other long term data from 5-year trials of pembrolizumab. The resulting predictions were validated as clinically plausible at an advisory board of eight UK clinicians from across the UK who treat advanced cervical cancer in their day to day practice. Since that advisory board, the estimates have been revised downwards be the use of a one-piece curve in the SoC arm and the imposition of a treatment waning assumption in the pembrolizumab + SoC arm. The experts at the Appraisal Committee Meeting (ACM) confirmed these newer, more conservative data were plausible (slide 20).

In section 3.7 of the ACD, it is stated that the company believe separate models might be justified based on pembrolizumab having a different mechanism of action to SoC. This is true, and it is well known that I/O survival curves have long tails compared to more traditional treatments, but we would also stress that the design of KEYNOTE-826 is not immunotherapy vs. another type of treatment. Pembrolizumab is used in addition to SoC and therefore provides not only a different mechanism of action but an additional mechanism of action by which patients can respond to treatment.

Results:
For the SoC arm the different approaches produced fairly consistent results, especially in the long term. The RBM tended to underestimate OS to begin with but this is largely accounted for when correcting for the probable overestimation of TTP in the NE/NA group (this sensitivity analysis is labelled “RBM2”). The long-term OS on all SoC models is consistent with the base case and therefore with clinical expectation.
In the Pem+SoC arm, the spline model estimates higher OS than the base case and the RBM lower. The treatment waning assumption controls the curves to the extent that 15y+ OS is very similar for all models. All models produce a reduction in OS from year 2 to year 5 that is conservative compared to observed data in other five-year pembrolizumab trials.

Table 3: Overall survival scenarios

		Overall Survival

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Scenario	Waning	2y	3y	5y	10y	15y	20y
Piecewise Pem+SoC	None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBM Pem+SoC	None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Pem+SoC	None	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise Pem+SoC (basecase)	5-7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBM Pem+SoC	5-7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBM2 Pem+SoC	5-7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Pem+SoC	5-7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Piecewise Pem+SoC	3-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBM Pem+SoC	3-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBM2 Pem+SoC	3-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline Pem+SoC	3-5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC - Piecewise	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC - One Piece	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBM SoC	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RBM2 SoC	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Spline SoC	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*NB waning is vs. the corresponding SoC model e.g. spline vs. spline

We conclude that all of these approaches produce curves that have clinically plausible long-term OS for both Pembrolizumab + SoC and SoC. The data for SoC are consistent with clinical expectation that there are a small number of patients who respond well to treatment and get durable response. The estimates for Pembrolizumab + SoC are well within a plausible range given data from five-year trials, UK clinical experience and the discussion at the NICE ACM. It is reassuring that different modelling approaches arrive at similar conclusions in terms of OS for both arms.

Cost-effectiveness Results

The company's base case model includes the following assumptions:-

- Pembrolizumab + SoC modelled piecewise from 37 weeks
- One piece model for SoC
- Treatment waning from 5-7 years post cessation
- Health state utility values with programming error corrected
- Other settings are the same as agreed prior to ACM

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Table 4: ICER

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
SOC	[redacted]	2.060	[redacted]	-	-	-	
PEM+SOC	[redacted]	4.247	[redacted]	[redacted]	[redacted]	[redacted]	**£40,203**

The results of the model are reassuringly below the cost-effectiveness threshold for End of Life medicines.
Having undertaken different modelling approaches, the company considers the above to be the most appropriate scenario for decision making. We present below results from numerous other approaches to demonstrate the consistency in estimated ICERs regardless of the modelling.

Table 5: Sensitivity/scenario analyses results

Scenario	Waning years	Mean LYs SoC	Mean LYs Pem+SoC	Inc. Costs	Inc. LYs	Inc QALYs	ICER
Piecewise (loglog) vs. One piece (basecase)	5-7	2.06	4.25	[redacted]	2.19	[redacted]	£40,203
Piecewise (lognorm) vs. One piece	5-7	2.06	4.45	[redacted]	2.39	[redacted]	£36,881
Piecewise (av. Loglog/weibull) vs. One piece	5-7	2.06	3.91	[redacted]	1.86	[redacted]	£46,081
Piecewise (loglog) vs. Piecewise	5-7	2.51	4.76	[redacted]	2.25	[redacted]	£41,821
RBM	5-7	2.00	3.74	[redacted]	1.74	[redacted]	£50,207
RBM2	5-7	2.13	3.92	[redacted]	1.79	[redacted]	£49,156
RBM3	5-7	2.15	3.92	[redacted]	1.77	[redacted]	£49,839
Spline (2 knot)	5-7	2.21	4.63	[redacted]	2.41	[redacted]	£34,773
Spline (3 knot)	5-7	2.15	4.59	[redacted]	2.44	[redacted]	£33,798
Piecewise (loglog) vs. One piece	3-5	2.06	3.95	[redacted]	1.89	[redacted]	£44,893
Piecewise (lognorm) vs. One piece	3-5	2.06	4.10	[redacted]	2.04	[redacted]	£41,605
Piecewise (av. Loglog/weibull) vs. One piece	3-5	2.06	3.75	[redacted]	1.69	[redacted]	£49,418
Piecewise (loglog) vs. Piecewise	3-5	2.51	4.56	[redacted]	2.05	[redacted]	£44,825
RBM	3-5	2.00	3.61	[redacted]	1.61	[redacted]	£53,213
RBM2	3-5	2.13	3.80	[redacted]	1.67	[redacted]	£51,686
RBM3	3-5	2.15	3.81	[redacted]	1.66	[redacted]	£52,414
Spline (2 knot)	3-5	2.21	4.19	[redacted]	1.97	[redacted]	£41,014
Spline (3 knot)	3-5	2.15	4.12	[redacted]	1.97	[redacted]	£40,332
RBM (GenGamma SoC CR)	3-5	2.40	4.01	[redacted]	1.60	[redacted]	£55,633

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Piecewise (loglog) vs. One piece (basecase)	None	2.06	5.31	[redacted]	3.25	[redacted]	£31,675

The scenario analyses tables shows the cost-effectiveness results using a wide array of different plausible approaches for extrapolating PFS and TTP. The results are reassuring in that they produce ICER estimates that are either close to or substantially below the cost-effectiveness threshold. Given there are several areas of value for patients, carers and dependents that are not captured in the model (see Theme 6), we are confident that pembrolizumab is a cost-effective addition to SoC in this indication.
Critically, the RBM validates the assumptions in the piecewise model which the company suggests is the most appropriate for decision making.

6

<u>Theme 2: Relationship between PFS and OS (ACD Section 3.6)</u>

The committee state in the ACD that one of the two key areas of uncertainty is "the level of benefit pembrolizumab will have on overall survival". We suggest this is only uncertain to the extent that gains in PFS are uncertain. To summarise why mean gains in PFS should be expected to translate into similar mean gains OS in this indication:-

1) For mean PFS gain not to lead to at least the same mean OS gain, post progression survival would have to be shorter in the pembrolizumab + SoC arm. The committee have confirmed the opposite; that their preferred assumption is that PPS is slightly longer in the pembrolizumab + SoC arm.

2) Clinical experts at ACM1 commented that the benefits of pembrolizumab might persist beyond progression. This fits with response data from the clinical trial that shows that the depth of response is greater in the pembrolizumab + SoC arm. Progression in the trial was assessed from the greatest extent of response and therefore patients entering the PD health state have less extensive disease on average after responding to pembrolizumab + SoC than SoC alone.

3) The observed PPS data in KEYNOTE-826 is relatively mature and is in line with data observed in GOG240.

4) The same PFS-OS phenomenon has been observed in this disease area before in GOG240. Clinicians at ACM1 confirmed this is in line with their experience using bevacizumab and that OS gains may be even greater than PFS gains (slide 17)

5) There are no effective second line treatments and second line treatments do not differ by arm, either in the study or in proposed clinical practice, therefore there is no confounding off efficacy due to subsequent treatment

6) The patient population is relatively young and non-cancer mortality does not influence survival

7) PFS and OS HRs are the same within the trial (~0.6)

These arguments also support the appropriateness of the state-transition model structure, where OS depends to a great extent on PFS rather than being modelling entirely independently of it as in a partitioned survival model.

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7	Theme 3: Plausibility of PFS and OS (ACD section 3.7) The ACD states "…the company's 2-piece approach led to an optimistic projection of people achieving long-term survival on pembrolizumab" (4). It is unclear the origin of this statement. The survival estimates predicted by the model are plausible and realistic based on all the information and insight the company has. To reiterate why we believe the PFS and OS estimates are plausible:- 1) They are validated by the Response Based Model, which, despite taking an different approach to extrapolation and model structure produces similar estimates for PFS and OS as the economic model and illustrates the changing nature of the hazard function over time as it transitions from being dominated by non-responders to responders. 2) MSD conducted an advisory board with 8 clinicians treating cervical cancer from across the UK who confirmed that the model's estimates are plausible. 3) The clinical experts at the NICE committee meeting confirmed that the model's results are plausible and in line with published data (slide 17, slide 20 of ACM slides). 4) The SoC model is validated by published longer term data from GOG240 and supported by the published description of patients with long term PFS on bevacizumab. 5) Both the absolute OS and magnitude of OS gain are within the range that has been seen in other 5-year trials of pembrolizumab in metastatic solid tumours (data were supplied in the company's TE response). 6) The Complete and Partial response data are some of the highest ever observed in an immunotherapy trial and a great cause for optimism about long term survival in patients who respond well to treatment. 7) Non-cancer mortality is not a factor in this relatively young population. 8) Uncertainty beyond 5 years is controlled by the imposition of the treatment waning assumption. 9) There is a consistent morphology for PFS curves across long term pembrolizumab trials. 10) The one piece model considered as part of the analyses for decision-making at ACM1 does not produce plausible results for the following reasons:- a. Poor visual fit to the KM data, especially in the pembrolizumab arm b. Estimated 4-year OS is [redacted]. This is only [redacted] higher than the 4-year OS observed in GOG240. An incremental benefit this small has never been observed in a long term study of pembrolizumab (see KM data from KEYNOTE-024, KEYNOTE-010 and KEYNOTE-006 submitted by the company at Technical Engagement). c. The one-piece curve leads to OS and PFS decreasing at a rate much greater than that observed in long term trials of pembrolizumab. Below are data from the advanced solid tumour trials the company presented at Technical

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Engagement and those published since. It can be seen that the company's base case piecewise model is within the range of other trials for PFS and conservative for OS. By contrast, the company considers the one-piece model to produce extraordinarily pessimistic results with OS and PFS being roughly one quarter of their two-year value by five years. Given the response data in KEYNOTE-826, it would be very surprising if PFS and OS declined faster than in other comparable pembrolizumab trial.

Table 6: 2 year and 5 year PFS and OS in pembrolizumab arms of advanced solid tumour trials

	PFS			OS			Ref
	2 years	5 years	Ratio	2 years	5 years	Ratio	(5)
KEYNOTE-024	*29%*	12.8%	0.44	50.0%	31.9%	0.64	(5)
KEYNOTE-010 TPS ≥50%	*30%*	18.2%	0.61	34.5%	25.0%	0.72	(5)
KEYNOTE-010 TPS ≥1%	*19%*	9.4%	0.49	22.9%	15.6%	0.68	(5)
KEYNOTE-006+	*35%*	*21.5%*	0.61	60.0%	45.0%	0.75	(5)
KEYNOTE-189*	23.1%	7.5%	0.32	45.7%	19.4%	0.42	(6)
KEYNOTE-407*	20.7%	10.8%	0.52	36.0%	18.4%	0.51	(7)
Company - KN826	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
One-piece model - KN826	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

+ projected from 26% at 4 years to 21.5% at 5
*included approximately 1/3 PDL1 negative patients

8

Theme 4: Treatment effect waning assumption (ACD section 3.9)

It is important to re-emphasise that treatment effect waning is an uncertain assumption. Although we understand the logic that at some point progression free patients may become qualitatively similar in each arm and exhibit the same hazards of progression, no empirical evidence exists on if and when that time point exists.

1) Although we understand that the committee consider 3-5 years post treatment to be their preferred assumption, it is important to keep in mind that there is no more empirical evidence for this than the 5-7 year assumption and indeed, no waning at all.

2) We emphasise that, given the data we showed on multiple 5-year trials of pembrolizumab showing no evidence of waning, 3-5 years post treatment cessation is the most conservative this assumption could be.

3) We have therefore continued to submit alternate waning scenarios for the committee's consideration and propose that waning at 5-7 years could be considered a 'middle ground'.

4) We note that the treatment waning assumption controls model uncertainty and

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	variability to a great degree. We further note that all the models we have submitted are at or below the decision-making threshold when this assumption is imposed.
9	Theme 5: PD utility value corrected (ACD section 3.10) MSD understand that the committee's preference is that the model uses health state utility values (HSUV) based on the Progression Free (PF) and Progressed Disease (PD) health states. We initially presented HSUVs only as a sensitivity analysis and have revisited our calculations in light of the committee's preferences. In the version of the model that was used to generate results for ACM1, this value was set to the beta coefficient for PD rather than the combination of the PF value and the coefficient i.e. the actual PD utility. We apologise for this error. Correcting this error reduces the ICER by a small amount.
10	Theme 6: Uncaptured Value (ACD section 3.16) The ACD states that 'all relevant benefits are captured in the QALY calculations' but these calculations only reflect data from the EQ-5D forms filled in by patients within the trial period (4). 1) We urge the committee to reconsider the evidence from Jo's Cervical Cancer Trust and BGCS that was discussed at the meeting (slide 7), 'This cancer mostly affects young women of working age. Many have families and dependents. Treatment can enable women to return to their daily lives, including work and their caring responsibilities' (8). The health related quality of life of patients' carers and those that they may care for, such as young children has not been included in the economic model. We consider that the benefit of prolonged response (particularly Complete Response) would add QALYs to both the patients' carers and children/dependents (9, 10) 2) Many of the QALYs in the model are accrued by patients who have remained progression free after the 2-year time point in KEYNOTE-826. There are no data on the utility of these patients from KEYNOTE-826 but it is likely that the ability to be free from treatment, to have long term progression free status and to "return to their daily lives" would lead to a significant increase in quality of life and therefore incremental QALYs. It is also likely that the cohort of progression free patients will become steadily more comprised of patients who achieved a Complete Response. It is logical that this "enriching" of the progression free population would increase incremental QALYs above what has been captured in the model. 3) Section 6.2.3 of NICE health technology evaluations: the manual states that non-health factors can be taken into account by the committee when contained within the NICE Principles . NICE Principle 9: Aim to reduce health inequalities would seem to be applicable (11) . For a variety of socio-economic reasons, metastatic cervical cancer is more common among the most deprived communities in society as well as ethnic minority groups and migrants who have low engagement with vaccination and screening programmes (12-16). A recommendation that generates QALYs for these groups will work towards reducing health inequalities.
11	Theme 7: Decision Threshold

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	MSD considers the decision threshold should be £50,000/QALY gained for the following reasons (specific reference to the decision-making considerations outlined in the NICE Methods Guide issued in 2013 6.3.3) (11): 1. Certainty about the appropriateness of the model structure. a. The economic model structure captures the natural history of the disease well because mean PFS and OS have a strong relationship in advanced cervical cancer (see Theme 2) b. The two-piece model is validated by the Response Based Model, a totally different modelling approach that explicitly accounts for response status and produces similar PFS and OS (Theme 1) 2. A relatively tightly defined range of plausible ICERs, all close to or below the threshold mean there is a low risk of decision error 3. Certain clinical benefit a. The data from the trial show separate and separating PFS and OS curves b. The CR and PR rates are some of the highest ever observed in an immunotherapy trial c. Close to 90% of CR patients are alive at two years 4. Uncaptured benefit, which would move the base case ICER downwards a. Carer QoL uncaptured b. Dependent QoL uncaptured c. Long term ability to return to daily activities uncaptured d. Enrichment of PFS health state by CR patients uncaptured 5. Pembrolizumab represents a badly needed innovation in advanced cervical cancer. There has been no new NICE approved treatment for 13 years. 6. Potential to reduce health inequalities by generating QALYs in a disease area that most affects certain vulnerable and disadvantaged groups.
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NICE National Institute for Health and Care Excellence

Pembrolizumab in combination with platinum-based chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 26 October 2022. Please submit via NICE Docs.

Appendix	**Appendix** [redacted]

Checklist for submitting comments

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

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

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Response from Jo's Cervical Cancer Trust

- **Has all of the relevant evidence been taken into account?**
- **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**
- **Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**
- **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

- We want to bring the faces and stories behind the models to the forefront of this consultation. Trial evidence shows pembrolizumab plus chemotherapy can slower progression, thus extending life.
- The fact evidence regarding how long this extension is should not be the factor that prohibits its approval
- The only advance in treatment options for this cohort of patients in many years has been the addition of bevacizumab. This has been shown to extend by a shorter amount of time than pembrolizumab at just over 3 months
- Patients are often young. Sima, below, is in her 30s and has a 4-year-old child. Pembrolizumab has given her a chance to have more time with her son. The other stories show the anguish and inequity faced by others with an advanced cancer diagnosis around accessing treatments

Sima*

I'd read some information online about a study showing that Pembro alongside the chemo showed an increase in response rate for advanced CC and through some social media networks that I'm part of, I was aware this was a standard first line treatment offered in the US and some other countries.
After finding out that I was PD-L1 positive and therefore a candidate for immunotherapy then I knew that this was something I wanted to get access to, to give me the best chance of more time with my loved ones and most importantly, time with my 4-year-old son.

It was very stressful in trying to gain access to the immunotherapy treatment option. I felt like I had to fight for a treatment that is currently a postcode lottery as I was aware of some ladies from Jo's being offered Pembro, depending on their cancer centre location. This felt very unfair and adding this on top of dealing with an incurable cancer diagnosis is an unnecessary mental pressure when we are already going through a lot.

I'd been offered the standard chemo to start at my local hospital in Newcastle but was told they were unable to offer immunotherapy as they had never offered this before as a first line option. I then had a private consultation with the Royal Marsden thanks to a private healthcare policy I had already - I went to the Royal Marsden as

the North East where I live doesn't have a private cancer hospital anymore. I'd made the decision that getting the treatment was the best thing for me so was very close to travelling from Newcastle to London to have this at the Royal Marsden. Logistically this would have been expensive for stays in London every 3 weeks but would also mean time away from my son and a big upheaval on our lives. Fortunately, after some searching, I was recommended a private consultant in the North East that offers treatment at home so was able to get access to the immunotherapy alongside chemotherapy. It was a big relief and my family, and I celebrated that I was getting access to this.

I do feel it's incredibly unfair that I have this option when so many women aren't getting the chance of immunotherapy on the NHS when they may benefit from it. As a cancer with only one line of standardised treatment for metastasis, we need more options and more of a focus on potential 'maintenance' treatments like they have with many other cancers. I know I'm not alone in finding it terrifying how little there is available to advanced CC women so it's great that Pembro is potentially coming available across the NHS in the future.

Catherine*

I'm 57 and living with advanced cervical cancer. I am currently going through carbo/paclitaxel and Avastin and am responding well, I'm tolerating it and after three cycles the tumour has shrunk by a third. I'm hoping for an NED but will be thinking about what to do next when the cancer inevitably comes back.

Other women I have spoken to have wanted to access Keytruda when it was in trial state but couldn't get funding or couldn't get it at their usual cancer treatment hospitals and missed out due to being unable to travel hundreds of miles. I live in a very rural area so my options are already limited in where I can access treatments. The fact that drugs which have shown such positive results may be refused to patients in the England is awful. Very few new drugs become available which work for cervical cancer, and this means women are left without options and hope. This drug being made widely available on the NHS would save the heartbreak and devastation suffered by their families. "

Ava*

The day I was diagnosed with stage 4 cervical cancer, my oncologist spoke to me about a new-to-cervical cancer drug, pembrolizumab, that was being administered to patients at the Marsden for the first time on compassionate basis, as agreed with the NHS. If I qualified, I would be one of a very, very small number of women receiving this novel treatment for cervical cancer in the UK. I agreed to waiting an extra week to have my tumour tested for PDL-1 to see if I qualified (which I did) and began treatment on 7 July. After three infusions, including carboplatin, taxol and bevacizumab alongside pembrolizumab, I was given a midpoint PET scan which showed a "complete metabolic response" – the very best possible outcome. There was no cancer activity visible, and my oncologist is fairly confident that the "chemo cocktail" including pembrolizumab is helping deliver good results. I went from an

initial diagnosis that included extensive lymphadenopathy, to having zero hotspots visible on my midway PET. As I near the finish line of this round of treatment, I am cautiously optimistic and beginning to think about the future again after so many months of worry, fear and utter despair. Pembrolizumab gives me hope that I can reclaim my life.

When I tell other women with advanced cervical cancer about being on pembrolizumab, all have said it was not made available to them, but they wished it were. I sometimes feel guilty for having been “at the right place, at the right time” because I certainly did nothing else to set me apart from these women to get access. Most of them wondered if I had gone the private route, which I hadn’t, and no one should not have to. I am very grateful to the Royal Marsden and the NHS for allowing me to receive this treatment, but why can’t my friends? To say we live in an unequal world is putting it mildly.

Sarah*

I was diagnosed with adenocarcinoma in December 2019 stage 2B followed by recurrent cervical cancer with multiple lung mets in June 2021. After my first line of treatment with carbo/taxol/avastin, I had to fight to get suitable follow up treatment and even paid for some private treatment at one point. For those living with advanced cancer, we often find we have to advocate loudly and forcefully ourselves within our own hospitals for treatment. At our most vulnerable, a huge amount of time and energy is used this way and on top of everything else, the financial burden can sometimes be crippling. There is a huge discrepancy as to what is already available across different parts of the UK. The addition of pembromizulab has been a very long time coming but it worries me that it may not be considered for use wherever, and at whatever stage, needed and that lack of funding might remain a barrier. There is so much inequality in access to treatments. Many on our side have ended up on trial after trial desperately in search of something that works. Some are left so ill, it is hard to tell where the treatment ends and the cancer begins.

We are a much under-funded minority in the world of cancer and woefully behind in research. There just aren’t the numbers of us to make it interesting or worthwhile, and it sometimes feels that as a 'woman’s illness’ further stigmatised by the mention of HPV, things just have not moved on for decades. We feel written off. Many of us are young; some have young children. It is heartbreaking to see. The idea that those lucky enough to have private health insurance have so much more available to them is never something I would have dreamt possible in this country. I had assumed that when we were at our most sick and vulnerable, the NHS would step up and give us the very best of care that was available anywhere. It has been a huge eye-opener. Little did we know that this would be the time when so little would be on offer, and we would feel written off as statistics. We are people, not numbers. The situation is desperate.

*Pseudonyms used for anonymity

Comments on the Appraisal Consultation Document from Dr Susan Lalondrelle, clinical expert

Comments on:

NICE Appraisal Consultation Document (ACD): consultees and commentators: Cervical cancer (metastatic, recurrent, persistent) - pembrolizumab (with chemotherapy) [ID3798]

In considering the draft consultation I would like to add the following comments.

The evidence provided by Keynote 826 demonstrates the benefit of pembrolizumab in this setting. Whilst the OS data may not be considered mature, the significant improvement in PFS is highly indicative of a similar OS benefit. In other trials of the same technology where a DFS benefit is seen, there is also an OS benefit. It is not logical to think that this would be different for this group of patients. It should also be highlighted that a proportion of patients are able to achieve a complete response - this is unprecedented in advanced cervical cancer. Data in the company submission highlights that in this cohort of responders the OS rate at 2 years is 90% - this figure is more in keeping with the responses expected with radically treated, earlier stage disease.

Extrapolations of OS for the SOC arm are in line with those observed in GOG240. This would support the model used by the company and are in line with clinically observed outcomes from my experience.

With regard to the waning effect; in my experience of use of this and similar technologies in other cancers, I have not observed a waning effect to the extent being considered here. i.e. patients who respond and are long term responders do not relapse subsequently.

I would like to emphasise the lack of therapeutic treatment options for this group of patients and therefore the significant impact that this technology could have on outcomes for them. Most eligible patients are young women, often with young families, facing a terminal diagnosis and progressive symptoms. When GOG240 reported an OS benefit for bevacizumab , this was a landmark of hope for these patients. There is now evidence of further PFS and OS gains with this new technology which should be granted to patients with cervical cancer, as it has been with many other tumour types, sometimes with less clinical benefit and wider treatment options. It should be remembered that this technology is not available as second line therapy in the UK and therefore approval in this first line setting would represent the only chance for these patients to access immunotherapy.

Dr Susan Lalondrelle

Committee Clinical Expert

26.10.22

• Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • Are the recommendations sound and a suitable basis for guidance to the NHS? • Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity

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

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

All relevant evidence has been taken into account but i strongly disagree with the outcome of this and think that this treatment will make a huge impact on our patients.
The KEYNOTE 826 paper is a seminal paper with massive significant improvements in outcomes in a patient cohort who have very limited treatment options and therefore is a huge area of unmet need. These patients are often young and fit with dependants/young families and therefore they tolerate treatment well and any disease control and survival improvements lead to significant QoL improvements. There are very limited treatment options despite fitness often with enrollment in phase 1 trials etc.
In view of the lack of second line treatment options in this patient cohort I do agree that the PFS benefit is very likely to be reflected in OS benefit and the not yet reached median OS of estimated 2 years in my view is groundbreaking for this patient cohort. Even if that is an overestimate it is the most dramatic impact and step forward since the addition of bevacizumab which has now been available for 8 years.
I am very disheartened and am concerned that the treatment i am able to deliver to this patient cohort is suboptimal if access to pembrolizumab is not possible despite the solid evidence.

Has all of the relevant evidence been taken into account?

yes it has

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

i disagree that the PFS is not likely to translate into OS benefit as these patients have no good second line treatment options and even if the calculations are an overestimate the improvements in survival still represent a massive step change for our treatment outcomes.

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

NO. I strongly believe that this drug should be available for this patient cohort who have a massive unmet need as this paper demonstrates seminal step change improvements in outcomes.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any

group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
no.

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I think that this decision is incorrect and doesn't take into account that this is an aggressive cancer with limited options.

This patient group needs more options and this trial represents the biggest improvement in progression free survival.

Has all of the relevant evidence been taken into account?

Yes

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I understand its an early result but at least it is showing some improvement in the progression free survival and it is significant. This is an area of unmet need and we don't have any strong alternatives or treatment options for this group of patients where mostly the population is very young. This is showing the way forward . Please consider it.

Single Technology Appraisal (STA)

Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

ERG Response: Review of the company's response to the appraisal consultation document

Produced by	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Date completed	01/12/22

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135578.

Declared competing interests of the authors

None.

Rider on responsibility for report

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

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, and all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

Table of Contents

1 OVERVIEW

The evidence review group (ERG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the appraisal consultation document (ACD) and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the ERG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. Specifically, the EGR has not fully validated several structural changes to the model outlined in the company's response to the ACD. Instead the ERG has conducted high-level checks of these proposed changes and ensured replication of the results presented by the company.

The company's response to the ACD covers seven themes summarised in Table 1 and presents a revised base case that accepts several of the committee's preferred assumptions. The company contests several preferences stated in the ACD, specifically around the magnitude and plausibility of benefits associated with pembrolizumab combination therapy. No new data is presented in support of the company's preferred assumptions; however, several new analyses are presented, which include an exploration of alternative extrapolation methods and an alternative model structure based on a response-based approach. The company's responses to each of the issues are discussed in Section 2, while Section 3 presents an overview of the company's revised base case and the updated ERG base case.

Table 1: Summary of the themes covered in the ACD

Theme	
1	PFS / TTP modelling approaches (ACD sections 3.7)
2	Relationship between PFS and OS (ACD Section 3.6)
3	Plausibility of PFS and OS (ACD section 3.7)
4	Treatment effect waning assumption (ACD section 3.9)
5	PD utility value corrected (ACD section 3.10)
6	Uncaptured Value (ACD section 3.16)
7	Decision Threshold

2 DESCRIPTION AND CRITIQUE OF RESPONSE

2.1 Theme 1: PFS / TTP modelling approaches

To explore the uncertainty in progression free survival (PFS) and time to progression (TTP), the company presents two sets of scenario analyses using spline-based extrapolation methods and a response-based model (RBM) to analyse the available PFS/TTP data. The company also provides

further commentary in support of the original piecewise model used in their base case analysis. No new data is available from KEYNOTE-826, and therefore all analyses use the same data cut as the company submission and technical engagement (TE) response.

Cubic spline models

The company explored one- two- and three-knot cubic spline models, with three alternative models (Normal, proportional hazards, and proportional odds) fitted for each. Selection of the most appropriate model considered statistical fit, visual fit, and plausibility of predictions. The same model was considered for both PFS and TTP, with priority also given to using the same model type in both treatment arms. The company considered all one-knot models inappropriate due to poor statistical visual fit and settled on the "hazard 2" model as the most appropriate (see Figure 1 for a graphical representation of model fits). The company noted that long-term PFS and OS estimates produced by the two- and three-knot models were more optimistic than those generated by the base case piecewise model.

Figure 1 "Hazard, 2" spline models fit to PFS KM data

2.1.1 The ERG's response

While the ERG notes the good statistical and visual fit of the presented spline models, it is important to emphasise that good fit to observed data does not mean that extrapolations are reliable. Spline models, much like piecewise models, are inherently more flexible than one-piece models because they fit to only part of the observed data. Because of this spline models will often visually fit data better than less flexible models. This also means that they tend to emphasise trends towards the end of follow-up, which is driven by very few events and small numbers at risk. The limitations of the spline models, therefore, reflect those of the piecewise approach. As previously outlined, the ERG considers the company's justification for adopting flexible models to be inadequate and to place too much

emphasis on visual fit to the pembrolizumab PFS data without appropriate consideration of the clinical plausibility of predictions. As the spline models are significantly more optimistic than the piecewise model applied in the company base case, they are unlikely to present more realistic predictions about long-term survival.

Response based model

In addition to the spline models, the company also presents a RBM. A RBM uses response status to predict long-term survival outcomes and is founded on the principle that response is a strong predictor of future survival (see Figure 1 of the company ACD response). In the presented RBM PFS data from KEYNOTE 826 is stratified into five response levels: complete response, partial response, stable disease, progressive disease and not available. Separate parametric models were fitted to each set of response data and then reweighted (by the proportion of patients in each group) to generate an overall PFSTTP curve. An important feature of the response-based analysis presented by the company is that it assumes a treatment specific relationship between response status and PFS/TTP.

The primary advantage of the RBM approach is that it allows parametric projections to reflect the distinct trajectories of patients with different levels of response and allows for greater flexibility than fitting a single curve to either the whole or part of the PFS/TTP data. The company consider the results of the RBM analysis to broadly align with those of the base-case piecewise approach and present it as supportive evidence.

2.1.2 The ERG's response

The ERG agrees broadly with the company's characterisation of the RBM and the stated advantages of this approach. The ERG also agrees that the outcomes better align with those of the piecewise model than the one-piece model though it is notable that projections are generally more pessimistic using the RBM than the company's preferred piecewise model, see Section 3 and confidential appendix.

Despite the advantages of the RBM, the ERG does have some concerns regarding the assumptions underpinning the RBM approach as presented in the ACD response.

Firstly, the response-based approach is applied only to TTP and PFS, not overall survival (OS). The model, therefore, retains the assumption that PFS is the main driver of benefit. Consequently, structural uncertainties discussed in the assessment group report remain. The company also presents OS curves extrapolated using an RBM approach, but these are not incorporated into the economic model. The company suggests that these analyses validate the predictions of the economic model. The ERG concurs with this conclusion but notes that the graphical presentation of this analysis and the

limited information regarding the parametric curves selected means it is difficult to fully appraise this comparison.

Secondly, the company assumes that there is a treatment-dependent relationship between response and TTP/PFS. This is an important assumption that is not justified in the ACD response. Examination of the presented figures appears to indicate numerically superior survival outcomes in favour of pembrolizumab combination therapy across some response categories. It is, however, difficult to formally assess differences without access to individual patient data, and it is unknown whether these differences are statistically significant. The clinical plausibility of a treatment-specific relationship between response and survival outcomes is also unclear. Given the available evidence, a more conservative approach may have been preferable, whereby a common (treatment-independent) relationship between response and TTP/PFS is assumed. This approach would also have the advantage of increasing sample sizes across response categories, increasing confidence in survival projections. It could have also allowed external data to be leveraged, which could increase confidence in long-term projections.

Thirdly, while the RBM approach increases flexibility in the parametric modelling of survival outcomes, it necessarily also increases uncertainty. The stratification of data significantly reduces sample sizes and the number of observed events, increasing uncertainty in projections. This issue is particularly acute in complete responders, where relatively few events are observed. This uncertainty is important because the complete response groups drive much of the benefit associated with pembrolizumab. Exploration of uncertainty in model predictions is also difficult in an RBM due to the large number of possible combinations of parametric curve selectable; in total there are 7776 alternative combinations of parametric curve choice under the specified RBM.

Piecewise approach – original base case

The company restate their preference for a piecewise approach to modelling PFS and that they consider this approach to generate the most clinically plausible estimates. The company also advocate for the differential use of a one-piece model in the SoC arm. The company highlight differences in the mechanisms of action that may justify this approach and note that immunotherapy treatments are generally associated with long tails in survival outcomes. The company also notes support from eight UK clinicians confirming the clinical plausibility of predictions in the SoC arm using the one-piece approach.

2.1.3 The ERG's response

The ERG agrees that a one-piece model generates more clinically plausible predictions in the SoC arm but urges caution in applying a different extrapolation approach across treatment arms. The ERG

is unaware of any precedent to support such an approach and is concerned by the assumptions implied. The NICE DSU technical documents(1) do not directly address the issue of using a piecewise model in only one arm but generally advise against the use of different parametric models in different arms, suggesting that "substantial justification" would be required to adopt such an approach. Therefore, if the committee prefer a piecewise extrapolation in the pembrolizumab arm, the ERG urges the committee to only consider scenarios where a piecewise model is applied in the SoC arm.

Regarding the plausibility of model predictions, the ERG continues to consider the piecewise model to be overly optimistic. Model predictions using a piecewise model remain inconsistent with parametric extrapolations of OS data which are consistently more conservative. Importantly, while the ERG is satisfied that the company have explored the full range of realistic approaches to survival analysis, these additional analyses do not address the fundamental limitations of the available data. The ERG considers the full resolution of this issue is not possible given the current data limitations but notes that future data cuts will contribute to reducing the associated uncertainty. The ERG maintains that the one-piece approach, while undoubtedly subject to limitations and conservative in its predictions, represents a useful counterpoint to the company's position that is both methodologically orthodox and generates predictions that are consistent with our expectations for current SoC.

2.2 Theme 2: Relationship between PFS and OS

The ACD states that there is uncertainty regarding the magnitude of OS benefits associated with pembrolizumab. The company contests this statement and highlights the principal uncertainty relates to PFS, not OS. The company further outlines that there is an expectation that PFS benefits will translate into OS gains citing evidence from KEYNOTE-826, GOG-240 and clinical opinion.

The ERG's response

As highlighted in the ERG report, the modelling approach taken by the company places significant emphasis on PFS, such that PFS is the main driver of OS benefits. The company is therefore correct in isolating PFS as the principal uncertainty in this appraisal. However, given the structural relationship between PFS and OS assumed in the model, it is equally accurate to characterise this as uncertainty about the magnitude of OS benefits.

Regarding the relationship between PFS and OS, the ERG agrees that is plausible that PFS gains will result in OS gains. This relationship is, however, subject to uncertainty, and PFS is not a validated surrogate for OS in this indication. The ERG considers it important to consider this uncertainty in decision-making.

2.3 Theme 3: Plausibility of PFS and OS

The company challenges the assertion that the two-piece approach to modelling PFS leads to optimistic estimates of long-term survival. The company lists a total of ten individual points in support of the piecewise approach, which includes highlighting the robustness of predictions to alternative modelling approaches (see Theme 1), clinical validation of predictions, and consistency with external data sources.

The ERG's response

The relative advantages and limitations of alternative extrapolation approaches including the two-piece approach have been discussed extensively in Theme 1 and are not revisited here. The ERG, however, addresses several specific points raised by the company with reference to the plausibility of the predictions generated by a piecewise approach:

- Points 4 and 10: The company highlight that they have used GOG-240 to validate the predictions of the economic analysis. The ERG reiterates concerns about the use of GOG-240 to inform model selection due to concerns about the representativeness of patients treated in this trial. The ERG also highlights that the company's revised base case does not align well with the predictions of GOG-240. OS predictions for SoC are substantively lower than observed in GOG-240 (9.41% vs 15.1% at 4 years).

  The company also suggests that the ERG's preferred one-piece model is overly pessimistic because it predicts 4-year OS on pembrolizumab to be only 5% higher than observed in GOG-240. The ERG rejects this argument. The highlighted issues with the GOG-240 study equally apply to comparisons with pembrolizumab and as previously indicated the results of GOG-240 do not align with NHS clinical experience which suggests few patients achieve such long-term freedom from progression and survival on current SoC. A 5% absolute improvement over GOG-240 is therefore not necessarily indicative of a small or pessimistic relative treatment effect.

- Points 5 and 10: The company presents a landmark analysis of PFS and OS from pembrolizumab trials. Based on descriptive analysis, these trials are consistent with declining hazard trends and the application of a piecewise approach. The ERG considers this analysis informative in understanding the evolution of hazard trends in patients receiving pembrolizumab. However, this analysis should not be over-interpreted. Inherent differences in disease biology, population (many patients with cervical cancer are heavily pre-treated), and availability of subsequent treatments (there are few subsequent treatment options in cervical

cancer) may all impact resulting hazard trends. Furthermore, the presented comparisons do not represent a systematic assessment of all evidence on long-term treatment effects in immunotherapies. As such, while the evidence presented is broadly supportive of the company's position, it is not conclusive evidence that this pattern of declining hazards will occur across all indications. The ERG also notes the ratio of 2-year to 5-year PFS predicted by the piecewise model is amongst the highest of the trials listed in the ACD response, which is consistent with the committee's conclusions regarding the relative optimism of the PFS extrapolations.

- Point 7: While cervical cancer disproportionately affects younger women, it is inaccurate to suggest that cervical cancer exclusively affects younger women. As discussed below in Theme 6, cervical cancer also affects older women, and therefore for a proportion of patients, non-cancer mortality will be relevant.

- Point 8: The company suggests that uncertainty is controlled by the imposition of treatment waning from five years. This is inaccurate and potentially misleading. Treatment effect waning is not a device that in of itself reduces or increases uncertainty. It is a structural assumption that reflects our beliefs about the persistence of the treatment effect and imposes these upon the modelled extrapolations. In the case of 5- to 7-year waning, it means beyond 7 years, we consider there to be no further advantage offered by pembrolizumab in terms of the rate at which patients progress or die. Under scenarios both with and without treatment effect waning, modelled benefits are primarily determined by the choice of parametric model used to extrapolate PFS, which is subject to uncertainty and is the primary driver of benefits throughout the model time horizon, including beyond the application of the waning effect (if applied).

2.4 Theme 4: Treatment effect waning assumption

The company summarise uncertainty around the treatment effect waning assumption and the lack of evidence to support treatment effect waning. The company base case assumes a 5 to 7-year waning as an appropriate middle ground between a 3 to 5-year waning period and no waning.

The ERG's response

The ERG accepts the biological plausibility of a durable treatment effect after stopping pembrolizumab. However, the duration of any such effect is highly uncertain, and there is no indication-specific evidence to support a sustained treatment effect. In the absence of such evidence

the ERG considers a 3 to 5-year waning period plausible and consistent with previous NICE appraisals.

2.5 Theme 5: PD utility value corrected

The company acknowledged the committee's preference for health state-based utility values. On inspection of the model, the company identified a minor error in the implementation of this scenario and has presented an updated analysis. The correction results in a small reduction to the ICER.

The ERG's response

The ERG thanks the company for highlighting the modelling error and can confirm that the updated model is correct.

2.6 Theme 6: Uncaptured value

The company outlines several arguments suggesting that there are uncaptured QALY benefits beyond those estimated in the economic analysis. In brief, these are as follows:

1) Cervical cancer mostly affects young women of working age many of whom have dependent children. The survival benefits associated with pembrolizumab are likely to enable women to return to their daily lives, including work and caring responsibilities with a commensurate effect on the health-related quality of life of both the patients' carers and children/dependents.
2) The modelled survival benefits of pembrolizumab suggest many complete responders will survive beyond 2 years. Quality of life in the progression-free health state is likely to be higher than for other patients who do not achieve a durable response. Modelled quality of life for these patients is therefore likely to be underestimated.
3) A positive recommendation for pembrolizumab will help reduce health inequalities as a consequence of the higher incidence of metastatic cervical cancer in women from deprived communities as well as ethnic minority groups and migrants.

The ERG's response

The ERG considers each of the arguments put forward by the company below.

1) The incidence of cervical cancer across different age groups is bi-modal with a peak at around the age of 35 and then increasing risk from around the age of 50.(2) The company is therefore correct that eligible cervical cancer patients will include many working-age women with dependent children. However, cervical cancer also affects many older women, 55% of patients KEYNOTE-826 were over 50 and 16.2% were over 65. Importantly, the routine

provision of the human papillomavirus vaccine means that the age of patients with cervical cancer is likely to increase over time.

The ERG considers it plausible that additional health-related quality-of-life benefits are associated with this younger population, but considers that the evidence provided is insufficient to conclude that the provision of pembrolizumab will generate additional benefits in this population. Moreover, the ERG notes there is lack of precedent for including additional carer benefits in cancer appraisals.(3)

2) The ERG agrees that is plausible there are additional benefits in patients surviving beyond two years as a consequence of the fact this patient group will not be in receipt of treatment and therefore not be subject to the adverse event burden associated with pembrolizumab combination treatment. However, this would also be true for patients receiving standard care who similarly at this point would not receive active treatment; the ERG acknowledges that more patients would survive beyond two years in receipt of pembrolizumab than on standard care. The magnitude of this benefit is, however, likely to be very small and inconsequential in terms of determining the ICER. This can be illustrated with reference to the adverse event disutility applied in the model, which in the pembrolizumab arm sums to just -0.013 QALYs over the entire time horizon.

3) The ERG accepts the points raised by the company regarding the incidence of cervical cancer being higher in women from deprived communities and ethnic minority groups. The ERG, however, notes that differences in incidence cannot be addressed by this technology appraisal. Nor, is there any suggestion that any recommendation for pembrolizumab would differentially impact individuals protected by equalities legislation. The ERG further notes that there is no reason to believe that additional QALYs will be generated as a consequence of addressing the highlighted inequalities.

2.7 Theme 7 Decision threshold

The company put forward several arguments asserting that a £50,000/QALY gained is appropriate for decision-making. In support of this assertion, the company highlights the lack of decision uncertainty, the significant clinical benefits associated with pembrolizumab, and the clinical unmet need in this population, as well as reiterating several points made in Theme 6 regarding the potential for additional benefits.

The ERG's response

The ERG does not agree with the assertion that decision uncertainty is small and considers there to be a high risk of decision error. Current follow-up from KEYNOTE 826 is limited and much of the modelled incremental benefit associated with pembrolizumab is in the extrapolated portion of the survival curve. Further, the nature of the company model makes additional assumptions that further propagate uncertainty. As such the committee cannot be confident that the modelled benefits will be realised within the NHS. Furthermore, while the ERG agrees that there is both a high unmet need in this population and that there would be substantive clinical benefits associated with a positive recommendation for pembrolizumab, these benefits have already been captured by the economic model. With regards to the issues raised under Theme 6, see section 2.6 above.

3 COMPANY REVISED BASE CASE AND UPDATED ERG BASE CASE

As part of the response, the company have provided a revised base case. The revised base case includes several changes from the base case presented at TE which are described in Table 2.

Table 2 Revisions to the company base case

Revised company base case	Previous base case (at TE)
Revised PAS discount	Old PAS discount
One-piece model for SoC	Piece wise approach used in both arms
Health state utility values with programming error corrected	Time dependent utility values
Treatment waning from 5-7 years post-cessation	Both 3 to 5 years and 5 to 7 years presented

3.1.1 Results of updated company analysis

Table 3 presents results for the company's revised base case. These results include only the confidential PAS discount for pembrolizumab and are exclusive of confidential commercial arrangements for the comparator treatments. Results with the PAS discounts for all comparators and subsequent treatments are provided in a confidential appendix to this report. The confidential appendix also includes all other exploratory analyses presented by the company as part of the ACD response inclusive of the comparator PAS discounts.

Table 3 Company's revised base case (Including Pembrolizumab PAS only)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Deterministic analysis							
SoC	[redacted]	2.060	[redacted]				
Pembrolizumab	[redacted]	4.247	[redacted]	[redacted]	2.187	[redacted]	£40,203
Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

3.1.2 Selected scenario analysis on company base case

For completeness the ERG presents several additional scenario analyses aligning with those presented in the ERG report. These are presented in Table 4 and as above are exclusive of confidential commercial arrangements for the comparator treatments.

Table 4 ERG Exploratory Scenario Analyses (Including Pembrolizumab PAS only)

Scenario	Technology	Incremental			ΔICER vs company BC
		Costs	QALYs	ICER	
Company base case	SoC				
	Pembrolizumab	[redacted]	[redacted]	£40,203	-
1. One-piece extrapolation of pembrolizumab (scenario 1 ERG report)	SoC				
	Pembrolizumab	[redacted]	[redacted]	£79,796	£39,593
2. Pooled survival curve for PPS using Weibull curve. (scenario 2 ERG report)	SoC				
	Pembrolizumab	[redacted]	[redacted]	£43,075	£2,873
3. GP/nurse visits, blood counts, and thyroid function tests costs (scenario 9 ERG report)	SoC				
	Pembrolizumab	[redacted]	[redacted]	£41,304	£1,102
4. All AEs of special interest occurring in more than 5% of patients modelled (scenario 10 ERG report)	SoC				
	Pembrolizumab	[redacted]	[redacted]	£40,621	£419

3.1.3 ERG base case

To reflect corrections to the executable model and the revised PAS discount,

Table 5 presents an updated ERG base case analysis. The assumptions used in this analysis are identical to those previously presented in the ERG report.

Table 5 ERG base case (Including Pembrolizumab PAS only)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs baseline (£/QALY)
Deterministic analysis							
SoC	[redacted]	2.08	[redacted]	[redacted]		[redacted]	
Pembrolizumab	[redacted]	2.90	[redacted]	[redacted]	0.82	[redacted]	£99,014
Abbreviations: SoC, Standard of care; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years.							

4 REFERENCES

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Single Technology Appraisal (STA)

Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer [ID3798]

Review of the company's response to the appraisal consultation document addendum

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Date 08th December 2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number ID3798.

Declared competing interests of the authors

None

Rider on responsibility for report

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

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

1 Additional analysis inclusive of Pembrolizumab PAS only

This addendum to the Evidence Review Group (ERG) report presents additional analysis requested by the NICE team following the submission of the ERG critique of the company's response to the appraisal consultation document. The results in Table 1 reflect the outcomes of analyses when the available patient access scheme (PAS) discount for pembrolizumab is applied but excludes available discounts for other treatments

Table 1: Additional analysis (Pembrolizumab as Only)

Scenario	**ICER (cumulative)**	**Δ ICER vs company BC**
Company base case following AC1	£40,203	-
1. 3-5 years waning	£44,893	£4,690
Scenario	**ICER (cumulative)**	**Δ ICER vs company BC**
2. ERG Model corrections	£44,900	£4,697
3. One-piece log-logistic extrapolation of the PFS and TTP curves in the model	£81,226	£41,023
4. GP visits, nurse/nurse specialist visits, blood counts, and thyroid function tests costs	£82,359	£42,156
5. All AEs of special interest occur >5% of patients	£83,811	£43,608