Single Technology Appraisal

Pembrolizumab with chemoradiotherapy for untreated locally advanced cervical cancer [ID6138]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with chemoradiotherapy for untreated locally advanced cervical cancer [ID6138]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Merck Sharp & Dohme**

2. **Comments on the Draft Guidance Document from experts:**
    a. Alexandra Taylor – Clinical expert, nominated by MSD

3. **External Assessment Group critique of company comments on the Draft Guidance**

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

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Consultation on the draft guidance document – deadline for comments 5pm on 24 February. 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 UK

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A submitting company
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]

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 would like to thank the committee, EAG, clinical experts, patient experts and the NICE team for the time taken to consider this appraisal. MSD is pleased that the committee recognise the unmet need for effective, innovative treatment options for untreated locally

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	advanced cervical cancer and that pembrolizumab in addition to CCRT is effective at improving progression-free survival (PFS) and overall survival. MSD emphasises the comments from clinical experts during and prior to Appraisal Committee Meeting 1 in which they expressed their view that pembrolizumab works well with CCRT, improves the probability that women are cured from cervical cancer and thereby would improve outcomes among certain disadvantaged groups in society. MSD understands the need to further address economic modelling related uncertainty within this consultation response and as such this response focuses on the two main areas highlighted by the committee in the Draft Guidance (DG): • Further validation of the assumption of cure, specifically looking at mixture cure modelling • Exploring the use of KEYNOTE-A18 post progression survival data to better model overall survival • Further exploration of immunotherapy rechallenge assumptions This response is accompanied by an updated cost-effectiveness model (CEM), all adaptations have been made to the model that was sent from the EAG back to the company with the EAG report, "ID6138 Pembrolizumab for high risk LACC_EAG model_061025 [CON]". New sheets have been coloured purple and a full list of adaptions is found in the response below along with instructions on operating new switches for certain sensitivity analyses.
2	**<u>Cure assumption</u>** A key structural assumption of the model is the presence of cure. Within the model, the cohort who are progression free at 5 years start to be classed as cured. A cured patient has a risk of progression of zero, and a risk of death equal to the England and Wales age-sex specific mortality rates (upweighted by an SMR to account for life long effects of disease and treatment exposure). At year 5, 0% of the progression free population are "cured" and this raises linearly up to 95% of those still progression free at 7 years. To allow

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for the most appropriate comparisons, we will refer to a figure equal to 95% of those progression free at 7 years in the economic model when discussing the cure proportions that it estimates. These assumptions are common to several other pembrolizumab appraisals in early stage oncology settings.

As stated in the company submission, feedback from clinicians was that concurrent chemo-radiotherapy (CCRT) was used with curative intent in all patients relevant to this decision problem, clinicians agreed that 5 years was an appropriate time point for cure, and this corresponded with when progression free patients are typically discharged from routine follow up care in NHS clinical practice. These assumptions were supported by the clinical experts at the committee meeting, with them commenting that in their experience, the cure point might actually occur even earlier than this.

As discussed at ACM1, the model does not estimate cure directly but rather a cure proportion is implied. It is important to note that some people who are cured will have already died in the economic model for reasons other than cancer and thus the cure proportions derived from the model are not directly comparable to a cure proportion derived from a mixture cure model.

The cure proportions estimated within the base-case modelling assumptions are found below, with the model suggesting roughly 44% of patients are cured within the CCRT arm and 53% in the pembrolizumab + CCRT arm, with a cure delta of 9%. The company/EAG base case PFS curves were validated by clinicians at ACM1, along with this expected delta in cure.

Table 1: Modelled cure proportions for the company/EAG basecase

	5 year progression free	7 year progression free	95% of 7 years progression free	Cure delta
CCRT arm	48.4%	46.3%	44.0%	
Pembrolizumab + CCRT arm	58.7%	55.8%	53.0%	9.0%

KEYNOTE-A18 response rate

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Table 2 below shows the complete response rates from KEYNOTE-A18, these are the patients that most closely relate to a cured population as at best response these patients will have had no sign of disease. The observed complete response sits [redacted] higher than the modelled cure proportion across both arms, but the CR delta is the same as the cure delta within the model. It should be noted that CR is not a true equivalent to cure as we would expect that some patients still recur after a complete response, this explains why the complete response rate is higher that the estimated cure proportions. As such we have also presented the number of complete responders that subsequently did not experience a progression or pre-progression death event up to maximum follow up. For this statistic the difference between each arm grows in the favour of pembrolizumab and the absolute figures are broadly inline with those modelled (Table 1). We also note that the prognosis of a CR is not equal between the arms in this, or in other pembrolizumab studies. In TA939, the CR-specific PFS Kaplan-meier curve was shown to be much higher in the pembrolizumab arm(1).

Table 2: Summary Complete Response based on Investigator Assessment per RECIST 1.1 (Participants with measurable disease at baseline)

	Pembrolizumab + CCRT	CCRT
Total patients	292	300
Complete Response (CR)	[redacted]	[redacted]
Complete response without progression or pre-progression death event at maximal follow up	[redacted]	[redacted]

Mixture cure modelling

A mixture cure model had originally been requested at clarifying questions, but due to the amount of work required in updating the model to include the newest data cut, delivery of the MCM was deprioritised and ultimately not conducted as part of the clarifying questions.

MSD still believe that based on feedback from clinicians, their understanding of the known natural history of the disease, the relatively long follow up from a relatively large RCT and the observed concordance between complete response rate and modelled cure proportion that the company's current approach is evidence based and holds face validity. We feel

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this is fundamentally a better and more testable method than using a statistical algorithm to detect a cure fraction, with all the limitations that entails. These limitations are discussed further below in the context of the data.

However, due to continued interest at the first committee meeting, we have conducted a suite of mixture cure modelling analyses on the KEYNOTE-A18 data. Mixture cure modelling has been conducted on KEYNOTE-A18 PFS. An MCM on OS is mentioned in the draft guidance but due to the immaturity of the observed OS in the trial, we considered that running an MCM would not be appropriate. Where time to event data are immature and where no substantial plateau is yet visible, MCM modelling will either not converge or produce wildly variable cure proportions that would not be easy to interpret(2). We considered that there is a known and substantial structural link between PFS and OS in this setting, that PFS are more mature and it is to the PFS outcome that cure assumptions are applied in the model.

For PFS, two scenarios have been run with regards to the hazard of an event in the cured population, one where risk of progression or death is equally to the England and Wales 2021-2023 age-sex specific risk of death and a second, and likely more appropriate, where the SMR (1.19), as used in the model, is applied to this population. MCMs have been modelled using the R package *flexsurv*, function *flexsurvcure(3)*.

It should be noted that this was an international trial and therefore the actual background mortality risk for patients may not be completely correctly parametrised by the England and Wales figures.

Table 3 and Table 3: MCM cure proportions on KEYNOTE-A18 PFS endpoint, with SMR adjustment to baseline hazard

Distribution	Pembrolizumab + CCRT	CCRT	Cure delta
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

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Table 4 detail the cure proportions and cure delta from the PFS MCM analyses, with curve fits and AIC statistics contained within the appendices.

Table 3: MCM cure proportions on KEYNOTE-A18 PFS endpoint, with SMR adjustment to baseline hazard

Distribution	Pembrolizumab + CCRT	CCRT	Cure delta
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

Table 4: MCM cure proportions on KEYNOTE-A18 PFS endpoint, without SMR adjustment to baseline hazard

Distribution	Pembrolizumab + CCRT	CCRT	Cure delta
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

The MCM shows an increased cure proportion in the pembrolizumab + CCRT arm across the majority of models (assuming the same distribution is picked between arms). Given this exercise is focused on validation, no specific curve distribution is preferred, although the generalised gamma can be rejected due to it estimating 0% cure in the pembrolizumab arm, a result that is clinically implausible. Similarly, the Gompertz can be rejected as it predicts markedly lower cure fractions in the pembrolizumab arm, which does not align with the observed improved PFS, OS, complete response and clinician feedback. Outside of this there is no evidence to pick one curve over another, TSD21 warns against AIC as a metric for model selection as this can be bias by selecting models that fit well to the start

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of curves, where there are greater N at risk, and not the tail which is more important for MCMs(2).

While these results are broadly supportive that pembrolizumab will increase the cure proportion, further analysis was conducted to assess the robustness of the results, exploring how a small number of late events might affect the cure proportion. In this scenario analysis we have treated all events after 200 weeks as a censoring event across both arms.

The choice of 200 weeks was arbitrary; and results in the censoring of late events in the pembrolizumab arm; a single late progression and a single late death.

Table 5: MCM cure proportion on KEYNOTE-A18 PFS endpoint, with SMR applied to baseline risk, 200 week sensitivity analysis

Distribution	Pembrolizumab + CCRT	CCRT	Cure delta
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

Table 6: MCM cure proportion on KEYNOTE-A18 PFS endpoint, without SMR applied to baseline risk, 200 week sensitivity analysis

Distribution	Pembrolizumab + CCRT	CCRT	Cure delta
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]

This sensitivity analysis increased the cure proportion in the pembrolizumab and the cure delta between the arms. For these analyses the censoring of a single disease progression

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	event and a single death event increased the cure proportion in the pembrolizumab arm by 3.5%-7% (excluding generalised gamma and Gompertz), highlighting the sensitive nature of the MCMs within this trial population. In the sensitivity analysis, the cure delta is quite consistent across models and nearly all the MCMs estimate higher cure deltas than the economic model. It should be noted that the possibility of a single death and a single progression event occurring at around 4 years and pembrolizumab still having a cure delta 9% higher than placebo is consistent with the economic model's assumptions. In totality, we believe the above results and analysis further support both the assumption of cure and the cure delta estimated within the model being reasonable. Response rate is an objective clinical outcome that supports comments already raised by both the clinical experts consulted by the company and at the committee meeting. The MCM analysis also provides a statistical grounding in the concept of a cure in the observed data. The different MCM analyses demonstrate that MCMs in this indication are sensitive to small adjustments, but that the range of observed cure fractions does support the assumption that the addition of pembrolizumab to CCRT can improve the cure proportion by the amount implied in the economic model.
3	**<u>Post progression survival and overall survival</u>** Within the original submission, the model used KEYNOTE-826 data to inform the post progression survival of patients at progression, a key reason for doing so was the relative maturity of KEYNOTE-826, compared to KEYNOTE-A18 PPS data. At the time of submission, using KEYNOTE-A18 interim analysis 2 PFS/TTP data with KEYNOTE-826 data provided modelled OS estimates that were in line with those observed at interim analysis 2 for KEYNOTE-A18. Upon viewing this relatively close alignment between modelled and observed OS, we concluded that our model was performing well. By the time of the second round of EAG clarification questions, however, final analysis data was available for KEYNOTE-A18. Once incorporated into the model the use of KEYNOTE-A18 PFS/TTP data and KEYNOTE-826 data resulted in modelled OS estimates that sat

	significantly below the observed OS results from KEYNOTE-A18, particularly in the pembrolizumab arm. As such a calibration factor was added to the model to downweigh KEYNOTE-826 hazards, so the OS in the model matched the OS observed in the trial. We believed this was a pragmatic solution that combined the best elements of a Partitioned Survival Model (close fit to the data) with the best elements of a Markov model (long term extrapolations that are based on testable combinations of assumptions about the natural history of the disease). While the EAG agreed this was a pragmatic approach to an issue that only arose from the newest data cut, this is a key area of uncertainty. To mitigate this, and in response to the requests of the committee in the DG, a new model adaptation has been submitted as part of the consultation that directly uses KEYNOTE-A18 PPS data. While KEYNOTE-A18 is at final analysis, this PPS data is too immature to populate a 4-state structure. As such, the model has been simplified into a 3-state transition model, using KEYNOTE-A18 PPS data rather than separating out PPS in the various subsets of outcomes need to satisfy a 4-state transition model. i.e. PPS has been preferred to preserve patient numbers vs splitting it out into transitions for PD1->PD2, PD1->PD2 or Death (prior to progression to PD2) and PD2->Death. Figure 1 shows that observed PPS in KEYNOTE-A18 was very similar between the arms. This was substantially different from what we had originally modelled, particularly in the pembrolizumab arm and is despite many more people receiving subsequent treatment in the placebo arm. This suggests that exposure to pembrolizumab has a profound post-progression treatment effect. This is potentially due to the long acting mechanism of action of pembrolizumab along with the likelihood that progressions took place from a deeper level of response in the pembrolizumab arm. The patients between the arms are therefore prognostically different and their outcomes are not merely determined by the treatments they received, as we had initially (and conservatively) modelled. A post-progression

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	treatment effect was also observed in KEYNOTE-826 and the NICE committee agreed it should be part of the base case assumptions in TA939. **Figure 1: Observed PPS from KEYNOTE-A18, compared to modelled PPS from KEYNOTE-A18 and KEYNOTE-826 (via PFS/TTP/PPS)**  Note: This PPS modelled from KEYNOTE-826 assumes the same subsequent treatment mix as observed in KEYNOTE-A18. PPS curve via KEYNOTE-826 constructed by starting all patients in PD1 state from cycle 1. **Implementation in the model** A new switch has been added in 'Controls!'I128 that allows for easy switching between the original 4STM model using KEYNOTE-826 and 3STM using KEYNOTE-A18 PPS. The method by which the model is simplified into a 3STM is by forcing the TTP2 hazards = 0, and feeding in new KEYNOTE-A18 PPS curves into the model in place of the KEYNOTE-826 PFS curves. By modelling TTP2 hazard as 0, patients' time in the PD1 health state can be dictated by a single survival curve, which is now fitted to the KEYNOTE-A18 PPS data. Therefore, once in the PD1 state the only transition out of this state is death, with no transitions into PD2. **Implementation** • A new =IF() was added to 'KN-826 TTP standard'!BA:BC to ensure hazards = 0 (functionally the TTP2 KM has been set to 1 across all time points) • 4 new sheets added: o KN-A18 PPS Standard – similar format to previous curve fitting sheets. This sheet is simplified from 'KN-826 Standard' as there is no longer a need for the sub treatment weighted hazard (previously columns AJ:BB). Functionality for waning remains. Waning inputs is linked to that used for KN- 826 PFS (Controls!I176) o KN-A18 Spline – As above but for splines. o KN-A18 KM – Separate sheet with KM data, this data is pulled through in the two sheet above to assess model fits and long term extrapolations

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	○ KN-A18 PPS data – Used to enable PSA iterations for PPS data for both parametric and splines If 3STM is selected in controls this feeds into a new = IF() in 'KN-826 PFS Standard'!BA:BC, pulling the KEYNOTE-A18 PSS curve into this sheet means no edits are needed to the trace. **Instructions for use** • Select "Use KN-A18 PPS (3 state model)" in 'Controls'!I128 • Headings for curve selection in Controls row146 and 165 auto update ○ The old KN-826 TTP curve selection, rows 146 to164, is obsolete ○ The old KN-826 PFS curve selection, rows 165 to 183 are now used for selecting KEYNOTE-A18 PPS data • The calibration factor is not utilised for these curves so there is no need to set these to 1 • The PD2 state is not used at all • Waning functionality has been included for KEYNOTE-A18 PPS, but in the basecase this is not applied. The PPS population uses a combination of standard chemotherapy +- IO and no treatment and the patients progressing into PPS health state appear to differ prognostically by treatment arm (outcomes appear more tied to pre-exposure to pembrolizumab than they are to downstream treatments), therefore the concept of waning one arm to another is not as straight forward as a strict IO vs non IO comparison. Hazards are also similar between the PPS curves. Given the prominence of waning in the draft guidance, scenarios with waning of PPS have been presented. **KEYNOTE-A18 post progression survival curves**

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	The transition probabilities starting from the progressed state were estimated based on survival analyses of individual patient-level data from the KEYNOTE-A18 trial in line with guidance from NICE DSU TSD 14. (4) Both parametric and splines were fit to the data All curve outputs can be found in the appendix of this response • All parametric curves across both arms fit the observed KM well, especially up to 2 years follow up, at which point there is spread across the distribution for longer term predictions (Figure 9 Figure 14) • The hazard profiles are relatively simple and flat across both arms (Figure 10 Figure 15). this may support exponential across both arms although given the declining pattern of hazards observed in KEYNOTE-826 this may not hold clinical validity. • All parametric curves within the pembrolizumab + CCRT arm have AIC within 2 of the lowest AIC (log-normal, Table 16). All parametric fits bar log-normal and Gompertz were within 2 AIC of the lowest AIC (Log-logistic) in the CCRT arm (Table 18). • Following the same approach as all other curves within the submission the same curve type has been selected in both arms. • When considering visual fit and AIC across both arms the log-logistic was deemed the most appropriate curve to explore in the base-case. Visual fit alone could not be used to differentiate most curves but log-logistic had the lowest AIC in the CCRT arm and was within 2 AIC points from the best fit in the pembrolizumab arm. • Exponential was explored in a scenario, the observed smoothed hazard was relatively flat in both arms with the AIC being within 2 of the lowest AIC in both arms. This also allows for the relaxation of time dependant transition probabilities after exiting the progression free state. • Splines have been presented for completeness but given the simple shape of the hazard function, and comparison of the AIC/BIC they do not provide any better fit compared to the standard parametric fits. Of all spines the 1-knot splines had the

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	best AIC and visual fit to the hazards, a scenario was explored using 1-knot hazard in both arms. **<u>Modelled OS using the KEYNOTE-A18 PPS data</u>** Figure 2 below shows the modelled overall survival using the new KEYNOTE-A18 PPS 3-state transition model against the observed KEYNOTE-A18 overall survival. The direct use of KEYNOTE-A18 PPS data has led to a marked improvement in fit. There is still some underfitting at the tails, however, particularly in the pembrolizumab arm, which suggests the model is underestimating PPS life years in the pembrolizumab arm to a greater degree than in the placebo arm and therefore over-estimating the ICER. Scatter plots comparing time to progression with time from first progression to second progression or death are presented in the appendices (Figure 7), these suggests that there is a small positive correlation between TTP and PPS. The slope of this relationship is flat enough as to not invalidate the Markov structure but may explain why directly using PPS has led to under-prediction of observed OS in the tails. The gradient of this correlation appeared to be greater in the pembrolizumab arm, which fits with the greater level of under-prediction in the tail of the OS KM. Although the absolute OS appears lower in both arms than in the 4STM, the delta in OS benefit appears quite similar.

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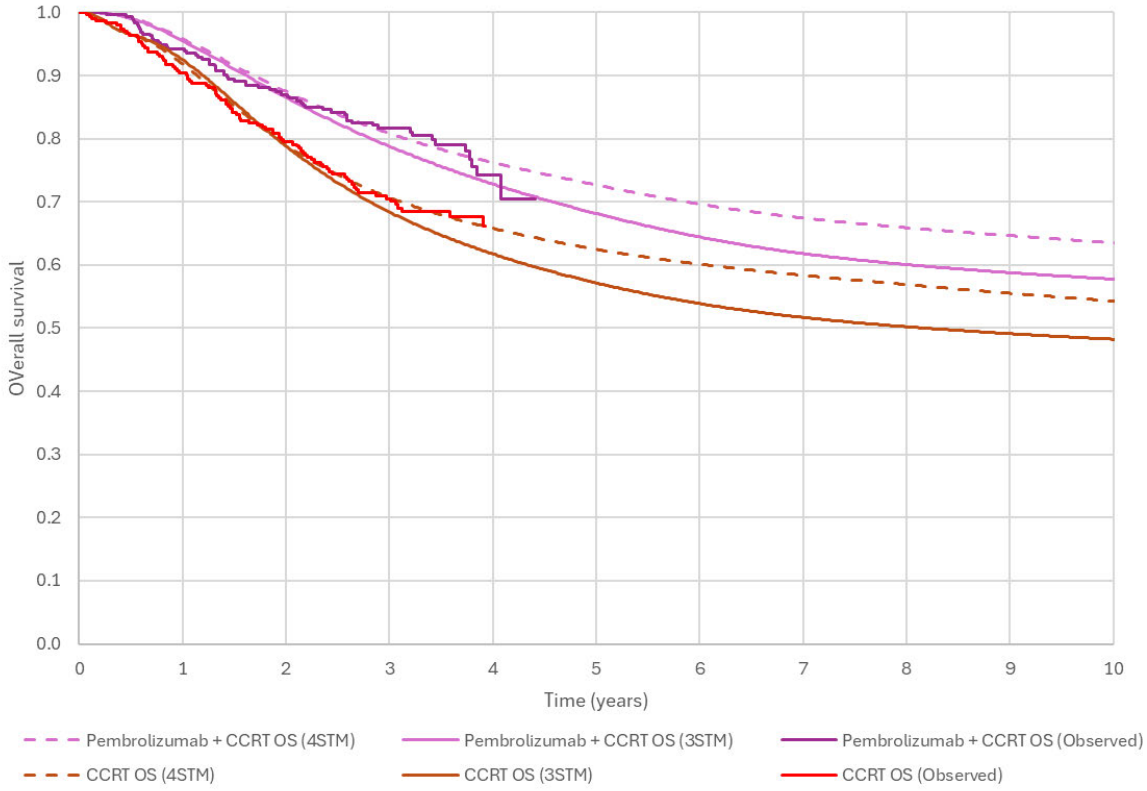
	Figure 2: Modelled overall survival (3 and 4 state transition models) vs observed OS  Note: 4-state transition model extrapolations assume calibration factor applied for 4 years
4	**<u>Dealing with different subsequent treatments</u>** When modelling using the 3-state transition model, PPS from the trial cannot be easily adjusted to account for differences in subsequent treatment patterns observed in the trial and expected in the UK without, for example, modifying individual patient survival times, which would have been too complex to do as part of a DG response and would have been based on uncertain evidence. As such, functionality has been added to the model to suitably adjust efficacy and some costs *post-hoc* by bolting on additional QALY and costs payoffs upon transition to the PPS health state. For clarity this method will be referred to as "*subsequent treatment trade-off*" throughout the rest of this response. A drop down box in Controls!E335 has been added to allow this adjustment. Methodology:

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	• The modelled discounted QALYs and costs from the 3 subsequent treatment options based on KEYNOTE-826 data are inputted into E339:E341. For costs these include non-treatment costs in the PD1 state and all costs in the PD2 state, PD1 treatment costs are dealt with by the model already. These have been calculated within the model itself by starting all patients in the PD1 state and recording the total discounted QALYs for 100% pembrolizumab + CT, 100% CT, and 100% no treatment respectively*. Half cycle correction was turned off and calibration factors were set to 1. These have been used to allow for adjustments to the total QALYs and costs within the model by comparing the trial subsequent treatment proportions with those being modelled. • A new sheet, "Trade-off calculations" has been added, within the sheet: o The first (left) table is the trial observed subsequent treatment proportions (Table) o The second (left-middle) table pulls through the model input subsequent treatments o The final 2 tables (right-middle, right) works out the difference between the observed and modelled subsequent treatments. These % differences are used alongside the subsequent treatment QALY and cost values (Controls!E339:F341) to create a weighted QALY/cost loss/gain trade off for each arm. • These arm specific QALY loss/gains are then applied to patients on entry to the PD1 state in the traces (Trace (1)!DM and GM, and Trace (2)!DB and GB) • These arm specific cost loss/gains are then applied to patients on entry to the PD1 state in the traces (Trace (1)!FI and ID, and Trace (2)!EX and HS) *functionally the no treatment proportion needs to be <100% to avoid a DIV/0 error, so a value of 0.99999 was used Scenarios have been added to the scenario analysis sheet that allow the EAG or NICE to recalculate the needed QALY and cost inputs if assumptions regarding KEYNOTE-826

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efficacy differ from the company base-case. The QALYs and costs can be found in 'Scenario Analyses'!AD:AD and 'Scenario Analyses'!S:S respectively.

While the disconnect between observed and modelled OS suggest that KN-826 is not a perfect method for predicting KN-A18 PPS, this approach has been taken as the most suitable and pragmatic solution to allow for the exploration of subsequent treatment mix when using KEYNOTE-A18 data. Importantly, it is unclear in what direction any mismatch in population affects the cost-effectiveness of pembrolizumab when used in the downstream setting as time on treatment and outcomes are both unknown if they are different from what was observed in the prior CRT patients in KEYNOTE-826.

Within the base case presented in this response, the *subsequent treatment trade-off* has been implemented as default, with scenarios exploring its removal and using the trial specific subsequent treatment-mix.

Table 7 and Table 8 below detail the base case subsequent treatment inputs and those observed in the trial.

Table 7: Observed second line treatment in KEYNOTE-A18

Observed	Pembrolizumab + CCRT	CCRT
Immunotherapy + CT	[redacted]	[redacted]
CT	[redacted]	[redacted]
No treatment	[redacted]	[redacted]

Values in brackets indicate the *% of those that get treatment* that get immunotherapy, this is the value inputted into 'Controls'!I238:K238

Table 8: Modelled second line treatment in KEYNOTE-A18

	Pembrolizumab + CCRT (early progressor)	Pembrolizumab + CCRT (early progressor)	CCRT
Immunotherapy + CT	0.0%	51.2% (64%)	51.2% (64%)
CT	80.0%	28.8%	28.8%
No treatment	20.0%	20.0%	20.0%

Values in brackets indicate the *% of those that get treatment* that get immunotherapy, this is the value inputted into 'Controls'!I238:K238.

5 **Pembrolizumab rechallenge**

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	In the DG, the committee indicated an interest in a scenario that explored a reduced efficacy for pembrolizumab rechallenge. MSD note that few patients are modelled to receive rechallenge in the model; only patients who have 2.5 years of PFS and subsequently have a relapse are eligible and only 51.2% of this late relapsing cohort are modelled to receive rechallenge. We have provided some arbitrary rechallenge scenarios but there are substantive issues with their interpretability:- • It is important to state that there is no robust evidence on the cost-effectiveness of retreatment with pembrolizumab in patients with cervical cancer on which to base this scenario. • If outcomes on retreatment were worse than in I/O naïve patients, this suggests that the time on treatment, and therefore the treatment cost would be lower as well. It does not automatically follow that reduced efficacy means reduced cost-effectiveness. • It is biologically plausible that the opposite effect might be true. Patients who have relapsed after >2.5 years progression free could have a) a cancer that has sensitivity to immunotherapy (possibly indicated by long PFS), b) a disease that is less aggressive than average or c) both. It is plausible that re-use of immunotherapy might actually be more effective in this group than in the I/O naïve patients observed in KEYNOTE-826. • Retreatment with pembrolizumab is commissioned on the NHS in other solid tumour settings following a prolonged period of PFS e.g. in lung cancer and melanoma and no adjustment to the cost-effectiveness of retreatment was made in the relevant NICE technology appraisals. The company is not aware of any evidence that cervical cancer should be considered differently to any other solid tumour settings in this regard. **<u>Methodology of reduced pembrolizumab methodology implementation:</u>** • New switching in 'Controls'!E344 that allows adjustment on immunotherapy rechallenge

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	• Controls!E346 is user input. The value is used to adjust the incremental benefit between pembrolizumab + chemotherapy vs chemotherapy in the *subsequent treatment trade-off* methodology. E.g. a value of 0.5 would reduce the incremental QALYs and costs of pembrolizumab + chemotherapy vs chemotherapy used within the *subsequent treatment trade-off* by a half, a value of 0 would mean pembrolizumab would add no benefit at all on top of chemotherapy and only treatment cost. • The switch and adjustment factor are fed into a function in the 'trade-off calculations'!R9. • Under this method only efficacy and cost related to the *subsequent treatment trade-off* method are altered with no change to time on pembrolizumab, unless manually changed in the normal place in the model. But it would stand to reason that reduced efficacy should also relate to reduced time on treatment, therefore potentially reducing both acquisition and administration costs. It is therefore likely that any scenario with reduced efficacy for rechallenge biases the ICER against pembrolizumab. Scenario exploring reduced pembrolizumab efficacy, a reduction in the % of progressors getting rechallenge and the complete removal of rechallenge have been presented in Table 11.

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6

Results

Focussing on the use of KEYNOTE-A18 PPS data, the updated company base-case is defined as:

- A 3-state transition model.
- KEYNOTE-A18 PPS data informing transition in the PD1 state, with log-logistic parametric curves across both arms being the preferred distribution.
- No waning of PPS in the base case.
- Subsequent treatments are modelled as per the original submission, based on clinical input, with a new adjustment being made to account for differences in expected QALY gain and costs between the modelled and observed subsequent treatment mixes. Trial observed subsequent treatment scenarios have been run, as have scenarios excluding the subsequent treatment adjustment.
- Immunotherapy rechallenge is still assumed after 2.5 years in the base case but scenarios removing IO rechallenge or reducing its efficacy have been presented.

Base case deterministic results

Table 9 shows the cost-effectiveness results for pembrolizumab + CCRT versus CCRT using the list prices of all treatments and the CAA price for pembrolizumab. The results show that pembrolizumab + CCRT is estimated to offer greater health benefits compared to CCRT alone, with an additional 1.77 LYs and 1.12 QALYs gained per patient lifetime. Treatment with pembrolizumab + CCRT is associated with incremental costs of [redacted], resulting in an ICER of £[redacted] per QALY gained.

Table 9: Deterministic sensitivity analysis results (CAA price)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER
CRT	[redacted]	10.69	[redacted]	-	-	-
Pembrolizumab + CRT	[redacted]	12.46	[redacted]	[redacted]	1.12	[redacted]

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

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Base-case probabilistic results

Key parameters were varied within appropriate probability distributions to examine the effect of joint uncertainty on the model's results, the PSA was run for 1,000 iterations. The incremental costs and QALYs were similar to the deterministic base-case.

Table 10: Probabilistic sensitivity analysis results (CAA price)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER
CCRT	[redacted]	10.67	[redacted]	-	-	-
Pembrolizumab + CCRT	[redacted]	12.49	[redacted]	[redacted]	1.15	[redacted]

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

Scenario analysis

Results from the scenario analysis can be found in Table 11. For clarity, all scenarios are run on the 3-state transition model using KEYNOTE-A18 PPS data.

Table 11: Results of scenario analyses explored in the cost effectiveness analysis

Scenario	Base case value	Rationale	ICER	% change
Base-case			[redacted]	
Company base-case from ACM1. 4-state transition model using KN-826 and calibration	3-state transition, using KN-A18 PPS, no calibration	-	[redacted]	-15.8%
A18 PPS, loglogistic, trial specific subsequent treatment	KN-A18 PPS = Log-logistic, original company submission subsequent treatment with subsequent treatment trade-off	Explore alternative subsequent treatment scenarios	[redacted]	-7.2%
A18 PPS loglogistic curve and original company submission subsequent treatment without subsequent treatment trade-off	KN-A18 PPS = Log-logistic, original company submission subsequent treatment with subsequent treatment trade-off	Explore alternative subsequent treatment scenarios	[redacted]	-17.4%

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	A18 PPS exponential curve and original company submission subsequent treatment with subsequent treatment trade-off	KN-A18 PPS = Log-logistic, original company submission subsequent treatment with subsequent treatment trade-off	Explore different PPS selections	[redacted]	-0.9%
	A18 PPS 1k hazard curve and original company submission subsequent treatment with subsequent treatment trade-off	KN-A18 PPS = Log-logistic, original company submission subsequent treatment with subsequent treatment trade-off	Explore different PPS selections	[redacted]	-0.9%
	Waning applied to KN-A18 PPS	Waning not applied to PPS	Explore effect of waning in PPS	[redacted]	<1%
	Applies a decrement factor of 0.7 to the efficacy of pembrolizumab rechallenge	No rechallenge efficacy decrement	Explore rechallenge assumptions in line with the DG	[redacted]	4.1%
	Applies a decrement factor of 0.8 to the efficacy of pembrolizumab rechallenge	No rechallenge efficacy decrement	Explore rechallenge assumptions in line with the DG	[redacted]	2.7%
	Applies a decrement factor of 0.9 to the efficacy of pembrolizumab rechallenge	No rechallenge efficacy decrement	Explore rechallenge assumptions in line with the DG	[redacted]	1.3%
	Half as many late progressors get pembrolizumab rechallenge (25% of progressors after 2.5 years get immunotherapy)	51% of progressors after 2.5 years get immunotherapy rechallenge	Explore rechallenge assumptions in line with the DG	[redacted]	2.0%
	Remove all rechallenge (0% of progressors after 2.5 years get immunotherapy)	51% of progressors after 2.5 years get immunotherapy rechallenge	Explore rechallenge assumptions in line with the DG	[redacted]	4.2%

Discussion

The company has tried to respond as fully as possible to the committee's requests for additional analyses and would like to make the following overarching comments:-

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	• The mixture cure models, while uncertain and able to be substantially influenced by two events in the very tail of the curve, seem to provide validation that the implied difference in cure proportions from the company's model are reasonable. This is further supported by additional data from the trial showing that difference in the proportion of patients still in a state of complete response at maximal follow up is similar to the estimated cure proportions in the economic model. The company feels these data are more clinically relevant than MCMs • The incorporation of A18 PPS data has increased the ICER somewhat versus the calibrated the previous 4STM base case. This may be because of slightly greater underestimation of OS in the pembrolizumab arm. However, the new base case offers a much improved fit over the uncalibrated 4STM without the need for calibration. • There is no evidence that rechallenging patients who have 2.5 years of PFS would be more or less cost-effective than were they I/O naïve. These patients are fundamentally prognostically different to those in the KEYNOTE-826 trial. There is substantial precedent for NICE committees to agree base case assumptions with no reduced efficacy for rechallenge and it is routinely commissioned by NHSE in other solid tumour settings. Few patients are modelled to receive rechallenge and the effect on the ICER appears to be small. • We would ask the committee to consider the strength of the KEYNOTE-A18 study and the large PFS and OS benefit, the relatively small variance in ICERs in plausible scenario analyses, the lower ICER of the 4STM and the health inequalities benefits of introducing pembrolizumab in this setting when determining their threshold ICER.
7	**<u>Additional minor model edits</u>**

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	• Above and beyond what has been detailed in sections above, a minor edit was made to the calculation of discounting, such that the factor is applied on a yearly basis i.e. 0% in the first year, 3.5% in the second year as opposed to having a continuous discount factor. • While the results presented in this response include the pembrolizumab net price, the submitted model does not include these and must be entered in both the "Drug Costs" and "Subsequent Tx Costs" sheets. Values in 'Controls'!E339:F341 will also need to be updated to reflect inputted discounts for pembrolizumab and bevacizumab.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [redacted]' in turquoise, and all information submitted as '[redacted]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- 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 draft guidance document, please submit these separately.

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1.1 Appendix

1.1.1 Mixture cure model outputs

1.1.1.1 Base-case PFS MCM

Figure 3: MCM curve fits for KN-A18 PFS using SMR adjustment, base-case (left pembrolizumab + CCRT, right CCRT)

[redacted]

Table 12: PFS using SMR MCM AIC statistic, by arm

AIC	Pembrolizumab + CCRT	CCRT
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Figure 4: MCM curve fits for KN-A18 PFS without SMR adjustment, base-case (left pembrolizumab + CCRT, right CCRT)

[redacted]

Table 13: PFS without SMR MCM AIC statistic, by arm

AIC	Pembrolizumab + CCRT	CCRT
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]

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Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

1.1.1.2 Sensitivity PFS MCM

Figure 5: MCM curve fits for KN-A18 PFS using SMR adjustment, sensitivity analysis (left pembrolizumab + CCRT, right CCRT)

[redacted]

Table 14: Sensitivity analysis PFS using SMR MCM AIC statistic, by arm

AIC	Pembrolizumab + CCRT	CCRT
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Figure 6: MCM curve fits for KN-A18 PFS using SMR adjustment, sensitivity analysis (left pembrolizumab + CCRT, right CCRT)

[redacted]

Table 15: Sensitivity analysis PFS without SMR MCM AIC statistic, by arm

AIC	Pembrolizumab + CCRT	CCRT
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

1.1.2 TTP to PPS correlation

[redacted] **Figure 7: Scatter-plots of TTP vs PPS1P2D, by arm**

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1.1.3 KEYNOTE-A18 PPS survival analysis

Figure 8: Kaplan–Meier curve and Schoenfeld residual KEYNOTE-A18 PPS – pembrolizumab + CCRT versus CCRT

[redacted]**Figure 9: Parametric fitting and extrapolation of long-term KEYNOTE-A18 PPS - Pembrolizumab + CCRT**

[redacted]**Figure 10: Smoothed hazard plot and standard parametric model hazards - PPS Pembrolizumab + CCRT**

[redacted]**Table 16: AIC/BIC of parametric fits, PPS, pembrolizumab + CCRT**

Model	[redacted]	[redacted]
Exponential		
Weibull		
Log-normal		
Log-logistic		
Gompertz		
Gamma		
Generalized Gamma		

[redacted]**Figure 11: Spline fits, PPS, pembrolizumab + CCRT**

[redacted]**Figure 12: Pembrolizumab + CCRT spline hazard fits - PPS**

[redacted]**Table 17: AIC/BIC of spline fits, PPS, pembrolizumab + CCRT**

AIC	knots=1	knots=2	knots=3	BIC	knots=1	knots=2	knots=3
hazard	[redacted]	[redacted]	[redacted]	hazard	[redacted]	[redacted]	[redacted]
odds	[redacted]	[redacted]	[redacted]	odds	[redacted]	[redacted]	[redacted]
normal	[redacted]	[redacted]	[redacted]	normal	[redacted]	[redacted]	[redacted]

[redacted]**Figure 13: Spline fits, PPS, CCRT**

[redacted]**Figure 14: Parametric fitting and extrapolation of long-term KEYNOTE-A18 PPS - CCRT**

[redacted]**Figure 15: Smoothed hazard plot and standard parametric model hazards - PPS CCRT**

[redacted]**Table 18: AIC/BIC of parametric fits, PPS, pembrolizumab + CCRT**

Model	AIC	BIC
Exponential		
Weibull		
Log-normal		
Log-logistic		
Gompertz		
Gamma		
Generalized Gamma		

Figure 16: CCRT spline hazard fits - PPS

[redacted]**Table 19: AIC/BIC of spline fits, PPS, CCRT**

AIC	knots=1	knots=2	knots=3	BIC	knots=1	knots=2	knots=3
hazard	[redacted]	[redacted]	[redacted]	hazard	[redacted]	[redacted]	[redacted]

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odds	[redacted]	[redacted]	[redacted]	odds	[redacted]	[redacted]	[redacted]
normal	[redacted]	[redacted]	[redacted]	normal	[redacted]	[redacted]	[redacted]

References

1. NICE. TA939: Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer. 'Comments on the Appraisal Consultation Document from MSD', Figure 6 2023 [Available from: www.nice.org.uk/guidance/ta939/documents/committee-papers-3.
2. Nice DSU. NICE DSU TSD 21: Flexible Methods for Survival Analysis 2020 [Available from: https://www.sheffield.ac.uk/nice-dsu/tsds/full-list.
3. Amdahl J. R package ‘flexsurvcure’, Flexible parametric mixture and non-mixture cure models for time-to-event data. 2025 [Available from: https://github.com/jrdnmdhl/flexsurvcure.
4. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data 2011 [Available from: http://www.nicedsu.org.uk.

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	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):	Clinical Expert

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	MSD: £1000 speaker fee on endometrial cancer BGCS 2025
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Alexandra Taylor

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The addition of pembrolizumab to chemoradiation for patients with locally advanced cervical cancer is an important advance that increases the likelihood of curing tumours that currently have a high risk of recurrence which is then incurable at relapse. The subset of patients with FIGO 2014

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	Stage 3 (extending to pelvic sidewall or lower vagina) and 4A is a small cohort in the UK and easily identified. We do now use FIGO 2018 Staging but always assess the local extent of disease (T staging in TNM staging).
2	In terms of radiotherapy doses in KEYNOTE A18 in comparison to UK practice, although a lower dose was allowed (primarily for the Japan cohort) the median doses delivered in the trial were comparable. It should be noted that stage T3 and T4A tumours are typically much larger and extensive than median volumes, and therefore these tumours have a higher likelihood of being inadequately treated with brachytherapy and failing to receive the target doses, which is why the addition of immunotherapy is so important for these patients.
3	The proportion of patients who would be rechallenged with immunotherapy in the event of relapse is likely to be very low – the vast majority of relapses of cervical cancer occur within 2-3 years of completing chemoradiation and also reasons for discontinuation will include IO-toxicity.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Addendum: EAG comments on the company's response to the NICE draft guidance

Produced by	Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield
Authors	Mon Mon Yee, Research Associate, SCHARR, Division of Population Health, University of Sheffield, UK
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Date completed	3rd March 2026

1. Introduction

In February 2026, NICE issued a negative draft recommendation for pembrolizumab with chemoradiotherapy (CCRT) (external beam radiation therapy [EBRT] followed by brachytherapy) for untreated International Federation of Gynecology and Obstetrics (FIGO) 2014 stage 3 to 4A locally advanced cervical cancer (LACC) in adults.[1] Section 1 of the draft guidance (DG) states that there are uncertainties in the economic model and its assumptions and consequently it is not possible to determine the most likely cost-effectiveness estimate for pembrolizumab plus CCRT. Section 3.16 of the DG states that the appraisal committee thought that the incremental cost-effectiveness ratios (ICERs) were highly uncertain due to: the cure assumptions applied in the model; the need for calibration to force modelled overall survival (OS) to fit the observed OS from KEYNOTE-A18[2] and assumptions regarding pembrolizumab retreatment. Section 3.17 of the DG states that the appraisal committee requested the following additional analyses to reduce uncertainty:

(1) A mixture-cure model (MCM) based on observed progression-free survival (PFS) and OS in KEYNOTE-A18.[2] The DG also states that using direct data from KEYNOTE-A18 rather than from KEYNOTE-826[3] for the pembrolizumab progressed disease states may help to reduce uncertainty.

(2) Sensitivity analyses exploring different rates of retreatment, including no retreatment, and reduced efficacy with pembrolizumab when used as retreatment.

Section 3.17 of the DG[1] also states that the appraisal committee's preferred assumptions related to these analyses were that a cure assumption was plausible and that treatment effect waning should be applied for pembrolizumab (the EAG notes that it is not fully clear whether the latter assumption is referring to the use of pembrolizumab when used as first-line therapy for untreated LACC, as subsequent therapy for progressed disease, or both).

In February 2026, the company submitted its response to the NICE DG. The company's DG response includes a written response form[4] and an updated executable economic model which includes an updated base case analysis. The company's DG response form includes:

(1) Details of the methods and results of MCMs fitted to PFS data from KEYNOTE-A18.[2] These MCMs have been conducted to provide supportive evidence for the cure assumptions applied in the company's economic model. The MCM survivor functions have not been applied in the company's economic model and the company's modelled cure assumptions remain unchanged.

(2) Details of an updated base case 3-state economic model which is informed by parametric survival models fitted to data on post-progression survival (PPS) from KEYNOTE-A18[2] to characterise outcomes for patients with disease progression without the need for calibration. This differs from the company's previous 4-state model which used parametric survival models fitted to data from KEYNOTE-826[3] and required calibration to force modelled OS to fit observed OS in KEYNOTE-

A18. The company's updated base model also includes the adjustment of quality-adjusted life years (QALYs) and costs of subsequent treatments received post-progression in an attempt to account for differences between the experience of KEYNOTE-A18 and current UK treatment pathways. The company's DG response reports the results of its updated base case model together with 11 additional scenario analyses which explore the use of: external data from KEYNOTE-826 (including calibration of PPS probabilities – i.e., the company's previous 4-state base case model at Appraisal Committee Meeting 1 [ACM1]); alternative assumptions regarding the distributions of subsequent treatments; alternative parametric survival models fitted to PPS data from KEYNOTE-A18; the inclusion of treatment effect waning assumptions applied to the model fitted to pembrolizumab plus chemotherapy PPS in KEYNOTE-A18; alternative assumptions of reduced effectiveness of pembrolizumab rechallenge and alternative proportions of patients receiving pembrolizumab rechallenge.

The company has not amended its Patient Access Scheme (PAS) discount for pembrolizumab; details of this discount can be found in CS Appendix J.[5]

2. Summary of additional analyses provided in the company's DG response

2.1 Mixture-cure modelling

The company fitted MCMs to the PFS data from KEYNOTE-A18;[2] MCMs were not fitted to the OS data due to immaturity and the absence of a substantial visible plateau in the Kaplan-Meier OS functions. The company fitted exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma MCMs. MCMs assume that the population comprises two latent groups: a cured group and an uncured patients. Cured patients are assumed to be cured from baseline (time zero) and their survival follows age/sex-matched general population hazards, while uncured patients have an excess risk of progression and/or death and their survival is modelled using a selected parametric survival distribution. The cure fraction is driven by the predicted convergence of modelled hazards to general population hazards. The company fitted two main sets of MCMs using general population hazards based on life tables for England and Wales 2021-2023,[6] with and without adjustment using a standardised mortality ratio (SMR) of 1.19 (note – this SMR was applied in the company's previous base case model at ACM1[7]). For each main MSM analysis set, sensitivity analyses were conducted whereby all events occurring after Week 200 were considered as censoring events across both arms. These late events (N=2) only occurred in the pembrolizumab plus CCRT group, therefore these sensitivity analyses do not affect the MCMs fitted to data for the CCRT group. The MCMs were fitted using the *flexsurvcure* function of the *flexsurv* package in R.

Plots of observed and MCM-predicted PFS for pembrolizumab plus CCRT and CCRT alone across the four sets of analyses are shown in Figure 1 to Figure 4. Akaike Information Criterion (AIC) statistics

for the fitted MCMs under each of the four scenarios are summarised in Table 1; Bayesian Information Criterion (BIC) statistics are not reported in the company's DG response.[4] Estimated cure fractions for all MCMs under each of the four scenarios are summarised in Table 2.

Figure 1: Observed and MCM-predicted PFS, pembrolizumab plus CCRT and CCRT alone, including SMR-adjustment

Figure 2: Observed and MCM-predicted PFS, pembrolizumab plus CCRT and CCRT alone, excluding SMR-adjustment

Figure 3: Observed and MCM-predicted PFS, pembrolizumab plus CCRT and CCRT alone, including SMR-adjustment, events censored after Week 200

Figure 4: Observed and MCM-predicted PFS, pembrolizumab plus CCRT and CCRT alone, excluding SMR-adjustment, events censored after Week 200

Table 1: AIC statistics for company's MCMs, KEYNOTE-A18, pembrolizumab plus CCRT and CCRT alone

MCM	1. Background mortality including SMR=1.19		2. Background mortality excluding SMR adjustment		3. Sensitivity analysis censoring events after Week 200, including SMR=1.19		4. Sensitivity analysis censoring events after Week 200, excluding SMR adjustment	
	Pembro+ CCRT	CCRT	Pembro+ CCRT	CCRT	Pembro+ CCRT	CCRT	Pembro+ CCRT	CCRT
Exponential	[redacted]							
Weibull	[redacted]							
Gompertz	[redacted]							
Log-normal	[redacted]							
Log-logistic	[redacted]							
Gamma	[redacted]							
Gen. gamma	[redacted]							

MCM - mixture-cure model; Pembro - pembrolizumab; CCRT - concurrent chemoradiotherapy; SMR - standardised mortality ratio; Gen. - generalised
Best-fitting model shown in bold

Table 2: Cure fractions obtained from company's MCMs, KEYNOTE-A18, pembrolizumab plus CCRT and CCRT alone

MCM	1. Background mortality including SMR=1.19			2. Background mortality excluding SMR adjustment			3. Sensitivity analysis censoring events after Week 200, including SMR=1.19			4. Sensitivity analysis censoring events after Week 200, excluding SMR adjustment		
	Pembro+ CCRT	CCRT	Difference	Pembro+ CCRT	CCRT	Difference	Pembro+ CCRT	CCRT	Difference	Pembro+ CCRT	CCRT	Difference
Exponential	[redacted]											
Weibull	[redacted]											
Gompertz	[redacted]											
Log-normal	[redacted]											
Log-logistic	[redacted]											
Gamma	[redacted]											
Gen. gamma	[redacted]											

MCM - mixture-cure model; Pembro - pembrolizumab; CCRT - concurrent chemoradiotherapy; SMR - standardised mortality ratio; Gen. - generalised

Across the two main sets of MCM analyses, the company ruled out the generalised gamma and Gompertz MCMs because they suggested implausible cure fractions in the pembrolizumab plus CCRT group. The inclusion of SMR adjustment had only a minor impact on the estimated cure fractions for the remaining MCMs:

- When the SMR of 1.19 was included in the analysis, the cure fractions ranged from [redacted] to [redacted] for pembrolizumab plus CCRT and from [redacted] to [redacted] for CCRT alone. When both arms were modelled with the same parametric distribution, the differences in cure fractions ranged from [redacted] to [redacted].
- When the SMR was excluded from the analysis, the cure fractions ranged from [redacted] to [redacted] for pembrolizumab plus CCRT and from [redacted] to [redacted] for CCRT alone. When both arms were modelled with the same parametric distribution, the differences in cure fractions ranged from [redacted] to [redacted].
- The scenario analyses indicate that the fitted MCMs are sensitive to the small number of late events in the pembrolizumab plus CCRT group, with these analyses suggesting comparatively higher cure fractions when these events are censored.

For comparison, the company states that its previous base case model at ACM1 suggested cure proportions of 53.0% for pembrolizumab plus CCRT and 44.0% for CCRT alone (difference = 9.0%). These cure proportions were derived as 95% of the modelled probability of being alive and progression-free at 7 years (i.e., 95% of the PF health state occupancy at 7 years). The company concludes that its MCM analysis supports both the assumption of cure and the estimated magnitude of the difference in the cure proportions generated by the company's base case model at ACM1.

EAG comments on the company's MCM analysis

The EAG notes the following points regarding the company's MCM analyses:

- The EAG considers that the company's MCM analyses for PFS are useful as they provide further evidence to support the assumption of a cure for pembrolizumab plus CCRT and CCRT alone in the target population.
- The EAG believes that whilst it may have been possible to conduct similar analyses for OS, the relative immaturity of the data would likely have led to highly uncertain cure fractions. Longer-term data collection beyond the Final Analysis data cut-off of KEYNOTE-A18[2] may be required to obtain reliable estimates of the cure fractions for OS in each treatment group; however, the EAG understands that no further data-cuts of KEYNOTE-A18 are anticipated.
- The EAG notes the company's claim that, in this disease setting, there is a substantial structural link between PFS and OS, implying that the estimated PFS cure fraction could be informative for OS if more mature data showed a clear, sustained plateau in OS. However, no specific supporting evidence was provided. The EAG's clinical experts advised that patients who remain

progression-free for a sufficiently long period may be considered cured. On this basis, the EAG considers the company's claim to be broadly reasonable.

- The results of the MCM sensitivity analyses are broadly consistent with the main analyses. However, the EAG notes that the higher cure fractions for PFS obtained from these analyses should be interpreted with caution because these analyses ignore two events occurring in the tail of the pembrolizumab plus CCRT group (one progression event and one death). Again, longer-term follow-up would be required to obtain more reliable estimates of the cure fractions for PFS.
- The company's estimate of the cured proportion from the economic model is calculated as 95% of those patients who remain alive and progression-free at 7 years (53% for pembrolizumab plus CCRT and 44% for CCRT alone). This approach may not be meaningful - after 7 years in the company's model, the application of the cure assumptions means that the risks of transitioning out of the PF state are reduced by 95%. This is not equivalent to multiplying the proportion of patients residing in the PF state at 7 years by 95%.
- The accompanying documentation for the *flexsurvcure* function (https://github.com/jrdnmdhl/flexsurvcure) notes that whilst the Gompertz and generalised gamma models are supported, they may not be reliable due to issues with convergence and numerical instability. This may explain the implausible cure fractions estimated for these two MCMs. The EAG considers it reasonable that the company ruled out these models.

2.1 Company's updated base case model using PPS data from KEYNOTE-A18

2.1.1 Company's updated model – structure

As part of its DG response,[4] the company adapted its economic model to use PPS data from KEYNOTE-A18,[2] rather than relying on parametric survival models fitted to external data from KEYNOTE-826.[3] The company's updated model uses a simplified structure based on three health states: (i) Progression-free (PF); (ii) Progressed disease (PD) and (iii) Dead. This differs from the company's previous base case model at ACM1 which included four health states, with two separate states for patients who have experienced disease progression (Progressed disease 1 [PD1] and Progressed disease 2 [PD2]).[7] The company's DG response states that this alternative model structure was adopted to preserve patient numbers in the PPS data from KEYNOTE-A18. As with its previous 4-state model, the company's updated 3-state model uses a semi-Markov state transition approach.

2.1.2 Company's updated model – transition probabilities

The company fitted parametric survival models to the PPS data for each randomised arm of KEYNOTE-A18.[2] The company's analysis included standard parametric survival models, including the exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma distributions, as well as

restricted cubic spline (RCS) models with 1, 2 or 3 knots, each fitted on the hazard, odds and normal scales.

Hazard plots for the standard parametric models fitted to PPS data for each randomised treatment group in KEYNOTE-A18[2] are shown in Figure 5 and Figure 6. Comparisons of observed and predicted OS for the standard parametric models for each randomised treatment group are shown in Figure 7 and Figure 8. AIC and BIC statistics are shown in Table 3. Hazard plots, AIC and BIC statistics and survival curves for the spline models are provided in the company's DG response;[4] for brevity, these have not been reproduced here.

The company selected the log-logistic model to represent PPS in both treatment groups in its updated base case model; the selection of this model was based on visual fit and AIC statistics across both arms. The company's DG response[4] states that due to the simple shape of the hazard functions, the use of RCS models did not improve model fit.

Figure 5: Empircal (smoothed) and modelled hazard functions for PPS, KEYNOTE-A18, pembrolizumab plus CCRT, standard parametric models

Figure 6: Empircal (smoothed) and modelled hazard functions for PPS, KEYNOTE-A18, CCRT alone, standard parametric models

Figure 7: Observed and model-predicted PPS, KEYNOTE-A18, pembrolizumab plus CCRT, standard parametric models

Figure 8: Observed and model-predicted PPS, KEYNOTE-A18, CCRT alone, standard parametric models

Table 3: AIC and BIC statistics, PPS, KEYNOTE-A18, both treatment groups

Model	Pembrolizumab plus CCRT		CCRT	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; CCRT - concurrent chemoradiotherapy; Gen. - generalised gamma

2.1.3 Company's updated model – implementation approach and subsequent treatment distributions and QALY and cost adjustments

Within the company's updated model, the PD2 state was functionally removed by forcing the hazards of transitioning into this health state to zero. Treatment effect waning assumptions for pembrolizumab when used as a subsequent treatment were excluded from the base case analysis, but were tested in sensitivity analyses.

The economic model was amended to use post-progression transition probabilities (PD1 to PD1 and PD1 to Dead) informed by the survival models fitted to the PPS data from KEYNOTE-A18.[2] At the time of disease progression in the model (i.e., on entry into the PD1 state), all patients are assumed to incur one-off drug acquisition and administration costs associated with first subsequent treatments. These costs were calculated as the product of the monthly cost, the mean treatment duration and the proportion of patients receiving each treatment component. In the company's updated base case analysis, the mix of first subsequent treatments was based on the distribution applied in the company's (post-clarification) 4-state model[7]; the observed subsequent treatment mix in KEYNOTE-A18 was explored in scenario analyses. Health state management costs for PD1 were applied in each model cycle, conditional on modelled PD health state occupancy. Table 4 summaries the proportions of patients receiving each first subsequent treatment in KEYNOTE-A18 and in the company's previous 4-state model.

Table 4: Subsequent treatment distributions in KEYNOTE-A18 and the company's previous 4-state model

Treatment group	Component	Pembrolizumab plus CCRT (early progressors)	Pembrolizumab plus CCRT (late progressors)	CCRT alone
Based on KEYNOTE-A18				
No treatment	-	[redacted]	[redacted]	[redacted]
Active treatment*	Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]
	Chemotherapy alone	[redacted]	[redacted]	[redacted]
Based on the company's 4-state model (intended to reflect UK treatment pathways)				
No treatment	-	20.00%	20.00%	20.00%
Active treatment*	Pembrolizumab plus chemotherapy	0.00%	51.20%	51.20%
	Chemotherapy alone	80.00%	28.80%	28.80%

CCRT - concurrent chemoradiotherapy
**Adjusted based on the proportion of patients receiving active treatment*

As summarised in Table 4, the proportions of patients receiving active subsequent treatment in KEYNOTE-A18[2] were generally lower than what would be expected in UK clinical practice (as reflected in the treatment pathways assumed in the company's previous 4-state model[7]). Therefore, the company included an adjustment to account for the higher expected use of active subsequent treatment (including pembrolizumab rechallenge) in terms of health outcomes and costs. This was done by "bolting on" additional QALY and cost payoffs to the expected outcomes in the 3-state model. The additional payoffs were estimated using an approach referred to by the company as the "subsequent treatment trade-off" method, which operates as follows:

Step 1: Calculating the net discounted QALY and cost payoffs using the company's 4-state model

- Based on the company's 4-state model,[7] the model was re-run with all patients starting in the PD1 state and receiving one of three subsequent treatment options: (i) pembrolizumab plus chemotherapy; (ii) chemotherapy alone or (iii) no treatment. No half-cycle correction was applied, calibration was removed and treatment waning for pembrolizumab was assumed. Total discounted QALYs and costs were then estimated for each of the subsequent treatment options. For the discounted costs, only non-treatment costs in the PD1 state and all costs in the PD2 state were included. Treatment costs for the PD1 state of the company's updated 3-state model did not require adjustment because the subsequent treatment mix for the PD1 state was already based on the distribution applied in the company's post-clarification 4-state model.[7]
- The differences in the proportions of patients receiving each subsequent treatment option between KEYNOTE-A18[2] and the company's 4-state model were calculated for both treatment groups (Table 5). For example, in the company's 4-state model, 51.20% of patients in the CCRT arm receive pembrolizumab plus chemotherapy as a subsequent treatment following disease progression, whereas in KEYNOTE-A18 this proportion was much lower at [redacted]. Therefore, an additional [redacted] of patients in the CCRT group would be expected to receive

pembrolizumab plus chemotherapy as subsequent treatment. The same calculations were applied to the other subsequent treatment options in both the pembrolizumab plus CCRT and CCRT alone groups.

- The net discounted QALY and cost payoffs associated with the additional/lower use of the three subsequent treatment options were estimated for both treatment groups (see Table 5).

Step 2: Applying the net discounted QALY and cost payoffs in the company's 3-state model

- The net QALY and cost payoffs were applied to the new progressors entering the PD1 state in each model cycle in the new 3-state model. The total expected QALY and cost payoffs were then calculated over the lifetime horizon. These were subsequently added to the total QALYs and costs accrued in the PD1 state of the 3-state model.

Table 5: QALY and cost payoffs for first subsequent treatments and differences in subsequent treatment distributions between the company's previous 4-state model and KEYNOTE-A18

Subsequent treatment option	Payoffs when 100% of patients receive each treatment option (calculated using the company's 4-state model)		Difference in the subsequent treatment distributions between the company's 4-state model and KEYNOTE-A18		
	QALYs (discounted)	Costs (discounted)	Pembrolizumab plus CCRT (early progressors)	Pembrolizumab plus CCRT (late progressors)	CCRT alone
Pembrolizumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net QALY payoffs (discounted)*			[redacted]	[redacted]	[redacted]
Net cost payoffs (discounted)*			[redacted]	[redacted]	[redacted]

QALY - quality-adjusted life year; CCRT - concurrent chemoradiotherapy
** Calculated as the sumproduct of the differences in subsequent treatment distribution between KEYNOTE-A18 and the company's previous 4-state model and the absolute QALYs and costs for each subsequent treatment option*

2.1.4 Company's updated model – results

The company's updated base case analysis includes the following features:

- Use of the simplified 3-state model structure
- Use of log-logistic models fitted to PPS data from KEYNOTE-A18[2]
- Exclusion of treatment effect waning for pembrolizumab as subsequent treatment
- Use of QALY and cost payoffs from the trade-off calculations.

The results of the company's updated base case analysis and scenario analyses are shown in Table 6 and Table 7, respectively. The probabilistic version of the company's updated base case model suggests that the ICER for pembrolizumab plus CCRT versus CCRT alone is expected to be [redacted] per QALY gained. The deterministic version of the updated model suggests a slightly lower ICER of [redacted] per

QALY gained. These ICERs are higher than the company's previous base case analysis using the 4-state model ([redacted] per QALY gained; see EAG report,[8] Additional Analysis 4). Across all scenario analyses, the ICER ranges from [redacted] to [redacted] per QALY gained.

Table 6: Company's updated 3-state base case model results following the DG

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Probabilistic							
Pembrolizumab plus CCRT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCRT alone	[redacted]	[redacted]	[redacted]	-	-	-	-
Deterministic							
Pembrolizumab plus CCRT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCRT alone	[redacted]	[redacted]	[redacted]	-	-	-	-

DG - draft guidance; LYG - life year gained; QALY - quality-adjusted life year; Inc. - incremental; ICER - incremental cost-effectiveness ratio; CCRT - concurrent chemoradiotherapy; ACM - Appraisal Committee Meeting

Table 7: Company's scenario analyses results following the DG

Scenario	Inc. QALYs	Inc. costs	ICER
Company's updated base case, deterministic	[redacted]	[redacted]	[redacted]
Company base-case from ACM1. 4-state model using KEYNOTE-826 data[3] including calibration for first 4 years*	[redacted]	[redacted]	[redacted]
KEYNOTE-A18 PPS, log-logistic, trial-specific subsequent treatment	[redacted]	[redacted]	[redacted]
KEYNOTE-A18 PPS log-logistic, original CS[9] subsequent treatment without subsequent treatment trade-off	[redacted]	[redacted]	[redacted]
KEYNOTE-A18 PPS exponential, original CS subsequent treatment with subsequent treatment trade-off	[redacted]	[redacted]	[redacted]
KEYNOTE-A18 PPS 1-knot hazard RCS, original CS subsequent treatment with subsequent treatment trade-off	[redacted]	[redacted]	[redacted]
Waning applied to KEYNOTE-A18 PPS	[redacted]	[redacted]	[redacted]
Decrement factor of 0.7 applied to pembrolizumab rechallenge effectiveness	[redacted]	[redacted]	[redacted]
Decrement factor of 0.8 applied to pembrolizumab rechallenge effectiveness	[redacted]	[redacted]	[redacted]
Decrement factor of 0.9 applied to pembrolizumab rechallenge effectiveness	[redacted]	[redacted]	[redacted]
Half as many late-progressors (32%) receive pembrolizumab rechallenge after 2.5 years	[redacted]	[redacted]	[redacted]
No pembrolizumab rechallenge	[redacted]	[redacted]	[redacted]

DG - draft guidance; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental; CS - company's submission; ACM - Appraisal Committee Meeting; PPS - post-progression survival
** This analysis was programmed based on the EAG's base case rather than the company's base case at ACM1. The EAG notes that the company applied the calibration factor to the TTP2 in CCRT group for only 2 years.The corrected ICER is [redacted] per QALY gained.*

EAG comments on the company's updated base case model and scenario analyses

The EAG notes the following points regarding the company's updated base case model:

- Figure 9 presents Kaplan-Meier plots of: (i) observed PPS in KEYNOTE-A18;[2] (ii) directly modelled estimates of PPS in KEYNOTE-A18 and (iii) modelled PPS based on the company's

previous 4-state model[7] which was informed by data from KEYNOTE-826[3] and adjusted to assume the KEYNOTE-A18 subsequent treatment distribution. The plot suggests that observed PPS was similar between the progressed patients in both randomised groups of KEYNOTE-A18 and that PPS was substantially higher for KEYNOTE-A18 patients compared with the PPS estimates derived from the company's previous 4-state model.[7]

- Basing the economic model on KEYNOTE-A18[2] is unlikely to fully reflect UK clinical practice due to the lower than expected proportion of patients in the CCRT alone group who received post-progression pembrolizumab ([redacted] versus 51.2% in KEYNOTE-A18 and the company's previous model, respectively) and the high proportion of patients in the pembrolizumab plus CCRT group who received no subsequent treatment ([redacted] versus 20% in KEYNOTE-A18 and the company's previous model, respectively). The EAG understands that the company's QALY and cost trade-off calculations represent an attempt to adjust for differences in the distributions of subsequent therapies between KEYNOTE-A18 and UK clinical practice. However, the EAG considers the company's QALY and cost adjustment approach to be somewhat inconsistent due to three reasons:
    (i) The estimates of PPS applied in the economic model trace and the resulting estimates of OS are calculated using analyses of PPS in KEYNOTE-A18, whereas the QALYs and costs associated with time spent in the PD state are partially driven by the company's original assumed subsequent treatment distribution and estimates of absolute QALYs and costs based on parametric survival models fitted to the KEYNOTE-826 data. There appear to be some prognostic differences between patients who progressed in KEYNOTE-A18 and patients who were randomised in KEYNOTE-826. Therefore, estimating the absolute QALY and cost payoffs for individual treatments using KEYNOTE-826 data and then applying these estimates to progressed patients from KEYNOTE-A18 is unlikely to overcome the inherent limitation that KEYNOTE-A18 does not reflect the UK subsequent treatment mix.
    (ii) The company's adjustment approach suggests that if patients in KEYNOTE-A18 had received subsequent treatments for progression in line with UK treatment pathways (i.e., more active treatment in the pembrolizumab plus CCRT group and more pembrolizumab plus chemotherapy in the CCRT alone group), they would gain additional QALYs over and above the QALYs suggested from the models directly fitted to the KEYNOTE-A18 data. These additional QALYs would come from additional survival time which is not reflected in the economic model trace (because the additional QALY estimates are "bolted-on" numerical estimates applied to patients in the PD1 state, rather than being estimated by adusting PPS directly). The company's plot of modelled OS is therefore misleading because it does not account for this implied additional survival time.

(iii) Treatment waning associated with the subsequent pembrolizumab treatment was not considered in the 3-state model in the company's updated base case; however, it was included when estimating the additional QALYs and costs using the subsequent treatment trade-off method. This means that treatment waning is only applied to a proportion of progressed patients (i.e., the differences shown in the right-hand columns of Table 5); the EAG considers this approach to be inconsistent. However, the company conducted a scenario analysis assuming treatment waning in the 3-state model and the impact on the cost-effectiveness results was minimal.

- The EAG remains concerned regarding the model fit for OS. Figure 10 presents a comparison of observed OS in KEYNOTE-A18,[2] modelled OS based on the company's previous 4-state model at ACM1, and modelled OS based on the company's updated 3-state model. Whilst the company's DG response[4] states that its updated 3-state base case model provides a marked improvement in fit (relative to its previous 4-state model excluding calibration), the EAG considers that this model still provides a poor fit to the observed data. The precise reasons for this are unclear, but may be a consequence of: (i) the company's decision not to properly account for competing risks in the derivation of progression and death risks or (ii) the misspecification of one or more parametric survival models used to inform any of the transition probabilities which inform OS (PFS, time to progression [TTP] and/or PPS).
- At ACM1, the company's base case model and the EAG's preferred model used external data from KEYNOTE-826[3] and included calibration. Given that the company's updated 3-state model using PPS data from KEYNOTE-A18[2] provides a worse fit to OS than the company's previous 4-state model, and remains partially reliant on absolute costs and QALYs estimated using data from KEYNOTE-826 applied in the previous 4-state model,[3] the EAG does not believe that the company's updated model is more suitable for decision-making than the company's previous base case model.
- The hazards of PPS in both treatment groups in KEYNOTE-A18[2] are almost flat over the observed period (see Figure 5 and Figure 6). As such, the EAG believes that the exponential model may be more appropriate than the company's selected log-logistic model. The use of the exponential model is however already explored within the company's scenario analyses. The ICER for this scenario is similar to the company's base case model using the log-logistic model (ICER using exponential model for PPS = [redacted] per QALY gained; ICER using log-logistic model for PPS = [redacted] per QALY gained; see Table 7).
- Despite the EAG's concerns regarding the company's new model, the range of scenario analyses conducted using the company's updated model address the other key concerns raised in the DG. None of the ICERs generated using the company's updated model are below £35,000 per QALY gained.

Figure 9: Observed PPS from KEYNOTE-A18, compared to modelled PPS from KEYNOTE-A18 and KEYNOTE-826 (via PFS/TTP/PPS)

Note – the dashed lines reflect estimates obtained by: (i) all patients entering the company's previous 4-state model in the PD1 health state and (ii) applying the subsequent treatment distribution from KEYNOTE-A18

Figure 10: Comparison of observed OS in KEYNOTE-A18 and modelled OS based on the company's previous base case model at ACM1 with and without calibration and the company's updated base case model following the DG

3. References

1. National Institute for Health and Care Excellence. Pembrolizumab with chemoradiotherapy for untreated locally advanced cervical cancer - Draft Guidance. NICE: London, UK; 2026.
2. Merck, Sharp, and Dohme. Health Technology Assessment (HTA) report of MK3475, Protocol A-18: A randomized, Phase 3, double-blind study of chemoradiotherapy with or without pembrolizumab for the treatment of high-risk, locally advanced cervical cancer - Rest of World (ROW) Report. Final analysis. MSD: London, UK; 2025.
3. Merck, Sharp, and Dohme. Clinical Study Report: P826V01MK3475: A Phase 3 randomized, double-blind, placebo-controlled trial of pembrolizumab (MK-3475) plus chemotherapy versus chemotherapy plus placebo for the first-line treatment of persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826). MSD: New Jersey, USA; 2021.
4. Merck SaD. Pembrolizumab with chemoradiotherapy for untreated locally advanced cervical cancer [ID6138]. Company's response to the NICE Draft Guidance MSD: London, UK; 2026.
5. Merck, Sharp, and Dohme. Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138] - CS appendices. MSD: London, UK; 2025.
6. Office for National Statistics. National life tables: England and Wales. ONS: London, UK. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables; 2025.
7. Merck, Sharp, and Dohme. Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138] - company's response to clarification questions from the EAG. MSD: London, UK; 2025.
8. Yee M, Simpson E, Chang JYA, Tappenden P, Ren S, Chanakira EZ*, et al.* Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138]. External Assessment Group Report. University of Sheffield: Sheffield, UK; 2025.
9. Merck, Sharp, and Dohme. Pembrolizumab with chemoradiation for untreated high-risk locally advanced cervical cancer [ID6138] - company's evidence submission. MSD: London, UK; 2025.