NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer [ID3811]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with lenvatinib for previously treated advanced or recurrent endometrial cancer [ID3811]

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.

Appraisal title

Single Technology Appraisal

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

Type of stakeholder:

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

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

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

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

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

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Consultee	MSD	**Overview of comments by MSD** MSD welcomes the opportunity to comment on the Appraisal Consultation Document (ACD), which confirms that: • Pembrolizumab plus lenvatinib improves overall survival (OS) and progression-free survival (PFS) compared with doxorubicin or paclitaxel monotherapy (ACD 3.4) • Patients benefit from pembrolizumab plus lenvatinib compared with doxorubicin or paclitaxel monotherapy in both mismatch repair subgroups (ACD 3.5) • Pembrolizumab with lenvatinib meets the end of life criteria (ACD 3.12) The draft decision not to recommend pembrolizumab plus lenvatinib is disappointing as it restricts physician and patient access to an efficacious treatment option in a setting where there is currently no standard of care and, therefore, a high unmet medical need. In response to the Committee's request, we provide novel analyses using the final database lock (Data Cut Off, 1 March 2022) that supports access to pembrolizumab plus lenvatinib (PEM + LEN) for these patients. The additional 18 months of follow-up provides strong and consistent evidence of the sustained longer-term benefits of treatment with PEM + LEN. Our ACD response addresses the following areas of uncertainty: • **Assessment of the overall survival extrapolations using the final data cut from the KEYNOTE-775 trial, including exploration of flexible spline models (ACD 3.7, 3.8).** The final data cut demonstrated sustained and consistent clinical benefits for the PEM + LEN group compared with the treating physician's choice (TPC) consisting of paclitaxel or doxorubicin group. Spline models provided an excellent fit to the observed data, tracked well to the smooth hazard plots, and provided clinically	Thank you for your comment. The committee noted the updated model which had incorporated the final database lock and for the company making other further changes. The specific points raised here have been addressed below in the relevant comments. The committee have considered the consultation comments and the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.

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			plausible extrapolations. As a result spline models are used in the revised base case. • **Adjusting for treatment-switching in patients who received subsequent immunotherapies in the TPC arm (ACD 3.8).** Multiple treatment-switching analyses were explored. These all approaches provided similar results. Hence adjustment for treatment-switching was included in the revised base case. • **Consideration of the plausibility of treatment effect waning assumptions and their impact (ACD 3.9).** There is no observed treatment waning in KEYNOTE-775 at the final database lock. As there is biological rationale supporting the persistence of treatment effects for pembrolizumab with lenvatinib, these highly conservative scenarios were not included in the base case analysis, consistent with the EAG approach. In addition to the above, we have explored the Committee's preferences with respect to the final two issues discussed in the ACD. These are applied in our revised base case analysis: • Using progression status to derive utilities • Using an average patient age of 67 that was preferred assumption by the committee. Finally, a technical addendum to this document provides full details of the updates made to the electronic version of the economic model to aid the EAG's review. The FA data from KEYNOTE-775 provides more certainty of the superior clinical effectiveness of PEM + LEN compared with TPC, with respect to PFS and OS (Table 1). The updated model, which now reflects the Committee's views, produces results which consistently demonstrate that pembrolizumab plus lenvatinib is likely to be a cost-effective use of NHS resources under a wide range of scenarios, including too pessimistic assumptions around the duration of treatment effect to enable the Committee to make a positive recommendation for baseline commissioning. This will facilitate rapid access to an innovative treatment for patients that currently lack effective treatment options.	
2	Consultee	MSD	**Assessment of the overall survival extrapolations using the final data cut from the KEYNOTE-775 trial** The company submission was based on the interim analyses (IA) of KEYNOTE-775 (data cut off [DCO], 26 October 2020). At the technical engagement stage, the company provided a clinical summary of the final	Thank you for your comment. The committee noted the updated model which had incorporated the final database

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			database lock of KEYNOTE-775 (DCO, 1 March 2022). The final analysis (FA) provided approximately 18 months of additional follow-up. The median duration of follow-up at the time of the FA (defined as the time from randomization to date of death or DCO) was 18.7 months (range: 0.3–43.0) in the PEM + LEN arm and 12.2 months (range: 0.3–42.4) in the TPC arm and was 14.7 months (range: 0.3–43.0) for all patients (see Table 1 for a summary of clinical effectiveness). Notably, at the time of the FA, compared with IA, a greater number of patients in the TPC arm of KEYNOTE-775 had switched over to receive subsequent in-study treatment with PEM + LEN or other subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies, thus confounding the unadjusted OS analysis from the trial. Without adjusting for treatment switching in the TPC arm of KEYNOTE-775, estimates of the OS benefit of PEM + LEN compared with TPC are underestimated. **Table 1: Clinical effectiveness summary (KEYNOTE-775 IA and FA)** Table removed In response to the ACD, we have incorporated the FA of KEYNOTE-775 into the economic model. This involved an update of all clinical inputs from the KEYNOTE-775 trial, including OS (with and without adjustment for treatment switching), PFS, time on treatment (TOT), adverse events (AEs) and subsequent therapies. **Full details of the FA update to the economic model are provided in a standalone technical addendum, while the following sections of this document are focused on responding to the issues discussed in the ACD**.	lock. Comments about treatment switching are addressed in the more detailed comment below.
3	Consultee	MSD	**<u>Alternative spline models for overall survival as per the Committee's request.</u>** ***ACD commentary on spline models*** The final analyses (FA) of the KEYNOTE-775 trial provides mature and consistent evidence of the sustained longer-term OS benefit associated with treatment with PEM + LEN compared with TPC in endometrial cancer. Median OS was significantly longer in the PEM + LEN arm compared with the TPC arm (18.7 and 11.9 months, respectively), with a hazard ratio (HR) of 0.65 (95% CI: 0.55, 0.77; p < 0.0001) and there is a consistent separation in the OS Kaplan–Meier curves for the entire duration of follow-up. Further details are	Thank you for your comment. The committee noted the company used more flexible spline models and agreed with the company's chosen extrapolations for both arms for both progression-free and overall survival.

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			provided in the economic addendum to this ACD response and in the clinical study report (CSR) update.(1) The ACD makes clear the importance of ensuring that the economic model uses survival extrapolations that track well to the underlying hazards. We understand that this provides confidence in the ability of the survival extrapolations to reflect realistic and clinically valid predictions beyond the observed period, as described in NICE DSU TSD14 and TSD21.(2, 3) In the original submission, this consideration led to our selection of a flexible two-piece survival modelling approach; in their response the EAG suggested that cubic spline models should also be considered and are likely to be preferable. The advantages of flexible spline models are well-documented.(3) They were developed to capture the underlying shape of hazard functions and have been used across many NICE technology appraisals in oncology for this reason. They can result in more realistic predictions of survival within the observed period, and, ideally, in the long-term extrapolations. ***Summary of OS spline models in the PEM + LEN and TPC arm*** The consideration of complex hazards remains relevant at the final database lock of KEYNOTE-775, which the one- and two-piece models are not able to resolve. Based on this view in the ACD, we have therefore focused on the Committee's suggestions: • Analyses of extrapolations based on spline models for OS using the FA data cut as the preferred approach for survival extrapolations to provide a better fit to the hazards (see summary below, and refer to technical addendum for details) o TPC arm (unadjusted for treatment switching) o TPC arm (adjusted for treatment switching; used in revised base case) o PEM + LEN arm (used in revised base case) • Incorporation of analyses into cost-effectiveness model (see technical addendum for details) Consistent with the recommendations in NICE DSU TSD 21 guidance, we used the package *flexsurvspline*, conducted with R statistical software and based on the Royston and Parmar (2002) methodology.(4) Flexible spline functions were individually fitted to each arm of the FA of KEYNOTE-775 trial data for OS and PFS. Splines were modelled on the 'odds', 'hazard' and 'normal' scales. Without knots, these correspond to single	

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			piece Weibull, log-logistic and log-normal models, respectively. For each of these scales we fitted spline models based on one, two or three internal knots (k=1, k=2, k=3) placed at uniformly distributed percentiles along uncensored log-times (the standard approach), resulting in a total of nine spline models for each treatment arm. The assessment of the OS spline models focused on both how well they captured the shape of the hazards and the plausibility of the extrapolated outcomes, using the following process: • Visual fit to the smooth spline hazard curve • Statistical fit by Akaike information criterion (AIC)/Bayesian information criterion (BIC) values • Visual fit of the predicted outcomes of the spline models to the observed data • Clinical plausibility of the fit to the smooth spline hazard curve and of the predicted outcomes Priority was given to retaining the same model type (number of knots and scale) between the arms, following NICE DSU TSD 14 advice.(2) When determining the number of knots among equally well-fitting models, preference was given to lower numbers of knots to ensure that the long-term extrapolations are based on a reliable and sufficient number of events while avoiding over-fitting to the data. **Based on the findings, the one-knot OS spline models (odds scale) provided an excellent fit to the hazards in the TPC and PEM + LEN arms (Figure 1 and Figure 2; see technical addendum for details). A summary is provided below:** • Overall, all of the spline models provided very good statistical and visual fit to the observed Kaplan–Meier data as well as the smooth hazard functions. • In the TPC arm (unadjusted for treatment switching), AIC/BIC values indicated that the odds and hazards models generally provided the best statistical fit to the data, with the lowest values for the one-knot odds model. The odds scale also provided a slightly better visual fit (Figure 1). This remained true when assessing spline models fit to the TPC arm after adjusting for treatment switching, which is used in the revised base case analysis (please see MSD ACD Response 4). • In the PEM + LEN arm, AIC/BIC values indicated that the odds and hazards models generally provided the best statistical fit to the data, with the lowest values for the one-knot odds model. The odds scale	

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			also provided a slightly better visual fit (Figure 2). • Of the spline models on the odds scale, there was minimal difference in visual fit when varying the number of knots. The AIC rankings trended in the opposite direction of the BIC rankings which is not surprising as a result of the way these statistics are calculated. Preference was given to the one-knot models as this would ensure that the long-term extrapolations are based on a reliable and sufficient number of events to capture the underlying shape, while avoiding over-fitting to the data.(4, 5) **Figure 1: Plot of OS hazard rates in the TPC arm, spline models unadjusted for treatment switching (KEYNOTE-775 FA)** Plots removed **Figure 2: Plot of OS hazard rates in the PEM+LEN arm, spline models (KEYNOTE-775 FA)** Plots removed **To provide clinical validation of the survival extrapolations based on the FA of KEYNOTE-775 in this ACD response, three individual 45-minute interviews were conducted in November 2022.** These validation interviews also included the results of the treatment switching analysis; described in more detail in the next section (MSD ACD Response 4). Briefly, three clinical experts were consulted to understand the appropriateness of using spline models and to discuss the plausibility of long-term projections. This included landmark survival estimates and mean predicted life years generated from each model. All clinical experts commented that the hazard plots look very similar, but that the odds scale provided a slightly better fit to the smooth hazards. Of the spline models on the odds scale, it was suggested that the one-knot spline model may provide the best fit over time. **In response to the ACD, following clinician input, we have fully incorporated the Committee's suggestion to explore the impact of treatment switching on OS in the TPC arm of KEYNOTE-775. These analyses are described in the next section (MSD ACD Response 4) and are included in the revised base case analysis instead of the unadjusted OS data**.	
4	Consultee	MSD	**Treatment switching adjustment for patients who received subsequent immunotherapies in the TPC arm of KEYNOTE-775** ***Overview***	Thank you for your comment. The committee noted the company's efforts to use treatment switching methods to adjust for subsequent

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			As noted in the ACD, allowing treatment switching in the control arm of clinical trials leads to increased OS compared with that which would be observed in UK practice. Based on the positive outcome of the OS analysis in KEYNOTE-775, participants in the TPC arm who experienced investigator-defined disease progression had the opportunity to crossover to receive PEM + LEN or other subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies. At the final database lock in March 2022, there were a total of [redacted] participants with disease progression in the TPC arm.(1) [redacted] participants randomized to the TPC arm received in-study treatment PEM + LEN or other subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies that are not currently reimbursed in this treatment setting in the UK. In clinical practice, these patients would not have received such treatment and their outcomes are likely to have been worse than seen in the trial. Without adjusting for treatment switching in the TPC arm of KEYNOTE-775 (as in MSD ACD Response 3), estimates of the OS benefit of PEM + LEN compared with TPC are underestimated. Consistent with the Committee's suggestion in the ACD to explore treatment switching analysis, there was consensus from the three clinical experts consulted in November 2022 that it is clinically reasonable to use the crossover-adjusted data in the TPC arm. Without such adjustment, TPC OS data are likely over-estimated. These analyses were conducted and incorporated into the revised base case, as described below. ***Summary of methods*** Following NICE DSU TSD16 guidance, we explored three common methods of adjusting for treatment switching to estimate the true OS benefit of PEM + LEN compared with TPC.(6) Each of the three methods rely on the applicability of various underlying assumptions to produce reliable and unbiased results. There is usually no clear best method for adjustment as it depends on study design, conduct and patient characteristics; therefore, we have tested all three methods using SAS statistical software and assessed the likelihood of the key underlying assumptions holding for each method with respect to the KEYNOTE-775 trial. A summary is provided below. The three methods are: • Inverse probability of censoring weights (IPCW) • Rank preserving structural failure time model (RPSFTM) • Two-stage estimation (TSE)	treatments used. The committee agreed that treatment switching methods were used but felt it was likely to be an overestimate of the result (see section 3.8 in the FAD).

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			Results of the treatment switching analysis An overlay of the unadjusted and adjusted counterfactual data of the TPC arm is presented in Figure 3. The analysis suggests that the unadjusted data overestimate outcomes in the TPC arm of KEYNOTE-775. Irrespective of the method used in the analysis, the adjusted estimates result in consistently lower OS across the entire duration of follow-up. **Figure 3: TPC, OS with and without adjusting for treatment switching (unadjusted KM; and adjusted counterfactual plots using TSE, RPSFT and IPCW methods) - KEYNOTE-775 FA** Figure removed Adjusted and unadjusted estimates of the HR for the PEM + LEN arm compared with the TPC arm are presented in Table 2, along with estimates of median OS for the TPC arm. These demonstrate a high degree of consistency in estimates of OS. The adjustment for treatment switching consistently leads to an improvement in the OS benefit of PEM + LEN compared with TPC by reducing the probability of death by approximately [redacted], in favour of PEM + LEN. The HRs for PEM + LEN versus TPC after adjustment for treatment switching ranged from [redacted]. **Table 2: Treatment switching analysis results based on final analysis of KEYNOTE-775** Table removed ***Discussion*** This section provides an abbreviated summary of the assessment of which treatment switching method to use in the revised base case, per NICE DSU TSD16 guidance (6). All other methods were tested in scenario analyses which demonstrated a small impact on the results. For further details, please refer to the technical addendum.	

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			Of the above methods: • The IPCW approach was excluded because it can be prone to error when there are small sample sizes assessed as switcher and non-switcher groups.(6) This is particularly relevant in this case, where there was a relatively small number of patients randomized to the TPC arm who received subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies ([redacted] out of [redacted] participants [redacted]). This figure is substantially smaller than seen in some other clinical trials in oncology. • The RPSFT approach was considered subject to considerable bias in the case of KEYNOTE-775. It is unclear whether the fundamental assumption of the 'common treatment effect' holds. When treatment switching is permitted after disease progression, the capacity for a patient to benefit in the post-progression stages may be different compared with pre-progression. The control arm of KEYNOTE-775 is also an active treatment. Both issues pose limitations to the RPSFT approach. • The TSE approach was preferred because it avoids the need of the 'common treatment effect' assumption and was considered less prone to bias. The timepoint used to determine the secondary baseline is based on disease progression, aligned to the trial protocol in the case of KEYNOTE-775. The median time from disease progression until switching was shorter than [redacted] months (approximately [redacted] days), reducing the likelihood of potential bias associated with time-dependent confounding. Although there was some variation in the time taken for participants to switch over, the bias was likely to be small because the majority of switching occurred shortly after disease progression. Finally, one practical advantage of TSE is that it does not require data to be collected on time-dependent covariates other than the timepoint of disease progression. **Based on the above assessment, whilst all methods provided similar estimates, the TSE approach was preferable because the IPCW and RPSFT methods were more prone to bias.** Methods of treatment switching adjustment with and without recensoring were also tested to assess the impact of informative censoring. The difference in HRs between TSE with and without recensoring was small; recensoring improved the HR by [redacted] in favour of PEM + LEN vs TPC. Additionally, current research suggests that the 'true' HR will fall between the values estimated with and without recensoring.(7) **In light of the range of HRs after adjusting for treatment switching (HRs between [redacted]), the TSE approach without**	

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			recensoring (HR = [redacted]) is likely to produce conservative estimates of the clinical and cost effectiveness of PEM + LEN, and was used in the base case to inform the updated cost-effectiveness results. Therefore, ICERs generated by the EAG once commercial arrangements are accounted for, should still be **considered as an upper limit of cost-effectiveness**. ***OS spline models in the TPC arm, adjusted for treatment switching (TSE without recensoring)*** With the availability of the counterfactual estimates from the treatment switching analysis, spline models were fitted directly to the counterfactual outputs of the TSE method without recensoring. The approach for fitting and assessing the spline models follows that previously described for the unadjusted dataset (see ACD Response 3 and refer to the technical addendum for further details). The one-knot spline on the odds scale continued to outperform the other spline models (Figure 4) and was also the preferred model to maintain consistency in the method of extrapolating OS for both the PEM + LEN arm and the unadjusted TPC arm. The extrapolations of OS using the spline models illustrate the similarity in the long-term predictions in the TPC OS estimates after adjusting for treatment switching (Figure 5). **Figure 4: Plot of OS hazard rates in the TPC arm, spline models adjusted for treatment switching (KEYNOTE-775 FA)** Figure removed **Figure 5: Final OS models in the revised base case, PEM + LEN (one-knot spline) and TPC arm (one-knot spline adjusted for treatment switching, TSE without recensoring) – KEYNOTE-775 FA** Figure removed Three UK clinical experts commented on the reliability of long-term projections, including landmark survival estimates and mean predicted life years generated from each flexible model.(8) Details are provided in the technical addendum, with a summary below: • TPC OS should be adjusted for treatment switching, both from a treatment pathway and clinical efficacy perspective. Clinicians expected the OS outcomes in the TPC arm to worsen, after applying	

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			the adjustment • The one-knot spline models (odds scale) provide a good fit to the observed data, and reasonable extrapolations in both the PEM + LEN and TPC arms • The spline models provided a good fit to the observed data, within the trial period. Additionally, all clinical experts commented that the hazard plots look very similar, but that the odds scale provided a better fit to the smooth hazard functions. This was more pronounced in the TPC arm • Of the spline models on the odds scale, clinical experts commented on the similarity of the plots when varying the number of knots. The one-knot spline models may provide a slightly better fit over time but it was difficult to differentiate between the plots in some cases • The long-term projections were also similar, based on visual assessment of the extrapolated curves, landmark survival estimates, median estimates and mean predicted life years generated from each flexible model. Based on the above assessment, the revised base case uses the one-knot spline model to extrapolate OS after adjusting for treatment switching in the TPC arm. **Table 3: OS estimates at landmark time points (KEYNOTE-775 FA)** Table removed ***Impact of analysis on cost-effectiveness results*** The treatment switching analysis was conducted to adjust for the impact on OS as a result of treatment switching in the TPC arm, to estimate the true benefit of PEM + LEN compared with TPC. This is considered more appropriate for a UK NHS setting where subsequent immunotherapies or VEGF/VEGFR inhibitor therapies are not available in clinical practice. Given the importance of these analyses from a clinical perspective, the results were incorporated into the revised base case in the economic model (see Figure 5 for an overlay of curves in the revised base case, with results summarised in Table 4). Further details are available in the technical addendum. For comparison purposes, we present a range of scenarios which demonstrate the small impact on the results (Table 4). Consistency in the ICERs across the selection of methods supports the reliability of the	

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			analyses for use in decision making. As previously noted, the base case ICER is likely to be over-estimated, due to the conservative approach of using the TSE method without recensoring. **Table 4: Revised base case using FA of KEYNOTE-775, incorporating OS spline model for PEM + LEN and HR adjusted for treatment switching in the TPC arm; see technical addendum for full details (with pembrolizumab CAA; costs and health outcomes discounted at 3.5%)** Table removed **Validating OS in the TPC arm based on real-world evidence (Heffernan, 2022)** To better understand the predicted outcomes in the TPC arm of the economic model, clinical experts were consulted to explore the comparability of the KEYNOTE-775 and Heffernan (2022) real-world study populations. Details of the Heffernan (2022) real-world study became available in the public domain after the initial company submission date for ID3811.(9) As a single-arm, real-world study, there remains severe limitations of the use of this data to validate the results from the Phase III randomized controlled trial, KEYNOTE-775. There is a degree of consistency in the naïve comparison of median OS results based on the full populations of each study. The median survival in Heffernan (2022) in the total assessed population was 10.3 months (95% confidence interval [CI], 9.2–11.1). When assessing the breakdown of results by type of treatment received in the second-line setting, median OS ranged from 4.9–14.2 months. Median OS reported in the TPC arm, based on the FA of KEYNOTE-775 trial, was 11.9 months. After adjusting for treatment switching in the TPC arm, median estimates ranged from [redacted] months. The EAG have previously queried the reasons for differences in the median OS values between patients who specifically received paclitaxel (n = 93) or liposomal doxorubicin monotherapy (n = 130) in Heffernan (2022). These cannot be explained with certainty, however, clinical experts suggested that: • ECOG PS was only reported for approximately half of the patients in the Heffernan (2022), which provides an incomplete view of the population on this measure alone and is ultimately a major limitation of this interpreting the types of patients or the results from this study. • Compared with KEYNOTE-775, the Heffernan (2022) population had a higher proportion of patients	

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			with serous histology type (25% vs 42%, respectively), a greater proportion of patients with initial diagnosis at Stage III or IV disease (65% vs 78%, respectively). These differences are likely to have a negative impact on prognosis in the Heffernan (2022) study population. • There could be some differences in the types of patients based on use of platinum doublet therapies; however, the baseline characteristics data are incomplete and there is no further information available to understand these differences. In summary, incomplete information from the real-world study prevents any useful interpretation of how this applies to the decision problem. **MSD believes that the Heffernan (2022) study has severe limitations for applicability for the KEYNOTE-775 and cannot be used to meaningfully validate or invalidate the outcomes for this appraisal.**	
5	Consultee	MSD	**Alternative scenarios for treatment waning** We understand the relevancy of this topic; however, there is no evidence of a treatment waning effect with PEM + LEN based on the KEYNOTE-775 trial. The OS and PFS results provide evidence of a sustained longer-term comparative benefit of PEM + LEN compared with TPC that is numerically consistent between the IA and FA data cuts.(1) **Long term available data showing no signs of waning** Biological reason: The marketing authorisation states that lenvatinib is administered until disease progression. There is biological evidence and rationale suggesting that lenvatinib helps shift the tumour microenvironment to an immune-stimulatory state by inhibiting VEGFR and FGFR.(10) In mouse models, lenvatinib plus PD-1 inhibition had significantly greater antitumour activity than either agent alone. On this basis, pembrolizumab with lenvatinib act in a synergistic way to provide a positive enhancement of the tumour microenvironment by improving the action of each drug given in isolation. This hypothesis is consistent with data for other IO agents and IO combinations, which offer robust evidence on the durability of the treatment effect associated with IOs in metastatic treatment (refer to table below for a summary of this).This treatment combination was not been subjected to treatment waning assumptions in another NICE technology appraisals (11). It is unclear why it would apply in this case since patients in KEYNOTE-775 may continue to receive lenvatinib monotherapy even after stopping treatment with pembrolizumab (at the last recorded time point around 3	Thank you for your comment. The committee noted the company used alternative treatment switching scenarios. The committee considered that some treatment effect waning was likely but expected that there was likely to be a period of sustained effect before waning was likely to start, possibly because of the continued use of lenvatinib. As a result, the committee preferred the assumptions made in the EAG's scenario analysis with all patients waning after 5 to 7 years from initiation of treatment. Please see discussion of the committee's considerations in sections 3.9 and 3.10 of the FAD.

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			years' follow-up, there were [redacted]% of patients still receiving lenvatinib in KEYNOTE-775). UK clinical experts consulted in November 2022 confirmed that a proportion of patients will have durable response to PEM + LEN. In addition, patients who are considered to benefit from further treatment may very well receive continued treatment with lenvatinib monotherapy even after pembrolizumab has stopped in a real-world setting, as in the KEYNOTE-775 trial. Long term data: A long- term OS data for endometrial patients treated with PEM+LEN is available for the KEYNOTE-146 (12). This is a multi-centre, open-label arm Phase Ib/II basket trial of selected solid tumours (n=108 had pre-treated EC) with a median follow-up 34.7 months. The observed data proved durable and sustained treatment effect beyond the 2-year treatment period with PEM+LEN. This is corroborated by data from KEYNOTE-775 (Document B Figure 9), which details distinct evidence of sustained OS for PEM+LEN in the form of a plateau with 30% of patients alive at 5 years. We do acknowledge there are some limitations for applicability, but this is longest available data for this treatment combination and therefore constitutes a key piece in the evidence under consideration around the durability of the treatment effect. Other pembrolizumab long term studies: The OS and PFS results provide evidence of a sustained longer-term comparative benefit of PEM + LEN compared with TPC that is numerically consistent between the IA and FA data cuts.(1) Multiple randomized controlled trials that have reported 5-year data for pembrolizumab. All of these demonstrated a sustained treatment effect, with two studies conducted specifically in the second-line treatment setting. **Table 5: 2 year and 5-year OS in pembrolizumab arms of advanced solid tumour trials** Table removed We have not conducted a full systematic literature review on long term treatment effect durability, however in addition to the studies reported above , there is additional long term clinical evidence from melanoma which demonstrate the durability of treatment effect for anti-CTLA4 agents. These work in a similar fashion to anti-PD-1 agents such as pembrolizumab. Schadendorf et al 2015 reports a durable clinical benefit starting from year 3 that is maintained up to year 10 for advanced melanoma. (19) Whilst these are different tumor	

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			microenvironments which limits the generalisability of this evidence, it is relevant for this advanced endometrial cancer assessment that there is biological plausibility to a plateau. To date there is no evidence suggesting why a similar plateau would not be observed in pembrolizumab + lenvatinib combinations. Considering also clinical evidence from KEYNOTE-146 which reports 5 year OS estimate of 30%. We therefore consider any waning of treatment effect to be implausible and inappropriate in this combination treatment. <u>Treatment effect and discontinuation of pembrolizumab:</u> It is important to note that long-term data support a sustained treatment effect post discontinuation of pembrolizumab. One of the examples with a long-term data is in melanoma patients. In KEYNOTE-006 a long-term survival benefit has been observed in patients with advanced melanoma who were treated with pembrolizumab for up to 2 years. In patients who ceased treatment after completing 35 doses of pembrolizumab at 2 years, 78.4% remained in progression-free survival for at least 24 months (censored) following discontinuation.(13) The long-term outcome seen in KEYNOTE-006 is generally consistent with the outcome seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule. (20) The cumulative and log-cumulative hazard plots below show that there is no structural difference between the hazards in these two trials (Figure 6, Figure 7 and Figure 8). This data points towards a sustained treatment effect post discontinuation of pembrolizumab in melanoma and other patients treated with pembrolizumab. **Figure 6: Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001** Figure removed **Figure 7: Cumulative and log-cumulative hazard plots for OS in KEYNOTE-006** Figure removed **Figure 8: Comparison of Overall Survival curves of KEYNOTE-001 and KEYNOTE-006 in advanced melanoma** Figure removed	

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			Same trends in hazards were observed in the KEYNOTE-024. The following tables show the PFS and OS hazard ratios from KEYNOTE-024 reported in the 1-, 2-, 3- and 5-year publications. If treatment waning began at 2 years we should expect some upward drift in the hazard ratios by the 5 year cut-off, which is not observed, despite crossover being allowed in the study and 66% of patients in the chemotherapy arm receiving immunotherapy on progression. **Table 6: KEYNOTE-024 PFS and OS HRs** Table removed The provided data from various long-follow up studies mentioned above provides no evidence in support of a treatment waning effect for which clinical evidence is collected. <u>Conditional survival</u> When discussing treatment effect waning one must consider conditional survival probability. Several studies reported conditional survival in endometrial patients. It is clear that there is a higher survival probability for long term survival which notes a decreasing risk of death over time. (24, 25) The conditional relative survival rates for patients with EC improved with increased time elapsed from diagnosis. The discussed treatment combination provides the additional time in PFS and OS. At FA KEYNOTE-775 patient have longer median PFS in the PEM + LEN arm versus TPC arm (7.3 months vs 3.8 moths in all-comer, HR: 0.56), a longer median duration of response (12.9 months vs 5.7 months in all-comer), and a longer median OS (18.7 months vs 11.9 months in all-comer, HR: 0.65) (26). <u>Waning scenarios:</u> Although MSD maintains its views around the durability of long-term treatment effect of PEM + LEN, we explored the potential impact on the results, as suggested by the Committee for scenarios on the basis of the clinical evidence presented above. Results are presented for the following scenarios (Table 7**Error! Reference source not found.**): • Waning effect from 5–7 years after stopping treatment, given no waning at all has been observed in	

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			KEYNOTE-775 or in the 5-year pembrolizumab trials in other indications to date • Application of the treatment waning effect to between 60-80% of patients in the PEM + LEN arm to reflect a small proportion of patients experiencing durable response and prolonged immunotherapeutic effect after stopping treatment with pembrolizumab, while a proportion of patients will also continue treatment with lenvatinib monotherapy. **Table 7: Scenarios exploring potential impact of treatment waning assumptions in the PEM + LEN arm (pembrolizumab CAA applied only, lenvatinib list price)** Table removed MSD urges the Committee to consider these cost-effectiveness analyses only as pessimistic scenarios for decision making purposes given the scarcity of robust clinical evidence in this topic and the totality of the arguments presented above.	
6	Consultee	MSD	**<u>Using progression status to derive utilities</u>** We are grateful for the Committee's careful consideration in the ACD regarding the methods used to predict utility, and the implications for use in health economic modelling. The ACD notes that the time-to-death (TTD) utility approach may provide more granular information but that the approach in the initial submission limited the amount of information informing the health states because it did not include disease progression as a predictive covariate. To address this issue, we have conducted further analysis using an extended approach to the initial TTD utility method with disease progression as a covariate to predict utility, and a scenario following the general approach and rationale in the dostarlimab appraisal (TA779). There was a small impact on the results. This analysis is based on the FA of KEYNOTE-775, with full details provided in the technical addendum. **Table 8: Scenario analyses exploring the impact of utilities assumptions (pembrolizumab CAA applied only, lenvatinib list price)**	Thank you for your comment. The committee noted the company's updated approach. However, the committee still preferred the EAG's method of deriving utilities using progression status. Please see discussion of the committee's considerations in section 3.11 of the FAD.

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			Table removed	
7	Consultee	MSD	**Using an average patient age in the model based on committee preferred value** We acknowledge the Committee's preferred assumption to use the average age of patients reported in the ECHO study. This was based on the view that the average patient age in clinical practice would be slightly higher than that used by the company (63.5 years, based on the KEYNOTE-775 trial) and less than that assumed by the EAG (75.0 years, based on the EAG's clinical advisor). Heffernan (2022) provides another alternative value for the mean age of this patient cohort, which sits between the lower and upper ranges.(9) This has been tested in scenario analyses, which demonstrate that the model results are not sensitive to the input value. The Committee's preference to assume a mean patient age of 67 years has been incorporated in the updated model, and applied in the revised base case (Table 9). Patient age is not a key driver of the cost-effectiveness of PEM + LEN versus TPC as it has only a small impact on the ICER. **Table 9: Scenarios exploring impact of patient age in the economic model (pembrolizumab CAA applied only, lenvatinib list price)** Table removed	Thank you for your comment. The committee noted the company had incorporated its preferred average age in the model. See section 3.12 of the FAD.
8	Consultee	MSD	**Revised base case analysis** The FA data of KEYNOTE-775 has been incorporated into a revised version of the economic model and we have provided a revised base case which incorporates the Committee's views. Full details are provided in a technical addendum to provide transparency and to aide review of the updates. In summary, the following updates have been incorporated in the revised base case analysis: • All clinical inputs updated with the KEYNOTE-775 FA data, including OS, PFS, TOT, lenvatinib dosing schedule, subsequent treatments and adverse events (ACD 3.8; MSD ACD Response 2 and technical addendum) • OS extrapolations based on a one-knot spline model for the PEM + LEN arm, which provides an	Thank you for your comment. As noted above, the committee noted the company's updates to the model. The committee's preferred assumptions are captured in the EAG's scenarios using treatment waning from 5 to 7 years after treatment with and without treatment switching. The committee have considered the consultation comments and the model amended by the company

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			excellent fit to the hazards for each arm (ACD 3.8; MSD ACD Response 3) • OS adjusted for treatment-switching in the TPC arm, to account for subsequent immunotherapies or PD1/VEGF inhibitors that are not reimbursed in the UK, using a one-knot spline models that provide a consistent approach with the PEM + LEN arm above (ACD 3.8; MSD ACD Response 4) • Utility values following a progression-based analysis by TTD (ACD 3.10; MSD ACD Response 6) • Mean patient age (67 years) based on the committee preferred age (ACD 3.11; MSD ACD Response 7) The results demonstrate that at the final database lock, PEM + LEN remains a cost-effective treatment option in a patient setting where there is a high unmet need and no current standard of care (Table 10). Further scenarios have been updated and provided to explore the impact of various assumptions in response to comments in the ACD. These have been collated in Table 11 below. **Table 10: Revised base case results (FA of KEYNOTE-775) including CAA for pembrolizumab (pembrolizumab CAA applied only, lenvatinib list price)** Table removed **Table 11: Scenario analyses (FA of KEYNOTE-775) including CAA for pembrolizumab (pembrolizumab CAA applied only, lenvatinib list price)** Table removed	which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.
9	Commentator	EISAI	Eisai is the marketing authorisation holder for lenvatinib in this indication. In section 3.9, pages 13-15 – the appraisal consultation document states that '*It is appropriate to assume some treatment waning in the model*'. Eisai believe it would be inappropriate to assume a treatment waning effect for lenvatinib plus pembrolizumab based on the following rationale: • Although pembrolizumab has a 35-cycle (24 month) stopping rule, it is important to note that lenvatinib can be administered until unacceptable toxicity or disease progression. • The Evidence Review Group report cites the application of a treatment waning effect in TA779 for dostarlimab (for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency) as justification for its application in this appraisal. However, it should be noted that dostarlimab is a monotherapy whereas lenvatinib plus pembrolizumab is a	Thank you for your comment. The committee has considered this alongside the comments from the company on the duration of the treatment effect. The committee considered that some treatment effect waning was likely but expected that there was likely to be a period of sustained effect before waning was likely to start, possibly because of the

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			combination therapy and as described above, lenvatinib can be administered until unacceptable toxicity or disease progression. Therefore, we do not believe TA779 is an appropriate analogue to justify the application of a treatment waning effect for lenvatinib plus pembrolizumab. • Kaplan-Meier curves for overall survival from the KEYNOTE-775 final analysis (data cut off: 01 March 2022) showed a sustained separation of the treatment arms over the follow-up (approximately 42 months; 3.5 years). This is supported by the Kaplan-Meier curves for duration of response, see Figures 1-2 below, which also show a sustained separation of the treatment arms over 3.5 years of follow-up. Therefore, Eisai believe there is no evidence of treatment waning effect for lenvatinib plus pembrolizumab and it would be inappropriate to assume this in the economic analysis. ***Figure 1: Kaplan-Meier estimate of overall survival, (all-comers, intention-to-treat population)*** Figure removed ***Figure 2: Kaplan-Meier estimate of duration of response (all-comers, intention-to-treat population)*** Figure removed ***Reference:*** (1). Makker, V., et al. "525MO Updated efficacy and safety of lenvatinib (LEN)+ pembrolizumab (pembro) vs treatment of physician's choice (TPC) in patients (pts) with advanced endometrial cancer (aEC): Study 309/KEYNOTE-775." *Annals of Oncology* 33 (2022): S785-S786.	continued use of lenvatinib. Please see discussion of the committee's considerations in sections 3.9 and 3.10 of the FAD.
10	Consultee	Peaches Womb Cancer Trust	**Introductory notes** Peaches Womb Cancer Trust is a charitable organisation dedicated to improving the lives of those affected by womb cancer through raising awareness, supporting those affected, and funding womb cancer research. Peaches Womb Cancer Trust also hosts 'Peaches Patient Voices', a patient and public involvement group for people affected by womb cancer. We work with, and advocate for, people affected by endometrial cancer – diagnosed at all stages – and their loved ones. Peaches Womb Cancer Trust has contributed the views, insights, and expertise of our patient voices network, and used our evidence to highlight the difficult situation many patients face when diagnosed with advanced or recurrent endometrial cancer. As an organisation, we have presented our evidence on the impact of advanced and recurrent endometrial cancer, and available treatments, on our patient voices community. In this instance, we are concerned that NICE's interim recommendation would not be in the interest of the approximately 1,200 people diagnosed with advanced endometrial cancer in England each year, or the approximately 1,000 people in whom endometrial cancer recurs. We are concerned that this decision will perpetuate the current situation, in which the majority of these patients face treatments with poor effectiveness and massive impacts on quality of life. Peaches Womb Cancer Trust is increasingly receiving enquiries about the availability of pembrolizumab and lenvatinib, which has highlighted to us how desperate	Thank you for your comments and contributions to this appraisal. The committee has carefully considered these comments as well as verbal contributions from the patient experts that attended the committee meetings. The committee have also considered the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.

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			patients are for a second line treatment that is more effective than chemotherapy. Peaches Womb Cancer Trust has valued the opportunity to use evidence obtained from members of Peaches Patient Voices to demonstrate the potential positive outcome for many people facing an advanced or recurrent endometrial cancer diagnosis. However, we are concerned that, although slide 8 titled 'Patient Perspective', presented at the Technology Appraisal Committee meeting on 11 October 2022, provided an overview of the range of symptoms and side effects of chemotherapy and radiotherapy experienced by patients with advanced or recurrent endometrial cancer, it did not adequately represent our patient experts' submissions. Additionally, our patient experts only had one working day in which to review the content of the 'Patient Perspective' slide, which gave them insufficient time to prepare for the committee meeting. Therefore, Peaches Womb Cancer Trust is putting forward this consultation response to ensure that the appraisal committee is able to most effectively include the patient perspective in its decision-making process. This response has been compiled from information obtained from our previous submissions, as well as new evidence obtained by questionnaire and survey from members of Peaches Patient Voices and Womb Cancer Support UK, a private Facebook peer support group for women who have been diagnosed with womb cancer. As the survey ran alongside free text questions, not all quotes provided below were included in the initial submission circulated. Key points in each section have not been changed and all main points were consulted on by respondents. A survey sent to members of Peaches Patient Voices and Womb Cancer Support UK who have been affected by womb cancer as either patient or carer confirmed that an overwhelming 43 out of 44 (97.7%) respondents are in agreement with our response, and 1 out of 44 (2.3%) respondents neither agrees nor disagrees with our response. Additional questions were asked to those who identified themselves as having advanced (stage 3 or 4), recurrent or metastatic cancer. In total, we have included quotes from 17 people affected by endometrial cancer. Most of the quotes and patient stories have been taken from this survey. Whilst we have provided names to help committee members identify different people in the patient and carer stories, these are pseudonyms and all identifying information has been removed.	
11	Consultee	Peaches Womb Cancer Trust	**The outcome we want to see** Peaches Womb Cancer Trust would like to see the approval of pembrolizumab and lenvatinib to give people affected by advanced or recurrent endometrial cancer access to treatments which support them to live longer and with fewer side effects which affect their day-to-day and overall quality of life. This would provide much-needed hope to patients and their loved ones of living well for longer and would also mean fairer access to more effective second-line treatment options, like those available for many other cancers.	Thank you for your comments and contributions to this appraisal. The committee acknowledged the advantages of this treatment over the current options including its role in providing hope to patients and their loved ones (see section 3.1 and 3.15 of the FAD).
12	Consultee	Peaches Womb Cancer Trust	**What a "yes" decision means to patients and their carers**	Thank you for your comments. The committee has carefully

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			• Patients would get access to effective treatments that would improve both survival and quality of life by better symptom control and fewer debilitating side effects than chemotherapy, which would allow them to maintain their independence longer and live life as fully as possible. • Living without fear of neutropenic sepsis and unplanned hospital admissions means that patients could continue to work and participate in activities that are meaningful to them such as spending quality time with family and friends, swimming, and travel. • Feeling well enough to undertake activities that are meaningful to a patient's life would promote mental wellbeing and allow them to thrive - to 'live with' cancer - which may help them to remain well for longer. • The combination of 3-weekly pembrolizumab 30-minute infusions and daily oral lenvatinib would be more convenient to patients as it is less burdensome than chemotherapy regimens, making it more accessible to people who cannot tolerate a longer duration infusion. • Remaining independent for longer, and the reduced frequency of planned and unplanned hospital visits, would reduce the caring burden for loved ones and improve their physical and mental wellbeing. • Staying well for longer would improve the likelihood of bridging to future treatments. **Patient story 1:** Hannah was diagnosed with stage 3c, grade 3 endometrial cancer in November 2019, age 30, and relapsed 6 months after finishing treatment for her primary cancer – with tumours in her bowel, scar tissue and one near her liver. After undergoing surgery which removed 3 of 4 tumours, she started pembrolizumab as a monotherapy which shrunk the final tumour so that there is nothing visible on her scans. Her scans have been clear for almost a year with no sign of the cancer. Hannah has also been able to live a "healthier and more fulfilling life" despite an incurable cancer diagnosis: travelling to Prague to visit a friend, getting a promotion at work, taking up climbing as a new hobby and open water swimming. Although there have been a couple of setbacks (mainly underactive thyroid due to the treatment) and some fatigue, the benefits much outweigh these – and are much easier to manage than those she experienced on chemotherapy. Hannah reported: *"Receiving pembrolizumab over the past year has been life-changing for me. My priorities for my life, as someone living with incurable cancer, is to live a full life, where I don't constantly feel like a cancer patient, and I am able to thrive for as long as possible. Over the past year, I have been able to live a nearly normal life – with the exception of needing to rest more and not 'over-do' it."*	considered these comments and patient stories. The committee have also considered the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.

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13	Consultee	Peaches Womb Cancer Trust	**What a "no" decision means to patients and their carers** • Patients with advanced or recurrent endometrial cancer are often already living with long-term side effects caused by previous treatment such as radiotherapy or first line chemotherapy. • Debilitating side effects caused by second line chemotherapy include nausea, vomiting and fatigue, which severely impact day-to-day living. • Symptoms of advanced or recurrent endometrial cancer (e.g. pain, vaginal bleeding, nausea, vomiting, bowel obstruction, fatigue) are often poorly controlled by chemotherapy, which impacts massively on quality of life. • Reduced quality of life means that patients are not able to enjoy the often-limited time they have left to live or take part in activities that are meaningful to them. • Frequent and extended planned and unplanned trips to medical settings disrupt patients' and their carers' lives which provokes anxiety and distress. The increased financial pressures of frequent visits to medical settings also create extra worry and stress for patients. • Fear of neutropenic sepsis makes patients feel vulnerable and severely limits activities such as meeting up with friends and family, swimming, going to work, and travelling due to the need to be within reach of hospital care. • For some patients, hair loss can have a profound impact on mental wellbeing. • For loved ones, there is a physical impact due to additional activities on top of their own day-to-day living, and psychologically due to constant worry and anxiety, including the risk of catching and transmitting an infection, as well as less time for themselves. **Carer story 2:** Lynn's mum had been diagnosed with advanced endometrial cancer which caused reduced mobility, pain and swelling. This meant that she was unable to leave the house or to live independently, which took its toll on her mum's mental health and quality of life. It also meant her mum needed to rely on family members for a number of daily living activities and reduced the quality of the family's remaining time spent together. Lynn describes how: *"Chemotherapy was THE only treatment option [for my mum]! She endured several different types of this toxic and archaic treatment option! She suffered physically, mentally, and so did all of her world, her children and young grandchildren! Chemo meant she couldn't go abroad on holiday, eat out in restaurants fearing the risk of infection. She slept more, she became depressed because of her want and need to live and no other alternative treatment! She had to choose in the end to suffer chemo and side effects or stop treatment and enjoy just a couple of quality months with her family!"*	Thank you for your comments. The committee has carefully considered these comments and patient stories. The committee have also considered the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.

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			Patient story 3: Julia was diagnosed with advanced endometrial cancer last year and feels grateful to have received surgery, chemotherapy and radiotherapy treatment. She says she would have done or suffered anything to have been treated; however: *"It resulted in a big interruption to my job (11 months off work) and to my husband's job [as] he drove me to every appointment. Obviously, we spent a lot on diesel over this time [including 5 weeks of radiotherapy] and although I was fortunate to have the first six months on full pay, the second five months were on half pay, so there was a considerable financial hit. I felt very isolated at times due to being very immunocompromised - especially during a time of covid and two treatments had to be delayed due to a low neutrophil count, which meant I cancelled even seeing family a couple of times. Although I coped reasonably well with the hair loss when I was in treatment, the 'growing back' phase has actually, for me, been so much harder. I look different, but to people who don't know my story, my appearance may look like a choice - but it isn't."* **Patient and carer quotes:** *i "A no decision from NICE would be nothing short of devastating."* *ii "I get a lot of pain and discomfort around my bladder and bowel following my op and first chemo which has caused nerve damage and incontinence."* *iii "I try to plan things like seeing friends [but] I have to cancel so often due to the pain, anxiety and constant tiredness."* *iv "I had to get a cleaner in and have help from my 74-year-old mother as I can't cope with daily living tasks."* *v "Chemotherapy meant [my mother] was unable to swim and enjoy meals out due to her immunocompromised situation."* *vi "I'm devastated watching my mum deteriorate and lose the independence that she has always had"* *vii "[I was] taken aback by how vulnerable it made me."*	

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			viii *"[It was] like living on a knife edge with constant anxiety about my future and that of the people I care about."* ix *"I […] found the period where my blood count during chemotherapy dropped incredibly stressful and anxiety-inducing, leading to panic attacks and lack of sleep."* x *"My sister and I shared the week between us staying over, including our young children, to care for Mum [and] to help her move and support with meals and medication."*	
14	Consultee	Peaches Womb Cancer Trust	**Current treatments are woefully lacking with no standard second line of treatment for endometrial cancer** • NICE recognises that there is a high unmet need for patients with previously treated advanced or recurrent endometrial cancer. • For those who can tolerate it, second line chemotherapy is an option, but this offers little promise of effectiveness ("only 10% to 15%" response rate according to the clinical experts) and serious and debilitating side effects severely impact quality of life. • A diagnosis of advanced or recurrent endometrial cancer is devastating enough, but when patients discover the lack of effective second line treatment options open to them, this provokes feelings of anger, frustration, abandonment and hopelessness. • Patients agree with clinical expert opinion that pembrolizumab and lenvatinib is a 'game changer' and a 'huge step change' in terms of effectiveness, real world patient experience suggesting it is a kinder treatment that will improve quality of life compared to chemotherapy. • There is a high unmet need for a treatment like this and patients justly feel they deserve access to this treatment, and to have hope of living well for longer. **Carer story 4:** John's wife was recently diagnosed with metastatic endometrial cancer, and he feels his life has been destroyed as the future he and his wife had planned, and their desire to grow old together, can no longer happen. Although he and his wife try to live day-by-day as best they can, each day is filled with the knowledge that current chemotherapy offers little hope; knowledge that causes him a great deal of "mental anguish". He describes how he is: *"…distraught by NICE's interim decision. This anguish is compounded by the knowledge that the*	Thank you for your comments. The committee has carefully considered these comments and patient stories. The committee acknowledged the limitations of the existing treatments and the resulting high unmet need (see section 3.1 and 3.15 of the FAD). The committee have also considered the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.

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			Scottish equivalent of NICE, SMC, has approved pembrolizumab and lenvatinib for treatment of my wife's cancer. When clinical experts testify to the committee on 11 October that pembrolizumab and lenvatinib were a 'game changer' and outlined clear benefits to this approach over existing treatment options, I was filled with hope. When the committee stated on 2 November they would not be recommending pembrolizumab and lenvatinib as a treatment this hope was dashed and I was distressed. I have to hide this interim decision from my wife as I know the impact on her will be devastating. *As experts in their field, the committee members know the current chemotherapy options provide little hope to patients like my wife. They know that treatment for patients with this cancer have not changed for decades. They know that immunotherapy is an exciting, developing and promising treatment option. They know their counterparts in Scotland have approved pembrolizumab and lenvatinib. They have listened to the clinical experts and patient representatives, and know the benefits of pembrolizumab and lenvatinib. I have listened to this evidence, and relayed it to my wife. This has had a very positive impact on her mental well-being. I dread that if the committee moves forward with its interim recommendation the impact on my wife will be devastating and she will be left with no hope."* **Patient story 5:** Anne had a recurrence of endometrial cancer that was treated with radiotherapy and chemotherapy but was told that, unfortunately, neither treatment had been successful, and her condition would deteriorate as there were no other treatment options left. Anne describes how at the: *"…last minute I was referred to [a] hospital, nearly 200 miles from where I lived for [a] last ditch operation. The impact this had on not only my life, but for my husband & children/grandchildren etc, was just unimaginable. I had two months of hospitalisation, not allowed visitors, to say I hit rock bottom is an understatement. I am now left incontinent, a permanent stoma and open wound in my back for which I have daily treatment. My life could have been so much better had this alternative treatment been available. Surely women with endometrial cancer deserve better, not to be treated as second class patients. We are worth more than that and what is available to us at the present time."* **Patient and carer quotes:**	

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			i *"I do not feel that there would have been many options available to me, had immunotherapy not been available, and that the conversations with my doctors would have been very different had my recurrence happened before it was available – particularly as I did not respond well to chemotherapy, resulting in a relapse shortly after finishing treatment. From conversations with my oncologist, it seems as though there would be few available options which is not a conversation that I wanted to have at 32." [Patient received pembrolizumab as a monotherapy through special licence].* ii *"My mother has recurrent incurable metastatic endometrial cancer, there is only top up chemotherapy available and psychologically, mentally, and emotionally we feel that there is no other treatment in place as the chemotherapy keeps weakening her and with no knowledge of whether it would help. We are desperate to find alternatives that would be cancer specific."* iii *"On my second chemo I nearly died from severe anaphylactic shock as it turns out I'm severely allergic to paclitaxel. When I saw my oncologist, he told me there are no other chemos to put me on. That feeling that there is medication there to help save my life, but I can't use, and there are no other medications available, it was worse than being told I had cancer. It took away some of the hope that I'm going to survive."* iv *"As a patient, and registered nurse, with recurrent womb cancer NICE should be exploring all options available as the incidence of womb cancer is increasing in the population. At 45 I am not prepared for a terminal diagnosis when there are other options available."* v *"[If NICE decided not to approve pembrolizumab with lenvatinib I would] feel terribly let down and frightened, for myself and for others. I think [people with advanced endometrial cancer] are entitled to have potentially life-saving treatment."* vi *"You hear about all these different treatments out there, and people losing their lives when there are no other treatments available, and then you hear about treatments out there that could save or extend your life but they won't be used because they're too expensive. Nobody can fully understand this without having been in that position themselves."*	
15	Consultee	Peaches Womb Cancer Trust	**There are fewer treatment options for patients facing advanced and recurrent endometrial cancer** • Patients feel that they are being treated unfairly compared to people with other cancers and that they deserve access to newer targeted and more effective treatments.	Thank you for your comments. The committee has carefully considered these comments and patient stories. The committee acknowledged the

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			Patient and carer quotes: *i* *"There are too few options for patients with recurrent endometrial cancer. We are the Cinderellas of the cancer world and deserve better options."* *ii* *"All the other cancers get 'ibs' and 'mabs' but we get nothing - we are the poor relation."* *iii* *"I was alarmed to realise that all I would be offered in both first and second line (if I progressed) would be just the bog-standard traditional chemotherapy. Not a level playing field!"* *iv* *"When I was re-diagnosed, I took a lot of courage and reassurance from others I followed on social media who were 'living with cancer' for many years, such as those with secondary breast cancer. I was horrified to learn that, if I hadn't had access to pembrolizumab, there would not have been any more options available beyond chemotherapy which hadn't been effective for me." [Patient received pembrolizumab as a monotherapy through special licence]* *v* *"What is the future strategy for women who have this cancer if the most promising treatment available is denied to them? What impact will this have on future research into immunotherapy for treating this type of cancer? In brief,* ***what next?*** *If the committee's interim recommendation not to recommend pembrolizumab and lenvatinib is their final decision, I know very well what is next for my wife: months, possibly years of hopelessness, followed by death."* *vi* *"It is my own working theory - from my experience of womb cancer and my husband's of prostate cancer - same time period, different London hospitals - that provision for prostate cancer is 'better' and more joined up." [Received by email from a Peaches Patient Voices member]* *vii* *"I am currently having the combination chemo of paclitaxel and carboplatin which, I am assured, has I good success rate and I have a good prognosis. However, further chemo is likely in the future and, as well as not being the most pleasant treatment, it affects life in so many ways."*	limitations of the existing treatments and the resulting high unmet need (see section 3.1 and 3.15 of the FAD). The committee have also considered the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.
16	Consultee	Peaches Womb Cancer Trust	**Equality of access** • Chemotherapy impacts patients' lives financially due to absence from employment secondary to illness, travel to and from and parking at the hospital, and the cost of living at home (e.g., heating) and alternative therapies. Pembrolizumab infusion is shorter duration and less frequent than chemotherapy which often requires carers to take less time off work to accompany their loved ones. • Chemotherapy is not suitable for many mostly older patients due to comorbidity, however,	Thank you for your comments. The committee has considered these. However, please note: - financial impact – In accordance with NICE's social value judgement principles, no

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 and lenvatinib is likely to be tolerated better than chemotherapy giving those people hope of accessing an effective treatment. • There is an urgent unmet need for patients with mismatch repair proficient tumours (the majority) to have access to an effective treatment. • Pembrolizumab with lenvatinib has recently been approved for use by the Scottish Medical Council. Without approval by NICE, there is a risk of geographical inequalities in access to a second line treatment for advanced and recurrent endometrial cancer.	priority is given based on individuals' income, social class, position in life or social roles in guidance developed for the NHS. NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare. - age and comorbidity – as this treatment has been recommended, it does not exclude any patients by age or comorbidity - there is an unmet need in both subgroups based on mismatch repair status. - geographical location is not a protected characteristic.
17	Consultee	Peaches Womb Cancer Trust	**People affected by endometrial cancer see pembrolizumab and lenvatinib as a source of hope for the future** • When we asked about the impact of potential approval of pembrolizumab and lenvatinib, many patients identified that this is a source of hope for the future and that they are fearful for a future that only includes the current standard treatments. People cited worries about side effects of these treatments and the low response rates and life expectancies on currently available treatments. **Patient and carer quotes:** i *"I feel as if there is a shadow over me and although I consider myself to be a resilient, well-rounded individual, who to all intents and purposes may appear healthy, I am haunted by the spectre of recurrence. If it does return, I would want to know that there were more and different options this time around - such as pembrolizumab and lenvatinib - because I would have little faith in chemotherapy a second time and also because the thought of withdrawing from a job that I love and friends and family again, would be such a hard thing to do. I'm really torn, asking for this, because I know only too well the pressures on the NHS and I know that everything has to be costed and*	Thank you for your comments. The committee has carefully considered these comments and patient stories. The committee acknowledged the advantages of this treatment over the current options including its role in providing hope to patients and their loved ones (see section 3.1 and 3.15 of the FAD). The committee have also considered the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.

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			funded. However, I do feel that if use of treatment other than chemotherapy begins to be the norm, then we can start to build a future where womb cancer can be lived with, alongside a normal life. Then the costs not only of the treatment itself, but costs related to long term collateral damage caused by chemotherapy, will also fall. Pembrolizumab and lenvatinib seem to me to provide the potential to return 'living a life' to endometrial cancer patients, rather than simply a chance of staying alive." *ii "I would be very disappointed [if NICE decided not to recommend pembrolizumab and lenvatinib], as my wife's carer since her diagnosis with womb cancer, and having gone on that journey with her, I strongly feel that any effective treatment should be utilised to fight this cancer as the cancer is extremely dangerous and I would imagine anyone concerned would want to know that there are effective treatments available to help."* *iii "I'd welcome anything that would prolong my life. I'm an active 63 year old and don't want to die from my [advanced endometrial] cancer."* *iv "Everyone deserves a chance at treatment - no matter. With [an advanced stage] cancer hanging over you I feel anything to help is paramount to the mental health of a patient."* *v "It is very important for these drugs to be available to give hope to us who appear to have no other form of treatment available."*	
18	Public	GSK (Company for dostarlimab)	Section 3.5 is titled 'Pembrolizumab plus lenvatinib may be better in dMMR disease than in pMMR disease but there is not enough evidence to conclude this', and the committee concludes 'The committee concluded that the study was not powered to consider subgroups based on MMR status and that the treatment pathways for routinely commissioned treatments for both subgroups are the same. It further concluded that both subgroups have had benefit from pembrolizumab plus lenvatinib compared with doxorubicin or paclitaxel monotherapy.' As noted within this ACD, dostarlimab is recommended via the Cancer Drugs Fund, and is therefore not considered a comparator within scope for this appraisal. GSK requests that the sentence 'However, it is possible that pembrolizumab plus lenvatinib is better than dostarlimab in the dMMR population, but there is no evidence to conclude this' is removed as no evidence or discussion regarding the comparative effectiveness of dostarlimab has been presented, and furthermore this sentence does not serve a purpose within this consultation document to add to the committees conclusions for this appraisal.	Thank you for your comments. The sentence referred to has now been amended to note that dostarlimab and pembrolizumab plus levantinib cannot be compared for this appraisal (see section 3.5).
19	Public – unknown	n/a	Has all of the relevant evidence been taken into account? The committee does not take into account the clear benefits of the technology to patients in reaching its recommendation. This is odd as they are clearly outlined in the documentation.	Thank you for your comment. The committee concludes that pembrolizumab plus lenvatinib improves overall and progression-free survival compared with doxorubicin or

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				paclitaxel monotherapy in (now section 3.4). It also concludes that it is a step change in the treatment of this condition in (now section 3.15).
20	Public – unknown	n/a	Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? No. The cost effectiveness of the therapy is barely mentioned in this documentation. Most of the discussion in the appraisal consultation document reflects discussion of the participants during the meeting on the most appropriate statistical methodology; not on the cost benefit of the technology. The conclusion appears to be ' The committee is unclear on the benefits of the technology in comparison to current treatments.' The outcome of current treatments are clear: dismal outcomes. The current treatments are clearly not cost-effective as the outcomes for patients are dismal. The conclusion of the committee appears to be based on their uncertainty of statistical models as opposed to the clear benefits from clinical practice and the real life experience of those who testified to the committee. The committee does not offer any evidence that the Technology is not cost-effective. They only appear to be able to state 'we can't tell if it's as good as the current treatment.' The current treatment is obviously not cost-effective, in terms of prolonging patients' overall survival rates; therefore, the comparison is nonsensical. The benefits are clear from Clinical practice and real life testimony, which the committee heard; supported by a review of the literature, viz. 'Lenvatinib plus pembrolizumab showed promising antitumor activity in patients with advanced endometrial carcinoma who have experienced disease progression after prior systemic therapy, regardless of tumor MSI status. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7479759/); Pembrolizumab and lenvatinib has emerged as an effective treatment for advanced, previously treated endometrial cancer (https://ijgc.bmj.com/content/32/1/93)'; Conclusions: In this exploratory analysis of pts with advanced EC enrolled in KEY- NOTE-146/study 111 treated with L + P, clinically meaningful responses were achieved regardless of biomarker status, including TMB status, and no gene expression sig- natures were associated with clinical outcomes. Clinical trial identification: NCT02501096; EudraCT 2017-000300-26. https://www.annalsofoncology.org/article/S0923-7534(21)03467-0/pdf; Similar to the global Study 309/KEYNOTE-775 results, this analysis suggested favorable efficacy and manageable safety with lenvatinib plus pembrolizumab after platinum-based chemotherapy in Japanese patients with advanced endometrial cancer and supports this combination as a new standard of care in this population. Lenvatinib plus pembrolizumab in Japanese patients with endometrial cancer: Results from Study 309/KEYNOTE-775 Cancer Science. 2022;113:3489–3497; Optimizing the use of lenvatinib in combination with pembrolizumab in patients with advanced endometrial carcinoma Front. Oncol., 21 September 2022 Sec. Gynecological Oncology https://doi.org/10.3389/fonc.2022.979519'	Thank you for your comment. The appraisals consultation document stated in section 3.13 that the most plausible cost-effectiveness estimate was unknown because the final data cut was not included. As the company has now included the final data cut in the model, the cost-effectiveness estimates are now discussed (see updated section 3.14). As noted above, the benefits of the technology are clearly noted in the guidance (now section 3.4 and 3.15). Concerns with existing treatments are noted (now section 3.1, 3.2 and 3.15). The committee have considered the consultation comments and the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.
21	Public – unknown	n/a	Are the recommendations sound and a suitable basis for guidance to the NHS? No. There is clear evidence that the use of this technology has a beneficial outcome for patients. The committee appears to be objecting to its usage based on a cost. What price a human life? What price for hope for those who have none? The clinicians who testified to the committee noted it was a game changer.	Thank you for your comment. The appraisals consultation document stated in section 3.13 that the most plausible

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			Patients and charities representing them noted the benefits of this technology. The evidence submitted by the committee on the cost model do not appear to be detailed. Current platinum based chemotherapy has dismal outcomes, yes it is fully funded by the NHS. The committee appears to be making its recommendation that it is not worth the money because the outcomes are not clear. The outcomes of not providing this treatment are very clear: death.	cost-effectiveness estimate was unknown because the final data cut was not included. As the company has now included the final data cut in the model, the cost-effectiveness estimates are now discussed (see updated section 3.14). The committee have considered the consultation comments and the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.
22	Public – unknown	n/a	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? This committee's recommendation clearly discriminates against patients who cannot afford private healthcare treatment.	Thank you for your comment. In accordance with NICE's social value judgement principles, no priority is given based on individuals' income, social class, position in life or social roles in guidance developed for the NHS. NICE's standard approach to economic modelling (the 'reference case') does not compare NHS healthcare with privately funded healthcare. However, the committee have considered the model amended by the company which incorporated updated discounts. Pembrolizumab plus lenvatinib is now recommended for this indication.

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NICE National Institute for Health and Care Excellence

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 23 November 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):	**Merck Sharp & Dohme (UK) Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

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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	**Overview of comments by MSD** MSD welcomes the opportunity to comment on the Appraisal Consultation Document (ACD), which confirms that: • Pembrolizumab plus lenvatinib improves overall survival (OS) and progression-free survival (PFS) compared with doxorubicin or paclitaxel monotherapy (ACD 3.4) • Patients benefit from pembrolizumab plus lenvatinib compared with doxorubicin or paclitaxel monotherapy in both mismatch repair subgroups (ACD 3.5) • Pembrolizumab with lenvatinib meets the end of life criteria (ACD 3.12) The draft decision not to recommend pembrolizumab plus lenvatinib is disappointing as it restricts physician and patient access to an efficacious treatment option in a setting where there is currently no standard of care and, therefore, a high unmet medical need. In response to the Committee's request, we provide novel analyses using the final database lock (Data Cut Off, 1 March 2022) that supports access to pembrolizumab plus lenvatinib (PEM + LEN) for these patients. The additional 18 months of follow-up provides strong and consistent evidence of the sustained longer-term benefits of treatment with PEM + LEN. Our ACD response addresses the following areas of uncertainty: • **Assessment of the overall survival extrapolations using the final data cut from the KEYNOTE-775 trial, including exploration of flexible spline models (ACD 3.7, 3.8).** The final data cut demonstrated sustained and consistent clinical benefits for the PEM + LEN group compared with the treating physician's choice (TPC) consisting of paclitaxel or doxorubicin group. Spline models provided an excellent fit to the observed data, tracked well to the smooth hazard plots, and provided clinically plausible extrapolations. As a result spline models are used in the revised base case. • **Adjusting for treatment-switching in patients who received subsequent immunotherapies in the TPC arm (ACD 3.8).** Multiple treatment-switching analyses were explored. These all approaches provided similar results. Hence adjustment for treatment-switching was included in the revised base case. • **Consideration of the plausibility of treatment effect waning assumptions and their impact (ACD 3.9).** There is no observed treatment waning in KEYNOTE-775 at the final database lock. As there is biological rationale supporting the persistence of treatment effects for

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

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	pembrolizumab with lenvatinib, these highly conservative scenarios were not included in the base case analysis, consistent with the EAG approach. In addition to the above, we have explored the Committee's preferences with respect to the final two issues discussed in the ACD. These are applied in our revised base case analysis: • Using progression status to derive utilities • Using an average patient age of 67 that was preferred assumption by the committee. Finally, a technical addendum to this document provides full details of the updates made to the electronic version of the economic model to aid the EAG's review. The FA data from KEYNOTE-775 provides more certainty of the superior clinical effectiveness of PEM + LEN compared with TPC, with respect to PFS and OS (Table 1). The updated model, which now reflects the Committee's views, produces results which consistently demonstrate that pembrolizumab plus lenvatinib is likely to be a cost-effective use of NHS resources under a wide range of scenarios, including too pessimistic assumptions around the duration of treatment effect to enable the Committee to make a positive recommendation for baseline commissioning. This will facilitate rapid access to an innovative treatment for patients that currently lack effective treatment options.
2	**Assessment of the overall survival extrapolations using the final data cut from the KEYNOTE-775 trial** The company submission was based on the interim analyses (IA) of KEYNOTE-775 (data cut off [DCO], 26 October 2020). At the technical engagement stage, the company provided a clinical summary of the final database lock of KEYNOTE-775 (DCO, 1 March 2022). The final analysis (FA) provided approximately 18 months of additional follow-up. The median duration of follow-up at the time of the FA (defined as the time from randomization to date of death or DCO) was 18.7 months (range: 0.3–43.0) in the PEM + LEN arm and 12.2 months (range: 0.3–42.4) in the TPC arm and was 14.7 months (range: 0.3–43.0) for all patients (see Table 1 for a summary of clinical effectiveness). Notably, at the time of the FA, compared with IA, a greater number of patients in the TPC arm of KEYNOTE-775 had switched over to receive subsequent in-study treatment with PEM + LEN or other subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies, thus confounding the unadjusted OS analysis from the trial. Without adjusting for treatment switching in the TPC arm of KEYNOTE-775, estimates of the OS benefit of PEM + LEN compared with TPC are underestimated.

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

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Table 1: Clinical effectiveness summary (KEYNOTE-775 IA and FA)

	Interim Analysis 1		Final Analysis	
	PEM+LEN (n=411)	**TPC (n=416)**	**PEM+LEN (n=411)**	**TPC (n=416)**
Progression-free survival				
Median months (95% CI)	7.2 (5.7-7.6)	3.8 (3.6-4.2)	7.3 (5.7-7.6)	3.8 (3.6-4.2)
HR (95% CI)	0.56 (0.47-0.66)		0.56 (0.48-0.66)	
P-value	*P* <0.0001		*P* <0.0001	
Overall survival				
Median months (95% CI)	18.3 (15.2-20.5)	11.4 (10.5-12.9)	18.7 (15.6-21.3)	11.9 (10.7-13.3)
HR (95% CI)	0.62 (0.51-0.75)		0.65 (0.55-0.77)	
P-value	*P* <0.0001		*P* <0.0001	

Key: CI: confidence interval; HR: hazard ratio; ITT, intention-to-treat; PEM+LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.

In response to the ACD, we have incorporated the FA of KEYNOTE-775 into the economic model. This involved an update of all clinical inputs from the KEYNOTE-775 trial, including OS (with and without adjustment for treatment switching), PFS, time on treatment (TOT), adverse events (AEs) and subsequent therapies. **Full details of the FA update to the economic model are provided in a standalone technical addendum, while the following sections of this document are focused on responding to the issues discussed in the ACD**.

3

Alternative spline models for overall survival as per the Committee's request.

ACD commentary on spline models

The final analyses (FA) of the KEYNOTE-775 trial provides mature and consistent evidence of the sustained longer-term OS benefit associated with treatment with PEM + LEN compared with TPC in endometrial cancer. Median OS was significantly longer in the PEM + LEN arm compared with the TPC arm (18.7 and 11.9 months, respectively), with a hazard ratio (HR) of 0.65 (95% CI: 0.55, 0.77; p < 0.0001) and there is a consistent separation in the OS Kaplan–Meier curves for the entire duration of follow-up. Further details are provided in the economic addendum to this ACD response and in the clinical study report (CSR) update.(1)

The ACD makes clear the importance of ensuring that the economic model uses survival extrapolations that track well to the underlying hazards. We understand that this provides confidence in the ability of the survival extrapolations to reflect realistic and clinically valid

	predictions beyond the observed period, as described in NICE DSU TSD14 and TSD21.(2, 3) In the original submission, this consideration led to our selection of a flexible two-piece survival modelling approach; in their response the EAG suggested that cubic spline models should also be considered and are likely to be preferable.
	
	The advantages of flexible spline models are well-documented.(3) They were developed to capture the underlying shape of hazard functions and have been used across many NICE technology appraisals in oncology for this reason. They can result in more realistic predictions of survival within the observed period, and, ideally, in the long-term extrapolations.
	
	Summary of OS spline models in the PEM + LEN and TPC arm
	
	The consideration of complex hazards remains relevant at the final database lock of KEYNOTE-775, which the one- and two-piece models are not able to resolve. Based on this view in the ACD, we have therefore focused on the Committee's suggestions:
	
	• Analyses of extrapolations based on spline models for OS using the FA data cut as the preferred approach for survival extrapolations to provide a better fit to the hazards (see summary below, and refer to technical addendum for details)
	  ○ TPC arm (unadjusted for treatment switching)
	  ○ TPC arm (adjusted for treatment switching; used in revised base case)
	  ○ PEM + LEN arm (used in revised base case)
	• Incorporation of analyses into cost-effectiveness model (see technical addendum for details)
	
	Consistent with the recommendations in NICE DSU TSD 21 guidance, we used the package *flexsurvspline*, conducted with R statistical software and based on the Royston and Parmar (2002) methodology.(4) Flexible spline functions were individually fitted to each arm of the FA of KEYNOTE-775 trial data for OS and PFS. Splines were modelled on the 'odds', 'hazard' and 'normal' scales. Without knots, these correspond to single piece Weibull, log-logistic and log-normal models, respectively. For each of these scales we fitted spline models based on one, two or three internal knots (k=1, k=2, k=3) placed at uniformly distributed percentiles along uncensored log-times (the standard approach), resulting in a total of nine spline models for each treatment arm.
	
	The assessment of the OS spline models focused on both how well they captured the shape of the hazards and the plausibility of the extrapolated outcomes, using the following process:
	
	• Visual fit to the smooth spline hazard curve
	• Statistical fit by Akaike information criterion (AIC)/Bayesian information criterion (BIC) values
	• Visual fit of the predicted outcomes of the spline models to the observed data
	• Clinical plausibility of the fit to the smooth spline hazard curve and of the predicted

outcomes

Priority was given to retaining the same model type (number of knots and scale) between the arms, following NICE DSU TSD 14 advice.(2) When determining the number of knots among equally well-fitting models, preference was given to lower numbers of knots to ensure that the long-term extrapolations are based on a reliable and sufficient number of events while avoiding over-fitting to the data.

Based on the findings, the one-knot OS spline models (odds scale) provided an excellent fit to the hazards in the TPC and PEM + LEN arms (Figure 1 and Figure 2; see technical addendum for details). A summary is provided below:

- Overall, all of the spline models provided very good statistical and visual fit to the observed Kaplan–Meier data as well as the smooth hazard functions.
- In the TPC arm (unadjusted for treatment switching), AIC/BIC values indicated that the odds and hazards models generally provided the best statistical fit to the data, with the lowest values for the one-knot odds model. The odds scale also provided a slightly better visual fit (Figure 1). This remained true when assessing spline models fit to the TPC arm after adjusting for treatment switching, which is used in the revised base case analysis (please see MSD ACD Response 4).
- In the PEM + LEN arm, AIC/BIC values indicated that the odds and hazards models generally provided the best statistical fit to the data, with the lowest values for the one-knot odds model. The odds scale also provided a slightly better visual fit (Figure 2).
- Of the spline models on the odds scale, there was minimal difference in visual fit when varying the number of knots. The AIC rankings trended in the opposite direction of the BIC rankings which is not surprising as a result of the way these statistics are calculated. Preference was given to the one-knot models as this would ensure that the long-term extrapolations are based on a reliable and sufficient number of events to capture the underlying shape, while avoiding over-fitting to the data.(4, 5)

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	Figure 1: Plot of OS hazard rates in the TPC arm, spline models unadjusted for treatment switching (KEYNOTE-775 FA) [redacted]**Key**: OS, overall survival; TPC, treatment of physician's choice. **Note:** x axis of all plots = time (weeks) **Figure 2: Plot of OS hazard rates in the PEM+LEN arm, spline models (KEYNOTE-775 FA)** [redacted]**Key:** OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib. **Note:** x axis of all plots = time (weeks) **To provide clinical validation of the survival extrapolations based on the FA of KEYNOTE-775 in this ACD response, three individual 45-minute interviews were conducted in November 2022.** These validation interviews also included the results of the treatment switching analysis; described in more detail in the next section (MSD ACD Response 4). Briefly, three clinical experts were consulted to understand the appropriateness of using spline models and to discuss the plausibility of long-term projections. This included landmark survival estimates and mean predicted life years generated from each model. All clinical experts commented that the hazard plots look very similar, but that the odds scale provided a slightly better fit to the smooth hazards. Of the spline models on the odds scale, it was suggested that the one-knot spline model may provide the best fit over time. **In response to the ACD, following clinician input, we have fully incorporated the Committee's suggestion to explore the impact of treatment switching on OS in the TPC arm of KEYNOTE-775. These analyses are described in the next section (MSD ACD Response 4) and are included in the revised base case analysis instead of the unadjusted OS data**.
4	**<u>Treatment switching adjustment for patients who received subsequent immunotherapies in the TPC arm of KEYNOTE-775</u>** ***Overview*** As noted in the ACD, allowing treatment switching in the control arm of clinical trials leads to increased OS compared with that which would be observed in UK practice. Based on the positive outcome of the OS analysis in KEYNOTE-775, participants in the TPC arm who experienced investigator-defined disease progression had the opportunity to crossover to receive PEM + LEN or other subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies. At the final database lock in March 2022, there were a total of [redacted] participants with disease progression in the TPC arm.(1) [redacted] participants randomized to the TPC arm received in-study treatment PEM + LEN or other subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies that are not currently reimbursed in this treatment setting in the UK. In clinical practice, these patients would not have received such treatment and their outcomes are likely to have been worse than seen in the trial. Without adjusting

for treatment switching in the TPC arm of KEYNOTE-775 (as in MSD ACD Response 3), estimates of the OS benefit of PEM + LEN compared with TPC are underestimated.

Consistent with the Committee's suggestion in the ACD to explore treatment switching analysis, there was consensus from the three clinical experts consulted in November 2022 that it is clinically reasonable to use the crossover-adjusted data in the TPC arm. Without such adjustment, TPC OS data are likely over-estimated. These analyses were conducted and incorporated into the revised base case, as described below.

Summary of methods

Following NICE DSU TSD16 guidance, we explored three common methods of adjusting for treatment switching to estimate the true OS benefit of PEM + LEN compared with TPC.(6) Each of the three methods rely on the applicability of various underlying assumptions to produce reliable and unbiased results. There is usually no clear best method for adjustment as it depends on study design, conduct and patient characteristics; therefore, we have tested all three methods using SAS statistical software and assessed the likelihood of the key underlying assumptions holding for each method with respect to the KEYNOTE-775 trial. A summary is provided below. The three methods are:

- Inverse probability of censoring weights (IPCW)
- Rank preserving structural failure time model (RPSFTM)
- Two-stage estimation (TSE)

Results of the treatment switching analysis

An overlay of the unadjusted and adjusted counterfactual data of the TPC arm is presented in Figure 3. The analysis suggests that the unadjusted data overestimate outcomes in the TPC arm of KEYNOTE-775. Irrespective of the method used in the analysis, the adjusted estimates result in consistently lower OS across the entire duration of follow-up.

Figure 3: TPC, OS with and without adjusting for treatment switching (unadjusted KM; and adjusted counterfactual plots using TSE, RPSFT and IPCW methods) - KEYNOTE-775 FA

[redacted] **Key:** KM, Kaplan-Meier; IPCW, inverse probability of censoring weights; OS, overall survival; RPSFT, rank preserving structural failure time model; TPC, treatment of physician's choice; TSE, two-stage estimation.

Adjusted and unadjusted estimates of the HR for the PEM + LEN arm compared with the TPC arm are presented in Table 2, along with estimates of median OS for the TPC arm. These demonstrate a high degree of consistency in estimates of OS. The adjustment for treatment switching

consistently leads to an improvement in the OS benefit of PEM + LEN compared with TPC by reducing the probability of death by approximately [redacted], in favour of PEM + LEN. The HRs for PEM + LEN versus TPC after adjustment for treatment switching ranged from [redacted].

Table 2: Treatment switching analysis results based on final analysis of KEYNOTE-775

Treatment switch adjustment methods	HR (PEM + LEN vs TPC)	Median OS, TPC (months)
Unadjusted	0.65	11.9
TSE – without recensoring	[redacted]	[redacted]
TSE – with recensoring	[redacted]	[redacted]
RPSFT – without recensoring	[redacted]	[redacted]
RPSFT – with recensoring	[redacted]	[redacted]
IPCW	[redacted]	[redacted]

Key: FA, final analyses; HR, hazard ratio; ICPW, inverse probability of censoring weighting; OS, overall survival; PEM + LEN, pembrolizumab plus lenvatinib; RPSFT, rank preserving structural failure time models; TPC, treatment of physician's choice; TSE, two-stage estimation.

Discussion

This section provides an abbreviated summary of the assessment of which treatment switching method to use in the revised base case, per NICE DSU TSD16 guidance (6). All other methods were tested in scenario analyses which demonstrated a small impact on the results. For further details, please refer to the technical addendum.

Of the above methods:

- The IPCW approach was excluded because it can be prone to error when there are small sample sizes assessed as switcher and non-switcher groups.(6) This is particularly relevant in this case, where there was a relatively small number of patients randomized to the TPC arm who received subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies ([redacted] out of [redacted] participants [redacted]). This figure is substantially smaller than seen in some other clinical trials in oncology.
- The RPSFT approach was considered subject to considerable bias in the case of KEYNOTE-775. It is unclear whether the fundamental assumption of the 'common treatment effect' holds. When treatment switching is permitted after disease progression, the capacity for a patient to benefit in the post-progression stages may be different compared with pre-progression. The control arm of KEYNOTE-775 is also an active treatment. Both issues pose limitations to the RPSFT approach.
- The TSE approach was preferred because it avoids the need of the 'common treatment effect' assumption and was considered less prone to bias. The timepoint used to determine

the secondary baseline is based on disease progression, aligned to the trial protocol in the case of KEYNOTE-775. The median time from disease progression until switching was shorter than [redacted] months (approximately [redacted] days), reducing the likelihood of potential bias associated with time-dependent confounding. Although there was some variation in the time taken for participants to switch over, the bias was likely to be small because the majority of switching occurred shortly after disease progression. Finally, one practical advantage of TSE is that it does not require data to be collected on time-dependent covariates other than the timepoint of disease progression.

Based on the above assessment, whilst all methods provided similar estimates, the TSE approach was preferable because the IPCW and RPSFT methods were more prone to bias. Methods of treatment switching adjustment with and without recensoring were also tested to assess the impact of informative censoring. The difference in HRs between TSE with and without recensoring was small; recensoring improved the HR by [redacted] in favour of PEM + LEN vs TPC. Additionally, current research suggests that the 'true' HR will fall between the values estimated with and without recensoring.(7) **In light of the range of HRs after adjusting for treatment switching (HRs between [redacted]), the TSE approach without recensoring (HR = [redacted]) is likely to produce conservative estimates of the clinical and cost effectiveness of PEM + LEN, and was used in the base case to inform the updated cost-effectiveness results. Therefore, ICERs generated by the EAG once commercial arrangements are accounted for**, should still be **considered as an upper limit of cost-effectiveness**.

OS spline models in the TPC arm, adjusted for treatment switching (TSE without recensoring)

With the availability of the counterfactual estimates from the treatment switching analysis, spline models were fitted directly to the counterfactual outputs of the TSE method without recensoring. The approach for fitting and assessing the spline models follows that previously described for the unadjusted dataset (see ACD Response 3 and refer to the technical addendum for further details).

The one-knot spline on the odds scale continued to outperform the other spline models (Figure 4) and was also the preferred model to maintain consistency in the method of extrapolating OS for both the PEM + LEN arm and the unadjusted TPC arm. The extrapolations of OS using the spline models illustrate the similarity in the long-term predictions in the TPC OS estimates after adjusting for treatment switching (Figure 5).

Figure 4: Plot of OS hazard rates in the TPC arm, spline models adjusted for treatment

switching (KEYNOTE-775 FA)

[redacted]**Key:** OS, overall survival; TPC, treatment of physician's choice.
Note: x axis of all plots = time (weeks)

Figure 5: Final OS models in the revised base case, PEM + LEN (one-knot spline) and TPC arm (one-knot spline adjusted for treatment switching, TSE without recensoring) – KEYNOTE-775 FA

[redacted]**Key:** adj, adjusted for treatment switching; KM, Kaplan-Meier; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice; TSE, two-stage estimation.

Three UK clinical experts commented on the reliability of long-term projections, including landmark survival estimates and mean predicted life years generated from each flexible model.(8) Details are provided in the technical addendum, with a summary below:

- TPC OS should be adjusted for treatment switching, both from a treatment pathway and clinical efficacy perspective. Clinicians expected the OS outcomes in the TPC arm to worsen, after applying the adjustment
- The one-knot spline models (odds scale) provide a good fit to the observed data, and reasonable extrapolations in both the PEM + LEN and TPC arms
- The spline models provided a good fit to the observed data, within the trial period. Additionally, all clinical experts commented that the hazard plots look very similar, but that the odds scale provided a better fit to the smooth hazard functions. This was more pronounced in the TPC arm
- Of the spline models on the odds scale, clinical experts commented on the similarity of the plots when varying the number of knots. The one-knot spline models may provide a slightly better fit over time but it was difficult to differentiate between the plots in some cases
- The long-term projections were also similar, based on visual assessment of the extrapolated curves, landmark survival estimates, median estimates and mean predicted life years generated from each flexible model. Based on the above assessment, the revised base case uses the one-knot spline model to extrapolate OS after adjusting for treatment switching in the TPC arm.

Table 3: OS estimates at landmark time points (KEYNOTE-775 FA)

TPC arm	1 yr	5 yr	10 yr	Mean (years)	Median (years)
Observed KM (KEYNOTE-775)	[redacted]	-	-	-	-
Unadjusted OS spline 1-knot[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Unadjusted OS spline 2-knot[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS spline 3-knot[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS spline 1-knot[a,b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS spline 2-knot[a,b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS spline 3-knot[a,b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS via HR[a,b,c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEM + LEN arm	**1 yr**	**5 yr**	**10 yr**	**Mean (years)**	**Median (years)**
Observed KM (KEYNOTE-775)	[redacted]	-	-	-	-
OS spline 1-knot[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS spline 2-knot[d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS spline 3-knot [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: FA, final analysis (of KEYNOTE-775); KM, Kaplan-Meier; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; TPC, treatment of physician's choice of paclitaxel or doxorubicin

Notes:

a. OS spline model on odds scale, independently fitted to the TPC data of KEYNOTE-775; based on best fit to the smooth hazard plot and observed data from trial
b. TSE method without recensoring; OS spline model independently fitted to the counterfactual estimates from the adjusted TPC arm; based on assessment of most reliable approach to minimise risk of bias in the results; further details available in technical addendum
c. TSE method (see above); HR estimate applied to the PEM + LEN arm as reference curve; further details available in technical addendum
d. OS spline model on odds scale, independently fitted to the PEM + LEN data of KEYNOTE-775; based on best fit to the smooth hazard plot and observed data from trial

Impact of analysis on cost-effectiveness results

The treatment switching analysis was conducted to adjust for the impact on OS as a result of treatment switching in the TPC arm, to estimate the true benefit of PEM + LEN compared with TPC. This is considered more appropriate for a UK NHS setting where subsequent immunotherapies or VEGF/VEGFR inhibitor therapies are not available in clinical practice. Given the importance of these analyses from a clinical perspective, the results were incorporated into the revised base case in the economic model (see Figure 5 for an overlay of curves in the revised base case, with results summarised in Table 4). Further details are available in the technical addendum.

For comparison purposes, we present a range of scenarios which demonstrate the small impact on the results (Table 4). Consistency in the ICERs across the selection of methods supports the reliability of the analyses for use in decision making. As previously noted, the base case ICER is likely to be over-estimated, due to the conservative approach of using the TSE method without recensoring.

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Table 4: Revised base case using FA of KEYNOTE-775, incorporating OS spline model for PEM + LEN and HR adjusted for treatment switching in the TPC arm; see technical addendum for full details (with pembrolizumab CAA; costs and health outcomes discounted at 3.5%)

Scenario	ICER (£ per QALY)	Difference vs revised base case
Revised base case • PEM + LEN OS: One-knot splines • TPC OS: One-knot splines (adjusted for treatment switching; TSE, without recensoring) • PFS, TOT, AEs, HRQL and subsequent treatments also updated using FA data cut (see technical addendum)	[redacted]	-
TPC OS: Scenarios testing for impact of alternative treatment switching adjustment methods in the TPC arm		
HR adjusted for treatment switching ([redacted]; TSE, without recensoring)	[redacted]	[redacted]
HR adjusted for treatment switching ([redacted]; TSE, **with** recensoring)	[redacted]	[redacted]
TPC OS: Scenarios testing for the impact of unadjusted TPC arm		
HR unadjusted for treatment switching ([redacted])	[redacted]	[redacted]
Unadjusted TPC one-knot spline model	[redacted]	[redacted]

Key: AE, adverse event; CAA, commercial access agreement; FA, final analyses; HR, hazard ratio; HRQL, health related quality of life; ICER, incremental cost-effectiveness ratio; ICPW, inverse probability of censoring weighting; OS, overall survival; PEM + LEN, pembrolizumab plus lenvatinib; PFS, progression-free survival; QALY, quality-adjusted life year; RPSFT, rank preserving structural failure time models; TOT, time on treatment; TPC, treatment of physician's choice; TSE, two stage estimation.

Notes: In addition to the new OS analyses, these results also incorporate other clinical endpoints that were updated to reflect the FA of KEYNOTE-775, including PFS, TOT, AEs, HRQL and subsequent treatments (please see technical addendum for full details).

Validating OS in the TPC arm based on real-world evidence (Heffernan, 2022)

To better understand the predicted outcomes in the TPC arm of the economic model, clinical experts were consulted to explore the comparability of the KEYNOTE-775 and Heffernan (2022) real-world study populations. Details of the Heffernan (2022) real-world study became available in the public domain after the initial company submission date for ID3811.(9) As a single-arm, real-world study, there remains severe limitations of the use of this data to validate the results from the Phase III randomized controlled trial, KEYNOTE-775.

There is a degree of consistency in the naïve comparison of median OS results based on the full populations of each study. The median survival in Heffernan (2022) in the total assessed population was 10.3 months (95% confidence interval [CI], 9.2–11.1). When assessing the breakdown of

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	results by type of treatment received in the second-line setting, median OS ranged from 4.9–14.2 months. Median OS reported in the TPC arm, based on the FA of KEYNOTE-775 trial, was 11.9 months. After adjusting for treatment switching in the TPC arm, median estimates ranged from [redacted] months. The EAG have previously queried the reasons for differences in the median OS values between patients who specifically received paclitaxel (n = 93) or liposomal doxorubicin monotherapy (n = 130) in Heffernan (2022). These cannot be explained with certainty, however, clinical experts suggested that: • ECOG PS was only reported for approximately half of the patients in the Heffernan (2022), which provides an incomplete view of the population on this measure alone and is ultimately a major limitation of this interpreting the types of patients or the results from this study. • Compared with KEYNOTE-775, the Heffernan (2022) population had a higher proportion of patients with serous histology type (25% vs 42%, respectively), a greater proportion of patients with initial diagnosis at Stage III or IV disease (65% vs 78%, respectively). These differences are likely to have a negative impact on prognosis in the Heffernan (2022) study population. • There could be some differences in the types of patients based on use of platinum doublet therapies; however, the baseline characteristics data are incomplete and there is no further information available to understand these differences. In summary, incomplete information from the real-world study prevents any useful interpretation of how this applies to the decision problem. **MSD believes that the Heffernan (2022) study has severe limitations for applicability for the KEYNOTE-775 and cannot be used to meaningfully validate or invalidate the outcomes for this appraisal.**
5	**<u>Alternative scenarios for treatment waning</u>** We understand the relevancy of this topic; however, there is no evidence of a treatment waning effect with PEM + LEN based on the KEYNOTE-775 trial. The OS and PFS results provide evidence of a sustained longer-term comparative benefit of PEM + LEN compared with TPC that is numerically consistent between the IA and FA data cuts.(1) **Long term available data showing no signs of waning** <u>Biological reason:</u> The marketing authorisation states that lenvatinib is administered until disease progression. There is biological evidence and rationale suggesting that lenvatinib helps shift the tumour microenvironment to an immune-stimulatory state by inhibiting VEGFR and FGFR.(10) In mouse models, lenvatinib plus PD-1 inhibition had significantly greater antitumour activity than either agent

alone. On this basis, pembrolizumab with lenvatinib act in a synergistic way to provide a positive enhancement of the tumour microenvironment by improving the action of each drug given in isolation. This hypothesis is consistent with data for other IO agents and IO combinations, which offer robust evidence on the durability of the treatment effect associated with IOs in metastatic treatment (refer to table below for a summary of this).This treatment combination was not been subjected to treatment waning assumptions in another NICE technology appraisals (11). It is unclear why it would apply in this case since patients in KEYNOTE-775 may continue to receive lenvatinib monotherapy even after stopping treatment with pembrolizumab (at the last recorded time point around 3 years' follow-up, there were [redacted]% of patients still receiving lenvatinib in KEYNOTE-775). UK clinical experts consulted in November 2022 confirmed that a proportion of patients will have durable response to PEM + LEN. In addition, patients who are considered to benefit from further treatment may very well receive continued treatment with lenvatinib monotherapy even after pembrolizumab has stopped in a real-world setting, as in the KEYNOTE-775 trial.

Long term data:

A long- term OS data for endometrial patients treated with PEM+LEN is available for the KEYNOTE-146 (12). This is a multi-centre, open-label arm Phase Ib/II basket trial of selected solid tumours (n=108 had pre-treated EC) with a median follow-up 34.7 months. The observed data proved durable and sustained treatment effect beyond the 2-year treatment period with PEM+LEN. This is corroborated by data from KEYNOTE-775 (Document B Figure 9), which details distinct evidence of sustained OS for PEM+LEN in the form of a plateau with 30% of patients alive at 5 years. We do acknowledge there are some limitations for applicability, but this is longest available data for this treatment combination and therefore constitutes a key piece in the evidence under consideration around the durability of the treatment effect.

Other pembrolizumab long term studies:

The OS and PFS results provide evidence of a sustained longer-term comparative benefit of PEM + LEN compared with TPC that is numerically consistent between the IA and FA data cuts.(1) Multiple randomized controlled trials that have reported 5-year data for pembrolizumab. All of these demonstrated a sustained treatment effect, with two studies conducted specifically in the second-line treatment setting.

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

	Tumour	OS		Reference
		2 years	5 years	
KEYNOTE-775 - Company model	Endometrial	40.6%	[redacted]%	-
KEYNOTE-146	Endometrial	42.0%	30.0%	(12)
KEYNOTE-006	Melanoma	60.0%	45.0%	(13)
KEYNOTE-010 TPS ≥50%	NSCLC	34.5%	25.0%	(14)

KEYNOTE-010 TPS ≥1%	NSCLC	22.9%	15.6%	(14)
KEYNOTE-024	NSCLC	50.0%	31.9%	(15)
KEYNOTE-189*	NSCLC	45.7%	19.4%	(16)
KEYNOTE-402 TPS ≥1%	NSCLC	38.9%	16.6%	(17)
KEYNOTE-407*	NSCLC	36.0%	18.4%	(18)
Key: NSCLC – Non-Small Cell Lung Cancer. TPS: Tumour Proportion Score *included approximately 1/3 PDL1 negative patients				

We have not conducted a full systematic literature review on long term treatment effect durability, however in addition to the studies reported above , there is additional long term clinical evidence from melanoma which demonstrate the durability of treatment effect for anti-CTLA4 agents. These work in a similar fashion to anti-PD-1 agents such as pembrolizumab. Schadendorf et al 2015 reports a durable clinical benefit starting from year 3 that is maintained up to year 10 for advanced melanoma. (19) Whilst these are different tumor microenvironments which limits the generalisability of this evidence, it is relevant for this advanced endometrial cancer assessment that there is biological plausibility to a plateau. To date there is no evidence suggesting why a similar plateau would not be observed in pembrolizumab + lenvatinib combinations. Considering also clinical evidence from KEYNOTE-146 which reports 5 year OS estimate of 30%. We therefore consider any waning of treatment effect to be implausible and inappropriate in this combination treatment.

Treatment effect and discontinuation of pembrolizumab:

It is important to note that long-term data support a sustained treatment effect post discontinuation of pembrolizumab. One of the examples with a long-term data is in melanoma patients. In KEYNOTE-006 a long-term survival benefit has been observed in patients with advanced melanoma who were treated with pembrolizumab for up to 2 years. In patients who ceased treatment after completing 35 doses of pembrolizumab at 2 years, 78.4% remained in progression-free survival for at least 24 months (censored) following discontinuation.(13) The long-term outcome seen in KEYNOTE-006 is generally consistent with the outcome seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule. (20) The cumulative and log-cumulative hazard plots below show that there is no structural difference between the hazards in these two trials (Figure 6, Figure 7 and Figure 8). This data points towards a sustained treatment effect post discontinuation of pembrolizumab in melanoma and other patients treated with pembrolizumab.

Figure 6: Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001

[redacted]

Figure 7: Cumulative and log-cumulative hazard plots for OS in KEYNOTE-006

[redacted]

Figure 8: Comparison of Overall Survival curves of KEYNOTE-001 and KEYNOTE-006 in advanced melanoma

[redacted]

Same trends in hazards were observed in the KEYNOTE-024. The following tables show the PFS and OS hazard ratios from KEYNOTE-024 reported in the 1-, 2-, 3- and 5-year publications. If treatment waning began at 2 years we should expect some upward drift in the hazard ratios by the 5 year cut-off, which is not observed, despite crossover being allowed in the study and 66% of patients in the chemotherapy arm receiving immunotherapy on progression.

Table 6: KEYNOTE-024 PFS and OS HRs

KN024 Analysis	PFS HR	OS HR	Source
1-year	0.5	0.62	(21)
2-year	NR	0.63	(22)
3-year	NR	0.65	(23)
5-year	0.5	0.60	(15)

The provided data from various long-follow up studies mentioned above provides no evidence in support of a treatment waning effect for which clinical evidence is collected.

Conditional survival

When discussing treatment effect waning one must consider conditional survival probability. Several studies reported conditional survival in endometrial patients. It is clear that there is a higher survival probability for long term survival which notes a decreasing risk of death over time. (24, 25) The conditional relative survival rates for patients with EC improved with increased time elapsed from diagnosis. The discussed treatment combination provides the additional time in PFS and OS. At FA KEYNOTE-775 patient have longer median PFS in the PEM + LEN arm versus TPC arm (7.3 months vs 3.8 moths in all-comer, HR: 0.56), a longer median duration of response (12.9 months vs 5.7 months in all-comer), and a longer median OS (18.7 months vs 11.9 months in all-comer, HR: 0.65) (26).

Waning scenarios:

Although MSD maintains its views around the durability of long-term treatment effect of PEM + LEN, we explored the potential impact on the results, as suggested by the Committee for scenarios on the basis of the clinical evidence presented above. Results are presented for the following scenarios (Table 7**Error! Reference source not found.**):

- Waning effect from 5–7 years after stopping treatment, given no waning at all has been

observed in KEYNOTE-775 or in the 5-year pembrolizumab trials in other indications to date

- Application of the treatment waning effect to between 60-80% of patients in the PEM + LEN arm to reflect a small proportion of patients experiencing durable response and prolonged immunotherapeutic effect after stopping treatment with pembrolizumab, while a proportion of patients will also continue treatment with lenvatinib monotherapy.

Table 7: Scenarios exploring potential impact of treatment waning assumptions in the PEM + LEN arm (pembrolizumab CAA applied only, lenvatinib list price)

Scenario	ICER (£ per QALY)	Difference vs revised base case
Revised base case	[redacted]	-
Waning between 5–7 years after stopping treatment (70% of patients)	[redacted]	[redacted]
Waning between 5–7 years after stopping treatment (60% of patients)	[redacted]	[redacted]
Waning between 5–7 years after stopping treatment (80% of patients)	[redacted]	[redacted]

MSD urges the Committee to consider these cost-effectiveness analyses only as pessimistic scenarios for decision making purposes given the scarcity of robust clinical evidence in this topic and the totality of the arguments presented above.

6

Using progression status to derive utilities

We are grateful for the Committee's careful consideration in the ACD regarding the methods used to predict utility, and the implications for use in health economic modelling. The ACD notes that the time-to-death (TTD) utility approach may provide more granular information but that the approach in the initial submission limited the amount of information informing the health states because it did not include disease progression as a predictive covariate.

To address this issue, we have conducted further analysis using an extended approach to the initial TTD utility method with disease progression as a covariate to predict utility, and a scenario following the general approach and rationale in the dostarlimab appraisal (TA779). There was a small impact on the results. This analysis is based on the FA of KEYNOTE-775, with full details provided in the technical addendum.

Table 8: Scenario analyses exploring the impact of utilities assumptions (pembrolizumab

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

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CAA applied only, lenvatinib list price)

Scenario	ICER (£ per QALY)	Difference vs. revised base case
Revised base case (TTD utilities with disease progression as covariate)	[redacted]	-
Alternative scenario: TTD utilities with disease progression as covariate (methodologically similar to the approach accepted in TA779)	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; with lenvatinib; QALYs, quality-adjusted life years		

7

Using an average patient age in the model based on committee preferred value

We acknowledge the Committee's preferred assumption to use the average age of patients reported in the ECHO study. This was based on the view that the average patient age in clinical practice would be slightly higher than that used by the company (63.5 years, based on the KEYNOTE-775 trial) and less than that assumed by the EAG (75.0 years, based on the EAG's clinical advisor). Heffernan (2022) provides another alternative value for the mean age of this patient cohort, which sits between the lower and upper ranges.(9) This has been tested in scenario analyses, which demonstrate that the model results are not sensitive to the input value.

The Committee's preference to assume a mean patient age of 67 years has been incorporated in the updated model, and applied in the revised base case (Table 9). Patient age is not a key driver of the cost-effectiveness of PEM + LEN versus TPC as it has only a small impact on the ICER.

Table 9: Scenarios exploring impact of patient age in the economic model (pembrolizumab CAA applied only, lenvatinib list price)

Scenario	ICER (£ per QALY)	Difference vs revised base case
Revised base case (mean age = 67)	[redacted]	-
Mean age in model: Scenarios testing alternative assumptions		
Mean age (years) = 63.5 (KEYNOTE-775; company submission)	[redacted]	[redacted]
Mean age (years) = 65.5 (Heffernan, 2022; company revised scenario)	[redacted]	[redacted]
Key: ICER, incremental cost-effectiveness ratio; with lenvatinib; QALYs, quality-adjusted life years		

8

Revised base case analysis

The FA data of KEYNOTE-775 has been incorporated into a revised version of the economic model and we have provided a revised base case which incorporates the Committee's views. Full details

are provided in a technical addendum to provide transparency and to aide review of the updates.

In summary, the following updates have been incorporated in the revised base case analysis:

- All clinical inputs updated with the KEYNOTE-775 FA data, including OS, PFS, TOT, lenvatinib dosing schedule, subsequent treatments and adverse events (ACD 3.8; MSD ACD Response 2 and technical addendum)
- OS extrapolations based on a one-knot spline model for the PEM + LEN arm, which provides an excellent fit to the hazards for each arm (ACD 3.8; MSD ACD Response 3)
- OS adjusted for treatment-switching in the TPC arm, to account for subsequent immunotherapies or PD1/VEGF inhibitors that are not reimbursed in the UK, using a one-knot spline models that provide a consistent approach with the PEM + LEN arm above (ACD 3.8; MSD ACD Response 4)
- Utility values following a progression-based analysis by TTD (ACD 3.10; MSD ACD Response 6)
- Mean patient age (67 years) based on the committee preferred age (ACD 3.11; MSD ACD Response 7)

The results demonstrate that at the final database lock, PEM + LEN remains a cost-effective treatment option in a patient setting where there is a high unmet need and no current standard of care (Table 10). Further scenarios have been updated and provided to explore the impact of various assumptions in response to comments in the ACD. These have been collated in Table 11 below.

Table 10: Revised base case results (FA of KEYNOTE-775) including CAA for pembrolizumab (pembrolizumab CAA applied only, lenvatinib list price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
PEM + LEN	[redacted]	[redacted]	[redacted]	-	-	-	-
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: FA, final analyses; CAA, commercial access agreement; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PEM+LEN, pembrolizumab with lenvatinib; QALYs, quality-adjusted life years; TPC, treatment of physician's choice.

Table 11: Scenario analyses (FA of KEYNOTE-775) including CAA for pembrolizumab (pembrolizumab CAA applied only, lenvatinib list price)

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

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Parameter	Base case	Scenario analysis	Justification	ICER (£ per QALY)	Difference vs. revised base case
Base case				[redacted]	
Time horizon, 30 years	40	30	NICE reference case, alternative time horizon	[redacted]	[redacted]
Discount rate (costs and utilities) – 1.5%	0	0	NICE reference case, alternative time discounting assumptions	[redacted]	[redacted]
Baseline characteristics					
Mean age (years) = 63.5 (KEYNOTE-775)	67.7	63.5	Testing for the impact of patient age	[redacted]	[redacted]
Mean age (years) = 65.5 (Heffernan, 2022)	67.7	65.5		[redacted]	[redacted]
OS (KEYNOTE-775 FA)					
TPC OS: HR adjusted for treatment switching ([redacted]; TSE, without recensoring)	One-knot splines (adjusted for treatment switching; TSE, without recensoring)	HR=0.60	Testing for impact of alternative treatment switching adjustment methods in the TPC arm	[redacted]	[redacted]
TPC OS: HR adjusted for treatment switching ([redacted]; TSE, with recensoring)		HR=0.55		[redacted]	[redacted]
TPC OS: HR unadjusted for treatment switching ([redacted]) Unadjusted TPC one-knot spline model		HR=0.65	Testing for the impact of unadjusted TPC arm	[redacted]	[redacted]
TPC OS: Unadjusted TPC one-knot spline model		Unadjusted TPC one-knot spline model		[redacted]	[redacted]
Treatment waning					
Waning between 5–7 years after stopping treatment (70% of patients)	No waning	5–7 years after stopping treatment (70% of patients)	Testing the impact of treatment waning assumptions	[redacted]	[redacted]
Waning between 5–7 years after stopping treatment (60% of patients)		5–7 years after stopping treatment (60% of patients)		[redacted]	[redacted]
Waning between 5–7 years after stopping		5–7 years after		[redacted]	[redacted]

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	treatment (80% of patients)		stopping treatment (80% of patients)			
	TOT (KEYNOTE-775 FA)					
	TOT: Next best plausible curve fit, Log-logistic (PEM), Weibull (LEN and TPC)	Generalized gamma	Log-logistic (PEM), Weibull (LEN and TPC)	Alternative structural assumptions surrounding TOT extrapolation	[redacted]	[redacted]
	TOT: Pembrolizumab and TPC KM	Capped by PFS	KM		[redacted]	[redacted]
	Utilities (KEYNOTE-775 FA)					
	Utility: Regression Model 4: TTD utilities with disease progression as covariate (methodologically similar to the approach accepted in TA779)	Model 3	Model 4	Alternative utility assumptions	[redacted]	[redacted]
	Safety: TTD utility, No disutilities	Model 3	Model 3		[redacted]	[redacted]
	Utility: Age-adjusted utilities, No	Yes	No		[redacted]	[redacted]
	Costs					
	Costs: Use caelyx to cost for doxorubicin, Yes	No	Yes	Alternative costing assumptions	[redacted]	[redacted]
	Safety: Include AE costs, No	Yes	No		[redacted]	[redacted]
	Costs: Vial sharing, Yes	No	Yes		[redacted]	[redacted]
	Key: AE, adverse event; CAA, commercial access agreement; FA, final analysis; HR, hazard ratio ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; PEM + LEN, pembrolizumab with lenvatinib; TOT, time on treatment; TPC, treatment of physician's choice; TSE, two stage estimation, time to death.					

Insert extra rows as needed

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(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
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Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 23 November 2022. Please submit via NICE Docs.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Technical addendum (model updates in response to the ACD)

November 2022

Contents

Tables and figures

Overview

Executive summary

- This addendum provides a description of all updates made to the economic model in response to the ACD. The model structure remains the same as in the company submission; all safety and efficacy inputs were updated to reflect the final analysis (FA) of KEYNOTE-775 (outlined in Table 1 and Table 2)
- Three key additional analyses were included in the updated economic model, based on the Committee's views in the ACD:
  - Flexible spline models were conducted to ensure that the extrapolations track well to the underlying hazards for overall survival (OS). For consistency in the methods, splines were also implemented for progression-free survival (PFS) (Section 1.2)
  - Treatment switching analyses were conducted to adjust for the receipt of subsequent programmed cell death protein 1/programmed death-ligand 1 (PD1/PD-L1) or vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) inhibitor therapies that are not currently reimbursed in this treatment setting in the UK. Without adjusting for treatment switching in the treatment of physician's choice (TPC) arm of KEYNOTE-775, estimates of the overall survival (OS) benefit of pembrolizumab with lenvatinib (PEM + LEN) compared with TPC are underestimated (Section 1.3.2)
  - Extended utility regression model that includes adverse events (AEs), time to death and disease progression as predictive variables. This approach is an extension of the utility models in the company submission, and similar to that accepted in a recent appraisal (Section 1.6)
- Furthermore, several scenario analyses have been incorporated to address some of the Committee's comments in the ACD (Section 1.9.3)
  - There continues to be no evidence to substantiate or quantify the potential impact of treatment waning assumptions for this appraisal, which is understood as the main reason for the External Assessment Group (EAG) not applying treatment waning in their base case at the technical engagement

stage. Nonetheless, in response to the ACD, treatment waning has been incorporated into the economic model as a gradual effect in the PEM + LEN arm (Section 1.5.2)

- **The availability of the evidence from the FA of KEYNOTE-775 provides certainty around the clinical and cost effectiveness of PEM + LEN** to enable the Committee to make a positive recommendation for baseline commissioning. This would enable rapid access to an innovative treatment for patients that currently lack effective treatment options
- **The revised base case analysis shows that PEM + LEN is estimated to offer a substantial incremental health benefit compared with TPC at an incremental cost-effectiveness ratio (ICER) of [redacted] per quality-adjusted life year (QALY) gained (including the commercial access agreement [CAS] for pembrolizumab)**
  - PEM + LEN is associated with an additional [redacted] years (LYs) and 0.96 QALYs per patient lifetime (a total of [redacted] LYs and [redacted] QALYs for PEM + LEN compared with [redacted] LYs and [redacted] QALYs for TPC)
  - This level of benefit supports the importance of PEM + LEN as a treatment for patients with advanced or recurrent endometrial cancer who have disease progression on or following prior treatment with a platinum-containing therapy who would otherwise face a poor prognosis under highly limited treatment options
  - As in the company submission, the ICERs are primarily driven by a longer duration of treatment for PEM + LEN coupled with the cost difference as a result of TPC being available in generic formulation

The economic model has been previously described in the Document B, Section B.3 of the initial submission. This technical addendum outlines any changes made to the model in response to the ACD. Unless specified otherwise, data presented in this addendum refer to the FA data cut. Table 1 provides an overview of the key data sources in the revised model. Updates to the model were implemented starting from the '*ID3811 PEM+LEN previously treated advanced EC ERG model EAGScenarios v2.2 22.06.22_pembro PAS removed (ACIC,no cPAS)*' version of the economic

model received by NICE on 22nd June 2022. Table 2 summarizes the changes applied to the company revised base case in response to the ACD.

Table 1: Overview of key data sources used in the economic model

Model input	Company submission (Document B)	Revised model (ACD response)	Reference in this document
OS	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.3
PFS	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.4
TOT	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.5
% Receiving subsequent treatment	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.8.2
% Distribution of subsequent treatment	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.8.2
AEs (safety)	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.7
Utilities	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.6
Unit costs	No change – NHS/UK databases (Schedule of Reference Costs)	No change required	N/A
Resource use type/frequency	No change – Assumptions/clinical opinion	No change required	N/A
Age at baseline	KEYNOTE-775 IA	Committee preferred age (see ACD)	N/A
Weight at baseline	KEYNOTE-775 IA	No change required	N/A
Lenvatinib dosing module	KEYNOTE-775 IA	KEYNOTE-775 FA	Section 1.8.1
Key: ACD, appraisal consultation document; AEs, adverse events; DCO, data cut off; FA, final analysis, (DCO March 2022); IA, interim analyses (DCO October 2020); OS, overall survival; PFS, progression-free survival; TOT, time on treatment; TTD, time to death.			

Table 2: Summary of changes incorporated into the updated base case analysis in response to ACD

ACD response	Committee's preferred analysis	Company's response	
		Reference in this document	Analysis provided
3.7	Assess the overall survival extrapolations using the final data cut from the KEYNOTE-775 trial*	Section 1.2	Incorporated in revised base case
3.8	Explore spline models to provide a better fit to the hazards from the KEYNOTE-775 trial	Section 1.3	Incorporated in revised base case

ACD response	Committee's preferred analysis	Company's response	
		Reference in this document	Analysis provided
3.8	Explore the impact of treatment-switching adjustment for patients who received subsequent immunotherapies in the TPC arm	Section 1.3.2	Scenario analysis
3.9	Explore scenarios for treatment waning	Section 1.5.2	Scenario analysis
3.11	Committee preferred mean age	N/A (see ACD)	Incorporated in revised base case
3.10	Utilities based on disease progression status	Section 1.6	Incorporated in revised base case
Note: *A complete update of the efficacy and safety data has been incorporated, using the final data cut from KEYNOTE-775.			

1. Economic analysis

The patient population, model structure, intervention technology and comparators remain the same as before. Please refer to Document B Section B.3.2 for a full description.

1.1. Overview of clinical data sources and outcomes in the economic model

The initial submission was based on the interim analyses (IA) of KEYNOTE-775 (data cut off [DCO], 26 October 2020). In response to the appraisal consultation document (ACD), the model has been updated to incorporate the final DCO of the trial (DCO, 1 March 2022). This is referred to as the final analysis (FA) from hereon.

The median duration of follow-up at the time of the FA (defined as the time from randomization to date of death or DCO) was 18.7 months (range: 0.3–43.0) in the pembrolizumab with lenvatinib (PEM + LEN) arm and 12.2 months (range: 0.3–42.4) in the treatment of physician's choice of paclitaxel or doxorubicin (TPC) arm and was 14.7 months (range: 0.3–43.0) for all patients.(1) With an additional 18 months of follow-up, the FA of the KEYNOTE-775 trial provides strong and consistent evidence of the sustained longer-term benefits associated with treatment with PEM + LEN compared with TPC in endometrial cancer.

All clinical parameters have been updated to reflect the FA of KEYNOTE-775 in the economic model (see Table 1 for an overview):

- Overall survival (OS)
- Progression-free survival (PFS)
- Time on treatment (TOT)
- Health-related quality of life (HRQL)
- Adverse events (AEs)
- Subsequent treatments

Table 3: Summary of OS and PFS models selected for economic analysis (PEM + LEN and TPC) – KEYNOTE-775 FA

Analysis	OS model	Justification	PFS model	Justification
Revised base case	PEM + LEN: One-knot splines TPC: One-knot splines (after adjusting for treatment switching)	Best visual fit to the short- and long-term smoothed hazard plots, especially in TPC arm but also PEM + LEN Supported by good statistical fit based on AIC/BIC values Excellent fit to the observed KM data for PEM + LEN and TPC Validated with clinical experts	PEM + LEN: One-knot splines TPC: One-knot splines	PFS data are highly mature for both arms and all curves fit well to the smoothed hazards and observed data For consistency with the OS approach, the same type of model is used for PFS(2)
Scenarios tested	TPC: HR adjusted for treatment switching, applied to PEM + LEN as reference curve	Demonstrate impact of method of treatment switching approach in the TPC arm	-	-
	TPC: One-knot splines (without adjusting for treatment switching)	Demonstrate impact of treatment switching in the TPC arm	-	-

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; FA, final analysis; HR, hazard ratio; KM, Kaplan–Meier, PEM + LEN, pembrolizumab with lenvatinib; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice.

1.2. Approach to time-to-event analysis

Key efficacy outcomes (OS, PFS and TOT) for PEM + LEN and TPC were modelled using patient-level data from KEYNOTE-775 (DCO, 1 March 2022).(1) In the ACD, the EAG and Committee preferred cubic splines methods to ensure that the extrapolations track well to the underlying hazards. The consideration of complex hazards remains relevant at the final database lock of KEYNOTE-775, which the one- and two-piece models will not be able to resolve.

Based on this view in the ACD and to streamline the number of analyses conducted over a relatively short amount of time, **this update focuses on the assessment and incorporation of flexible spline models as the preferred approach to extrapolating survival in the ACD**.

Consistent with the recommendations in NICE DSU TSD21 guidance, we used the package *flexsurvspline*, conducted with R statistical software and based on the Royston and Parmar (2002) methodology.(3, 4) Flexible splines functions were individually fitted to each arm of the FA of KEYNOTE-775 trial data for OS and PFS. Splines were modelled on the 'odds', 'hazard' and 'normal' scales. Without knots, these would correspond to single piece Weibull, log-logistic and log-normal models. For each of these scales we fitted spline models based on one, two or three knots (k=1, k=2, k=3), resulting in a total of nine spline models for each treatment arm.

The assessment of the OS spline models focused on how well they captured the shape of the hazards by statistical and visual fit, reflecting the EAG and Committee's considerations summarized in the ACD. The following process was used to assess suitability of the spline models for incorporation in the cost-effectiveness model:

- Visual fit to the smooth spline hazard curve
- Best statistical fit based on Akaike information criterion/Bayesian information criterion (AIC/BIC) values
- Visual fit of the predicted outcomes of the spline models to the observed data
- Clinical plausibility of the fit to the smooth spline hazard curve and of the predicted outcomes

Priority was given to same model type (number of knots, scale) between the arms, following NICE DSU TSD14 advice.(2) For simplicity, the same model type for PFS was assumed.

1.3. Overall survival

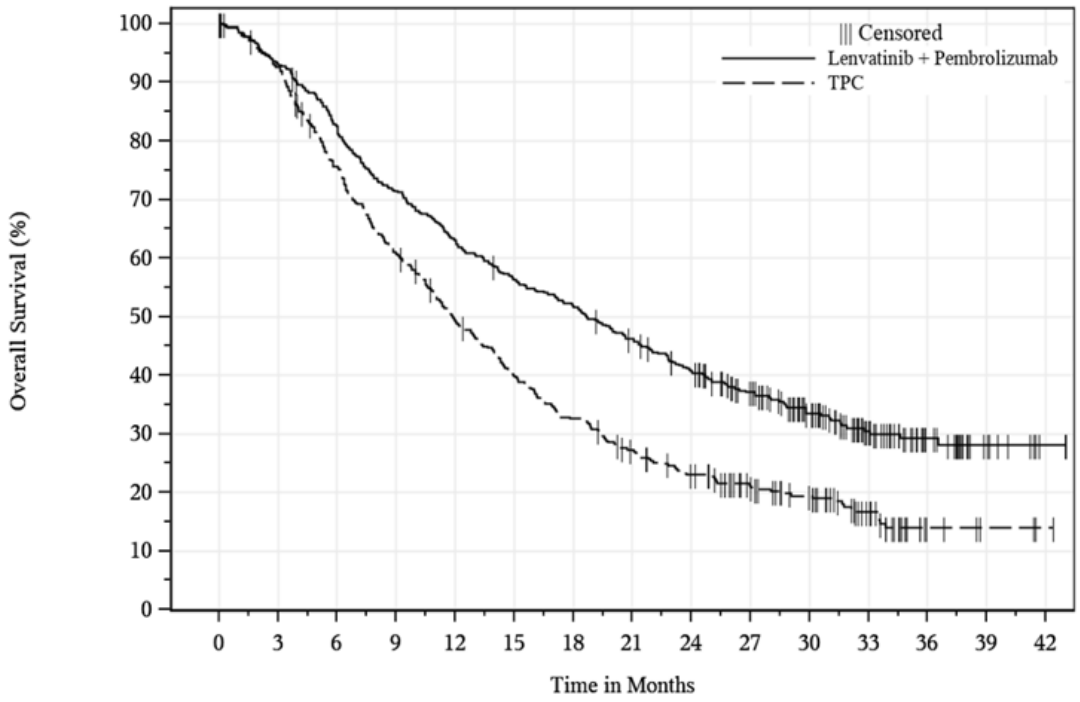
Given the level of maturity of the OS data in this update (Table 4), the FA of KEYNOTE-775 provides strong and consistent evidence of the sustained longer-term OS benefits associated with treatment with PEM + LEN compared with TPC. Median OS was significantly longer in the PEM + LEN group compared with the TPC group (18.7 and 11.9 months, respectively), with a hazard ratio (HR) of 0.65 (95% confidence interval [CI]: 0.55, 0.77; $p < 0.0001$). There is a consistent separation in the PEM + LEN and TPC Kaplan–Meier curves for the entire duration of follow-up (Figure 1). Full details are provided in the clinical study report (CSR) update.(1)

Table 4: Number of events and level of maturity of OS in KEYNOTE-775 (IA and FA)

Endpoint	Outcome	Interim analysis (October 2020)		Final analysis (March 2022)	
		PEM + LEN n = 411	TPC n = 416	PEM + LEN n = 411	TPC n = 416
OS	Number of events	[redacted]	[redacted]	[redacted]	[redacted]
	Maturity (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: FA, final analysis; IA, interim analyses; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.

Figure 1: PEM + LEN and TPC – OS, KM plot (KEYNOTE-775 FA)



n at risk

Lenvatinib + Pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
TPC	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 01MAR2022
Source: [P775V01MK3475: adam-adsl; adtte]

Key: FA, final analysis; KM, Kaplan–Meier; n, number; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.

The following sections are structured as follows:

- TPC arm
  - OS spline models (unadjusted for treatment switching)
  - OS spline models (adjusted for treatment switching)
    - Treatment switching analysis
    - Assessment of OS spline models
    - Application in the economic model
- PEM + LEN arm
  - OS spline models

1.3.1. OS spline models (TPC arm, unadjusted for treatment switching)

Following the process described in Section 1.2 above, the odds splines had the best visual fit to the smooth hazard plots in the TPC arm (Figure 2). The AIC/BIC values also indicated that the one-knot spline models consistently outperformed the two- and three-knot spline models with respect to statistical fit to the observed data (Table 5).

Figure 2: Plot of hazard rates in the TPC arm, OS unadjusted for treatment switching (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; OS, overall survival; TPC, treatment of physician's choice.
Note: x axis of all plots = time (weeks)

Table 5: TPC OS, AIC/BIC values for statistical fit of spline models

Spline model		TPC*		
Scale	**Knots**	**AIC**	**BIC**	**Average**
Hazard	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; TPC, treatment of physician's choice.
Note: *Unadjusted for treatment switching in the TPC arm.

Figure 3 shows that the spline model on the odds scale provided an excellent fit to the observed data for the entire trial period. Based on the above assessment, the choice of curve for the TPC arm is unlikely to have a large impact on the modelled results. As there was minimal difference in the visual fit across the spline models on the odds scale, preference was given to the one-knot splines to ensure that the long-term extrapolations are based on a reliable and sufficient number of events to capture the underlying shape, while avoiding over-fitting to the data.

Figure 3: OS spline models for TPC (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice.

1.3.2. OS spline models (TPC arm, adjusted for treatment switching)

1.3.2.1. Treatment switching analysis

1.3.2.2. Methods of treatment switching adjustment

In the trial protocol, participants in the TPC arm who experienced investigator-defined disease progression had the opportunity to crossover to receive PEM + LEN.(5) As noted in the ACD, treatment switching can lead to confounded results in the OS analysis of the observed data for the TPC arm.

At the final database lock in March 2022, there were a total of [redacted] participants in the TPC arm with disease progression.(1) [redacted] participants randomized to the TPC arm received in-study treatment PEM + LEN or other subsequent programmed cell death protein 1/programmed death-ligand 1 (PD1/PD-L1) or vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) inhibitor therapies that are not currently reimbursed in this treatment setting in the UK. In clinical practice, these patients would not have received such treatment and their outcomes are likely to have been worse than seen in the trial. Without adjusting for treatment switching in the TPC arm of KEYNOTE-775, estimates of the OS benefit of PEM + LEN compared with TPC are underestimated.

Following NICE DSU TSD16 guidance (6), three common methods of adjusting for treatment switching were explored to estimate the true OS benefit of PEM + LEN compared with TPC. Each of the three methods rely on the applicability of various underlying assumptions to produce reliable and unbiased results. There is usually no clear best method for adjustment as it depends on study design, conduct and patient characteristics; therefore, all analyses were conducted and the likelihood of the key underlying assumptions were assessed. For details of each methodology, please refer to NICE DST TSD16.(6) [Methodological details are provided in the treatment switching reports, embedded in the technical addendum]. The results are presented first, followed by a discussion of the most robust approach.

- Two-stage estimation (TSE)
- Rank preserving structural failure time model (RPSFTM)
- Inverse probability of censoring weights (IPCW)

1.3.2.3. Results

Figure 4 shows the unadjusted Kaplan–Meier OS, and counterfactual plots after adjusting for treatment switching in the TPC arm. The HR of OS results are presented in Table 6.

The counterfactual plots and the HR estimates demonstrate a high degree of consistency in the treatment switching results. The adjustment for treatment switching consistently leads to an improvement in the OS benefit of PEM + LEN compared with the unadjusted TPC data. The impact of the treatment switching

analysis resulted in a reduction of the comparative probability of death in the PEM + LEN arm compared with TPC by approximately [redacted] to [redacted]%, in favour of PEM + LEN. The HRs for PEM + LEN versus TPC after adjustment for treatment switching ranged from [redacted].

Figure 4: TPC, OS with and without adjusting for treatment switching (unadjusted KM; and adjusted counterfactual plots using TSE, RPSFT and IPCW methods) - KEYNOTE-775 FA

[redacted]**Key:** KM, Kaplan-Meier; IPCW, inverse probability of censoring weights; OS, overall survival; RPSFT, rank preserving structural failure time model; TPC, treatment of physician's choice; TSE, two-stage estimation.

Table 6: OS HR estimates after adjusting for treatment switching (KEYNOTE-775 FA)

Treatment switch adjustment methods	HR (PEM + LEN vs TPC)	Median OS, TPC (months)
Unadjusted	0.65	11.9
TSE – without re-censoring	[redacted]	[redacted]
TSE – with re-censoring	[redacted]	[redacted]
RPSFT – without re-censoring	[redacted]	[redacted]
RPSFT – with re-censoring	[redacted]	[redacted]
IPCW	[redacted]	[redacted]

Key: FA, final analysis; HR, hazard ratio; IPCW, inverse probability of censoring weighting; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib; RPSFT, rank preserving structural failure time models; TPC, treatment of physician's choice; TSE, two-stage estimation.

1.3.2.4. Discussion

The assessment of the most robust method for the treatment switching analysis is presented in the ACD response and repeated here for ease of viewing.

Of the three methods, the IPCW approach was excluded because it can be prone to error when there are small sample sizes when assessed as switcher and non-switcher groups. This is particularly relevant in this case, where there was a relatively small number of patients randomized to the TPC arm who received subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies ([redacted] out of [redacted] participants [[redacted]]). This figure is substantially smaller than seen in some other clinical trials in oncology.

The RPSFT approach was considered. It is unclear whether the fundamental assumption of the 'common treatment effect' holds. In the case of KEYNOTE-775, treatment switching is often only permitted after disease progression and the capacity for a patient to benefit in the post-progression stages may be different compared with pre-progression. Furthermore, following NICE DSU TSD16(6) guidance, the RPSFT approach is less appropriate when the control arm is an active treatment, which is applicable to KEYNOTE-775. Additionally, patients with different stages of disease were randomized into the trial, which is a key prognostic consideration in endometrial cancer. On this basis, the RPSFT approach was considered prone to bias.

The TSE method avoids the need of the 'common treatment effect' assumption. It instead relies on the existence of an appropriate secondary baseline, such that there is a clearly defined timepoint before which treatment switching could not occur. This timepoint is often selected to be based on disease progression in oncology trials; this is aligned to the trial protocol in the case of KEYNOTE-775. Another key consideration for the TSE approach is whether the length of delay between disease progression and occurrence of the switch introduces potential bias associated with time-dependent confounding. The median time from disease progression until switching was shorter than [redacted] months (approximately [redacted] days). Although there was some variation in the time taken for participants to switch over, the bias was likely to be small because the majority of switching occurred shortly after disease progression. One practical advantage of TSE is that it does not require data to be collected on time-dependent covariates other than the timepoint of disease progression.

Based on the above assessment, the TSE approach is preferable because the IPCW and RPSFT approaches were considered more prone to bias due to limitations associated with the underlying assumptions. Furthermore, the results were tested with and without re-censoring to assess the impact of informative censoring, which demonstrated that re-censoring is not considered necessary. The OS data from KEYNOTE-775 are mature, the estimates from the analysis were relatively consistent across the approaches, and the application of re-censoring leads to a loss of longer-term survival information.

1.3.2.5. Assessment of OS spline models, adjusted for treatment switching (TSE without re-censoring)

With the availability of the counterfactual estimates from the treatment switching analysis, spline models were fitted to the counterfactual data following methods described in Section 1.2 and assessed for suitability following the process outlined in Section 1.3.1. The one-knot spline on the odds scale continued to outperform the other models based on fit to the smooth hazard function (Figure 5), statistical fit based on AIC/BIC values (Table 7), and was also the preferred model to maintain consistency in the method of extrapolating OS with the PEM + LEN arm (see Section 1.3.3 below). The extrapolations of OS using the spline models illustrate the similarity in the long-term predictions in the TPC OS estimates after adjusting for treatment switching (Figure 6).

Figure 5: Plot of OS hazard rates in the TPC arm, adjusted for treatment switching (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; OS, overall survival; TPC, treatment of physician's choice.
Note: x axis of all plots = time (weeks)

Table 7: TPC OS, AIC/BIC values for statistical fit of spline models, adjusted for treatment switching

Spline model		TPC		
Scale	**Knots**	**AIC**	**BIC**	**Average**
Hazard	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; TPC, treatment of physician's choice.

Figure 6: Spline models for TPC, OS adjusted for treatment switching (KEYNOTE-775 FA)

[redacted]**Key:** adj, adjusted for treatment switching; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician's choice; TSE, two-stage estimation.

1.3.2.6. Application of treatment switching adjustment for OS in the TPC arm of the model

The treatment switching analyses using the TSE without re-censoring method were incorporated into the economic model to extrapolate outcomes in the TPC arm. Two approaches were implemented:

- One-knot spline model fitted to the counterfactual estimates of OS in the TPC arm (Section 1.3.2.5)
- By applying the adjusted HR of OS to the PEM + LEN arm as reference curve (Sections 1.3.2.1 and 1.3.3)

For comparison purposes, scenarios have been tested with and without treatment switching analyses in the economic model. The results demonstrate an improvement in the ICER after adjusting for treatment switching in the TPC arm (Section 1.9.3, Table 29).

1.3.3. OS spline models (PEM + LEN arm)

Based on visual assessment, all spline models fit well to the smooth hazard plots in the PEM + LEN arm (Figure 7). The models on the odds scale provide a slightly better fit to both the short- and long-term smooth hazard plots, and was preferred on the basis of consistency with the assessment of spline models in the TPC arm (Figure 7). Figure 8 illustrates how well the spline models fit to the observed data.

As with the TPC models, the one-knot splines were preferred because the AIC/BIC values for the PEM + LEN splines in Table 8 indicated that the one-knot models consistently outperformed the two- and three-knot spline models with respect to statistical fit to the observed data, and reducing the number of knots helps to ensure a reliable and sufficient number of events while avoiding over-fitting to the data.

Figure 7: Plot of hazard rates in the PEM + LEN arm, OS (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib.
Note: x axis of all plots = time (weeks)

Table 8: PEM + LEN OS, AIC/BIC values for statistical fit of spline models

Spline model		PEM + LEN		
Scale	**Knots**	**AIC**	**BIC**	**Average**
Hazard	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]
	3	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.
Note: Unadjusted for treatment switching in the TPC arm.

Figure 8: OS spline models for PEM + LEN (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; KM, Kaplan-Meier; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib

1.3.4. Validation of the OS curves in the revised model

1.3.4.1. Comparison of results across models

The relevant spline models provided highly consistent estimates of OS at landmark time points (Table 9), at 1-, 5- and 10-years for each treatment arm in the model. This supports the general robustness of the one-knot spline model. In the TPC arm, there was a difference in just 1% across the lowest and highest 5-years OS estimates after adjusting for treatment switching, and a 1% difference across the respective 10-year estimates. Median OS predicted by the model after adjusting for treatment switching was slightly lower than the observed median in the FA of KEYNOTE-775. Mean life-years were very similar in the extrapolations of OS after adjusting for treatment switching, ranging from [redacted] to [redacted]. These findings are similar when looking at the set of unadjusted OS models (which are not considered relevant for decision making).

There was also a high degree of consistency in the OS estimates for the PEM + LEN arm (Table 9), with up to a 2% difference in the range of 5-year estimates (range [redacted]%) and just 1% difference in the 10-year estimates (range [redacted]%).

Similar to the TPC arm, median OS in the model was highly consistent with the observed median OS, although slightly underpredicted. Mean life-years were generally consistent, supporting the general robustness of the one-knot spline model in the PEM + LEN arm.

Figure 9 presents an overlay of the final OS models which were considered to be most reliable for extrapolating outcomes in the PEM + LEN and TPC arms in the revised base case analysis. The curves provide an excellent fit to the Kaplan-Meier data and were validated by UK clinical experts (Section 1.3.4.2).

Table 9: OS estimates at landmark time points (KEYNOTE-775 FA)

TPC arm	1 yr	5 yr	10 yr	Mean (years)	Median (years)
Observed KM (KEYNOTE-775)	[redacted]	-	-	-	[redacted]
Unadjusted OS spline 1-knot[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS spline 2-knot[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unadjusted OS spline 3-knot[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS spline 1-knot[a,b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS spline 2-knot[a,b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS spline 3-knot[a,b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjusted OS via HR[a,b,c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEM + LEN arm	**1 yr**	**5 yr**	**10 yr**	**Mean (years)**	**Median (years)**
Observed KM (KEYNOTE-775)	[redacted]	-	-	-	[redacted]
OS spline 1-knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS spline 2-knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS spline 3-knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: FA, final analysis (of KEYNOTE-775); KM, Kaplan-Meier; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; TPC, treatment of physician's choice of paclitaxel or doxorubicin; yr, years.

Notes:

a. OS spline model on odds scale, independently fitted to the TPC data of KEYNOTE-775; based on best fit to the smooth hazard plot and observed data from trial
b. TSE method without re-censoring, OS spline model independently fitted to the counterfactual estimates from the adjusted TPC arm; based on assessment of most reliable approach to minimise risk of bias in the results
c. TSE method (see above); HR estimate applied to the PEM + LEN arm as reference curve
d. OS spline model on odds scale, independently fitted to the PEM + LEN data of KEYNOTE-775; based on best fit to the smooth hazard plot and observed data from trial

Figure 9: Final OS models in the revised base case, PEM + LEN (one-knot spline) and TPC arm (one-knot spline adjusted for treatment switching, TSE without re-censoring) – KEYNOTE-775 FA

[redacted]**Key:** adj, adjusted for treatment switching; KM, Kaplan-Meier; OS, overall survival; PEM + LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice; TSE, two-stage estimation.

1.3.4.2. Additional clinical expert validation

To provide a clinical perspective and input around the OS estimates based on the FA of KEYNOTE-775, individual 45-minute interviews were conducted in November 2022 (see Section 1.10 for further information).

In summary, the clinical experts considered the one-knot spline models (odds scale) to provide a good fit to the observed data, and reasonable extrapolations in both the PEM + LEN and TPC arms (adjusted for treatment switching). A summary of the feedback is provided below:

- All three clinical experts confirmed that it is clinically reasonable to use the adjusted data in the TPC arm, both from a treatment pathway and clinical efficacy perspective. Without such adjustment, TPC OS data are confounded by the administration of subsequent PD1/PD-L1 or VEGF/VEGFR inhibitor therapies, and therefore the trial data are likely to overpredict the true outcomes in the TPC arm. The clinical experts confirmed that they expected the OS outcomes in the TPC arm to worsen, after adjusting for treatment switching.
- There was consensus that the spline models provided a good fit to the observed data, within the trial period. Additionally, all clinical experts commented that the

hazard plots look very similar, but that the odds scale provided a better fit to the smooth hazard functions which was more pronounced in the TPC arm.

- Of the spline models on the odds scale, clinical experts commented on the similarity of the plots when varying the number of knots. It was suggested that the one-knot spline models may provide a slightly better fit over time but it was difficult to differentiate between the plots in some cases.
- The long-term projections were also similar across the models, based on visual assessment of the extrapolated curves, landmark survival estimates, median estimates and mean predicted life years generated from each flexible model. It was difficult to identify which curve produced the most reliable outcomes as KEYNOTE-775 provides the longest follow-up data to inform the estimates.

Additionally, Heffernan (2022) became available in the public domain after the initial company submission date for ID3811.(7) As a single-arm, real-world study, there remains severe limitations of the use of Heffernan (2022) to validate the results from the Phase III randomized controlled trial, KEYNOTE-775. Incomplete information from the real-world study prevents any useful interpretation of how this applies to the decision problem. In totality, MSD believes that the Heffernan (2022) study cannot be used to meaningfully validate or invalidate the outcomes for this appraisal.

There is a degree of consistency in the naïve comparison of median OS results based on the full populations of each study. The median survival in Heffernan (2022) in the total assessed population was 10.3 months (95% confidence interval [CI], 9.2–11.1).(7) When assessing the breakdown of results by type of treatment received in the second-line setting, median OS ranged from 4.9–14.2 months. Median OS reported in the TPC arm, based on the FA of KEYNOTE-775 trial, was 11.9 months. After adjusting for treatment switching in the TPC arm, median estimates ranged from 10.6–11.4 months. Any differences across the trial populations cannot be explained with certainty, however, in a disease setting where there are limited treatment options, slight differences in the baseline characteristics of the study populations may lead to variations in prognosis.

Clinical expert opinion was sought regarding the appropriateness of using the Heffernan (2022) study to validate modelled outcomes in the TPC arm of KEYNOTE-

775. Clinical experts provided the following feedback, when discussing the comparability of the study populations of Heffernan (2022) and KEYNOTE-775 (TPC arm):

- Compared with KEYNOTE-775, the Heffernan (2022) population had a higher proportion of patients with serous histology type (25% vs 42%, respectively), a greater proportion of patients with initial diagnosis at Stage III or IV disease (65% vs 78%, respectively). These differences are likely to have a negative impact on prognosis in the Heffernan (2022) study population.
- However, ECOG PS was only reported for approximately half of the patients in the Heffernan (2022), which provides an incomplete view of the population on this measure alone and is ultimately a major limitation of this interpreting the types of patients or the results from this study.
- There could be some differences in the types of patients based on use of platinum doublet therapies; however, the data on ECOG PS are incomplete and there is no further information available to understand these differences.

1.4. Progression-free survival

PFS was significantly improved with PEM + LEN compared with TPC (Figure 10), and was mature at the time of the final data cut (Table 10). As with OS, based on the FA of KEYNOTE-775, there is a consistent separation in the Kaplan–Meier curves for the entire duration of follow-up. The median PFS (per RECIST 1.1 by blinded independent central review [BICR]) remained significantly improved with PEM + LEN with an HR of 0.56 (95% CI: 0.48, 0.66; p < 0.0001). Further details are also provided in the CSR update.(1)

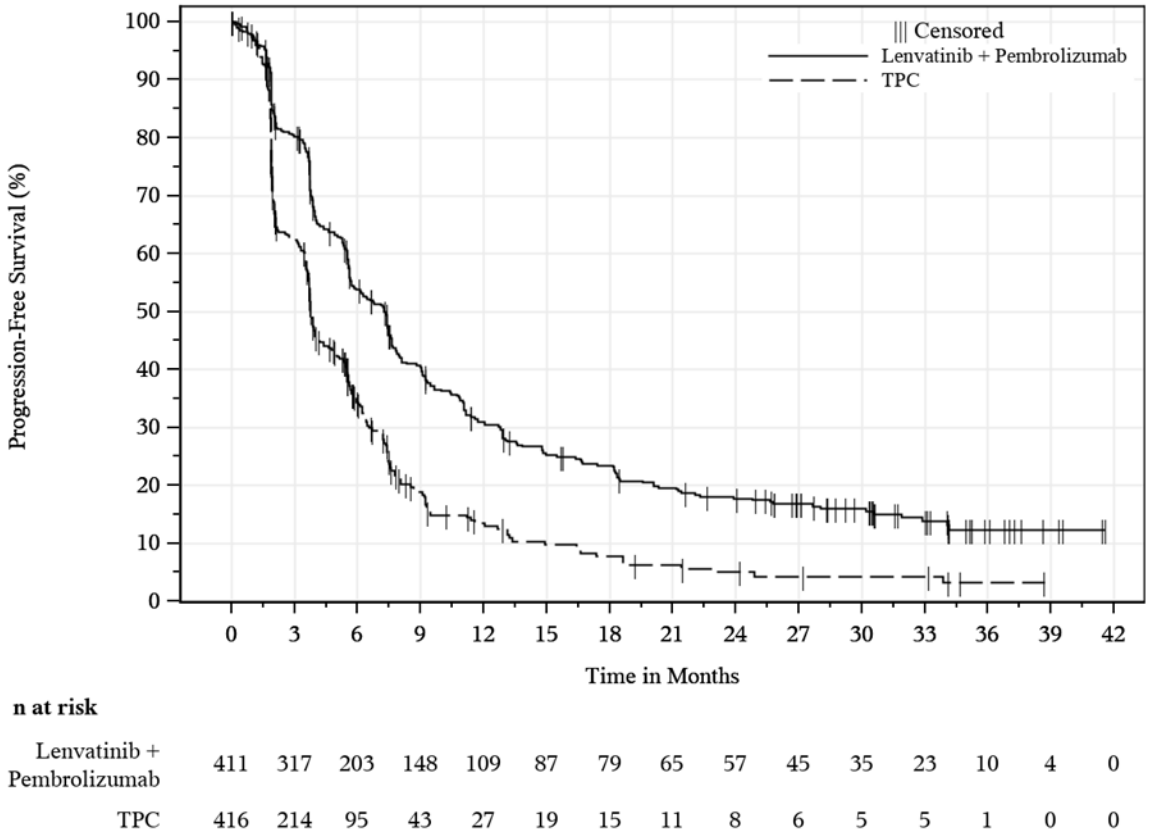
Table 10: Number of events and level of maturity of PFS in KEYNOTE-775 (IA and FA)

Endpoint	Outcome	Interim analysis (October 2020)		Final analysis (March 2022)	
		PEM + LEN n = 411	TPC n = 416	PEM + LEN n = 411	TPC n = 416
PFS	Number of events	[redacted]	[redacted]	[redacted]	[redacted]

	Maturity (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: IA, interim analyses; FA, final analysis; PFS, progression-free survival; PEM + LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.

Figure 10: PEM + LEN and TPC – PFS, KM plot (KEYNOTE-775 FA)



n at risk

Lenvatinib + Pembrolizumab	411	317	203	148	109	87	79	65	57	45	35	23	10	4	0
TPC	416	214	95	43	27	19	15	11	8	6	5	5	1	0	0

TPC = Treatment Physician´s Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 01MAR2022
Source: [P775V01MK3475: adam-adsl; adtte]

Key: FA, final analysis; KM, Kaplan–Meier; n, number; PEM + LEN, pembrolizumab with lenvatinib; PFS, progression-free survival; TPC: treatment of physician's choice.

1.4.1. Assessment of PFS spline models (TPC arm)

As the PFS data are highly mature, and the survival curves displaying very similar visual fits to the observed Kaplan–Meier data, there is a reduced level of variation across predictions with the PFS models and, therefore, greater certainty around the results.

For simplicity and consistency in the methods applied in the economic model, the same spline approach identified in Section 1.3.1 and 1.3.3 was selected for PFS.

The visual fit of the spline models to the observed data in the TPC and PEM + LEN arms and respective AIC/BIC statistics are presented in Figure 11, Figure 12, and Table 11. The hazard plots are provided in Figure 13 and Figure 14 below.

Table 11: PFS, AIC/BIC values for statistical fit of spline models (KEYNOTE-775 FA)

Distribution		PEM + LEN			TPC		
		AIC	BIC	Average	AIC	BIC	Average
Hazard	1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	2 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	3 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; FA, final analysis; OS, overall survival; PFS, progression-free survival; PEM + LEN, pembrolizumab with lenvatinib; TPC, treatment of physician's choice.

Figure 11: PFS spline models for TPC (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice.

Figure 12: PFS spline models for PEM + LEN (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; KM, Kaplan-Meier; OS, overall; PEM + LEN, pembrolizumab with lenvatinib; PFS, progression-free survival.

Figure 13: Plot of hazard rates in the TPC arm, PFS (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; OS, overall survival; PFS, progression-free survival; TPC, treatment of physician's choice.
Note: x axis of all plots = time (weeks

Figure 14: Plot of hazard rates in the PEM + LEN arm, PFS (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; PEM + LEN, pembrolizumab with lenvatinib; PFS, progression-free survival.

Note: x axis of all plots = time (weeks)

1.5. Time on treatment

There has been no change in the methods for modelling TOT data (please refer to Document B, Section B.3.3.5 for a full description) with the exception of incorporating the EAG's preference to ensure that TOT does not exceed PFS.

Consistent with the approach in the initial company submission, TOT is modelled based on individual components in the PEM + TPC arm and based on the combined components for TPC. Standard one-piece extrapolations were fitted to the full dataset of FA of KEYNOTE-775 and updated in the model(2):

- Pembrolizumab: One-piece models applied up to a maximum duration of 2 years (capped by PFS)
- Lenvatinib: One-piece models applied for the model time horizon (capped by PFS)
- TPC: One-piece models applied for the model time horizon, up to maximum cumulative dose for doxorubicin (capped by PFS)

Of note, the TOT data are almost complete for each arm in KEYNOTE-775. Median TOT remains almost the same at the time of the final analysis compared with IA (Table 13).

Table 12: Summary of TOT models selected for economic analysis

Analysis	TOT model[a]	TOT stopping rules and justification
Base case	**PEM:** Generalized gamma **LEN:** Generalized gamma **TPC:** Generalized gamma	PEM: maximum duration of 2 years per anticipated licence and KN-775 TPC: maximum cumulative doxorubicin dose of 500 mg/m^2 (5.75 months)
TOT distribution scenarios	**PEN:** Log-logistic **LEN:** Weibull **TPC:** Weibull	
Other TOT scenarios	KM data directly for pembrolizumab and TPC TPC: maximum of six paclitaxel cycles (5.52)	

Key: KM, Kaplan–Meier; LEN, lenvatinib; PEM, pembrolizumab; PFS, progression-free survival; TOT, time on treatment; TPC, treatment of physician's choice.

Note: [a]Consistent with treat-to-progression rule, this applies a constraint that does not allow TOT to exceed PFS (in line with changes to the company's cost effectiveness estimate at the technical engagement stage [Key issue 6a]).

Table 13: KN-775 median TOT (KEYNOTE-775 FA)

	KEYNOTE-775 IA		KEYNOTE-775 FA	
Treatment	**Weeks**	**Months**	**Weeks**	**Months**
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]

Key: FA, final analysis; PEM + LEN, pembrolizumab with lenvatinib; IA, interim analyses; TOT, time on treatment; TPC, treatment of physician's choice.

An overlay of the one-piece parametric models and observed Kaplan–Meier data for pembrolizumab, lenvatinib and TPC are shown in Figure 15, Figure 16 and Figure 17 respectively. The AIC and BIC statistics corresponding to the parametric models fitted to KEYNOTE-775 FA are provided in Table 14. The most appropriate and clinically plausible models for TOT were used in the base case analysis, with alternative clinically plausible models tested in scenario analyses which had a nominal impact on the results (Table 12):

- **PEM + LEN arm:**
  - Pembrolizumab: the generalized gamma model provided the best visual and statistical fit to the entire observed period from KEYNOTE-775. However, when considering the first 2 years of the trial data which resembles the maximum duration of treatment in clinical practice, the log-logistic model also seemed plausible
  - Lenvatinib: the Gompertz and log-logistic models provided the best statistical fits; however, these estimates are clearly implausible and unrealistic with patients remaining on treatment beyond 5 years. The generalized gamma provided the next best statistical fit
- **TPC arm:**
  - The generalized gamma, exponential, Weibull and Gompertz models all overlap and each provide a plausible fit to the TOT data in the TPC arm of KEYNOTE-775. There is no visible difference between curves; for consistency with the PEM + LEN components, the generalized gamma distribution was considered appropriate

Figure 15: TOT parametric curves for pembrolizumab (KEYNOTE-775 FA)

[redacted]**Key:** KM, Kaplan–Meier; PEM + LEN, pembrolizumab with lenvatinib; TOT, time on treatment.

Figure 16: TOT parametric curves for lenvatinib (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; KM, Kaplan–Meier; PEM + LEN, pembrolizumab with lenvatinib; TOT, time on treatment.

Figure 17: TOT parametric curves for TPC (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; KM, Kaplan–Meier; TOT, time on treatment; TPC, treatment of physician's choice.

Table 14: TOT, AIC/BIC values for statistical fit of parametric models (KEYNOTE-775 FA)

Treatment	PEM		LEN		TPC	
Extrapolation	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; FA, final analysis; LEN, lenvatinib; PEM, pembrolizumab; SOC, standard of care; TOT, time on treatment; TPC, treatment of physician's choice
Note: Shaded cells represent the models with the best statistical fit.

1.5.1. Summary of modelled extrapolations

Following the above assessment, the most appropriate and clinically plausible models for TOT were the generalized gamma distributions for all components (PEM, LEN and TPC). These are used in the base case analysis, shown in Figure 18. Alternative models and extrapolation methods tested in scenario analyses are summarized in Table 12 and Section 1.9.3.

Figure 18: Selected TOT curve fits – overall population (KEYNOTE-775 FA)

[redacted]**Key:** FA, final analysis; KM, Kaplan–Meier; PEM + LEN, pembrolizumab with lenvatinib; TOT, time on treatment.

1.5.2. Treatment stopping rule and duration of treatment effect

As described in Section 1.5.1 there has been no change to the application of treatment stopping rules in the economic model (Document B Section B.3.3.5.3).

In the ACD, the Committee has suggested exploring treatment waning assumptions in the economic model. The company understands the relevancy of this topic; however, there does not appear to be evidence of a treatment waning effect with PEM + LEN based on the KEYNOTE-775 trial. The FA results of KEYNOTE-775 provide evidence of a sustained longer-term comparative PFS and OS benefit of PEM + LEN compared with TPC that is numerically consistent between the IA and FA data cuts (MSD ACD Response 2)(1).

1.5.2.1. Biological reason

The marketing authorisation states that lenvatinib is administered until disease progression. There is biological evidence and rationale suggesting that lenvatinib helps shift the tumour microenvironment to an immune-stimulatory state by inhibiting VEGFR and FGFR.(8) In mouse models, lenvatinib plus PD-1 inhibition had significantly greater antitumour activity than either agent alone. On this basis, pembrolizumab with lenvatinib act in a synergistic way to provide a positive enhancement of the tumour microenvironment by improving the action of each drug given in isolation. This hypothesis is consistent with data for other IO agents and IO combinations, which offer robust evidence on the durability of the treatment effect associated with IOs in metastatic treatment (refer to table below for a summary of this).This treatment combination was not been subjected to treatment waning assumptions in another NICE technology appraisals.(9) It is unclear why it would apply in this case since patients in KEYNOTE-775 may continue to receive lenvatinib monotherapy even after stopping treatment with pembrolizumab (at the last recorded time point around 3 years' follow-up, there were [redacted]% of patients still receiving lenvatinib in KEYNOTE-775). UK clinical experts consulted in November 2022 confirmed that a proportion of patients will have durable response to PEM + LEN. In addition, patients who are considered to benefit from further treatment may very well

receive continued treatment with lenvatinib monotherapy even after pembrolizumab has stopped in a real-world setting, as in the KEYNOTE-775 trial.

1.5.2.2. Long term data

A long- term OS data for endometrial patients treated with PEM+LEN is available for the KEYNOTE-146 (10). This is a multi-centre, open-label arm Phase Ib/II basket trial of selected solid tumours (n=108 had pre-treated EC) with a median follow-up 34.7 months. The observed data proved durable and sustained treatment effect beyond the 2-year treatment period with PEM+LEN. This is corroborated by data from KEYNOTE-775 (Document B Figure 9), which details distinct evidence of sustained OS for PEM+LEN in the form of a plateau with 30% of patients alive at 5 years. We do acknowledge there are some limitations for applicability, but this is longest available data for this treatment combination and therefore constitutes a key piece in the evidence under consideration around the durability of the treatment effect.

1.5.2.3. Other pembrolizumab long term studies

The OS and PFS results provide evidence of a sustained longer-term comparative benefit of PEM + LEN compared with TPC that is numerically consistent between the IA and FA data cuts.(1) Multiple randomized controlled trials that have reported 5-year data for pembrolizumab. All of these demonstrated a sustained treatment effect, with two studies conducted specifically in the second-line treatment setting.

Table 15: 2 year and 5-year OS in pembrolizumab arms of advanced solid tumour trials

	Tumour	OS		Reference
		2 years	5 years	
KEYNOTE-775 - Company model	Endometrial	40.6%	[redacted]	-
KEYNOTE-146	Endometrial	42.0%	30.0%	(10)
KEYNOTE-006	Melanoma	60.0%	45.0%	(11)
KEYNOTE-010 TPS ≥50%	NSCLC	34.5%	25.0%	(12)
KEYNOTE-010 TPS ≥1%	NSCLC	22.9%	15.6%	(12)
KEYNOTE-024	NSCLC	50.0%	31.9%	(13)
KEYNOTE-189*	NSCLC	45.7%	19.4%	(14)
KEYNOTE-402 TPS ≥1%	NSCLC	38.9%	16.6%	(15)

KEYNOTE-407*	NSCLC	36.0%	18.4%	(16)
Key: NSCLC – Non-Small Cell Lung Cancer. TPS: Tumour Proportion Score *included approximately 1/3 PDL1 negative patients				

We have not conducted a full systematic literature review on long term treatment effect durability, however in addition to the studies reported above, there is additional long term clinical evidence from melanoma which demonstrate the durability of treatment effect for anti-CTLA4 agents. These work in a similar fashion to anti-PD-1 agents such as pembrolizumab. Schadendorf et al 2015 reports a durable clinical benefit starting from year 3 that is maintained up to year 10 for advanced melanoma. (17) Whilst these are different tumor microenvironments which limits the generalisability of this evidence, it is relevant for this advanced endometrial cancer assessment that there is biological plausibility to a plateau. To date there is no evidence suggesting why a similar plateau would not be observed in pembrolizumab + lenvatinib combinations. Considering also clinical evidence from KEYNOTE-146 which reports 5 year OS estimate of 30%. We therefore consider any waning of treatment effect to be implausible and inappropriate in this combination treatment.

1.5.2.4. Treatment effect and discontinuation of pembrolizumab

It is important to note that long-term data support a sustained treatment effect post discontinuation of pembrolizumab. One of the examples with a long-term data is in melanoma patients. In KEYNOTE-006 a long-term survival benefit has been observed in patients with advanced melanoma who were treated with pembrolizumab for up to 2 years. In patients who ceased treatment after completing 35 doses of pembrolizumab at 2 years, 78.4% remained in progression-free survival for at least 24 months (censored) following discontinuation.(11) The long-term outcome seen in KEYNOTE-006 is generally consistent with the outcome seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule. (18) The cumulative and log-cumulative hazard plots below show that there is no structural difference between the hazards in these two trials (Figure 19, Figure 20 and Figure 21). This data points towards a sustained treatment effect post discontinuation of pembrolizumab in melanoma and other patients treated with pembrolizumab.

Figure 19: Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001

Figure 20: Cumulative and log-cumulative hazard plots for OS in KEYNOTE-006

Figure 21: Comparison of Overall Survival curves of KEYNOTE-001 and KEYNOTE-006 in advanced melanoma

Same trends in hazards were observed in the KEYNOTE-024. The following tables show the PFS and OS hazard ratios from KEYNOTE-024 reported in the 1-, 2-, 3- and 5-year publications. If treatment waning began at 2 years we should expect some upward drift in the hazard ratios by the 5 year cut-off, which is not observed, despite crossover being allowed in the study and 66% of patients in the chemotherapy arm receiving immunotherapy on progression.

Table 16: KEYNOTE-024 PFS and OS HRs

KN024 Analysis	PFS HR	OS HR	Source
1-year	0.5	0.62	(19)
2-year	NR	0.63	(20)
3-year	NR	0.65	(21)
5-year	0.5	0.60	(13)

The provided data from various long-follow up studies mentioned above provides no evidence in support of a treatment waning effect for which clinical evidence is collected

1.5.2.5. Conditional survival

When discussing treatment effect waning one must consider conditional survival probability. Several studies reported conditional survival in endometrial patients. It is clear that there is a higher survival probability for long term survival which notes a decreasing risk of death over time. (22, 23) The conditional relative survival rates for

patients with EC improved with increased time elapsed from diagnosis. The discussed treatment combination provides the additional time in PFS and OS. At FA KEYNOTE-775 patient have longer median PFS in the PEM + LEN arm versus TPC arm (7.3 months vs 3.8 moths in all-comer, HR: 0.56), a longer median duration of response (12.9 months vs 5.7 months in all-comer), and a longer median OS (18.7 months vs 11.9 months in all-comer, HR: 0.65) (24).

1.5.2.6. Waning scenarios

Although we maintain our views around the long-term treatment effect of PEM + LEN, we have explored the potential impact on the results, as suggested by the Committee. Treatment waning has been incorporated as a gradual effect in the PEM + LEN arm. This option directly uses the EAG modifications to the model with an additional input to account for the proportion of patients experiencing a treatment waning effect. Controls and details are provided in *'EAG Scenarios'* tab, cell rows 23:25 and cell D32 ('*cont_trt_wan_pct_pts'*). This assumes that the risk of progression or death (PFS) and risk of death (OS) in the PEM + LEN arm converges over time with that in the TPC arm. The following scenarios, which are considered extremely conservative and/or implausible, were tested:

- Waning effect from 5–7 years after stopping treatment, given no waning at all has been observed in KEYNOTE-775 or in the 5-year pembrolizumab trials in other indications to date
- Application of the treatment waning effect to between 60-80% of patients in the PEM + LEN arm to reflect a small proportion of patients experiencing durable response and prolonged immunotherapeutic effect after stopping treatment with pembrolizumab, while a proportion of patients will also continue treatment with lenvatinib monotherapy.

1.6. Health-related quality-of-life data from clinical trials

As described in Document B, Section B.3.4 the EQ-5D data collected from the KEYNOTE-775 trial were conducted based on the final data cut. Linear mixed effects regression models were formally fitted to the data and updated in the economic model.

The Committee's view in the ACD was that a time-to-death (TTD) utility approach may provide more granular information relative to the health state utility approach (provided by the company in the original submission), but that this limited the amount of information informing the health states as it did not include disease progression as a predictive covariate. In response to the ACD, the initial utility regression models were extended to include TTD analyses including disease progression as a covariate. An additional scenario was tested using an approach that is methodologically similar to that accepted in a recent appraisal TA779, this also includes disease progression as a covariate but only two TTD categories (TTD <180 days and TTD ≥ 180 days).(25) There was a small impact on the results.

In summary, the updated model includes four utility models based on the FA of KEYNOTE-775:

- Utility Model 1: AE and progression status (Document B, Section B.3.4.2.2)
- Utility Model 2: AE and TTD (Document B, Section B.3.4.2.1)
- **Utility Model 3 (base case):** AE and TTD with progression status as covariate (extension of Model 2 above, in response to the ACD)
- Utility Model 4 (scenario): AE and TTD with progression status as covariate (methodologically similar to the approach accepted in TA779)

The estimated coefficients from each regression model demonstrate that all predictive variables were statistically significant at the 95% confidence level, $p < 0.05$ (Table 21). The TTD approach with AEs and progression status as covariates (Model 3) was used in the revised base case analysis (Table 17), reflecting the discussion in the ACD. An alternative TTD approach (also including AEs and progression status as covariates) similar to the approach accepted in TA779 (Table 18) was tested in scenario analyses (Section 1.9.3).

Methods for calculating and applying AE utility decrements remain the same as in Document B, Section B.3.4.4. Based on the updated analysis of KEYNOTE-775, the AE utility decrement was [redacted] for the TTD by progression status approach (Model 3) in the base case and [redacted] for the alternative TTD by progression status approach (Model 4) in scenario analysis (Table 18). AE utility decrements are not a driver of the results and have negligible impact on the ICER.

Table 17: Revised base case; Utility Model 3 – Mean utility values based on time to death and progression status (KEYNOTE-775 FA), applied in the economic model

Progression status	TTD	Mean	LB	UB
Pre-progression	< 30 days	[redacted]	[redacted]	[redacted]
	30–89 days	[redacted]	[redacted]	[redacted]
	90–179 days	[redacted]	[redacted]	[redacted]
	180–269 days	[redacted]	[redacted]	[redacted]
	270–359 days	[redacted]	[redacted]	[redacted]
	≥ 360 days	[redacted]	[redacted]	[redacted]
Post-progression	< 30 days	[redacted]	[redacted]	[redacted]
	30–89 days	[redacted]	[redacted]	[redacted]
	90–179 days	[redacted]	[redacted]	[redacted]
	180–269 days	[redacted]	[redacted]	[redacted]
	270–359 days	[redacted]	[redacted]	[redacted]
	≥ 360 days	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; LB, lower bound; TTD, time to death; UB, upper bound.				

Table 18: Scenario analyses; Utility Model 4 – Mean utility values based on time to death and progression status (KEYNOTE-775 FA), applied in the economic model

Progression status	TTD	Mean	LB	UB
Pre-progression	< 180 days	[redacted]	[redacted]	[redacted]
	≥ 180 days	[redacted]	[redacted]	[redacted]
Post-progression	< 180 days	[redacted]	[redacted]	[redacted]
	≥ 180 days	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; LB, lower bound; TTD, time to death; UB, upper bound.				

Table 19: Utility Model 1 – Mean utility values based on health state (KEYNOTE-775 FA)

Health state	Mean health state utility value	LB	UB
PF	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; LB, lower bound; PD, progressed disease; PF, progression free; UB, upper bound.			

Table 20: Utility Model 2 – Mean utility values based on time to death (KEYNOTE-775 FA)

Time to death	Mean time to death utility value	LB	UB
< 30 days	[redacted]	[redacted]	[redacted]
30–89 days	[redacted]	[redacted]	[redacted]
90–179 days	[redacted]	[redacted]	[redacted]
180–269 days	[redacted]	[redacted]	[redacted]
270–359 days	[redacted]	[redacted]	[redacted]
≥ 360 days	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; LB, lower bound; TTD, Time to death; UB, upper bound.			

Table 21: Utility regression model coefficients for HRQL analyses (KEYNOTE-775 FA)

Parameter	Coefficients				SE				P-value			
Model	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No Grade3+ AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD, 360 days or more	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD, 270 to 360 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD, 180 to 270 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD, under 180 days	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD, 90 to 180 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD, 30 to 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD, under 30 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: AE, adverse event; FA, final analysis; HRQL, health-related quality of life; SE, standard error; TTD, time to death.												

1.7. Adverse reactions

AE data were updated in the model to reflect the FA of KEYNOTE-775. The method for including AEs in the model, calculating per cycle probability and AE utility decrements remains unchanged (Document B, Section B.3.4.4). Consistent with the approach in the company submission, Grade 3+ AEs that occurred in ≥ 5% of patients in either PEM + LEN or TPC treatments arm were included (Table 2). Further details regarding the number of episodes per patient, AE duration, and utility decrements are presented in Table 22–Table 24.

Table 22: Summary of Grade 3+ AEs occurring In 5% or more patients in either treatment arm (KEYNOTE-775 IA vs FA)

Adverse event	KEYNOTE-775 FA			
	PEM + LEN (n = 406)		TPC (n = 388)	
	N	%	N	%
Hypertension	159	39%	10	3%
Weight decreased	44	11%	1	0%
Decreased appetite	31	8%	2	1%
Diarrhoea	33	8%	8	2%
Lipase increased	[redacted]			
Anaemia	[redacted]			
Asthenia	[redacted]			
Proteinuria	21	5%	1	0%
Hypokalaemia	[redacted]			
Fatigue	22	5%	12	3%
Neutrophil count decreased	[redacted]			
Neutropenia	[redacted]			
White blood cell count decreased	[redacted]			
Febrile neutropenia	[redacted]			
Leukopenia	[redacted]			
Alanine aminotransferase increased[a]	[redacted]			
Aspartate aminotransferase increased[a]	[redacted]			

Key: AE: adverse event; FA, final analysis; IA, interim analyses; N, number of patients; PEM + LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.
Note: [a] Increased alanine aminotransferase or aspartate aminotransferase were not included in the IA model (original company submission) as these AEs did not meet the ≥ 5% incidence threshold in either arm of the trial at the IA.

Table 23: Number of episodes per patient (KEYNOTE-775 FA)

Adverse event	Number of episodes	SE
Hypertension	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]
Key: FA, final analysis; SE, standard error.		

Table 24: Adverse event duration (KEYNOTE-775 FA)

Adverse event	N	Mean (days)	SD
Hypertension	[redacted]	[redacted]	[redacted]
Weight decreased	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Proteinuria	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; N, number of patients; SD, standard deviation.			

1.8. Cost and healthcare resource use identification, measurement and valuation

There has been no change to the cost categories, dosing schedules, unit costs or data sources (see to Document B, Section 3.5). The only inputs that were updated that specifically affect cost calculations are those related to the observed dosing data for lenvatinib and the proportion of patients receiving subsequent treatments based on the FA of KEYNOTE-775, as described below.

1.8.1. Observed dosing data for lenvatinib

KEYNOTE-775 FA provided an additional 70 weeks of data for the dose administration of lenvatinib for all patients treated with PEM+LEN. Consistent with the approach in the initial submission (Document B, Section 3.5.1.2), to accurately estimate the total costs associated with the PEM+LEN arm, the patient level dosing data for the lenvatinib component from KEYNOTE-775 FA was implemented in the model.

1.8.2. Subsequent therapy

At the time of final analysis, 50% of patients in the TPC arm and 40% of patients in the PEM + LEN arm had received at least one subsequent anticancer therapy. Consistent with the approach in the initial submission (Document B, Section 3.5.4) the proportion of subsequent treatments received by patients at the final data cut adjusted to the UK setting is provided in Table 25.

Table 25: Distribution of subsequent therapies – adjusted to UK setting (KEYNOTE-775 IA vs FA)

Subsequent therapy	KEYNOTE-775 IA		KEYNOTE-775 FA	
	PEM + LEN (n = 411)	TPC (n = 416)	PEM + LEN (n = 411)	TPC (n = 416)
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Anastrozole	[redacted]	[redacted]	[redacted]	[redacted]
Letrozole	[redacted]	[redacted]	[redacted]	[redacted]
Medroxyprogesterone	[redacted]	[redacted]	[redacted]	[redacted]
Megestrol	[redacted]	[redacted]	[redacted]	[redacted]

Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Tamoxifen	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab*	[redacted]	[redacted]	[redacted]	[redacted]
Bevacizumab*	[redacted]	[redacted]	[redacted]	[redacted]
Lenvatinib*	[redacted]	[redacted]	[redacted]	[redacted]
Hormonal therapy+	[redacted]	[redacted]	[redacted]	[redacted]

Key: FA, final analysis; IA, interim analyses; PEM + LEN, pembrolizumab with lenvatinib; TPC: treatment of physician's choice.
Notes:
*Proportion of patients receiving pembrolizumab, bevacizumab and lenvatinib reweighted uniformly across other treatment options.
⁺Patients receiving hormonal therapy can receive one of five individual treatments (anastrozole, letrozole, medroxyprogesterone, megestrol and tamoxifen). The proportion of patients receiving each therapy was calculated based by taking a weighted average of the observed use of treatments in KN-775.(5)
ˣProportion patients receiving systemic therapy agents, excluding investigational treatments and those that are not reimbursed in the UK.(26)

1.9. Revised base case results

All results presented in this section include the commercial access agreement (CAA) currently in place for pembrolizumab; all other treatments are included at list prices.

The cost-effectiveness results for PEM + LEN versus TPC are presented in Table 27. The results show that PEM + LEN is estimated to offer a substantial incremental health benefit compared with TPC, with an additional [redacted] life years (LYs) and [redacted] quality-adjusted life years (QALYs) per patient lifetime ((a total of [redacted] LYs and [redacted] QALYs for PEM + LEN compared with [redacted] LYs and [redacted] QALYs for TPC). This level of benefit supports the importance of PEM + LEN as a treatment for patients with advanced or recurrent endometrial cancer who have disease progression on or following prior treatment with a platinum-containing therapy who would otherwise face a poor prognosis under highly limited treatment options. The incremental cost-effectiveness ratios (ICERs) are primarily driven by a longer duration of treatment for PEM + LEN coupled with the cost difference as a result of TPC being available in generic formulation.

These ICERs should be considered in the context of PEM + LEN being an innovative, end-of-life technology that presents a step-wise improvement for patients with advanced or recurrent endometrial cancer who have received prior platinum-containing therapy.

The revised sensitivity analyses including the revised scenarios are presented in Sections 1.9.1, 1.9.2 and 1.9.3, respectively. The results demonstrate that PEM + LEN is plausibly to be a cost-effective use of NHS resources, even when considering unrealistically pessimistic scenarios around the duration of treatment effect.

1.9.1. Probabilistic sensitivity analyses

Table 26: Pairwise probabilistic results - (pembrolizumab CAA applied only, lenvatinib list price; KEYNOTE-775 FA)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental, PEM + LEN versus comparator			Pairwise ICER (PEM + LEN vs TPC)
				Costs	LYs	QALYs	
PEM + LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAA, commercial access agreement; ICER, incremental cost-effectiveness ratio; LY, life years; LYG, life years gained; PEM + LEN, pembrolizumab with lenvatinib; QALYs, quality-adjusted life years; TPC, treatment of physician's choice.

Figure 22: Cost-effectiveness acceptability curve – (pembrolizumab CAA applied only, lenvatinib list price; KEYNOTE-775 FA)

[redacted]

Key: FA, final analysis; PEM + LEN, pembrolizumab with lenvatinib; QALY, quality-adjusted life year; TPC, treatment of physician's choice.

1.9.2. Deterministic sensitivity analyses

Table 27: Discounted pairwise deterministic results - including CAA for pembrolizumab (pembrolizumab CAA applied only, lenvatinib list price; KEYNOTE-775 FA)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental, PEM + LEN versus comparator			Pairwise ICER (PEM + LEN vs TPC)
				Costs	LYs	QALYs	
PEM + LEN	[redacted]	[redacted]	[redacted]				

TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAA, commercial access agreement; ICER, incremental cost-effectiveness ratio; LY, life years; LYG, life years gained; PEM + LEN, pembrolizumab with lenvatinib; QALYs, quality-adjusted life years; TPC, treatment of physician's choice.

Table 28: Undiscounted pairwise deterministic results - including CAA for pembrolizumab (pembrolizumab CAA applied only, lenvatinib list price; KEYNOTE-775 FA)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental, PEM + LEN versus comparator			Pairwise ICER (PEM + LEN vs TPC)
				Costs	LYs	QALYs	
PEM + LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAA, commercial access agreement; ICER, incremental cost-effectiveness ratio; LY, life years; LYG, life years gained; PEM + LEN, pembrolizumab with lenvatinib; QALYs, quality-adjusted life years; TPC, treatment of physician's choice.

Figure 23 shows tornado diagrams depicting the 10 parameters that have the greatest influence on the ICER for PEM + LEN versus TPC. The key drivers of the deterministic sensitivity analysis results include those related to survival curve fits, specifically one-knot splines and generalised gamma distributions.

Figure 23: OWSA tornado diagram (pembrolizumab CAA applied only, lenvatinib list price; KEYNOTE-775 FA)

[redacted]

Key: AE, adverse event; FA, final analysis; ICER, incremental cost-effectiveness ratio; PEM + LEN, pembrolizumab with lenvatinib; MRU, medical resource use; OWSA, one-way sensitivity analysis; TPC, treatment of physician's choice.

1.9.3. Scenario analysis

Table 29: Scenario analysis – PEM + LEN versus SoC – including CAA for pembrolizumab (pembrolizumab CAA applied only, lenvatinib list price; KEYNOTE-775 FA)

Parameter	Base case	Scenario analysis	Justification	ICER (£ per QALY)	Difference vs. revised base case
Base case	-	-	-	[redacted]	[redacted]
Time horizon, 30 years	40	30	NICE reference case, alternative time horizon	[redacted]	[redacted]
Discount rate (costs and utilities) – 1.5%	0	0	NICE reference case, alternative time discounting assumptions	[redacted]	[redacted]
Baseline characteristics					
Mean age (years) = 63.5 (KEYNOTE-775)	67.7	63.5	Testing for the impact of patient age	[redacted]	[redacted]
Mean age (years) = 65.5 (Heffernan, 2022)	67.7	65.5		[redacted]	[redacted]
OS (KEYNOTE-775 FA)					
TPC OS: HR adjusted for treatment switching ([redacted]); TSE, without recensoring)	One-knot splines (adjusted for treatment switching; TSE, without recensoring)	HR=0.60	Testing for impact of alternative treatment switching adjustment methods in the TPC arm	[redacted]	[redacted]
TPC OS: HR adjusted for treatment switching ([redacted]; TSE, with recensoring)		HR=0.55		[redacted]	[redacted]
TPC OS: HR unadjusted for treatment switching ([redacted]) Unadjusted TPC one-knot spline model		HR=0.65	Testing for the impact of unadjusted TPC arm	[redacted]	[redacted]
TPC OS: Unadjusted TPC one-knot spline model		Unadjusted TPC one-knot spline model		[redacted]	[redacted]
Treatment waning					
Waning between 5–7 years after stopping treatment (70% of patients)	No waning	5–7 years after stopping treatment (70% of patients)	Testing the impact of treatment waning assumptions	[redacted]	[redacted]
Waning between 5–7 years after stopping		5–7 years after		[redacted]	[redacted]

Parameter	Base case	Scenario analysis	Justification	ICER (£ per QALY)	Difference vs. revised base case
treatment (60% of patients)		stopping treatment (60% of patients)			
Waning between 5–7 years after stopping treatment (80% of patients)		5–7 years after stopping treatment (80% of patients)		[redacted]	[redacted]
TOT (KEYNOTE-775 FA)					
TOT: Next best plausible curve fit, Log-logistic (PEM), Weibull (LEN and TPC)	Generalized gamma	Log-logistic (PEM), Weibull (LEN and TPC)	Alternative structural assumptions surrounding TOT extrapolation	[redacted]	[redacted]
TOT: Pembrolizumab and TPC KM	Capped by PFS	KM		[redacted]	[redacted]
Utilities (KEYNOTE-775 FA)					
Utility: Regression Model 4: TTD utilities with disease progression as covariate (methodologically similar to the approach accepted in TA779)	Model 3	Model 4	Alternative utility assumptions	[redacted]	[redacted]
Safety: TTD utility, No disutilities	Model 3	Model 3		[redacted]	[redacted]
Utility: Age-adjusted utilities, No	Yes	No		[redacted]	[redacted]
Costs					
Costs: Use caelyx to cost for doxorubicin, Yes	No	Yes	Alternative costing assumptions	[redacted]	[redacted]
Safety: Include AE costs, No	Yes	No		[redacted]	[redacted]
Costs: Vial sharing, Yes	No	Yes		[redacted]	[redacted]

Key: AE, adverse event; CAA, commercial access agreement; FA, final analysis; HR, hazard ratio ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; PEM + LEN, pembrolizumab with lenvatinib; TOT, time on treatment; TPC, treatment of physician's choice; TSE, two stage estimation, time to death.

1.10. Further clinical validation conducted after receiving the ACD

To provide a clinical perspective and input around the OS estimates based on the FA of KEYNOTE-775, individual 45 minute interviews were conducted in November 2022. In the individual interviews, three clinical experts were shown:

- Reported baseline characteristics and top-line OS results from the Heffernan (2022) real-world study compared with KEYNOTE-775
- Graphs of smooth hazard plots related to OS spline models in the PEM + LEN and TPC arms
- Graphs and HR of OS in the TPC arm of KEYNOTE-775 with and without adjustment for treatment switching
- Observed OS in the FA of KEYNOTE-775, modelled OS at landmark time points in the PEM + LEN and TPC arm and median and mean life-years predicted by the model

Clinical opinion and feedback were sought to provide clarity on the following key topics:

- Overall comparability of Heffernan (2022) and KEYNOTE-775 study populations; appropriateness for validating modelled outcomes in the TPC arm
- Expected impact of subsequent PD1/PDL-1 or VEGF/VEGFR inhibitor therapies on OS in the TPC arm; appropriateness of adjusting OS in the TPC arm of KEYNOTE-775 for treatment switching and the HR results after such adjustment
- Clinical perspectives on the ability of the OS spline models to track the underlying hazards (smooth hazard plots) in the PEM + LEN and TPC arms, individually; most appropriate spline model based on hazard plots
- Clinical perspectives on the OS extrapolations based on visual fit to the observed data from KEYNOTE-775, against Heffernan (2022), and at 5- and 10-year landmarks along with median and mean life-year predictions

The feedback has been taken into consideration as part of the revised base case analysis, referred to throughout this technical addendum:

- It is clinically reasonable to use the adjusted data in the TPC arm, both from a treatment pathway and clinical efficacy perspective. Without such adjustment, TPC OS data are confounded by the administration of subsequent PD1/PD-L1 or

VEGF/VEGFR inhibitor therapies, and therefore the trial data are likely to overpredict the true outcomes in the TPC arm. The clinical experts confirmed that they expected the OS outcomes in the TPC arm to worsen, after adjusting for treatment switching.

- The one-knot spline models (odds scale) provided a good fit to the observed data, and reasonable extrapolations in both the PEM + LEN and TPC arms (adjusted for treatment switching). There was consensus that the spline models provided a good fit to the observed data, within the trial period. Additionally, all clinical experts commented that the hazard plots look very similar.
- Of the spline models on the odds scale, clinical experts commented on the similarity of the plots when varying the number of knots. It was suggested that the one-knot spline models may provide a slightly better fit over time but it was difficult to differentiate between the plots in some cases.
- The long-term projections were also similar across the models, based on visual assessment of the extrapolated curves, landmark survival estimates, median estimates and mean predicted life years generated from each flexible model. It was difficult to identify which curve produced the most reliable outcomes as KEYNOTE-775 provides the longest follow-up data to inform the estimates.
- Compared with KEYNOTE-775, the Heffernan (2022) population had a higher proportion of patients with serous histology type (25% vs 42%, respectively), a greater proportion of patients with initial diagnosis at Stage III or IV disease (65% vs 78%, respectively). These differences are likely to have a negative impact on prognosis in the Heffernan (2022) study population.
- However, ECOG PS was only reported for approximately half of the patients in the Heffernan (2022), which provides an incomplete view of the population on this measure alone and is ultimately a major limitation of this interpreting the types of patients or the results from this study.
- There could be some differences in the types of patients based on use of platinum doublet therapies; however, the data on ECOG PS are incomplete and there is no further information available to understand these differences.
- A proportion of patients will have durable response to PEM + LEN. In addition, patients who are considered to benefit from further treatment may very well receive continued treatment with lenvatinib monotherapy, even after

pembrolizumab has stopped in a real-world setting, as was the case in KEYNOTE-775.

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NICE National Institute for Health and Care Excellence

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 23 November 2022. Please submit via NICE Docs.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eisai Limited
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]

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	Eisai is the marketing authorisation holder for lenvatinib in this indication. In section 3.9, pages 13-15 – the appraisal consultation document states that '*It is appropriate to assume some treatment waning in the model*'. Eisai believe it would be inappropriate to assume a treatment waning effect for lenvatinib plus pembrolizumab based on the following rationale: • Although pembrolizumab has a 35-cycle (24 month) stopping rule, it is important to note that lenvatinib can be administered until unacceptable toxicity or disease progression. • The Evidence Review Group report cites the application of a treatment waning effect in TA779 for dostarlimab (for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency) as justification for its application in this appraisal. However, it should be noted that dostarlimab is a monotherapy whereas lenvatinib plus pembrolizumab is a combination therapy and as described above, lenvatinib can be administered until unacceptable toxicity or disease progression. Therefore, we do not believe TA779 is an appropriate analogue to justify the application of a treatment waning effect for lenvatinib plus pembrolizumab. • Kaplan-Meier curves for overall survival from the KEYNOTE-775 final analysis (data cut off: 01 March 2022) showed a sustained separation of the treatment arms over the follow-up (approximately 42 months; 3.5 years). This is supported by the Kaplan-Meier curves for duration of response, see Figures 1-2 below, which also show a sustained separation of the treatment arms over 3.5 years of follow-up. Therefore, Eisai believe there is no evidence of treatment waning effect for lenvatinib plus pembrolizumab and it would be inappropriate to assume this in the economic analysis. ***Figure 1: Kaplan-Meier estimate of overall survival, (all-comers, intention-to-treat population)***

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Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

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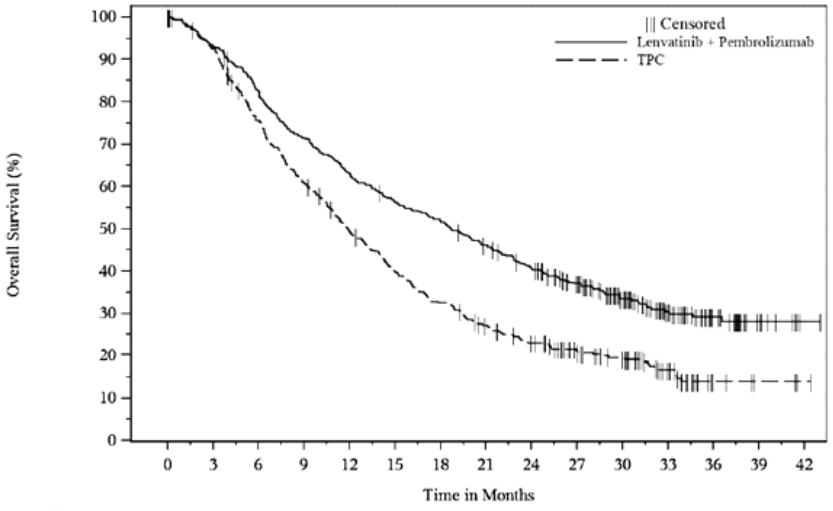


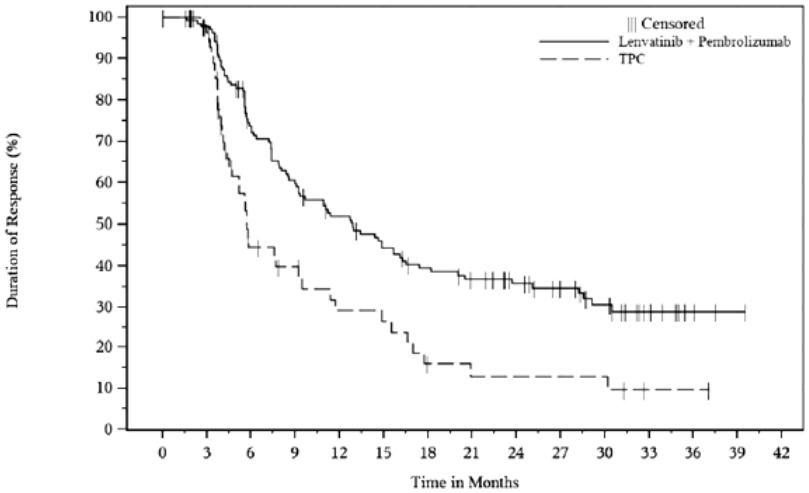
n at risk

Lenvatinib + Pembrolizumab	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
TPC	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 01MAR2022
Source: [P775V02MK3475: adam-adsl; adtte]

[Reference: Study 309/NICE ID3811 committee meeting slides, slide 16; Makker et al, ESMO 2022(1)]

Figure 2: Kaplan-Meier estimate of duration of response (all-comers, intention-to-treat population)



n at risk

Lenvatinib + Pembrolizumab	139	132	95	78	64	54	46	41	34	28	21	10	3	1	0
TPC	61	53	20	16	11	10	5	4	4	4	4	1	1	0	0

TPC = Treatment Physician's Choice of doxorubicin or paclitaxel.
Database Cutoff Date: 01MAR2022
Source: [P775V02MK3475: adam-adsl; adtte]

[Reference: Study 309/KEYNOTE-775 Clinical Study Report (final data cut), (Figure 11-16); Makker et al, ESMO 2022(1)]

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NICE National Institute for Health and Care Excellence

Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 23 November 2022. Please submit via NICE Docs.

	Reference: (1). Makker, V., et al. "525MO Updated efficacy and safety of lenvatinib (LEN)+ pembrolizumab (pembro) vs treatment of physician's choice (TPC) in patients (pts) with advanced endometrial cancer (aEC): Study 309/KEYNOTE-775." *Annals of Oncology* 33 (2022): S785-S786.

NICE National Institute for Health and Care Excellence

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Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 23 November 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):	Peaches Womb Cancer Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to disclose
Name of commentator person completing form:	[redacted]

Comment number	Comments

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Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 23 November 2022. Please submit via NICE Docs.

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Introductory notes** Peaches Womb Cancer Trust is a charitable organisation dedicated to improving the lives of those affected by womb cancer through raising awareness, supporting those affected, and funding womb cancer research. Peaches Womb Cancer Trust also hosts 'Peaches Patient Voices', a patient and public involvement group for people affected by womb cancer. We work with, and advocate for, people affected by endometrial cancer – diagnosed at all stages – and their loved ones. Peaches Womb Cancer Trust has contributed the views, insights, and expertise of our patient voices network, and used our evidence to highlight the difficult situation many patients face when diagnosed with advanced or recurrent endometrial cancer. As an organisation, we have presented our evidence on the impact of advanced and recurrent endometrial cancer, and available treatments, on our patient voices community. In this instance, we are concerned that NICE's interim recommendation would not be in the interest of the approximately 1,200 people diagnosed with advanced endometrial cancer in England each year, or the approximately 1,000 people in whom endometrial cancer recurs. We are concerned that this decision will perpetuate the current situation, in which the majority of these patients face treatments with poor effectiveness and massive impacts on quality of life. Peaches Womb Cancer Trust is increasingly receiving enquiries about the availability of pembrolizumab and lenvatinib, which has highlighted to us how desperate patients are for a second line treatment that is more effective than chemotherapy. Peaches Womb Cancer Trust has valued the opportunity to use evidence obtained from members of Peaches Patient Voices to demonstrate the potential positive outcome for many people facing an advanced or recurrent endometrial cancer diagnosis. However, we are concerned that, although slide 8 titled 'Patient Perspective', presented at the Technology Appraisal Committee meeting on 11 October 2022, provided an overview of the range of symptoms and side effects of chemotherapy and radiotherapy experienced by patients with advanced or recurrent endometrial cancer, it did not adequately represent our patient experts' submissions. Additionally, our patient experts only had one working day in which to review the content of the 'Patient Perspective' slide, which gave them insufficient time to prepare for the committee meeting. Therefore, Peaches Womb Cancer Trust is putting forward this consultation response to ensure that the appraisal committee is able to most effectively include the patient perspective in its decision-making process. This response has been compiled from information obtained from our previous submissions, as well as new evidence obtained by questionnaire and survey from members of Peaches Patient Voices and Womb Cancer

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	Support UK, a private Facebook peer support group for women who have been diagnosed with womb cancer. As the survey ran alongside free text questions, not all quotes provided below were included in the initial submission circulated. Key points in each section have not been changed and all main points were consulted on by respondents. A survey sent to members of Peaches Patient Voices and Womb Cancer Support UK who have been affected by womb cancer as either patient or carer confirmed that an overwhelming 43 out of 44 (97.7%) respondents are in agreement with our response, and 1 out of 44 (2.3%) respondents neither agrees nor disagrees with our response. Additional questions were asked to those who identified themselves as having advanced (stage 3 or 4), recurrent or metastatic cancer. In total, we have included quotes from 17 people affected by endometrial cancer. Most of the quotes and patient stories have been taken from this survey. Whilst we have provided names to help committee members identify different people in the patient and carer stories, these are pseudonyms and all identifying information has been removed.
2	**The outcome we want to see** Peaches Womb Cancer Trust would like to see the approval of pembrolizumab and lenvatinib to give people affected by advanced or recurrent endometrial cancer access to treatments which support them to live longer and with fewer side effects which affect their day-to-day and overall quality of life. This would provide much-needed hope to patients and their loved ones of living well for longer and would also mean fairer access to more effective second-line treatment options, like those available for many other cancers.
3	**What a "yes" decision means to patients and their carers** • Patients would get access to effective treatments that would improve both survival and quality of life by better symptom control and fewer debilitating side effects than chemotherapy, which would allow them to maintain their independence longer and live life as fully as possible. • Living without fear of neutropenic sepsis and unplanned hospital admissions means that patients could continue to work and participate in activities that are meaningful to them such as spending quality time with family and friends, swimming, and travel. • Feeling well enough to undertake activities that are meaningful to a patient's life would promote mental wellbeing and allow them to thrive - to 'live with' cancer - which may help them to remain well for longer. • The combination of 3-weekly pembrolizumab 30-minute infusions and daily oral lenvatinib would be more convenient to patients as it is less burdensome than chemotherapy regimens, making it more accessible to people who cannot tolerate a longer duration infusion. • Remaining independent for longer, and the reduced frequency of planned and unplanned hospital visits, would reduce the caring burden for loved ones and

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	improve their physical and mental wellbeing. • Staying well for longer would improve the likelihood of bridging to future treatments. **Patient story 1:** Hannah was diagnosed with stage 3c, grade 3 endometrial cancer in November 2019, age 30, and relapsed 6 months after finishing treatment for her primary cancer – with tumours in her bowel, scar tissue and one near her liver. After undergoing surgery which removed 3 of 4 tumours, she started pembrolizumab as a monotherapy which shrunk the final tumour so that there is nothing visible on her scans. Her scans have been clear for almost a year with no sign of the cancer. Hannah has also been able to live a "healthier and more fulfilling life" despite an incurable cancer diagnosis: travelling to Prague to visit a friend, getting a promotion at work, taking up climbing as a new hobby and open water swimming. Although there have been a couple of setbacks (mainly underactive thyroid due to the treatment) and some fatigue, the benefits much outweigh these – and are much easier to manage than those she experienced on chemotherapy. Hannah reported: *"Receiving pembrolizumab over the past year has been life-changing for me. My priorities for my life, as someone living with incurable cancer, is to live a full life, where I don't constantly feel like a cancer patient, and I am able to thrive for as long as possible. Over the past year, I have been able to live a nearly normal life – with the exception of needing to rest more and not 'over-do' it."*
4	**What a "no" decision means to patients and their carers** • Patients with advanced or recurrent endometrial cancer are often already living with long-term side effects caused by previous treatment such as radiotherapy or first line chemotherapy. • Debilitating side effects caused by second line chemotherapy include nausea, vomiting and fatigue, which severely impact day-to-day living. • Symptoms of advanced or recurrent endometrial cancer (e.g. pain, vaginal bleeding, nausea, vomiting, bowel obstruction, fatigue) are often poorly controlled by chemotherapy, which impacts massively on quality of life. • Reduced quality of life means that patients are not able to enjoy the often-limited time they have left to live or take part in activities that are meaningful to them. • Frequent and extended planned and unplanned trips to medical settings disrupt patients' and their carers' lives which provokes anxiety and distress. The increased financial pressures of frequent visits to medical settings also create extra worry and stress for patients.

- Fear of neutropenic sepsis makes patients feel vulnerable and severely limits activities such as meeting up with friends and family, swimming, going to work, and travelling due to the need to be within reach of hospital care.
- For some patients, hair loss can have a profound impact on mental wellbeing.
- For loved ones, there is a physical impact due to additional activities on top of their own day-to-day living, and psychologically due to constant worry and anxiety, including the risk of catching and transmitting an infection, as well as less time for themselves.

Carer story 2:

Lynn's mum had been diagnosed with advanced endometrial cancer which caused reduced mobility, pain and swelling. This meant that she was unable to leave the house or to live independently, which took its toll on her mum's mental health and quality of life. It also meant her mum needed to rely on family members for a number of daily living activities and reduced the quality of the family's remaining time spent together.

Lynn describes how:

> *"Chemotherapy was THE only treatment option [for my mum]! She endured several different types of this toxic and archaic treatment option! She suffered physically, mentally, and so did all of her world, her children and young grandchildren! Chemo meant she couldn't go abroad on holiday, eat out in restaurants fearing the risk of infection. She slept more, she became depressed because of her want and need to live and no other alternative treatment! She had to choose in the end to suffer chemo and side effects or stop treatment and enjoy just a couple of quality months with her family!"*

Patient story 3:

Julia was diagnosed with advanced endometrial cancer last year and feels grateful to have received surgery, chemotherapy and radiotherapy treatment. She says she would have done or suffered anything to have been treated; however:

> *"It resulted in a big interruption to my job (11 months off work) and to my husband's job [as] he drove me to every appointment. Obviously, we spent a lot on diesel over this time [including 5 weeks of radiotherapy] and although I was fortunate to have the first six months on full pay, the second five months were on half pay, so there was a considerable financial hit. I felt very isolated at times due to being very immunocompromised - especially during a time of covid and two treatments had to be delayed due to a low neutrophil count, which meant I cancelled even seeing family a couple of times. Although I coped reasonably well with the hair loss when I was in treatment, the 'growing back' phase has actually, for me, been so much*

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	harder. I look different, but to people who don't know my story, my appearance may look like a choice - but it isn't." **Patient and carer quotes:** *i "A no decision from NICE would be nothing short of devastating."* *ii "I get a lot of pain and discomfort around my bladder and bowel following my op and first chemo which has caused nerve damage and incontinence."* *iii "I try to plan things like seeing friends [but] I have to cancel so often due to the pain, anxiety and constant tiredness."* *iv "I had to get a cleaner in and have help from my 74-year-old mother as I can't cope with daily living tasks."* *v "Chemotherapy meant [my mother] was unable to swim and enjoy meals out due to her immunocompromised situation."* *vi "I'm devastated watching my mum deteriorate and lose the independence that she has always had"* *vii "[I was] taken aback by how vulnerable it made me."* *viii "[It was] like living on a knife edge with constant anxiety about my future and that of the people I care about."* *ix "I […] found the period where my blood count during chemotherapy dropped incredibly stressful and anxiety-inducing, leading to panic attacks and lack of sleep."* *x "My sister and I shared the week between us staying over, including our young children, to care for Mum [and] to help her move and support with meals and medication."*
5	**Current treatments are woefully lacking with no standard second line of treatment for endometrial cancer** • NICE recognises that there is a high unmet need for patients with previously treated advanced or recurrent endometrial cancer. • For those who can tolerate it, second line chemotherapy is an option, but this offers little promise of effectiveness ("only 10% to 15%" response rate according to the clinical experts) and serious and debilitating side effects severely impact quality of life.

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- A diagnosis of advanced or recurrent endometrial cancer is devastating enough, but when patients discover the lack of effective second line treatment options open to them, this provokes feelings of anger, frustration, abandonment and hopelessness.
- Patients agree with clinical expert opinion that pembrolizumab and lenvatinib is a 'game changer' and a 'huge step change' in terms of effectiveness, real world patient experience suggesting it is a kinder treatment that will improve quality of life compared to chemotherapy.
- There is a high unmet need for a treatment like this and patients justly feel they deserve access to this treatment, and to have hope of living well for longer.

Carer story 4:

John's wife was recently diagnosed with metastatic endometrial cancer, and he feels his life has been destroyed as the future he and his wife had planned, and their desire to grow old together, can no longer happen. Although he and his wife try to live day-by-day as best they can, each day is filled with the knowledge that current chemotherapy offers little hope; knowledge that causes him a great deal of "mental anguish".

He describes how he is:

> *"…distraught by NICE's interim decision. This anguish is compounded by the knowledge that the Scottish equivalent of NICE, SMC, has approved pembrolizumab and lenvatinib for treatment of my wife's cancer. When clinical experts testify to the committee on 11 October that pembrolizumab and lenvatinib were a 'game changer' and outlined clear benefits to this approach over existing treatment options, I was filled with hope. When the committee stated on 2 November they would not be recommending pembrolizumab and lenvatinib as a treatment this hope was dashed and I was distressed. I have to hide this interim decision from my wife as I know the impact on her will be devastating.*
>
> *As experts in their field, the committee members know the current chemotherapy options provide little hope to patients like my wife. They know that treatment for patients with this cancer have not changed for decades. They know that immunotherapy is an exciting, developing and promising treatment option. They know their counterparts in Scotland have approved pembrolizumab and lenvatinib. They have listened to the clinical experts and patient representatives, and know the benefits of pembrolizumab and lenvatinib. I have listened to this evidence, and relayed it to my wife. This has had a very positive impact on her mental well-being. I dread that if the committee moves forward with its interim recommendation the impact on my wife will be devastating and she will be left with no hope."*

Patient story 5:

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	Anne had a recurrence of endometrial cancer that was treated with radiotherapy and chemotherapy but was told that, unfortunately, neither treatment had been successful, and her condition would deteriorate as there were no other treatment options left. Anne describes how at the: *"…last minute I was referred to [a] hospital, nearly 200 miles from where I lived for [a] last ditch operation. The impact this had on not only my life, but for my husband & children/grandchildren etc, was just unimaginable. I had two months of hospitalisation, not allowed visitors, to say I hit rock bottom is an understatement. I am now left incontinent, a permanent stoma and open wound in my back for which I have daily treatment. My life could have been so much better had this alternative treatment been available. Surely women with endometrial cancer deserve better, not to be treated as second class patients. We are worth more than that and what is available to us at the present time."* **Patient and carer quotes:** i *"I do not feel that there would have been many options available to me, had immunotherapy not been available, and that the conversations with my doctors would have been very different had my recurrence happened before it was available – particularly as I did not respond well to chemotherapy, resulting in a relapse shortly after finishing treatment. From conversations with my oncologist, it seems as though there would be few available options which is not a conversation that I wanted to have at 32." [Patient received pembrolizumab as a monotherapy through special licence].* ii *"My mother has recurrent incurable metastatic endometrial cancer, there is only top up chemotherapy available and psychologically, mentally, and emotionally we feel that there is no other treatment in place as the chemotherapy keeps weakening her and with no knowledge of whether it would help. We are desperate to find alternatives that would be cancer specific."* iii *"On my second chemo I nearly died from severe anaphylactic shock as it turns out I'm severely allergic to paclitaxel. When I saw my oncologist, he told me there are no other chemos to put me on. That feeling that there is medication there to help save my life, but I can't use, and there are no other medications available, it was worse than being told I had cancer. It took away some of the hope that I'm going to survive."* iv *"As a patient, and registered nurse, with recurrent womb cancer NICE should be exploring all options available as the incidence of womb cancer is increasing in the population. At 45 I am not prepared for a terminal diagnosis when there are other*

	options available." v *"[If NICE decided not to approve pembrolizumab with lenvatinib I would] feel terribly let down and frightened, for myself and for others. I think [people with advanced endometrial cancer] are entitled to have potentially life-saving treatment."* vi *"You hear about all these different treatments out there, and people losing their lives when there are no other treatments available, and then you hear about treatments out there that could save or extend your life but they won't be used because they're too expensive. Nobody can fully understand this without having been in that position themselves."*
6	**There are fewer treatment options for patients facing advanced and recurrent endometrial cancer** • Patients feel that they are being treated unfairly compared to people with other cancers and that they deserve access to newer targeted and more effective treatments. **Patient and carer quotes:** i *"There are too few options for patients with recurrent endometrial cancer. We are the Cinderellas of the cancer world and deserve better options."* ii *"All the other cancers get 'ibs' and 'mabs' but we get nothing - we are the poor relation."* iii *"I was alarmed to realise that all I would be offered in both first and second line (if I progressed) would be just the bog-standard traditional chemotherapy. Not a level playing field!"* iv *"When I was re-diagnosed, I took a lot of courage and reassurance from others I followed on social media who were 'living with cancer' for many years, such as those with secondary breast cancer. I was horrified to learn that, if I hadn't had access to pembrolizumab, there would not have been any more options available beyond chemotherapy which hadn't been effective for me." [Patient received pembrolizumab as a monotherapy through special licence]* v *"What is the future strategy for women who have this cancer if the most promising treatment available is denied to them? What impact will this have on future research into immunotherapy for treating this type of cancer? In brief,* ***what next?*** *If the committee's interim recommendation not to recommend pembrolizumab and lenvatinib is their final decision, I know very well what is next for my wife: months,*

	possibly years of hopelessness, followed by death." vi *"It is my own working theory - from my experience of womb cancer and my husband's of prostate cancer - same time period, different London hospitals - that provision for prostate cancer is 'better' and more joined up." [Received by email from a Peaches Patient Voices member]* vii *"I am currently having the combination chemo of paclitaxel and carboplatin which, I am assured, has I good success rate and I have a good prognosis. However, further chemo is likely in the future and, as well as not being the most pleasant treatment, it affects life in so many ways."*
7	**Equality of access** • Chemotherapy impacts patients' lives financially due to absence from employment secondary to illness, travel to and from and parking at the hospital, and the cost of living at home (e.g., heating) and alternative therapies. Pembrolizumab infusion is shorter duration and less frequent than chemotherapy which often requires carers to take less time off work to accompany their loved ones. • Chemotherapy is not suitable for many mostly older patients due to comorbidity, however, pembrolizumab and lenvatinib is likely to be tolerated better than chemotherapy giving those people hope of accessing an effective treatment. • There is an urgent unmet need for patients with mismatch repair proficient tumours (the majority) to have access to an effective treatment. • Pembrolizumab with lenvatinib has recently been approved for use by the Scottish Medical Council. Without approval by NICE, there is a risk of geographical inequalities in access to a second line treatment for advanced and recurrent endometrial cancer.
8	**People affected by endometrial cancer see pembrolizumab and lenvatinib as a source of hope for the future** • When we asked about the impact of potential approval of pembrolizumab and lenvatinib, many patients identified that this is a source of hope for the future and that they are fearful for a future that only includes the current standard treatments. People cited worries about side effects of these treatments and the low response rates and life expectancies on currently available treatments. **Patient and carer quotes:** i *"I feel as if there is a shadow over me and although I consider myself to be a resilient, well-rounded individual, who to all intents and purposes may appear healthy, I am haunted by the spectre of recurrence. If it does return, I would want to*

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	know that there were more and different options this time around - such as pembrolizumab and lenvatinib - because I would have little faith in chemotherapy a second time and also because the thought of withdrawing from a job that I love and friends and family again, would be such a hard thing to do. I'm really torn, asking for this, because I know only too well the pressures on the NHS and I know that everything has to be costed and funded. However, I do feel that if use of treatment other than chemotherapy begins to be the norm, then we can start to build a future where womb cancer can be lived with, alongside a normal life. Then the costs not only of the treatment itself, but costs related to long term collateral damage caused by chemotherapy, will also fall. Pembrolizumab and lenvatinib seem to me to provide the potential to return 'living a life' to endometrial cancer patients, rather than simply a chance of staying alive." ii *"I would be very disappointed [if NICE decided not to recommend pembrolizumab and lenvatinib], as my wife's carer since her diagnosis with womb cancer, and having gone on that journey with her, I strongly feel that any effective treatment should be utilised to fight this cancer as the cancer is extremely dangerous and I would imagine anyone concerned would want to know that there are effective treatments available to help."* iii *"I'd welcome anything that would prolong my life. I'm an active 63 year old and don't want to die from my [advanced endometrial] cancer."* iv *"Everyone deserves a chance at treatment - no matter. With [an advanced stage] cancer hanging over you I feel anything to help is paramount to the mental health of a patient."* v *"It is very important for these drugs to be available to give hope to us who appear to have no other form of treatment available."*

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more

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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.

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Pembrolizumab with lenvatinib for previously treated advanced, metastatic or recurrent endometrial cancer [ID3811]

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

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

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

Section 3.5 is titled ‘Pembrolizumab plus lenvatinib may be better in dMMR disease than in pMMR disease but there is not enough evidence to conclude this’, and the committee concludes ‘The committee concluded that the study was not powered to consider subgroups based on MMR status and that the treatment pathways for routinely commissioned treatments for both subgroups are the same. It further concluded that both subgroups have had benefit from pembrolizumab plus lenvatinib compared with doxorubicin or paclitaxel monotherapy.’ As noted within this ACD, dostarlimab is recommended via the Cancer Drugs Fund, and is therefore not considered a comparator within scope for this appraisal. GSK requests that the sentence ‘However, it is possible that pembrolizumab plus lenvatinib is better than dostarlimab in the dMMR population, but there is no evidence to conclude this’ is removed as no evidence or discussion regarding the comparative effectiveness of dostarlimab has been presented, and furthermore this sentence does not serve a purpose within this consultation document to add to the committees conclusions for this appraisal.

.

Name	
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

The committee does not take into account the clear benefits of the technology to patients in reaching its recommendation. This is odd as they are clearly outlined in the documentation.

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

No. The cost effectiveness of the therapy is barely mentioned in this documentation. Most of the discussion in the appraisal consultation document reflects discussion of the participants during the meeting on the most appropriate statistical methodology; not on the cost benefit of the technology. The conclusion appears to be ' The committee is unclear on the benefits of the technology in comparison to current treatments.' The outcome of current treatments are clear: dismal outcomes. The current treatments are clearly not cost-effective as the outcomes for patients are dismal. The conclusion of the committee appears to be based on their uncertainty of statistical models as opposed to the clear benefits from clinical practice and the real life experience of those who testified to the committee. The committee does not offer any evidence that the Technology is not cost-effective. They only appear to be able to state 'we can't tell if it's as good as the current treatment.' The current treatment is obviously not cost-effective, in terms of prolonging patients' overall survival rates; therefore, the comparison is nonsensical. The benefits are clear from Clinical practice and real life testimony, which the committee heard; supported by a review of the literature, viz. 'Lenvatinib plus pembrolizumab showed promising antitumor activity in patients with advanced endometrial carcinoma who have experienced disease progression after prior systemic therapy, regardless of tumor MSI status.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7479759/);
Pembrolizumab and lenvatinib has emerged as an effective treatment for advanced, previously treated endometrial cancer
(https://ijgc.bmj.com/content/32/1/93)';
Conclusions: In this exploratory analysis of pts with advanced EC enrolled in KEY-NOTE-146/study 111 treated with L + P, clinically meaningful responses were achieved regardless of biomarker status, including TMB status, and no gene expression sig- natures were associated with clinical outcomes.
Clinical trial identification: NCT02501096; EudraCT 2017-000300-26.
https://www.annalsofoncology.org/article/S0923-7534(21)03467-0/pdf;
Similar to the global Study 309/KEYNOTE-775 results, this analysis suggested favorable efficacy and manageable safety with lenvatinib plus pembrolizumab after platinum-based chemotherapy in Japanese patients with advanced endometrial cancer and supports this combination as a new standard of care in this population.
Lenvatinib plus pembrolizumab in Japanese patients with endometrial cancer: Results from Study 309/KEYNOTE-775 Cancer Science. 2022;113:3489–3497;

Optimizing the use of lenvatinib in combination with pembrolizumab in patients with advanced endometrial carcinoma Front. Oncol., 21 September 2022 Sec. Gynecological Oncology https://doi.org/10.3389/fonc.2022.979519'

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

No. There is clear evidence that the use of this technology has a beneficial outcome for patients. The committee appears to be objecting to its usage based on a cost. What price a human life? What price for hope for those who have none? The clinicians who testified to the committee noted it was a game changer. Patients and charities representing them noted the benefits of this technology. The evidence submitted by the committee on the cost model do not appear to be detailed. Current platinum based chemotherapy has dismal outcomes, yes it is fully funded by the NHS. The committee appears to be making its recommendation that it is not worth the money because the outcomes are not clear. The outcomes of not providing this treatment are very clear: death.

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?

This committee's recommendation clearly discriminates against patients who cannot afford private healthcare treatment.

PEMBROLIZUMAB WITH LENVATINIB FOR PREVIOUSLY TREATED ADVANCED, METASTATIC OR RECURRENT ENDOMETRIAL CANCER [ID3811]

EAG critique of the company's updated economic analysis using final data (Post AC 1)

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter.
EX1 2LU

Authors

Brian O'Toole[1]
Maxwell S. Barnish[1]
Edward C.F Wilson[1]
Justin Matthews[1]
Helen Coelho[1]
Naomi Shaw[1]
Melanie Powell[2]
Neil Ryan[3]
Emma Crosbie[4]
Alexandra Taylor[5]
Louise Crathorne[1]
G.J. Melendez-Torres[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
[2] Consultant Clinical Oncologist, St Bartholomew's Hospital, London
[3] Specialty Registrar in Obstetrics and Gynaecology, Severn Deanery

[4] NIHR Advanced Fellow, Professor and Honorary Consultant in Gynaecological Oncology, Manchester
[5] Consultant in Clinical Oncology, The Royal Marsden NHS Foundation Trust

Correspondence to Brian O'Toole
3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; b.otoole@exeter.ac.uk

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1. INTRODUCTION

Following Appraisal Committee (AC) 1, pembrolizumab plus lenvatinib, was not recommended for treating advanced or recurrent endometrial cancer in adults who have disease progression on or after platinum-based chemotherapy and who cannot have surgery or radio therapy. As outlined in Sn 3.16 of the draft NICE guidance, the committee requested that the company make several changes to their cost effectiveness analysis in order to reflect NICE's preferred assumptions. NICE preferences included the following.

- Use results from the final data cut (March 2022) to inform the economic analysis.
- Ideally use more sophisticated, flexible models to allow the committee to see how this may affect the choice of extrapolation for both arms and the justification of waning in the model
- The impact of different treatment effect waning scenarios on the ICER

In response to NICE's concerns, the company has subsequently provided a revised economic analysis (base case and scenario analyses) based NICE's recommendations. However, the EAG has noted that some changes made to the company's base case are extensive, whilst others were not explicitly requested by NICE (see Section 2). The purpose of this document is to critically appraise the array of changes made by the company and determine their appropriateness for decision making.

The EAG has already provided a critique of the company's clinical data (OS and PFS) using the final data cut in the response to Technical Engagement, so this is not repeated here. At that stage, the final clinical data were not incorporated into the economic model. The EAG considered that the final data cut did not change the conclusions of the clinical evidence compared to the interim data cut used at that time in the economic model. Following AC1, the company has been asked to incorporate the final data cut into the economic model, and therefore a revised analysis has been provided.

2. COMPANY'S REVISED ANALYSIS POST AC 1

Following AC 1, the company submitted a revised base case and scenario analyses to address uncertainty raised by the NICE committee. Key changes to the company's base case include the following:

- Clinical data have been updated to reflect the final analysis data cut (see Table 1 in the company's supplementary economic addendum). Updated model inputs based on the final analysis data cut include OS, PFS, ToT, AE's, percentage and distribution receiving subsequent treatment, utilities, and lenvatinib dosing. It should be noted that mean patient weight is based on Interim analysis data from KEYNOTE-775 i.e. 70.5kg. NICE considered KEYNOTE-775 to be generalisable to NHS clinical practice.
- For both Pem+Len and TPC, OS and PFS have been extrapolated using an alternative modelling approach (one knot Splines)
- OS in the TPC arm has been adjusted to account for crossover/treatment switching
- Utilities have been estimated using a combined progression and TTD approach
- Mean age has been updated to reflect NICE preference (mean age=67)

Table 1 provides a summary of NICE committee preferences (post AC 1), EAG preferences, the company's revised changes to their economic model (post AC 1) and outlines whether these changes are consistent with NICE preferences.

Table 1: NICE committee preferences (post AC 1), EAG preferences and company revised base case (post AC1)

	NICE committee Preferences (post AC1)	EAG preferred base case	Company revised base case (post AC 1)	Company changes align with NICE preference?
Clinical data	Analysis should be based on the final data cut	Interim data cut used in EAG base case. However, preference for final data cut to be used	Key clinical parameters in the model were updated to reflect the final data cut and included in the revised base case.	☑
Model type	Committee preferred the EAG's model for TPC arm when using Interim data (KM+Log logistic). But unclear how curve fit changed in	Two-piece model used in EAG base case (KM+Log logistic). However, EAG preference was for more flexible models (such as Splines) to be used	Spline models used in the company's revised base case to estimate PFS and OS for both Pem+Len and TPC arms	Unclear

	both arms when using final data cut Suggested exploration of more sophisticated flexible models			
Treatment waning	The committee agreed that there was unlikely to be a continuing effect with no waning so preferred some treatment waning in the model. The committee concluded that it preferred EAG's waning scenario but wanted to see alternative treatment waning scenarios in a model that incorporates the final data cut.	Treatment waning explored by EAG as a scenario analysis. The EAG presented a preferred base case analysis with and without waning.	Treatment waning not included in the base case. The company provided alternative waning scenario analyses for consideration	☒
Utilities	NICE agreed with the EAG's approach to estimating utilities (utilities based on progression status) The committee considered that TTD limited the amount of information informing health states i.e. it may be granular but more uncertain	Base case utility values estimated based on progression status	In the company's revised base case, utilities were estimated for pre progression and post progression (and also incorporated a TTD element)	☒
Mean age	Committee preferred average age to be 67	Mean age used in EAG base case was 75	Mean age of 67 used in the company's revised base case analysis	☑
TPC arm adjusted for treatment switching	No preference stated However, the committee noted that having immunotherapy as subsequent treatment in the comparator arm had not been explored	Accepted the subsequent treatments and proportions received in the clinical trial.	OS in the TPC arm adjusted for treatment switching in the company's revised base case.	☒

As noted in Table 1, several of the company's revised changes did not reflect NICE preferences. Furthermore, some changes represent a substantial departure from the

company’s original modelling approach i.e. extrapolation of OS and PFS has changed from a piece wise approach to Spline approach and OS data in the TP arm has now been adjusted for treatment switching/crossover. In Section 3, the EAG provides a critique of the changes made by the company to determine their appropriateness.

3. EAG CRITIQUE OF THE COMPANY'S REVISED BASE CASE AND SCENARIO ANALYSES

3.1. Appropriateness of one knot Spline models and validation of OS and PFS estimates

In response to the EAG and the committee's preference for more flexible extrapolation on OS and PFS data, the company produced a set of estimates using the final data cut and drawing on hazard, odds and normal distributions (which could be viewed as 'more complex' versions of Weibull, log-logistic and log-normal distributions respectively). The company explored the use of one, two and three knots (essentially, where the 'break points' are for the survival functions to be joined up) and compared these on the basis of visual fit, AIC/BIC estimates and plausibility. This was undertaken for the TPC arm without adjustment for treatment switching, the TPC arm with adjustment for treatment switching, and the PEM+LEN arm.

The EAG regarded that the company's approach to undertaking this process was defensible and produced curve fits and extrapolations that had greater credibility. The EAG also broadly agreed with the company's chosen base case curves for OS data, but noted that alternative scenarios for PFS extrapolation were plausible.

3.1.1. OS data

Curve fits for TPC (whether adjusted or unadjusted) were all broadly similar on the basis of visual fit; however, extrapolations generated by the class of models using an odds scale had generally better fit to the smoothed hazard function at the end of the observed time period. AIC and BIC estimates did not demonstrate large differences between the included models, suggesting that the most parsimonious fit (i.e. with one knot) should be chosen. This was the company's base case, as supported by additional expert validation. The EAG agreed with this view, though noted that justification as to the placement of the knot was not provided and is thus an outstanding area of uncertainty.

In contrast, visual validation of curve fits for PEM+LEN was less straightforward. Similarly to the TPC curve fits, AIC/BIC estimates preferred fewer knots. Extrapolations consistently predicted a higher hazard than observed towards the end of the observed time period. Of note, inclusion of additional knots did not appear to improve fit. The company cited, among other reasons, consistency with the chosen TPC extrapolation as a rationale for the choice

of a one-knot spline on the odds scale. The EAG agreed that this was the most appropriate fit on the basis of lowest AIC/BIC scores and 'least bad' visual fit to the curves.

The resultant curve fits are shown in Figure 1, and reflect appropriate fit over the length of the survivor functions. In addition, landmark survival estimates in Table 2 suggest that chosen curve fits match the observed data and produce generally consistent long-term landmark survival estimates. For completeness, the EAG has conducted additional scenario analyses using a two knot Spline to estimate OS in the TPC arm (see Section 5.1 for results).

Figure 1: Final OS models in the revised base case, PEM + LEN (one-knot spline) and TPC arm (one-knot spline adjusted for treatment switching, TSE without re-censoring) – KEYNOTE-775 FA

Table 2: OS estimates at landmark time points

TPC arm	1 yr	5 yr	10 yr	Mean (years)	Median (years)
Observed KM (KEYNOTE-775)		-	-	-	
Unadjusted OS spline 1-knot[a]					
Unadjusted OS spline 2-knot[a]					
Unadjusted OS spline 3-knot[a]					
Adjusted OS spline 1-knot[a,b]					
Adjusted OS spline 2-knot[a,b]					
Adjusted OS spline 3-knot[a,b]					

Adjusted OS via HR[a,b,c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEM + LEN arm	**1 yr**	**5 yr**	**10 yr**	**Mean (years)**	**Median (years)**
Observed KM (KEYNOTE-775)	[redacted]	-	-	-	[redacted]
OS spline 1-knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS spline 2-knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS spline 3-knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: FA, final analysis (of KEYNOTE-775); KM, Kaplan-Meier; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; TPC, treatment of physician's choice of paclitaxel or doxorubicin; yr, years.

Notes:

a. OS spline model on odds scale, independently fitted to the TPC data of KEYNOTE-775; based on best fit to the smooth hazard plot and observed data from trial

b. TSE method without re-censoring, OS spline model independently fitted to the counterfactual estimates from the adjusted TPC arm; based on assessment of most reliable approach to minimise risk of bias in the results

c. TSE method (see above); HR estimate applied to the PEM + LEN arm as reference curve

d. OS spline model on odds scale, independently fitted to the PEM + LEN data of KEYNOTE-775; based on best fit to the smooth hazard plot and observed data from trial

3.1.2. PFS data

Citing consistency with OS data, the company asserts that the optimal base case for PFS extrapolations is a one-knot model on an odds scale. Ultimately, long-term visualisations of different knots used in the odds scale did not suggest meaningful differences (see **Error! Reference source not found.** and Figure 3), and AIC/BIC values reported in company addendum Table 11 suggested that the class of models on the odds scale was generally better fitting for the PEM + LEN arm; this was less clear for the TPC arm. Comparisons via landmark survival were not provided between models; however, visual plots of spline-based hazard functions against smoothed spline functions (company addendum Figures 13 and 14) suggested that models fit the TPC arm better than the PEM + LEN arm. Because of the limited time available to explore the range of fits, the EAG could not identify a coherent basis to prefer an alternative PFS extrapolation as a base case.

To explore uncertainty, the EAG considered testing sensitivity of the EAG base case to the worst-fitting PFS fits via AIC/BIC; specifically, one-knot spline on the normal scale for PEM+LEN and the three-knot normal for TPC. However, the company's model only allowed for the odds scale to be used i.e. it was not possible to select a normal distribution.

Figure 2: PFS extrapolation using Spline models (PEM + LEN arm)

Figure 3: PFS extrapolation using Spline models (TPC arm)

3.2. Appropriateness of adjusting OS in the TPC arm for cross over/treatment switching

Treatment switching is intended to adjust where there is permission within the trial protocol for patients in the control arm to switch to the treatment arm allocation. The adjustment produces an estimate of treatment effect in which the switching patients have, counterfactually, not switched.

Analysis for treatment switching was not presented in original CS but is alluded to in company's survival curve analysis, where it is stated that "Due to some participants in the TPC arm of KEYNOTE-775 receiving subsequent PD-1/PD-L1 and VEGF/VEGFR inhibitor therapies that are not routinely available in the UK, the OS estimates may be overestimated in the trial. This could underestimate the incremental benefit of PEM+LEN versus TPC although it is not possible to test and adjust for the potential impact without introducing substantial uncertainty in the analysis" (doc B, p86). At AC 1, the Committee considered that an exploratory analysis of treatment switching would be useful, though treatment switching was not outlined as a NICE preference for inclusion in the revised base case.

In the KEYNOTE-775 trial, patients were allocated to TPC in the control arm and Pembrolizumab + Lenvatinib in the treatment arm. In practice treatment switchers in the trial may alternatively have received Pembrolizumab or Lenvatinib, or similar (PD1/PD-L1 class or VEGF/VEGFR class) as single drugs. The company reports (KN-775_FA_2STG_report_V2) that [redacted] patients in the TPC arm switched, and that: "In protocol 775, 416 participants were randomized to the TPC arm of which [redacted]

The company tried three approaches post ACD all of which are set out in TSD 16. These are Rank Preserving Structural Failure Time Models (RPSFTM); Inverse Probability of Censoring Weights (IPCW); and a 2 Stage analysis (TSE). The company opted for adjustment by TSE because of concerns about the 'common treatment effect' assumption in RPSFTM, and about small sample sizes with IPCW.

The adjusted HRs are given in table 6 of the company response. The company selects the result for TSE 'without re-censoring' (see below), giving a hazard ratio of [redacted] compared to the ITT analysis (no adjustment for treatment switching) of [redacted].

A further issue relates to the application of ‘re-censoring’ within analysis, applied at an earlier time point to avoid informative censoring. Re-censoring in the TSE leads to a hazard ratio of [redacted]. The company argues that this sensitivity analysis ‘demonstrated that re-censoring is not considered necessary’, and opts for ‘without re-censoring’ as primary analysis. The EAG can see no clear reason to avoid the re-censoring step, but acknowledges that the differences in HR are small in magnitude and that this is a conservative selection (that is, it results in the selection of a lesser treatment effect estimate).

The EAG agrees that an analysis for treatment switching is reasonable in principle, and further that TSE may be the most defensible of the three approaches.

The EAG notes however that in this setting the treatment switchers in the trial do not homogeneously receive the trial-allocated treatment (Pembrolizumab + Lenvatinib), but this or a diversity of related treatments: VEGR/VEGFR inhibitors (bevacizumab, lenvatinib , Sorafenib) and PD-1/PD-L1 drugs (atezolizumab, dostarlimab, durvalumab, lodapolimab, nivolumab, pembrolizumab, retifanlimab). This suggests a more complex treatment response, and a more complex risk profile at the point of switching, than the model two-arm trial considered in TSD16. Within the TSE in this analysis, the estimated acceleration factor used to adjust survival among switching patients relates to (counterfactually) not receiving treatment from an uncontrolled ensemble of drugs, rather than a single homogenous allocated treatment. It therefore becomes less clear whether all prognostic covariates have been observed and adjusted for in the ‘first stage’, opening questions of residual bias. It should be noted though that adjustment for a number of prognostic variables has been carried out in the company analysis (table 4 of the company response).

The EAG’s preferred approach is to provide base case results with and without treatment switching, in order to characterize uncertainty and demonstrate how these assumptions impact the results. See Section 5.1 for results.

3.3. Appropriateness of estimating utilities based on progression status and TTD

In Section 3.10 of the draft NICE appraisal consultation document, the committee noted that the TTD approach used by the company may be more granular, however it limits the amount of information informing health states, increasing uncertainty and obscuring the difference between each of the TTD categories. The committee therefore preferred the EAG’s approach of modelling utility based on progression status.

As part of the revised base case analysis the company opted to revert to a TTD approach and extend the initial utility regression models to include progression as a covariate (See Table 3). This model is referred to as Utility Model 3 by the company. Additionally, the company also provided three alternative utility models, as outlined in Tables 17 to 20 of the supplementary economic addendum provided by the company. The EAG also noted, that based on the updated analysis of KEYNOTE-775, the AE utility decrement decreased from [redacted] previously to [redacted].

Although the company has incorporated progression status into their revised base case utility estimation approach, the EAG noted that NICE's concern remains relevant i.e. the data used to inform each of the six TTD categories (per health state) is limited which adds uncertainty to these values. Furthermore, estimating utilities based on progression status alone i.e., pre-progression and post progression aligns with the company's model structure (as highlighted by the EAG in the initial appraisal). As part of the EAG's preferred base case, utility values based on progression status alone were selected for use (these are the values provided by company's Utility Model 1 as outlined in Table 4).

As a scenario analysis the company estimated utilities based on an approach similar to the one used in the dostarlimab (TA779) appraisal i.e. utility values were estimated based on progression status and only two TTD categories (<180 days and ≥180 days), see Table 5 for mean utility values used in the model. In the initial report, the EAG considered this approach to be more reasonable than the TTD used in the company's original base case. To explore uncertainty surrounding modelled utility values, the EAG has conducted a scenario analysis using the mean utility values presented by Utility Model 4.

Table 3: Utility Model 3, utility values used in the company's revised base case (final data cut from KEYOTE-775)

Progression status	TTD	Mean	LB	UB
Pre-progression	< 30 days	[redacted]	[redacted]	[redacted]
	30–89 days	[redacted]	[redacted]	[redacted]
	90–179 days	[redacted]	[redacted]	[redacted]
	180–269 days	[redacted]	[redacted]	[redacted]
	270–359 days	[redacted]	[redacted]	[redacted]
	≥ 360 days	[redacted]	[redacted]	[redacted]
Post-progression	< 30 days	[redacted]	[redacted]	[redacted]
	30–89 days	[redacted]	[redacted]	[redacted]
	90–179 days	[redacted]	[redacted]	[redacted]
	180–269 days	[redacted]	[redacted]	[redacted]
	270–359 days	[redacted]	[redacted]	[redacted]

	≥ 360 days	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; LB, lower bound; TTD, time to death; UB, upper bound.				

Table 4: Utility Model 1, mean utility values based on progression status (final data cut from KEYOTE-775)

Health state	Mean health state utility value	LB	UB
PF	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; LB, lower bound; TTD, time to death; UB, upper bound.			

Table 5: Utility Model 4, mean utility values based on progression status and TTD (final data cut from KEYOTE-775)

Progression status	TTD	Mean	LB	UB
Pre-progression	< 180 days	[redacted]	[redacted]	[redacted]
	≥ 180 days	[redacted]	[redacted]	[redacted]
Post-progression	< 180 days	[redacted]	[redacted]	[redacted]
	≥ 180 days	[redacted]	[redacted]	[redacted]
Key: FA, final analysis; LB, lower bound; TTD, time to death; UB, upper bound.				

3.4. Appropriateness of the company's approach to testing treatment waning uncertainty

In their response, the company maintained that treatment waning was not relevant for inclusion in the base case, *as 'there does not appear to be evidence of a treatment waning effect with PEM+LEN, based on the KEYNOTE-775 trial'* and that *'The FA results of KEYNOTE-775 provide evidence of a sustained longer-term comparative PFS and OS benefit of PEM + LEN compared with TPC that is numerically consistent between the IA and FA data cuts*'. Additionally, the company stated that patients may stop pembrolizumab, but continue to receive lenvatinib, which adds to sustainability of response.

To highlight the durability of response, the company provided a comparison of 2 and 5 year OS in pembrolizumab arms of advanced solid tumour trials (endometrial, melanoma and NSCLC, see Table 6). The EAG noted that modelled 5 year OS for PEM +LEN in the KEYNOTE-775 showed some evidence of a sustained response (OS: [redacted]), however this was lower than the sustained response reported in the only other PEM+LEN study, KEYNOTE 146 (OS: 30%).

As further supportive evidence, the company referred to data from two pembrolizumab monotherapy trials for the treatment of advanced melanoma, KEYNOTE 006 and KEYNOTE 001. In KEYNOTE 006, pembrolizumab was stopped at two years and in KEYNOTE 001 there was no stopping rule. The company stated that there was no structural difference between the cumulative and log cumulative hazard plots for OS, indicating a sustained treatment effect post discontinuation of pembrolizumab. Whilst this observation is noteworthy, the EAG do not consider it appropriate to generalize these findings to the current population under review due to differences in patient characteristics, disease severity, prior treatment history etc.

The company provided three scenario analyses which tested alternative treatment waning assumptions i.e. treatment waning was assumed to occur from 5-7 years and apply to 60%, 70% and 80% respectively (see Section 4 for results).

Table 6: Two and five year OS in pembrolizumab arms of advanced solid tumour trials

	Tumour	OS		Reference
		2 years	5 years	
KEYNOTE-775 - Company model	Endometrial	40.6%	[redacted]	-
KEYNOTE-146	Endometrial	42.0%	30.0%	(10)
KEYNOTE-006	Melanoma	60.0%	45.0%	(11)
KEYNOTE-010 TPS ≥50%	NSCLC	34.5%	25.0%	(12)
KEYNOTE-010 TPS ≥1%	NSCLC	22.9%	15.6%	(12)
KEYNOTE-024	NSCLC	50.0%	31.9%	(13)
KEYNOTE-189*	NSCLC	45.7%	19.4%	(14)
KEYNOTE-402 TPS ≥1%	NSCLC	38.9%	16.6%	(15)
KEYNOTE-407*	NSCLC	36.0%	18.4%	(16)
Key: NSCLC – Non-Small Cell Lung Cancer. TPS: Tumour Proportion Score *included approximately 1/3 PDL1 negative patients				

The EAG acknowledged the company's additional justification for a sustained treatment effect and note that there appears to be some evidence to support some duration of effect after stopping pembrolizumab. However, differences between studies with respect to treatments, patient characteristics, disease severity and the small patient numbers alive at 5 years (in KEYNOTE-146), precludes the EAG from assuming there will be no waning in effect over time.

Furthermore, the EAG noted that NICE's preference was to include some treatment waning in the model and that the committee preferred the EAG's scenario whereby waning was applied over 3 years, after stopping treatment with pembrolizumab. This approach to waning is also consistent with waning assumptions preferred by NICE in other immunotherapies. Therefore, as part of the EAG preferred base case, waning has been applied from years 3 to 5. However, to explore uncertainty (as per NICE consideration in the draft guidance) the EAG has conducted two alternative waning scenarios to demonstrate how results are impacted by alternative treatment waning assumptions (see Section 5.2).

3.5. Appropriateness of altering mean modelled age to 67

The EAG considered that the company's decision to use a mean patient age of 67 to be reflective of NICE preferences, and therefore appropriate for use in their revised base case.

4. COMPANY REVISED BASE CASE RESULTS

The company's revised base case results are presented in Table 7 and Table 8. Results were based on the most up to date pembrolizumab Patient Access Scheme (PAS) discount and list price for lenvatinib (see the cPAS appendix for results using confidential comparator discounts). Company scenario analyses results are outlined in Table 9. The EAG noted that scenarios which had the largest upward impact on the ICER included the use of unadjusted OS data in the TPC arm (resulting in a HR of [redacted]), and incorporating a treatment waning effect for pembrolizumab (assumed to apply to 70% of patients after stopping treatment, from year 5 to year 7). NICE should be aware that several calculation errors were identified in the company's percentage change from the revised base case column (final column in Table 9).

Table 7: Revised company base case results (probabilistic results)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental, PEM + LEN versus comparator			Pairwise ICER (PEM + LEN vs TPC)
				Costs	LYs	QALYs	
PEM + LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAA, commercial access agreement; ICER, incremental cost-effectiveness ratio; LY, life years; LYG, life years gained; PEM + LEN, pembrolizumab with lenvatinib; QALYs, quality-adjusted life years; TPC, treatment of physician's choice.

Table 8: Revised company base case results (deterministic results)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental, PEM + LEN versus comparator			Pairwise ICER (PEM + LEN vs TPC)
				Costs	LYs	QALYs	
PEM + LEN	[redacted]	[redacted]	[redacted]				
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAA, commercial access agreement; ICER, incremental cost-effectiveness ratio; LY, life years; LYG, life years gained; PEM + LEN, pembrolizumab with lenvatinib; QALYs, quality-adjusted life years; TPC, treatment of physician's choice.

Table 9: Company scenario analyses results (deterministic analyses)

Parameter	Base case	Scenario analysis	Justification	ICER (£ per QALY)	Difference vs. revised base case

Base case	-	-	-	[redacted]	[redacted]
Time horizon, 30 years	40	30	NICE reference case, alternative time horizon	[redacted]	[redacted]
Discount rate (costs and utilities) – 1.5%	3.5%*	1.5%*	NICE reference case, alternative time discounting assumptions	[redacted]	[redacted]
Baseline characteristics					
Mean age (years) = 63.5 (KEYNOTE-775)	67.0*	63.5	Testing for the impact of patient age	[redacted]	[redacted]
Mean age (years) = 65.5 (Heffernan, 2022)	67.0*	65.5		[redacted]	[redacted]
OS (KEYNOTE-775 FA)					
TPC OS: HR adjusted for treatment switching ([redacted]; TSE, without recensoring)	One-knot splines (adjusted for treatment switching; TSE, without recensoring)	HR=0.60	Testing for impact of alternative treatment switching adjustment methods in the TPC arm	[redacted]	[redacted]
TPC OS: HR adjusted for treatment switching ([redacted]; TSE, with recensoring)		HR=0.55		[redacted]	[redacted]
TPC OS: HR unadjusted for treatment switching ([redacted]) Unadjusted TPC one-knot spline model		HR=0.65	Testing for the impact of unadjusted TPC arm	[redacted]	[redacted]
TPC OS: Unadjusted TPC one-knot spline model		Unadjusted TPC one-knot spline model		[redacted]	[redacted]
Treatment waning					
Waning between 5–7 years after stopping treatment (70% of patients)	No waning	5–7 years after stopping treatment (70% of patients)	Testing the impact of treatment waning assumptions	[redacted]	[redacted]
Waning between 5–7 years after stopping treatment (60% of patients)		5–7 years after stopping treatment (60% of patients)		[redacted]	[redacted]
Waning between 5–7 years after stopping treatment (80% of patients)		5–7 years after stopping treatment (80% of patients)		[redacted]	[redacted]
TOT (KEYNOTE-775 FA)					
TOT: Next best plausible curve fit, Log-logistic (PEM), Weibull (LEN and TPC)	Generalized gamma	Log-logistic (PEM), Weibull (LEN and TPC)	Alternative structural assumptions surrounding TOT extrapolation	[redacted]	[redacted]

TOT: Pembrolizumab and TPC KM	Capped by PFS	KM		[redacted]	[redacted]
Utilities (KEYNOTE-775 FA)					
Utility: Regression Model 4: TTD utilities with disease progression as covariate (methodologically similar to the approach accepted in TA779)	Model 3	Model 4	Alternative utility assumptions	[redacted]	[redacted]
Safety: TTD utility, No disutilities	Model 3	Model 3		[redacted]	[redacted]
Utility: Age-adjusted utilities, No	Yes	No		[redacted]	[redacted]
Costs					
Costs: Use caelyx to cost for doxorubicin, Yes	No	Yes	Alternative costing assumptions	[redacted]	[redacted]
Safety: Include AE costs, No	Yes	No		[redacted]	[redacted]
Costs: Vial sharing, Yes	No	Yes		[redacted]	[redacted]
Key: AE, adverse event; CAA, commercial access agreement; FA, final analysis; HR, hazard ratio ICER, incremental cost-effectiveness ratio; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; PEM + LEN, pembrolizumab with lenvatinib; TOT, time on treatment; TPC, treatment of physician's choice; TSE, two stage estimation, time to death.					

** typographical error in company submission table. Corrected values stated*

5. EAG PREFERRED BASE CASE RESULTS AND SCENARIO ANALYSES

5.1. EAG preferred base case results

As noted in Section 3, the EAG considered that several of the company's revisions did not adequately reflect NICE preferences and therefore may not be appropriate for decision making. Due to uncertainty surrounding the appropriateness of OS adjustment in the TPC arm, the EAG has opted to conduct two base cases for the committees consideration (one which adjusts OS in the TPC arm and one which does not adjust OS in the TPC arm). This approach highlights the impact of treatment switching on results. For the full list of EAG preferences see Table 10.

The probabilistic and deterministic results for EAG preferred base case 1, are outlined in Table 11 and Table 12 respectively. For base case 2, the probabilistic and deterministic results are presented in Table 13 and Table 14 respectively. All results are based on discounted costs and QALYs. For results using the appropriate cPAS discounts, see the accompanying appendix document.

Table 10: EAG preferred base case assumptions

	EAG preferred base case 1	**EAG preferred base case 2**
Clinical data	Final data cut analysis used. Additionally, patient weight based on KEYNOTE-775 and mean age of 67.	As per EAG preferred base case 1
Model used to estimate OS and PFS (both treatment arms)	Pem+Len: OS estimated using one knot Spline. PFS estimated using one knot Spline TPC: OS estimated using one knot Spline. PFS estimated using one knot Spline	
Treatment waning effect	Pembrolizumab treatment waning applied from year 3 to year 5 (as per NICE preference, applied to 100% of patients)	
Utility estimation approach	Based on progression status only (company Utility Model 1)	
Mean age	67	
OS for TPC	OS in the TPC arm not adjusted for treatment switching/crossover	OS in the TPC arm adjusted for treatment switching/crossover (using TSE adjustment method without re-censoring)

EAG: Evidence Assessment Group, TPC: The physician's choice, OS: Overall survival, PFS: Progression free survival

Table 11: EAG preferred base case 1 (probabilistic results including pembrolizumab PAS and lenvatinib list price)

	Total cost	Total life years	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pem+Len	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TPC: The physician's choice

Table 12: EAG preferred base case 1 (deterministic results including pembrolizumab PAS and lenvatinib list price)

	Total cost	Total life years	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pem+Len	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TPC: The physician's choice

Table 13: EAG preferred base case 2 (probabilistic results includes pembrolizumab PAS and lenvatinib list price)

	Total cost	Total life years	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pem+Len	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TPC: The physician's choice

Table 14: EAG preferred base case 2 (deterministic results includes pembrolizumab PAS and lenvatinib list price)

	Total cost	Total life years	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pem+Len	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TPC: The physician's choice

5.2. EAG Scenario analyses

The EAG acknowledged that there may still be some uncertainty surrounding key model parameters. To explore uncertainty, the EAG has conducted additional scenario analysis testing alternative assumptions for treatment waning, model choice for extrapolating OS in the TPC arm, and approach to estimating utilities. All results are based on discounted costs and QALYs. For results using the appropriate cPAS discounts, see the accompanying appendix document.

Table 15: EAG scenario analyses (EAG preferred base case 1, probabilistic results)

Scenarios	Incremental costs	Incremental LYs	Incremental QALYs	ICER
EAG base case 1	[redacted]	[redacted]	[redacted]	[redacted]
Alternative waning assumptions for pembrolizumab				
a. Waning applied from year 5 to year 7 (applied to 100% of patients in the pembrolizumab arm)	[redacted]	[redacted]	[redacted]	[redacted]
b. No treatment waning assumed	[redacted]	[redacted]	[redacted]	[redacted]
Two knot Spline model (odds, unadjusted) used to estimate OS in the TPC arm	[redacted]	[redacted]	[redacted]	[redacted]
Utilities estimated based on TTD and progression status (company Utility Model 4)	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TTD: Time to death, TPC: The physician's choice, OS: Overall survival, PFS: Progression free survival

Table 16: EAG scenario analyses (EAG preferred base case 1, deterministic results)

Scenarios	Incremental costs	Incremental LYs	Incremental QALYs	ICER
EAG base case 1	[redacted]	[redacted]	[redacted]	[redacted]

Alternative waning assumptions for pembrolizumab				
a. Waning applied from year 5 to year 7 (applied to 100% of patients in the pembrolizumab arm)	[redacted]	[redacted]	[redacted]	[redacted]
b. No treatment waning assumed	[redacted]	[redacted]	[redacted]	[redacted]
Two knot Spline model (odds, unadjusted) used to estimate OS in the TPC arm	[redacted]	[redacted]	[redacted]	[redacted]
Utilities estimated based on TTD and progression status (company Utility Model 4)	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TTD: Time to death, TPC: The physician's choice, OS: Overall survival, PFS: Progression free survival

Table 17: EAG scenario analyses (EAG preferred base case 2, probabilistic results)

Scenarios	Incremental costs	Incremental LYs	Incremental QALYs	ICER
EAG base case 2	[redacted]	[redacted]	[redacted]	[redacted]
Alternative waning assumptions for pembrolizumab				
a. Waning applied from year 5 to year 7 (applied to 100% of patients in the pembrolizumab arm)	[redacted]	[redacted]	[redacted]	[redacted]
b. No treatment waning assumed	[redacted]	[redacted]	[redacted]	[redacted]
Two knot Spline (odds, adjusted) model used to estimate OS in the TPC arm	[redacted]	[redacted]	[redacted]	[redacted]
Utilities estimated based on TTD and progression status (company Utility Model 4)	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TTD: Time to death, TPC: The physician's choice, OS: Overall survival, PFS: Progression free survival

Table 18: EAG scenario analyses (EAG preferred base case 2, deterministic results)

Scenarios	Incremental costs	Incremental LYs	Incremental QALYs	ICER
EAG base case 2	[redacted]	[redacted]	[redacted]	[redacted]
Alternative waning assumptions for pembrolizumab				
a. Waning applied from year 5 to year 7 (applied to 100% of patients in the pembrolizumab arm)	[redacted]	[redacted]	[redacted]	[redacted]
b. No treatment waning assumed	[redacted]	[redacted]	[redacted]	[redacted]
Two knot Spline (odds, adjusted) model used to estimate OS in the TPC arm	[redacted]	[redacted]	[redacted]	[redacted]
Utilities estimated based on TTD and progression status (company Utility Model 4)	[redacted]	[redacted]	[redacted]	[redacted]

LYs: Life years, QALYs: Quality adjusted life year, ICER: Incremental cost effectiveness ratio, TTD: Time to death, TPC: The physician's choice, OS: Overall survival, PFS: Progression free survival

6. EAG RESPONSE TO COMMENTS TO STAKEHOLDERS

EISAI, the manufacturer of lenvatinib, has commented that it is inappropriate to include treatment waning within the model on the basis that pembrolizumab is given as a combination therapy with lenvatinib. The company therefore states that patients will stop pembrolizumab at 24 months but continue to receive lenvatinib (and ultimately a continued treatment effect), until they experience unacceptable toxicity or disease progression. The company also state that the sustained separation of Kaplan Meier curves at 3.5 years (in KEYNOTE-775) is sufficient evidence of a sustained treatment effect.

The EAG acknowledges the company's comments, however as noted in the draft NICE guidance, NICE preference is for treatment waning to be considered. The EAG also consider that despite the final data analysis from KEYNOTE-775, there is some uncertainty surrounding the assumption of a sustained treatment effect over a longer time frame (see Section 3.1.4). For the committee's consideration, the EAG has provided scenario analyses testing alternative assumptions surrounding treatment waning.