Single Technology Appraisal (STA)

Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer (Rapid Review of TA885) [ID6279]

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD

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None

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Rider on responsibility for report

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

Contributions of authors

Matthew Walton and Robert Hodgson critiqued the company's model and submitted economic evidence, and co-authored Sections 1, 3, and 4 of the report. Robert Hodgson took overall responsibility for the cost effectiveness sections. Helen Fulbright provided information support. Mark Rodgers critiqued the clinical evidence and wrote Section 2 of the report. Alison Eastwood provided advice, commented on drafts of the report and took overall responsibility for the clinical effectiveness sections.

Note on the text

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

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1 Introduction and Overview

In this report, the external assessment group (EAG) has reviewed the company submission for the Rapid Review of TA885 which presents updated clinical and cost-effectiveness results using the KEYNOTE-826 trial Final Analysis (FA) data cut. The Final Appraisal Document for TA885, Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer, was published on 29 March 2023.

This overview provides a brief summary of the key issues identified by the EAG as being important for decision-making.

The EAG had no substantive concerns with the implementation of the FA data cut from KEYNOTE-826 in accordance with the committee's preferences as set out in the Final Appraisal Document (FAD) in TA885. Whilst a number of parameters relating to the trial data have been updated, they do not indicate any need for a departure from the committees preferred assumptions established in TA885.

However, the EAG identified three primary uncertainties with a potentially significant impact on the cost-effectiveness of pembrolizumab, and which may affect the interpretation of the cost-effectiveness estimates presented by the company.

1.1 Key Issue 1: Ongoing immaturity of OS data in KEYNOTE-826

In the TA885 FAD, the committee considered the continued use of a state transition model to be potentially inappropriate when final KEYNOTE-826 data became available. The EAG therefore requested that the company incorporate the FA data cut into a partitioned survival model structure for this rapid review. However, OS remained too immature to generate extrapolations with plausible long-term hazard rates with respect to established PFS trends. The assumptions necessary to maintain the PSM structure (i.e. many patients die immediately upon progression) given this immaturity are likely to be overly conservative. The cost-effectiveness results produced under these assumptions remain relatively robust. The model structure is therefore unlikely to be a key driver of uncertainty in this appraisal, however, the immaturity of the FA data cut means much of the benefit of pembrolizumab remains within the extrapolated portion of the survival curves, and is therefore subject to continuing uncertainty. This issue is discussed in Sections 2.2 and 3.2.

1.2 Key Issue 2: Generalisability of KEYNOTE-826 outcomes

Long-term PFS and OS outcomes on SoC predicted by the company's model remain much better than are likely to be expected in practice. This was highlighted as a concern by the company's clinical advisers, who estimated median survival of 9 to 12 months in this population, where median OS in

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KEYNOTE-826 was 16.5 months. The EAG is concerned that this may be indicative of a trial population selected for greater fitness and propensity to a more durable treatment response, and therefore may overestimate the proportion of patients able to achieve such durable responses on either treatment in practice. This is likely to overestimate the cost-effectiveness of pembrolizumab in practice. This issue is discussed in Section 3.2.

1.3 Key Issue 3: Applicability of the end of life criteria

The committee considered that the end of life (EoL) criteria could be applied in TA885 despite mean OS on SoC being in excess of two years (2.06 years). With the KEYNOTE-826 FA data cut, SoC now offers mean survival of 2.65 years, well above the usual EoL criteria threshold. Furthermore, whilst the present appraisal is to be run using pre-2022 methods, the EAG is uncomfortable applying EoL given that NICE moved away from this approach in recognition of the lack of evidence that society places additional value on treatments at the end of life. This issue is discussed in Section **Error! Reference source not found.**.

2 Description and critique of new clinical evidence

This summary refers to the updated clinical results from KEYNOTE-826 Final Analysis (FA), and their relationship to the Interim Analysis (IA1) data previously considered by the NICE committee. For the EAG's broader commentary on the KEYNOTE-826 trial, please refer to the Evidence Review Group's Report for TA885 Pembrolizumab with chemotherapy for treating recurrent, persistent or metastatic cervical cancer.[1]

The company submission for the Rapid Review of TA885 reported the following endpoints from the final planned analysis of KEYNOTE-826:

- Progression free survival (PFS)
- Time to progression
- Overall survival (OS)
- Response rate
- Subsequent treatments
- Post progression survival (PPS)
- Adverse events

In response to the EAG's request for clarification, the company also provided FA data from KEYNOTE 826 for the remaining outcomes that were reported in the original company submission for TA885:

- Duration of response

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- Health related quality of life outcomes
- Subgroup analyses for PFS and OS

2.1 Progression free survival (PFS) and time to progression (TTP)

Table 1 shows that the final analysis PFS data from the company submission are similar to the interim analysis data presented in the original appraisal (ID3798). Final analysis Kaplan-Meier estimates for PFS and TTP (which differs from PFS in that deaths are considered censors rather than events) are presented in the company submission.

The original company submission for TA885 cited the GOG-240 trial[2] which reported median PFS of 6.0 months for cisplatin plus paclitaxel chemotherapy and 8.2 months with the addition of bevacizumab. The median PFS for SoC patients in KEYNOTE-826 (63% of whom received bevacizumab) is 8.2 months (95% CI 6.3 to 8.5), suggesting that PFS in the SoC arm of KEYNOTE-826 is towards the upper end of that previously observed.

Table 1 PFS in the KEYNOTE-826 trial (CPS ≥1 population)

	Interim analysis		**Final analysis**	
	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	**Placebo + chemotherapy ± bevacizumab (n = 275)**	**Pembrolizumab + chemotherapy ± bevacizumab (n = 273)**	**Placebo + chemotherapy ± bevacizumab (n = 275)**
Number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI, months) [a]	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)	10.5 (9.7, 12.3)	8.2 (6.3, 8.5)
PFS HR (95% CI) [b]	0.62 (0.50, 0.77)		0.58 (0.47, 0.71)	
p-value [c]	< 0.0001		<0.0001	
6-month PFS, % (95% CI)	[redacted]	[redacted]	81.5 (76.2, 85.7)	67.1 (61.0, 72.4)
12-month PFS, % (95% CI)	45.5 (39.2, 51.5)	34.1 (28.3, 40.0)	45.6 (39.3, 51.6)	33.7 (27.9, 39.5)
18-month PFS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month PFS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; CPS, combined positive score; FIGO, International Federation of Gynaecology and Obstetrics; HR, hazard ratio; PD-L1, Programmed death-ligand 1; PFS, progression-free survival.
Notes: [a] From product-limit (Kaplan–Meier) method for censored data. [b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10). [C] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10).

2.2 Overall survival (OS)

In the original company submission for TA885 reported the KEYNOTE IA1 data cut in which OS data were immature, with median OS yet to have been reached for the pembrolizumab arm in the

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presented interim analysis. In the final analysis, median OS has been reached in both pembrolizumab and placebo arms: 28.6 months (95% CI: 22.1, 38.0) vs 16.5 months (95% CI: 14.5, 20.0).

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Table 2 shows that the interim and final analysis OS data are similar. Final analysis Kaplan-Meier estimates for OS are presented in the company submission.

GOG-240 trial[2] reported a median OS of 13.3 months for cisplatin plus paclitaxel chemotherapy and 16.8 months with the addition of bevacizumab. The median OS for SoC patients in KEYNOTE-826 (63% of whom received bevacizumab) is 16.5 months (95% CI 14.5 to 20.0), suggesting that OS in the SoC arm of KEYNOTE-826 was towards the upper end of that previously observed.

In response to a clarification question from the EAG, the company consulted with two clinicians currently treating advanced cervical cancer in the NHS, asking the question "how long would you normally expect a patient in the KN826 disease setting to survive?" and received the following responses:-

"For the patients eligible for bevacizumab my expectation would be around 12-15 months; but if a patient can tolerate only sub-optimal treatment – 9 months and if none of the treatment can be tolerated – 3-6 months."

"I would expect median overall survival for these patients to be around 9-12 months. The prognosis depends on a patients age and health status, and de novo vs recurrent metastatic cervical cancer."

Consequently, it appears that survival on SoC in KEYNOTE-826 is longer than would be expected in NHS practice. This could potentially be attributable to the subsequent treatments received by patients in this study arm (see section 2.4), though as noted in section 2.1, PFS (which would not be influenced by subsequent treatments) is also longer than observed in GOG-240.

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Table 2 OS in the KEYNOTE-826 trial (CPS ≥1 population)

	Interim analysis		Final analysis	
	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	**Placebo + chemotherapy ± bevacizumab (n = 275)**	**Pembrolizumab + chemotherapy ± bevacizumab (n = 273)**	**Placebo + chemotherapy ± bevacizumab (n = 275)**
Number of events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI, months) [a]	NR ([redacted])	16.3 ([redacted])	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
OS HR (95% CI) [b]	0.64 (0.50, 0.81)		0.60 (0.49, 0.74)	
p-value [c]	0.0001		<0.0001	
6-month OS, % (95% CI)	[redacted]	[redacted]	91.9 (88.0, 94.6)	85.5 (80.7, 89.1)
12-month OS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month OS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month OS, % (95% CI)	53.0 (46.0, 59.4)	41.7 (34.9, 48.2)	53.5 (47.4, 59.2)	39.4 (33.6, 45.2)

Key: CI, confidence interval; CPS, combined positive score; FIGO, International Federation of Gynaecology and Obstetrics; HR, hazard ratio; PD-L1, Programmed death-ligand 1; PFS, progression-free survival.
Notes: [a] From product-limit (Kaplan–Meier) method for censored data. [b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10). [C] One-sided p-value based on log-rank test stratified by metastatic at initial diagnosis (FIGO [2009] stage IVB) (yes or no), bevacizumab use (yes or no) and PD-L1 status (CPS < 1, CPS 1 to < 10, CPS >=10).

2.3 Response rate

Table 3 shows the reported response rate data from the interim and final analyses of KEYNOTE-826. As for other endpoints, the response rates in the pembrolizumab and comparator arms are similar for the two analyses. The company submission presents Kaplan Meier estimates of PFS and OS separated by response category. As in the original appraisal, a patient's response status is highly prognostic of both OS and PFS, with poorer outcomes observed for each decrease in response category.

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Table 3 Confirmed objective response based on investigator assessment per RECIST 1.1 (CPS ≥ 1 population)

	Interim analysis		Final analysis	
	Pembrolizumab + chemotherapy ± bevacizumab (n = 273)	**Placebo + chemotherapy ± bevacizumab (n = 275)**	**Pembrolizumab + chemotherapy ± bevacizumab (n = 273)**	**Placebo + chemotherapy ± bevacizumab (n = 275)**
Number of confirmed OR	[redacted]	[redacted]	[redacted]	[redacted]
ORR, % (95% CI)	68.1 (62.2, 73.6)	50.2 (44.1, 56.2)	[redacted]	[redacted]
CR, n (%)	62 (22.7)	36 (13.1)	[redacted]	[redacted]
PR, n (%)	124 (45.4)	102 (37.1)	[redacted]	[redacted]
SD, n (%)	58 (21.2)	88 (32.0)	[redacted]	[redacted]
PD, n (%)	9 (3.3)	29 (10.5)	9 (3.3)	29 (10.5)
Not evaluable n (%)	NR	NR	1 (0.4)	2 (0.7)
No assessment n (%)	NR	NR	19 (7.0)	18 (6.5)
Difference in percentage pembrolizumab group versus placebo group	[redacted]		17.6 (NR)	
p-value	[redacted]		NR	

Key: CI, confidence interval; CPS, combined positive score; OR, objective response; ORR, objective response rate; RECIST 1.1, response evaluation criteria in solid tumours version 1.1.

2.4 Subsequent treatments

The company submission reported subsequent oncologic treatments received by KEYNOTE-826 participants. Notably [redacted] patients in the SoC arm and [redacted] in the pembrolizumab arm had subsequent immunotherapies. The company suggested that since no immunotherapies are currently available for advanced cervical cancer in the UK, the KEYNOTE-826 data is likely to overestimate outcomes (particularly post-progression survival) in the SoC arm versus what would be seen in the UK setting.

2.5 Post progression survival (PPS)

The submission reported median PPS of [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]) for the pembrolizumab combination and SoC arms, respectively. The associated Kaplan-Meier curves were presented in the submission.

2.6 Adverse events

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Table 4 summarises the number of adverse events (AEs) and serious adverse events (SAEs), both overall and related to study drugs for the interim and final analyses of KEYNOTE-826. Observed AEs and SAEs were almost identical between analyses.

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Table 4 Summary of adverse events (APaT population) – interim and final analyses

	Interim analysis				Final analysis			
	Pembrolizumab + chemotherapy ± bevacizumab (n = 307)		Placebo + chemotherapy ± bevacizumab (n = 309)		Pembrolizumab + chemotherapy ± bevacizumab (n = 307)		Placebo + chemotherapy ± bevacizumab (n = 309)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
No. of patients, n (%)								
≥ 1 AE	305 (99.3)	251 (81.8)	307 (99.4)	232 (75.1)	305 (99.3)	253 (82.4)	307 (99.4)	233 (75.4)
≥ 1 drug-related AE	298 (97.1)	210 (68.4)	300 (97.1)	198 (64.1)	298 (97.1)	212 (69.1)	300 (97.1)	201 (65.0)
SAEs	[redacted] (49.8)	–	[redacted] (42.4)	–	157 (51.1)	–	132 (42.7)	–
Drug-related SAEs	[redacted]	–	[redacted]	–	94 (30.6)	–	73 (23.6)	
Death due to drug-related AEs	2 (0.7)	–	4 (1.3)	–	2 (0.7)	–	4 (1.3)	–
Discontinued any drug due to an AE	NR	–	NR	–	125 (40.7)	–	91 (29.4)	–
Key: AE, adverse event; APaT, all patients as treated; SAE, serious adverse event.								

2.7 Duration of response

In response to a request from the EAG, the company provided data on duration of response (DoR) from the final analysis. The median DoR was 19.2 months and 10.4 months in the pembrolizumab combination and SoC arms, respectively. The median DoR for the pembrolizumab arm increased by 1.2 months compared with the first interim analysis, with no change between the analyses for the SoC arm.

2.8 Health related quality of life outcomes

As in the interim analysis, the between group differences in least-squares mean change from baseline over the same period did not significantly differ between the pembrolizumab and SoC arms ([redacted]).

No additional data were reported for the principal pre-specified HRQoL measure for the trial (EORTC QLQ-C30 global score).

2.9 Subgroup analyses for PFS and OS

On the request of the EAG, the company provided PFS and OS data for the following subgroups: Metastatic at initial diagnosis (yes/no); bevacizumab use (yes/no); age (< 65 years/ ≥ 65 years); race (white/ non-white); and ECOG performance status (0/1).

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The pattern of subgroup effects was very similar to those observed in the interim analyses and discussed in section 3.2.3.1 of the ERG report for TA885 (i.e. hazard ratios comparing pembrolizumab to placebo were less than 1 in all subgroups, and were consistent with the overall hazard ratio. However, the 95% CI for patients who were metastatic at initial diagnosis and the 95% CI for patients aged ≥65 years intersected the line of "null effect" for both PFS and OS).

Points for critique

The key clinical uncertainty addressed by the company submission relates to OS, with median OS having been reached for the pembrolizumab arm after a further 17 months of follow-up. These data significantly favoured pembrolizumab over SoC.

All reported endpoints from the final analyses were similar to the interim analyses: effect sizes were generally similar in magnitude with greater precision due to the additional observed events.

3 Description and critique of new economic evidence

3.1 Model structure

The economic model presented alongside the company submission maintained the state transition model (STM) structure adopted in TA885. A key rationale for adopting this structure over a partitioned survival model (PSM) was the comparative maturity of PFS data compared to OS. Overall survival data are now significantly more mature. The EAG noted the committee's conclusion in the Final Appraisal Determination for TA885, that '*although the company's model may be adequate for decision making with the data currently available, when further data becomes available from KEYNOTE-826, the most appropriate modelling approach may change*'. In light of this, the EAG requested that the company explore the plausibility of a PSM approach using the FA data cut.

In their clarification response, the company reiterated their preference for a STM but also presented a PSM which integrated the FA results. The company noted that the best-fitting extrapolations of these data continue to result in the crossing of OS and PFS curves when around 15% of patients are predicted to remain progression free in the Pem + SoC arm. Indeed, all reasonable extrapolations result in the crossing of OS and PFS curves. This is because while a plateau in PFS is well developed, it is only starting to become emergent on OS, and thus hazard rates adopted by most parametric models naturally result in the intersection of OS and PFS extrapolations.

This requires a judgment to be made as to whether to cap PFS at OS, or assume the hazard trends observed on PFS better represent long-term outcomes, and thus assume OS follows PFS beyond the point the curves cross (i.e. patients die upon progression). In the presented PSM base case, the company assume the latter, using PFS curves to model OS when these curves intersect. However, this

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means that the committee's conclusion that patients on pembrolizumab would have 'at least a modest benefit in post-progression survival compared with placebo' is not reflected in the model.

Points for critique

The EAG acknowledges the company's concerns regarding the limitations of the final data cut. The results support the assumption that a substantial proportion of patients in the KEYNOTE-826 trial achieve a long-term reduction in PFS hazards which is yet to be reflected in the less mature OS data. The EAG considers this analysis an informative demonstration of the immaturity of OS and the relative robustness of cost-effectiveness outcomes to the structural implementation of the FA results. The EAG agrees that the PSM analysis is likely to fail to capture post-progression survival outcomes.

3.2 Survival analysis

Consistent with the STM model structure, the company base-case analysis applies parametric extrapolations of TTP, PFS and PPS to inform health state occupancy. In the alternative PSM structure presented by the company in their clarification response, OS was modelled directly in place of PPS. Each outcome was informed by data from the KEYNOTE-826 trial, which was the primary data source for the economic analysis. All model inputs from the KEYNOTE-826 trial are based on the FA data set.

3.2.1 Approach to extrapolations

The company considered a range of extrapolations including one piece, two piece, and spline-based models. Evaluation of alternative extrapolation approaches and curve selection was conducted considering visual fit to the observed data, statistical fit (Akaike information criterion (AIC) and Bayesian information criterion (BIC)) as well as the clinical plausibility of long-term survival estimates. As per committee preferences in TA885 all extrapolations of TTP, PFS and OS assumed a phased waning of the treatment effect between 3 and 5 years.

3.2.2 TTP and PFS

Following evaluation of standard one-piece parametric models, the company concluded that a single piece model (a parametric distribution fitted to the whole KM curve) had poor visual fit to the observed data and was unable to appropriately capture the complexity of the hazard functions for TTP and PFS.

The company therefore considered more flexible modelling approaches, including two-piece and spline-based approaches. Consistent with TA885, the company explored a range of two-piece models in which transition probabilities up to 37 weeks were modelled directly using observed TTP and PFS KM data, followed by the use of parametric models fitted to the remaining data. Using the criteria outlined above, the log-logistic model was selected as the most appropriate curve of the simple

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parametric models. Scenario analysis was also presented using the generalised gamma (considered the 2nd choice curve). The company further explored a range of spline-based models including 1, 2 and 3 knot spline models on the normal, hazard and odds scales. The company selected a 3-knot spline model on the hazard scale as their preferred extrapolation and applied this in their base case analysis. The rationale for selecting a spline model in favour of a two-piece model was not described. Scenario analysis, however, explored two-piece alternatives and demonstrated that a 3-knot spline model is a more conservative choice (i.e. generated a higher ICER).

3.2.3 PPS

The company base case used standard one-piece parametric models to extrapolate PPS data from KEYNOTE-826, more flexible models were considered unnecessary. The company's base case uses generalised gamma curves fitted to each treatment arm independently.

3.2.4 OS

Extrapolations of OS were provided following a request from the EAG at points for clarification (PFC B1). These are subsequently used in the alternative PSM model structure, which was also provided at clarification. The company's approach to extrapolating OS adopted a similar approach to that used to evaluate TTP, PFS and PPS extrapolations but also considered the plausibility of post-progression survival predictions as an additional selection criterion. The company explored both one-piece and spline-based models. Two-piece models appear not to have been considered. The EAG is not overly concerned by this omission as spline and two-piece models represent similarly flexible approaches. The company did not consider one-piece models appropriate to model OS, noting poor visual and statistical fit. Clinical expert advice also considered that all one-piece models were likely to underestimate survival on Pem+SoC. The company's preferred extrapolation was based on the 3-knot spline model using the hazards scale.

Points for critique

The EAG is generally satisfied with the company's approach to extrapolating the observed survival data for use in the PSM. In TA885, concerns were raised about the suitability of flexible parametric models, highlighting limited evidence to support a sustained plateau in PFS hazards. The longer follow-up in the FA analysis provides stronger support for the plateau in PFS, though this remains largely absent from the observed OS data. The EAG concurs with the company's assessment that one-piece parametric models inadequately capture the complex hazard trends observed in the Pem+SoC arm and considers that the company-preferred base-case spline models for both PFS and OS offer good visual and statistical fit to the observed data. The EAG, however, makes the following observations.

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Firstly, the clinical plausibility of the selected extrapolations depends upon additional assumptions made regarding the waning of the treatment effect. The landmark estimates of OS predicted by the model (Tables 9 and 12 of the CS) are therefore conditional on a treatment waning effect also being applied. In the absence of this treatment waning, predicted OS is substantially higher. For example, 5-, 10- and 20-year survival using the company's preferred extrapolations without waning are [redacted] respectively. These are highly optimistic predictions of OS driven by a sharp decline in modelled PFS events. The clinical plausibility of these predictions is important because these extrapolations determine the proportion of patients that transition to SoC hazards following the waning period, which, as outlined below, also suggests sharply declining hazards and very long survival.

Secondly the company's preferred extrapolations of PFS also results in highly optimistic predictions of OS on SoC, generating 10-year survival predictions of [redacted] This is acknowledged by the company as clinically unrealistic and was highlighted as a concern by the company's clinical advisory panel. This is important because hazards modelled for the SoC arm are ultimately applied to both treatment arms following the application of effect waning. It is unclear whether these long tails predicted by the spline (and two-piece) models are clinically realistic and may result in OS being overestimated in both the Pem+SoC and SoC arms of the model.

Thirdly, the optimistic estimates of PFS and OS on SoC are not wholly attributable to the extrapolation approach. The observed PFS and OS data from the KEYNOTE-826 trial is relatively mature, and thus these predictions simply reflect the observed data. Outcomes for patients in the SoC arm appear to be better than those in clinical practice. Indeed, the company highlights that median survival is substantially longer in KEYNOTE-826 than that estimated by their clinical experts (16.5 months vs. 9 to 12 months predicted by clinical experts). The EAG is concerned that this indicates that the KEYNOTE-826 trial recruited a highly optimised population and may overrepresent the proportion of patients who are able to achieve durable responses in practice (on either treatment). This would tend to favour Pem+SoC and is a critical concern because so much of the modelled benefit is as a result of a proportion of patients achieving sustained survival benefits.

In summary, while the final analysis has helped resolve some uncertainties regarding the benefits of Pem+SoC much of this benefit remains within the extrapolated portion of the survival curves and as such remains uncertain.

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3.3 Other updated model inputs

3.3.1 Time on treatment

Time on treatment outcomes were updated using the FA data cut. Mean time on treatment was slightly longer on pembrolizumab than at IA1, which results in a small increase in incremental costs. The EAG is satisfied that the company's implementation of the updated data cut is appropriate.

3.3.2 Health-related quality of life

The company analysed the final EQ-5D-5L data collected from KEYNOTE-826, which were mapped onto the 3L scale using the Hernandez-Alava *et al*. algorithm. The company's base-case approach adopts the progression-based linear mixed effects model preferred by the company in TA885, and generates utilities with only negligible differences to those accepted in that appraisal. The EAG is satisfied that the company's preferred utility set based on the FA data cut is appropriate.

3.3.3 Resource use

The company have made no material changes to the costs adopted in the model with the exception of those inputs affected by the updated data cut, namely relative dose intensity (RDI) and the duration of treatment with subsequent therapies. These updates had a minimal impact on total costs. The EAG is satisfied that the company's implementation of the updated data is appropriate.

3.4 End of life

In the analyses considered by the committee in TA885, mean overall survival on the standard of care was 2.06 years. Given the influence of the long tail on mean survival, and that 58.3% patients had died at 24 months, the committee concluded that on balance the end of life (EoL) criteria could be applied on the basis of the TA788 appeal decision, in which the committee were obliged to consider other measures of life expectancy.

In the company's base-case analysis incorporating the final data cut from KEYNOTE-826, SoC generated mean discounted life years (LYs) of 2.65, i.e. ~32 months. This is considerably longer than mean OS in the previous appraisal, and for consistency with previous appraisals, and the usual interpretation of life expectancy and QALY gain, should not be considered EoL.

Median OS was 16.5 months in KEYNOTE-826. It is unclear whether it could be argued that survival is 'normally less than 24 months', when 40% of patients remain alive in the model at two years. Given the significant extension to OS on SoC in the latest data cut, the EoL criteria may not continue to be applicable in the present appraisal.

As discussed in Section 3.2, survival on SoC appeared to be substantially longer in KEYNOTE-826 than would be expected in practice, which indicates the trial population is healthier than might be expected in practice. This may mean the trial overestimates real-world OS on SoC to the extent that

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the EoL criteria may be applicable. However, in such a scenario, current cost-effectiveness estimates should no longer be interpreted as presented. The outcomes on the Pem+SoC arm are unlikely to be representative of those achieved in practice, as long-term (i.e. post-waning) PFS hazards are based on those achieved on SoC. Whether or not the KEYNOTE-826 trial can sufficiently represent achievable outcomes in the NHS population presents a potentially significant uncertainty with regards to both the interpretation of cost-effectiveness outcomes, and the application of the EoL criteria.

Furthermore, the EAG is uncomfortable with applying EoL despite the present appraisal running on pre-2022 methods. The current NICE methods were developed in recognition of evidence that society does not place additional value on treatments at the end of life. It is therefore unclear whether it is appropriate to make decisions on the basis of a £50,000 willingness-to-pay threshold, particularly when the EoL criteria are not strictly met.

4 Updated economic model

The company's cost-effectiveness model adopts all of the assumptions agreed by the committee in the TA885 FAD, updating only the inputs derived directly from KEYNOTE-826, as discussed over the previous sections. Note that all results presented in this document are inclusive only of the currently approved patient access scheme (PAS) for pembrolizumab. A confidential appendix is provided which presents results inclusive of all available confidential commercial arrangements.

The company states the key assumptions of the company's base case as follows:

- PFS and TTP extrapolated using 3-knot spline models
- Treatment waning between 3-5 years
- PPS using individual generalised gamma curves
- Progression-based utilities using the linear mixed effects model
- Costs using exact dosing

These assumptions are consistent with those preferred by the committee in TA885.

4.1 Results of company base-case analysis

4.1.1 Deterministic analysis

The cost-effectiveness results for the company's base-case analysis are presented in Table 5.

Table 5 Company base case (deterministic)

Treatment	Totals per treatment arm			Incremental results			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Company base case							

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SoC	[redacted]	2.65	[redacted]				
Pem+SoC	[redacted]	5.33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.1.2 Probabilistic sensitivity analysis

The company's probabilistic sensitivity analysis (PSA) results are presented in Table 6 using 5,000 model iterations. Pembrolizumab had a [redacted] probability of being the most cost-effective treatment option at a willingness-to-pay threshold of £50,000 per QALY gained. This drops to [redacted] at a threshold of £30,000.

Table 6 Company base case (probabilistic)

Treatment	Totals per treatment arm			Incremental results			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Company base case							
SoC	[redacted]	2.51	[redacted]				
Pem+SoC	[redacted]	5.11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1 Cost-effectiveness plane (company base case)
[REDACTED]

4.1.3 Scenario analyses

In their submission and clarification response, the company present a range of scenario analyses which explore the impact of alternative extrapolations, waning assumptions, utility sets, and the imposition of a PSM structure upon cost-effectiveness estimates. A selection of the results presented across the two submission documents are reproduced in

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Table 7. These results include only the currently available PAS discount for pembrolizumab, and are replicated inclusive of all commercial arrangements available to the NHS in the confidential appendix to the report.

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Table 7 Company scenario analyses (deterministic)

Treatment	Totals per treatment arm			Incremental results			ICER (£/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Company base case							
SoC	[redacted]	2.65	[redacted]				
Pem+SoC	[redacted]	5.33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS/TTP 1-knot spline							
SoC	[redacted]	2.50	[redacted]				
Pem+SoC	[redacted]	4.84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS/TTP 2-knot spline							
SoC	[redacted]	2.73	[redacted]				
Pem+SoC	[redacted]	5.73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS modelled using exponential curve							
SoC	[redacted]	2.65	[redacted]				
Pem+SoC	[redacted]	5.01	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning applied between 5-7 years							
SoC	[redacted]	2.65	[redacted]				
Pem+SoC	[redacted]	5.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pooled PPS curve							
SoC	[redacted]	2.46	[redacted]				
Pem+SoC	[redacted]	4.72	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSM structure (OS 3-knot spline)							
SoC	[redacted]	2.70	[redacted]				
Pem+SoC	[redacted]	4.91	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 References

1. National Institute for Health and Care Excellence. *Pembrolizumab plus chemotherapy with or without bevacizumab for persistent, recurrent or metastatic cervical cancer [TA885]*: NICE; 2023. Available from: https://www.nice.org.uk/guidance/ta885/

2. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017;**390**:1654-63.

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