Single Technology Appraisal

Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma [ID3742]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma [ID3742]

Contents:

The following documents are made available to stakeholders:

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

NICE National Institute for Health and Care Excellence

Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma [ID3742]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5:00pm on Wednesday 3 January 2024. 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 (MSD)

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
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	Draft Guidance (DG) consultation document Section 3.3, Page 7, please note that the draft guidance currently states that randomisation occurred based on PD-L1 status which included a combined positive score (CPS) of CPS of 0, which is incorrect. In the

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	KEYNOTE-811 trial, randomisation was stratified according to the PD-L1 status: positive (i.e. CPS ≥1) versus negative (i.e. CPS <1).
2	**Clinical effectiveness data and updated cost-effectiveness analyses are provided based on longer-term follow-up from the recently published Interim Analysis 3 (IA3) of the KEYNOTE-811 trial. The longer-term data supports the company choice of survival curves previously based on IA2; additionally, MSD has conducted extensive clinical validation of our base case assumptions in the updated cost-effectiveness analyses based on the longer-term IA3 data cut.** DG consultation document Sections 3.4, 3.7, 3.14, 3.17: The committee has requested that additional analyses be conducted based on data from the recently published Interim Analysis 3 of the KEYNOTE-811 trial. MSD can confirm that IA3 data, which was unavailable at the time of the original company submission, has since become available. This provides overall survival data with longer duration of follow-up compared to IA2 which formed the basis of the original company submission. As requested by the Committee, this data is now presented with MSD's response to the DG consultation document. A summary of the clinical effectiveness data from the analysis is presented below (see pages 8-13). Additionally, MSD have updated the cost-effectiveness analysis with these data. The results are presented in Table 11 and Table 12.
3	**Treatment duration in the company economic model no longer applies a treatment cap for trastuzumab, in line with the committee preferred assumption.** Section 3.9 of the DG consultation document states that the committee concluded that it is appropriate to model trastuzumab drug costs based on the time-to-treatment discontinuation curve from KEYNOTE-811 with no cap applied. The updated cost-effectiveness analyses based on IA3 presented by MSD with this response (see Table 11 and Table 12) no longer applies a treatment cap for trastuzumab in either arm, however

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	MSD reiterate that patients are expected to receive less trastuzumab in clinical practice than in the trial, based on clinical expert opinion.
4	**In order to reflect NHS practice, PD-L1 testing costs should not be included in the base case: clinical expert feedback confirms that in the majority of cases, PD-L1 and HER2 testing occurs in parallel, hence MSD consider this to be reflective of the majority of NHS practice.** Section 3.11 of the DG consultation document states that the committee concluded that PD-L1 testing costs should be included in the economic model. In a correction of a statement made in MSD's response to clarification questions, the correct per-patient testing cost to be applied to the intervention arm in the model is £62.28. This reflects the fact that all HER2-positive patients would subsequently receive a PD-L1 test in the committee's preferred sequential approach. Based on the KEYNOTE-811 trial, 85.1% of HER2-positive patients have tumours which express a CPS≥1. Hence for each positive result, 1.18 (i.e. 1/0.851) tests must be offered, costing £53 each in current prices. A scenario which includes a testing cost of £62.28 per patient in the intervention arm increases the ICER (see Table 12). However, based on feedback received directly from UK clinicians to inform our response to the DG document, as summarised below, MSD considers it inappropriate to include this cost. The company spoke to 22 experts from 21 different NHS clinical centres across the UK (including 2 in Scotland) regarding this issue. A range of experts including oncologists, pathologists and advanced clinical practitioners from large teaching hospitals and cancer centres were consulted; 17 of the experts (77%) stated that PD-L1 and HER2 testing is done in parallel in their centre, i.e. they do not wait for a HER2 result before requesting PD-L1 testing and therefore for these centres there will be no increase in the number of PD-L1 tests required. 5/22 (22%) stated that PD-L1 testing was conducted post-HER2

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	testing; furthermore 2 of the experts within that group stated their centre plans to move to parallel testing. Further to these clinical interviews, results from market research (2) are available regarding testing in upper GI cancers, including metastatic/locally advanced HER2-positive gastric and gastro-oesophageal junction cancers. There were a total of 50 respondents from more than 27 UK centres; of these 92% stated that PD-L1 testing and HER2 testing were done in parallel. Based on the above, MSD believes that the vast majority of centres conduct parallel testing of HER2 and PD-L1. If recommended, addition of pembrolizumab to standard of care, i.e. trastuzumab and platinum and fluoropyrimidine based chemotherapy, will not increase the number of PD-L1 tests required for the vast majority of centres. The company accepts the committee view that there are regional variations in testing, however the sequential approach represents a minority of centres, which is expected to diminish further in the future.

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 [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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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MSD response to the Draft guidance document

Appendix

January 2024

File name	Version	Contains confidential information	Date
MSD response to the Draft guidance document (ID3742) [REDACTED]	V 1	No	03 January 2024

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CLINICAL DATA FROM KEYNOTE-811 IA3

KEYNOTE-811 trial interim analysis 3 results in non-Asia region PD-L1 CPS ≥1 population

During the course of the appraisal, the interim analysis 3 (IA3) data based on data-cut of 29 March 2023 became available. The DG consultation document confirms that at the first appraisal committee meeting, the appraisal committee concluded that non-Asia region population is generalisable to NHS clinical practice and is appropriate for decision-making. Consequently, as this is now considered a settled point the results based on the IA3 data cut of 29 March 2023 for primary efficacy endpoints specifically in the non-Asia region population, with CPS ≥1 are reported in this document.

As of the data cut-off date (29 March 2023) for IA3 CPS ≥1 population, the median duration of follow up (defined as the time from randomisation to the date of death or the database cut-off date if the participant is still alive) was 20 months (0.6 to 51.7 months) in the pembrolizumab plus SoC group and 18.2 months (0.3 to 51.7 months) in the SoC group. The DG consultation document refers to the KEYNOTE-811 Janjigian et al (1) publication which reports IA3 data in ITT and CPS ≥1. It should be noted that median duration of follow up in the publication was defined slightly differently, as the time from randomisation to database cut-off date. Therefore, the median follow-up duration between the data provided in this document and the Janjigian et al (1) publication differs. The difference in the definitions of median duration of follow up does not impact on the efficacy results.

As of the data cut-off date for IA3, 594 participants were randomized in the PD-L1 CPS ≥1 trial population; most participants (99.8%) were treated. 80.9% of participants in pembrolizumab plus SOC group and 88.8% of participants in the SOC group discontinued from study intervention. The proportion of participants who discontinued from study intervention was generally comparable for the pembrolizumab plus SOC group and the SOC group. The most common reason for discontinuation from study intervention was progressive disease.

The primary efficacy endpoints were analysed in the ITT population, and the hypotheses on PFS and OS were evaluated by comparing the experimental group to the control group using a stratified log-rank test. The HR was estimated using a stratified Cox regression model with Efron's tie handling method. Event rates over time were estimated within each treatment group using the Kaplan-Meier (KM) method.

Primary efficacy endpoints

At IA3, KEYNOTE-811 efficacy results showed that pembrolizumab plus SoC continued to provide a clinically meaningful improvement in both PFS and OS compared with SoC in previously untreated participants with locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma.

Progression-free Survival per RECIST 1.1 by BICR – PD-L1 CPS≥1 non-Asia region population (IA3 data cut)

Results in the PD-L1 CPS ≥1non-Asia region subgroup showed:

- Pembrolizumab in combination with SOC provided clinically meaningful improvement in PFS as demonstrated by a 36% reduction in the risk of disease progression or death compared with SOC (HR=0.64 [95% CI: 0.51, 0.80]; p<0.0001).
- The median PFS was longer for the pembrolizumab plus SOC group compared with the SOC group (9.9 months vs 6.4 months, respectively).
- By KM estimation, the PFS rates were higher in the pembrolizumab plus SOC group compared with the SOC group at 6, 12, 24 months.
- Based on KM analysis, a PFS treatment effect in favour of pembrolizumab plus SOC was observed as demonstrated by early separation of the curves that continued throughout the evaluation period.

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Table 1. Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS ≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC	SOC
	(N=202)	(N=200)
Number of Events (%)	155 (76.7)	161 (80.5)
Death	26 (12.9)	27 (13.5)
Documented progression	129 (63.9)	134 (67.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	9.9 (8.3, 11.4)	6.4 (5.6, 7.4)
[Q1, Q3]	[5.5, 17.8]	[4.0, 11.6]
Person-months	2565.7	1663.3
Event Rate / 100 Person-months	6.0	9.7
vs SOC		
Hazard Ratio (95% CI)[b]	0.64 (0.51, 0.80)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	71.1 (64.1, 76.9)	53.1 (45.6, 60.0)
PFS Rate at month 12 (%) (95% CI)	42.3 (35.1, 49.2)	24.3 (18.2, 31.0)
PFS Rate at month 18 (%) (95% CI)	24.9 (18.8, 31.4)	14.9 (9.9, 20.9)
PFS Rate at month 24 (%) (95% CI)	19.5 (14.0, 25.6)	9.5 (5.4, 15.0)

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.
c One-sided p-value based on log-rank test.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 29MAR2023

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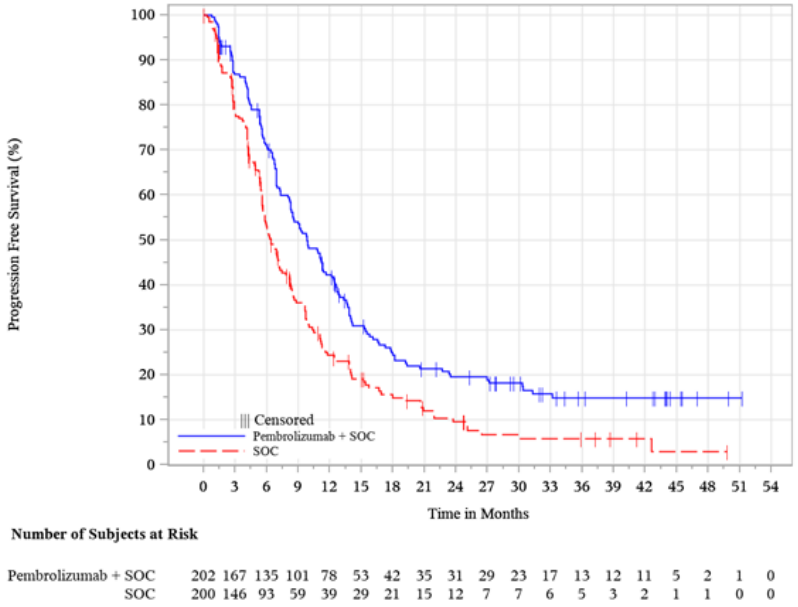
Figure 1. Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS>=1 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)



Overall Survival - PD-L1 CPS ≥1 non-Asia region population (IA3 data cut)

Results in the PD-L1 CPS ≥1 non-Asia region subgroup showed:

- Pembrolizumab in combination with SOC showed a clinically meaningful improvement in OS, in favour of pembrolizumab plus SOC, as demonstrated by a 30% reduction in the risk of death compared with SOC; the upper bound of the 95% CI did not cross 1 (HR=0.70 [95% CI: 0.56, 0.87]; *p*=0.0007).

- The median OS was longer for the pembrolizumab plus SOC group compared with the SOC group (18.6 months vs 12.06 months, respectively).

- By KM estimation, the OS rates were higher in the pembrolizumab plus SOC group compared with the SOC group at 6, 12, and 24 months.

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- Based on KM analysis, an OS treatment effect in favour of pembrolizumab plus SOC was observed as demonstrated by early separation of the curves that continued throughout the evaluation period.

Table 2. Analysis of Overall Survival (CPS ≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC	SOC
	(N=202)	(N=200)
Number of Events (%)	149 (73.8)	165 (82.5)
Death	149 (73.8)	165 (82.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	18.6 (15.5, 21.2)	12.6 (11.1, 14.9)
[Q1, Q3]	[9.7, 36.2]	[7.5, 25.1]
Person-months	4169.8	3232.5
Event Rate / 100 Person-months	3.6	5.1
vs SOC		
Hazard Ratio (95% CI)[b]	0.70 (0.56, 0.87)	
p-value[c]	0.0007	
OS Rate at month 6 (%) (95% CI)	89.1 (83.9, 92.7)	79.0 (72.7, 84.0)
OS Rate at month 12 (%) (95% CI)	66.3 (59.4, 72.4)	53.0 (45.9, 59.6)
OS Rate at month 18 (%) (95% CI)	52.0 (44.9, 58.6)	36.0 (29.4, 42.6)
OS Rate at month 24 (%) (95% CI)	39.7 (32.8, 46.4)	26.7 (20.7, 33.0)

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.
c One-sided p-value based on log-rank test.
Database Cutoff Date: 29MAR2023

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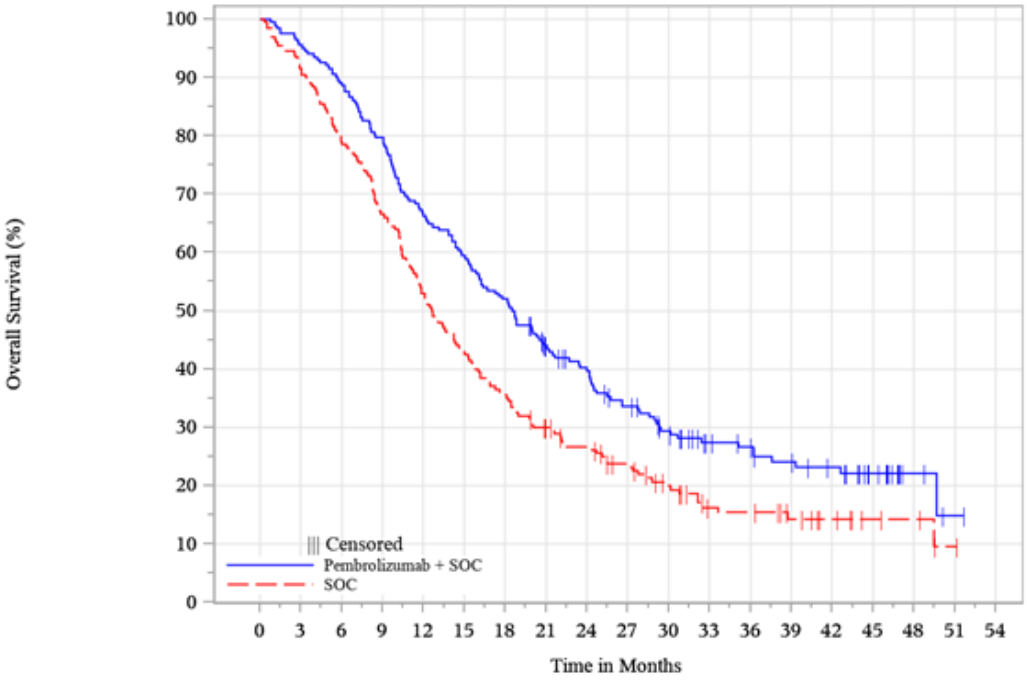
Figure 2. Kaplan-Meier Estimates of Overall Survival (CPS ≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)



Number of Subjects at Risk

Pembrolizumab + SOC	202	193	180	161	134	120	105	83	72	59	48	37	34	27	23	14	5	1	0
SOC	200	183	158	133	106	86	72	57	48	38	29	19	18	13	9	5	4	1	0

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COST-EFFECTIVENESS ANALYSIS USING IA3 DATA

The analysis has been updated with IA3 data and the longer-term data supports the company choice of survival curves previously based on IA2. Additionally, MSD has conducted extensive clinical validation of our base case survival predictions in the updated cost-effectiveness analyses based on the longer-term IA3 data cut.

Overall survival

Proportional hazards (PH) assumption

The PH assumption, i.e., that hazards are proportional over time, implying that treatment effect is constant over time, was evaluated for both treatment arms. As with IA2, MSD believes the PH assumption may not be valid for this comparison during the trial period, based on:

- clinical argument that the PH assumption may not be valid for immunotherapy versus non-immunotherapy comparisons due to differing biological mechanisms of action
- the Schoenfeld Residuals Plot (Figure 3): the plot itself is not linear indicating that the PH assumption may not be valid ($p<0.19$). Also, based on the log cumulative hazard plot (Figure 4), the hazards are further apart at the start of the trial
- reliance on the PH assumption is reduced when IPD are available, as per TSD 14.

For these reasons, independently fitted models, which do not assume a constant treatment effect over time, are preferred to jointly fitted (dependent) models. This was also the view of the EAG in their report.

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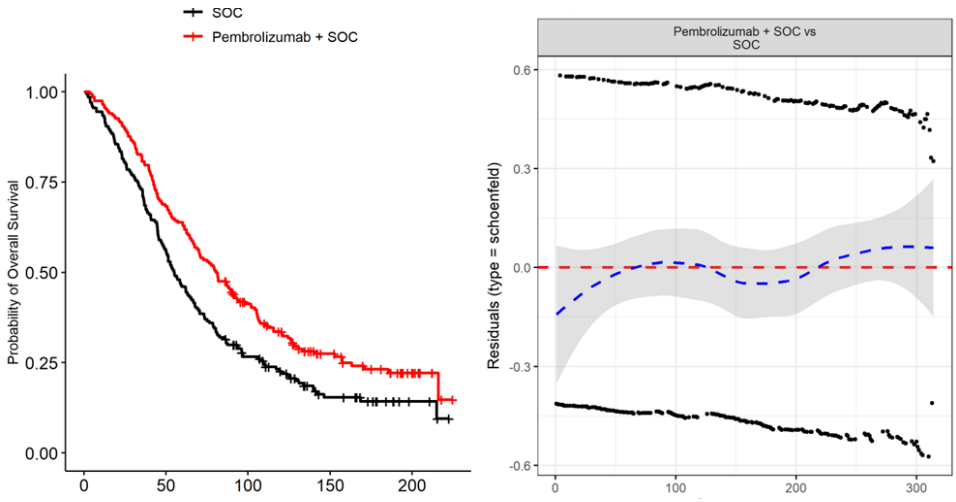
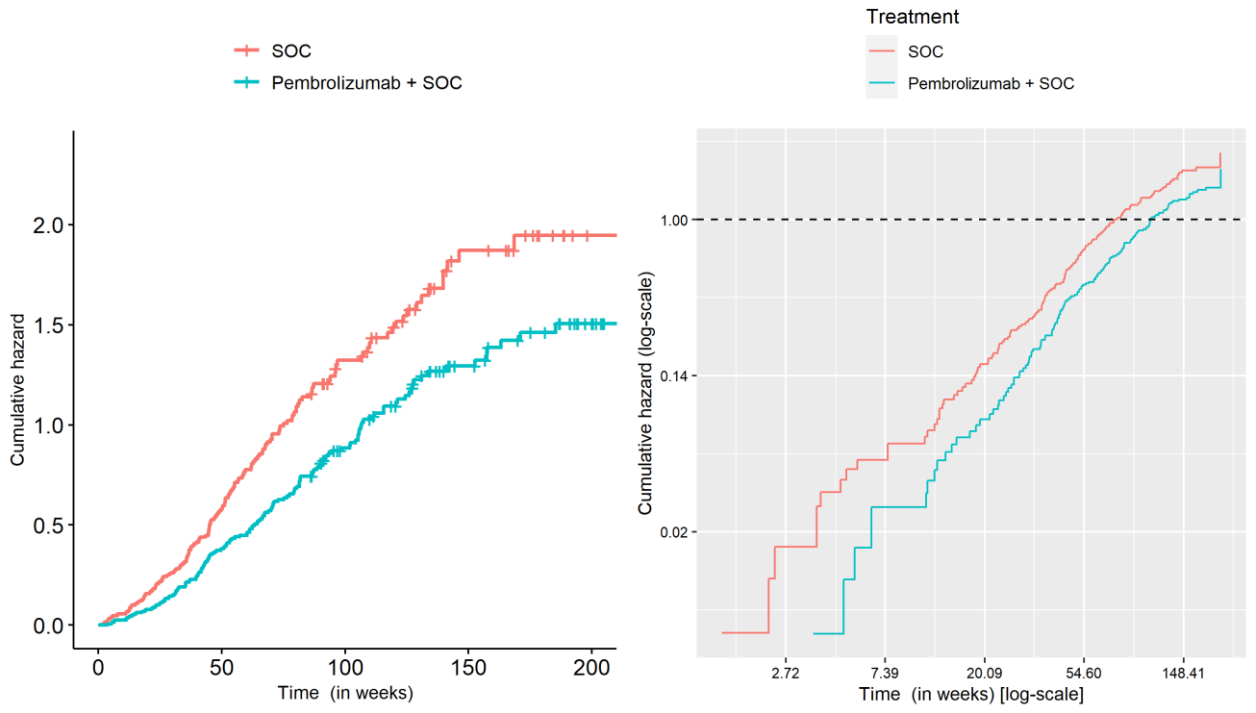
Figure 3. KM curve and Schoenfeld Residuals Plot for assessment of proportional hazards in OS (IA3)



Key: KM, Kaplan-Meier; OS, overall survival; SOC, standard of care

Figure 4. Cumulative hazard in OS over time between the intervention and comparator arm



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Key: OS, overall survival; SOC, standard of care

As requested by the committee, MSD have conducted a series of validation meetings with clinicians treating patients in England. Findings from these interviews are discussed at relevant points below.

Trastuzumab plus chemotherapy (SoC)

As with IA2, the Weibull standard parametric model is selected in the base case. The Weibull model reports similar survival to the KM rate at 2 years (29% vs. 27% of patients alive), at 3 years (14% vs. 15%) and predicts an OS rate of 3% at 5 years (Table 3). Discussions with clinicians revealed that patients who survive to 5 years while receiving the current SoC are very exceptional and that this curve aligns more closely with their expectations than the EAG base case curve. The other curves appear to predict overly optimistic survival for SoC at 5 years and any curve which predicts alive patients at 10 years should be excluded. The EAG base case (1-knot normal) predicts 5% of patients to be alive at 5 years.

In validation interviews, eleven clinical experts were asked to choose between the Weibull and 1-knot normal curves for SoC; nine of these selected the Weibull curve as more plausible, one selected the 1-knot normal curve and one was indifferent between them.

Table 3. OS predictions (trastuzumab plus chemotherapy)

Data	Year 1	Year 2	Year 3	Year 4	Year 5	Year 10
KM	53%	27%	15%	-	-	-
Parametric						
Exponential	54	30%	16%	9%	5%	0%
Gamma	0%	0%	0%	0%	0%	0%
Generalized gamma	55%	28%	15%	9%	5%	0%
Gompertz	54%	30%	16%	9%	5%	0%
Log-logistic	54%	27%	16%	11%	8%	3%
Log-normal	53%	29%	18%	12%	8%	2%
Weibull ***(company base case)***	57%	29%	14%	7%	3%	0%
Spline						
1k hazard	54%	28%	16%	9%	5%	0%

2k hazard	53%	26%	17%	12%	9%	3%
3k hazard	54%	25%	16%	12%	9%	3%
1k odds	54%	27%	15%	10%	7%	0%
2k odds	53%	26%	17%	12%	9%	4%
3k odds	54%	25%	16%	12%	10%	0%
1k normal ***(EAG base case)***	55%	28%	15%	9%	5%	0%
2k normal	53%	27%	17%	12%	8%	3%
3k normal	55%	25%	16%	12%	10%	4%
Key: *KM, Kaplan Meier; OS, overall survival*						

As shown in Table 4, the best-fitting parametric curve based on goodness-of-fit statistics is the log-logistic. Amongst the spline models, the 2-knot models provide the best fit according to goodness-of-fit statistics and the best visual fit to the KM curve (Figure 7) and hazard plot (Figure 8). However as discussed, these curves overestimate long-term survival in the SoC arm at 5 years and are considered clinically implausible.

Table 4. Statistical fit for OS (trastuzumab plus chemotherapy)

Distribution	AIC	BIC
Parametric		
Exponential	1798.8	1802.1
Weibull	1796.8	1803.4
LogNormal	1794.7	1801.3
LogLogistic	1784.2	1792.8
Gompertz	1800.8	1807.4
GenGamma	1792.1	1802.0
Spline		
1k hazard	1792.0	1801.9
2k hazard	1785.9	1799.1
3k hazard	1788.1	1804.6
1k odds	1787.4	1797.3
2k odds	1786.7	1799.9
3k odds	1788.0	1804.5
1k normal	1790.4	1800.3
2k normal	1787.1	1800.3
3k normal	1787.8	1804.3
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival		

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Figure 5. OS parametric extrapolations for trastuzumab plus chemotherapy

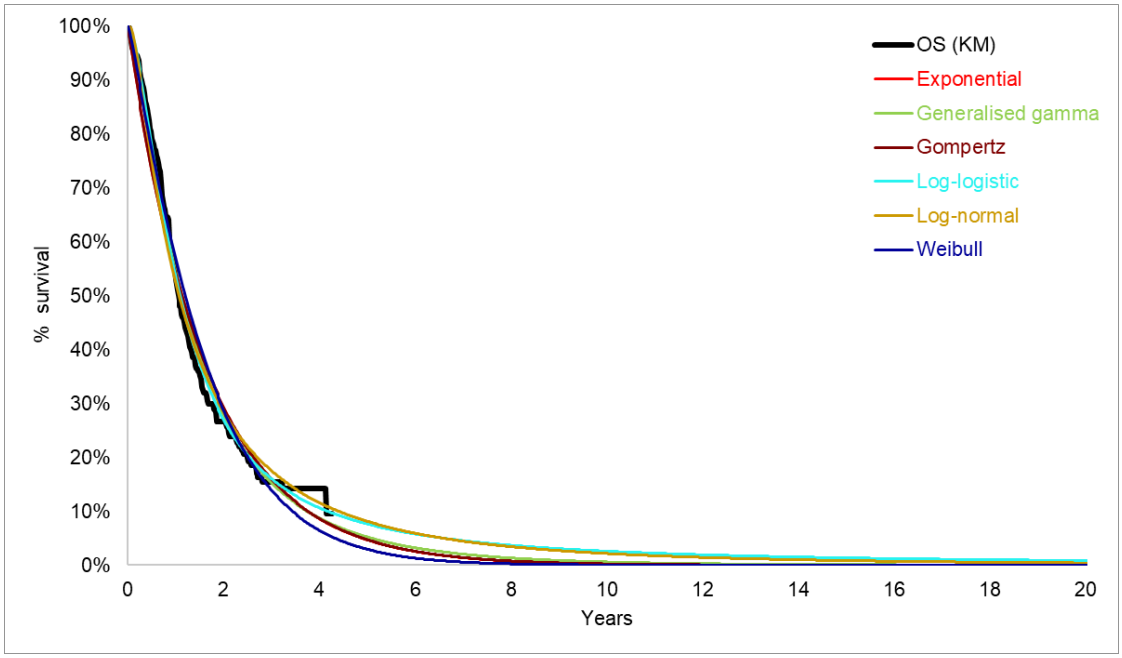
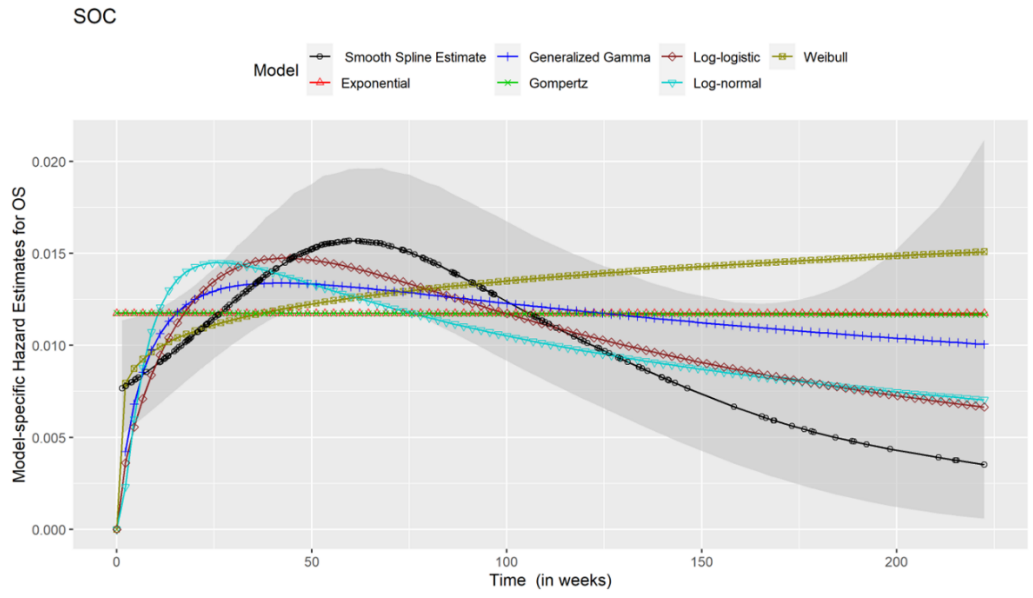


Figure 6. OS parametric smoothed hazards for trastuzumab plus chemotherapy



Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma [ID3742]

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Figure 7. OS spline extrapolations for trastuzumab plus chemotherapy

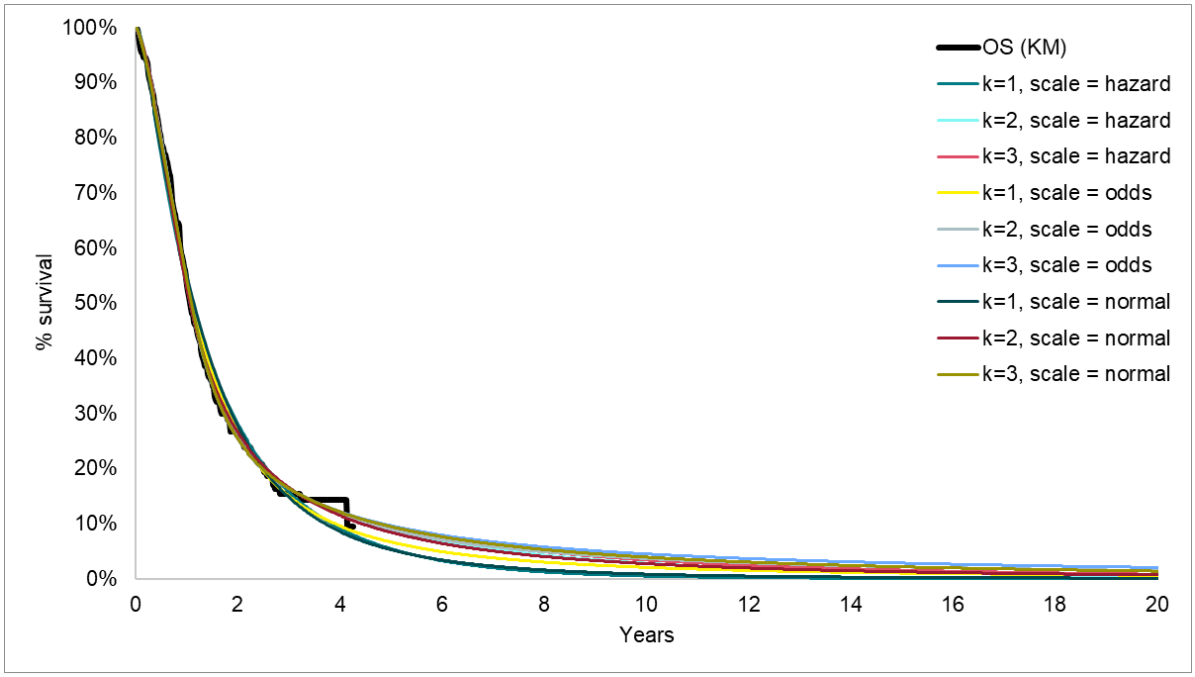
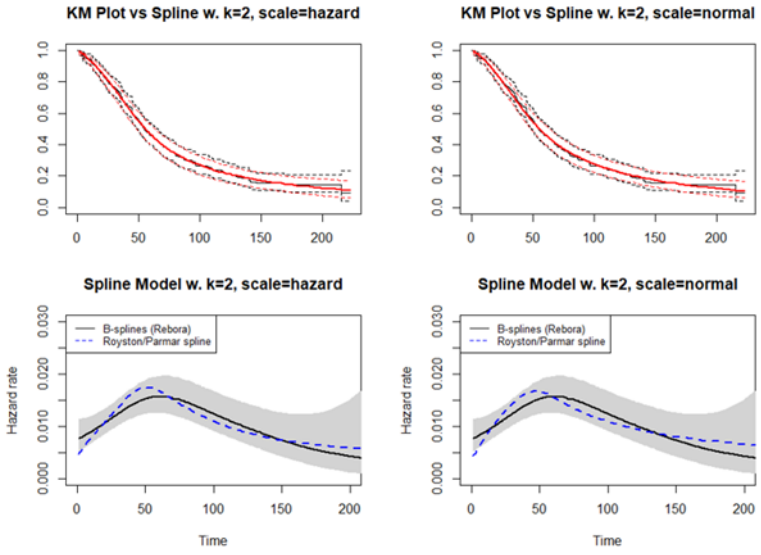


Figure 8. OS spline smoothed hazards for trastuzumab plus chemotherapy



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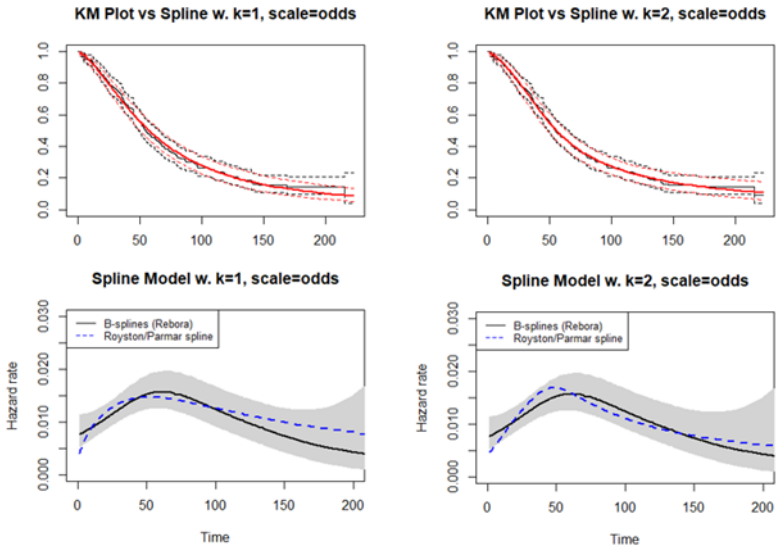

Pembrolizumab with trastuzumab plus chemotherapy

As with IA2, the 2-knot odds spline model is selected in the base case. Compared to the survival rates reported by the KEYNOTE-811 KM data (Table 5), the 2-knot odds model slightly overestimates survival at 1 year (68% vs 66%) but slightly underestimates survival at 2 years (39% vs 40%) and 3 years (25% vs 27%). The model predicts higher survival estimates at later timepoints than are seen in current clinical practice i.e., 15% at 5 years and 7% at 10 years. Although currently there are no available immunotherapy treatments for advanced HER2-positive GC against which to validate these estimates, this combination represents a step change in the treatment paradigm for these patients, and together with the established pattern of survival tails seen with pembrolizumab use in other cancers, this lends support to the plausibility of higher 5-year and 10-year survival estimates.

In validation interviews, eleven clinical experts were asked to choose between the company base case (2-knot odds) and EAG base case (1-knot hazard) curves; nine experts selected the 2-knot odds as the more plausible curve, two others were uncertain about which to choose.

Table 5. OS predictions (pembrolizumab with trastuzumab plus chemotherapy)

Data	Year 1	Year 2	Year 3	Year 4	Year 5	Year 10
KM	66%	40%	27%	-	-	-

Parametric						
Exponential	65%	43%	28%	18%	12%	1%
Gamma	0%	0%	0%	0%	0%	0%
Generalized gamma	68%	41%	26%	18%	12%	3%
Gompertz	66%	43%	27%	17%	10%	0%
Log-logistic	68%	40%	25%	17%	12%	4%
Log-normal	67%	41%	27%	18%	13%	4%
Weibull	70%	43%	25%	14%	8%	0%
Spline						
1k hazard ***(EAG base case)***	67%	40%	27%	18%	13%	3%
2k hazard	68%	39%	26%	20%	15%	5%
3k hazard	68%	38%	26%	20%	16%	6%
1k odds	68%	40%	26%	18%	14%	5%
2k odds ***(company base case)***	68%	39%	26%	20%	15%	7%
3k odds	68%	39%	26%	20%	16%	7%
1k normal	68%	41%	26%	17%	12%	3%
2k normal	68%	39%	26%	20%	15%	6%
3k normal	68%	39%	26%	20%	16%	7%
Key: *KM, Kaplan Meier; OS, overall survival*						

As with IA2, the best-fitting parametric curve based on goodness-of-fit statistics (Table 6) is the log-logistic. Amongst the spline models, the 1-knot odds models provide the best fit according to goodness-of-fit statistics. However, based on additional validation meetings conducted following the first committee meeting, the base case curve aligns more closely with clinical expert expectations.

Table 6. Statistical fit for OS (pembrolizumab with trastuzumab plus chemotherapy)

Distribution	AIC	BIC
Parametric		
Exponential	1730.8	1734.1
Weibull	1725.0	1731.6
LogNormal	1714.6	1721.2
LogLogistic	1712.3	1718.9
Gompertz	1732.4	1735.7

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GenGamma	1716.2	1721.2
Spline		
1k hazard	1715.3	1725.2
2k hazard	1714.8	1728.0
3k hazard	1716.3	1732.8
1k odds	1713.9	1723.6
2k odds	1714.7	1727.9
3k odds	1716.4	1732.9
1k normal	1716.0	1725.9
2k normal	1714.6	1727.9
3k normal	1716.2	1732.7
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival		

Figure 9. OS parametric extrapolations for pembrolizumab with trastuzumab plus chemotherapy

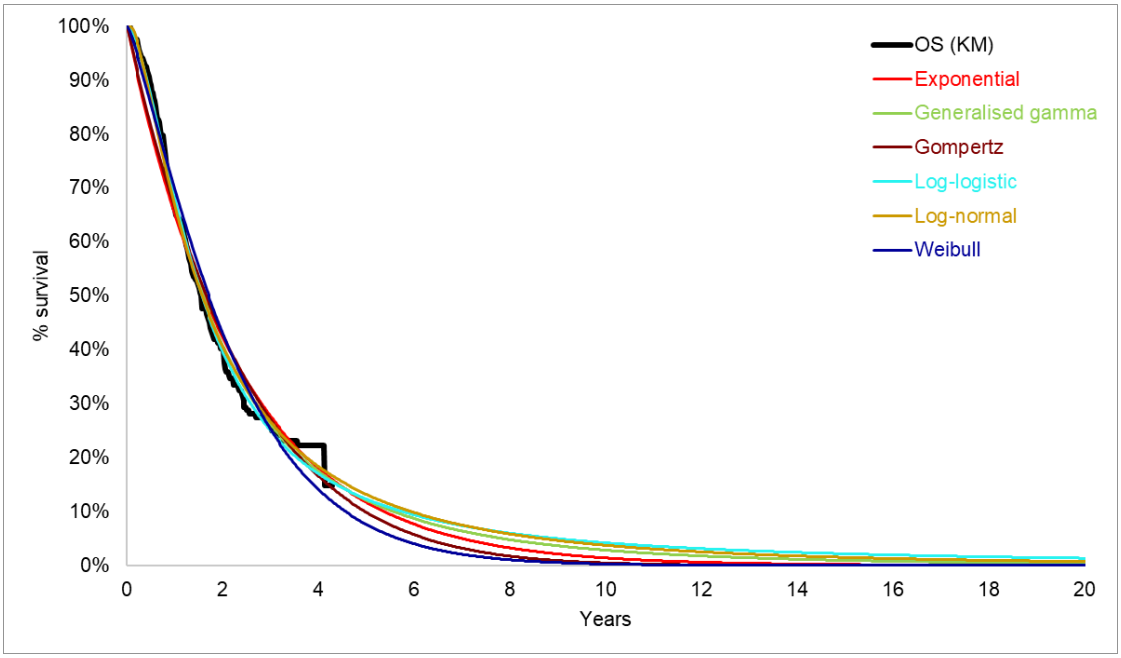

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Figure 10. OS parametric smoothed hazards for pembrolizumab with trastuzumab plus chemotherapy

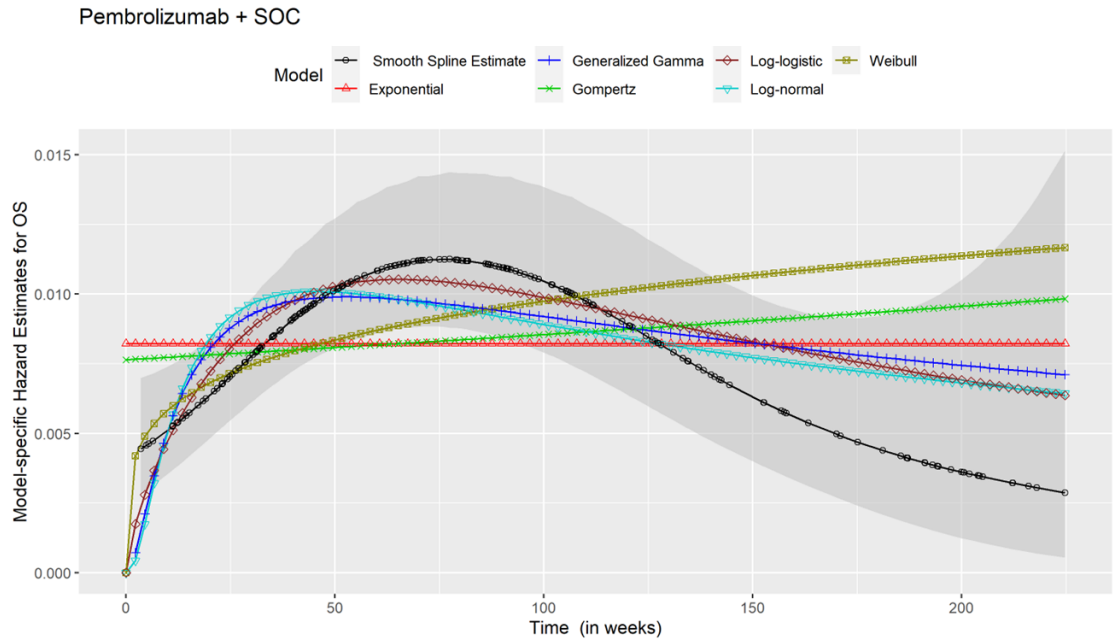

Figure 11. OS spline extrapolations for pembrolizumab with trastuzumab plus chemotherapy

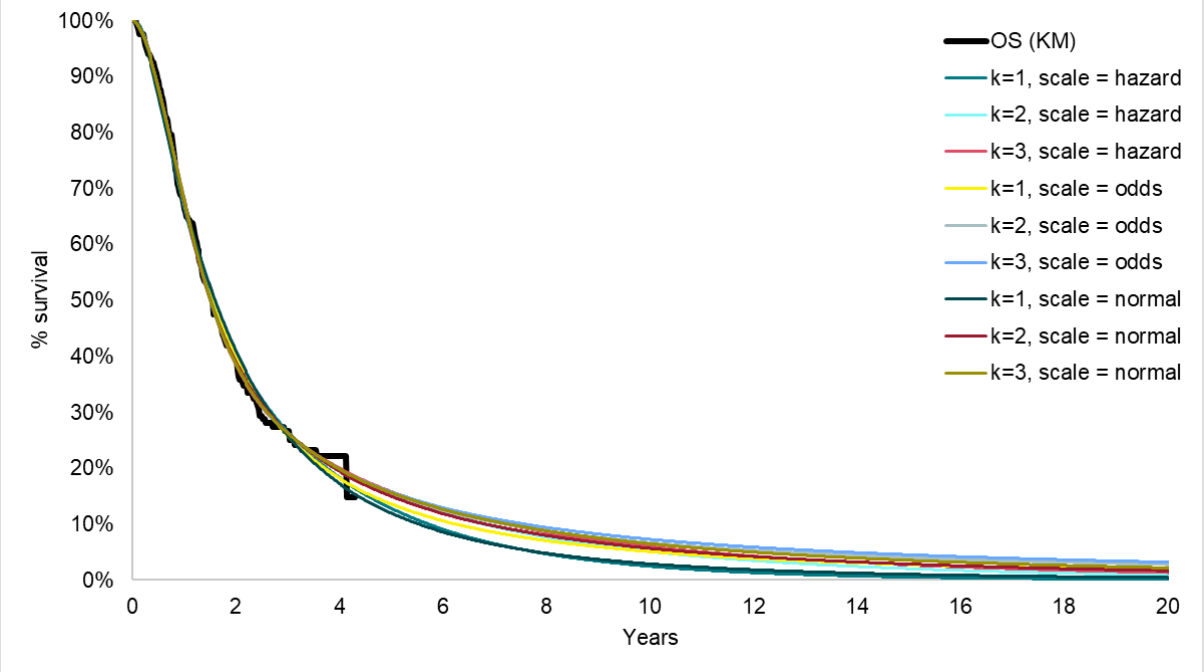

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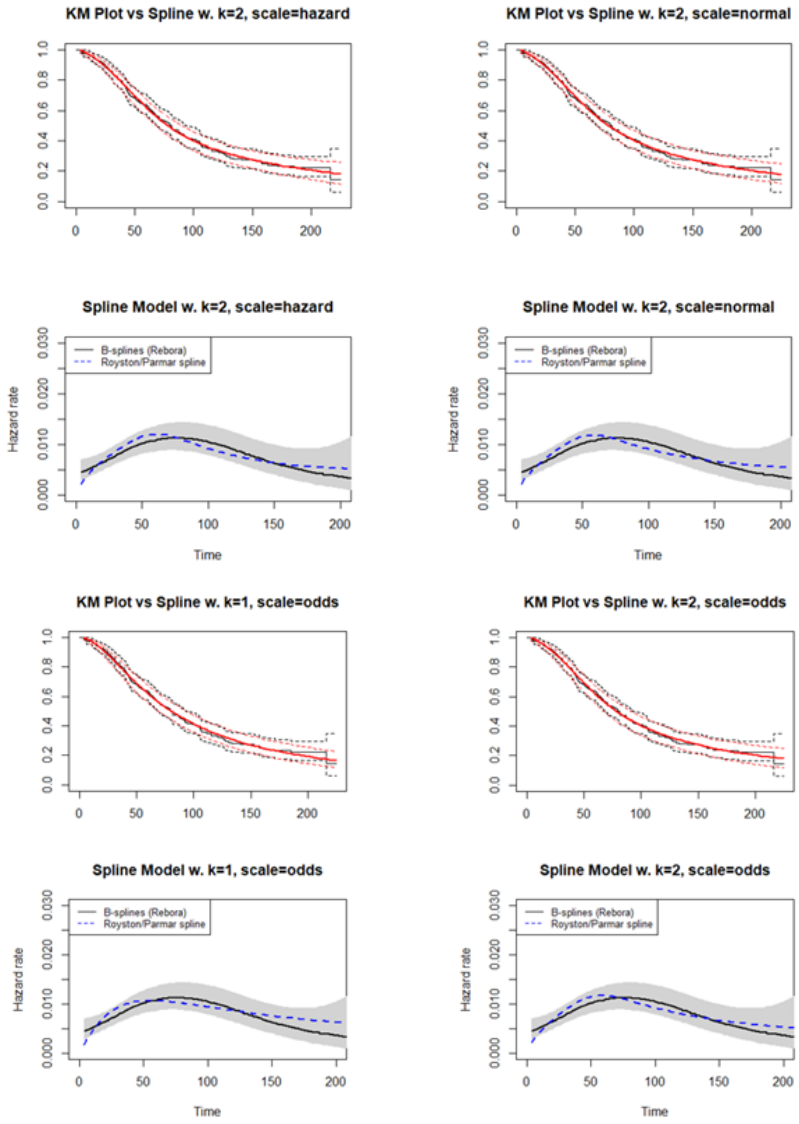
Figure 12. OS spline smoothed hazards for pembrolizumab with trastuzumab plus chemotherapy



Progression-free survival

Due to the completeness of the PFS data from the KEYNOTE-811 trial, MSD note that the impact of the PFS model selection on the cost-effectiveness outcome is minor and is not considered to be a model driver. Furthermore, at the first ACM the company and EAG were in agreement about the choice of survival curve.

Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma [ID3742]

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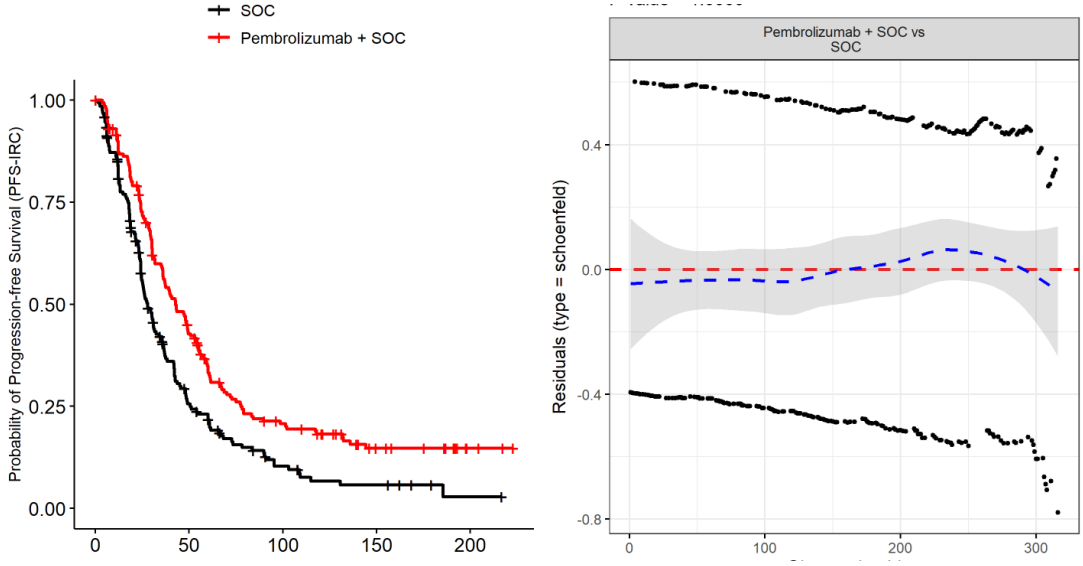
Proportional hazards (PH) assumption

As with IA2, independently fitted models, which do not assume a constant treatment effect over time, are preferred to jointly fitted (dependent) models.

Using IA3 data, the Schoenfeld residuals plot is predominantly linear (Figure 13). The evidence suggested that the proportional hazards assumption may be valid (p=0.393) for BICR-assessed PFS over time for those between the groups treated with each trial arm. Thereafter, log-cumulative hazards are roughly parallel from about 20 weeks onwards, after the protocol-driven evaluations (Figure 14), however the log-cumulative hazards are non-parallel during the first part of the trial period up to approximately 20 weeks, likely due to the protocol-driven tumour assessment schedules. Independently fitted models are preferred.

Figure 13. KM curve and Schoenfeld residual plot for diagnosis of proportional hazards in BICR-assessed PFS



Key: BICR, blinded independent central review; KM, Kaplan-Meier; PFS, progression-free survival; SOC, standard of care

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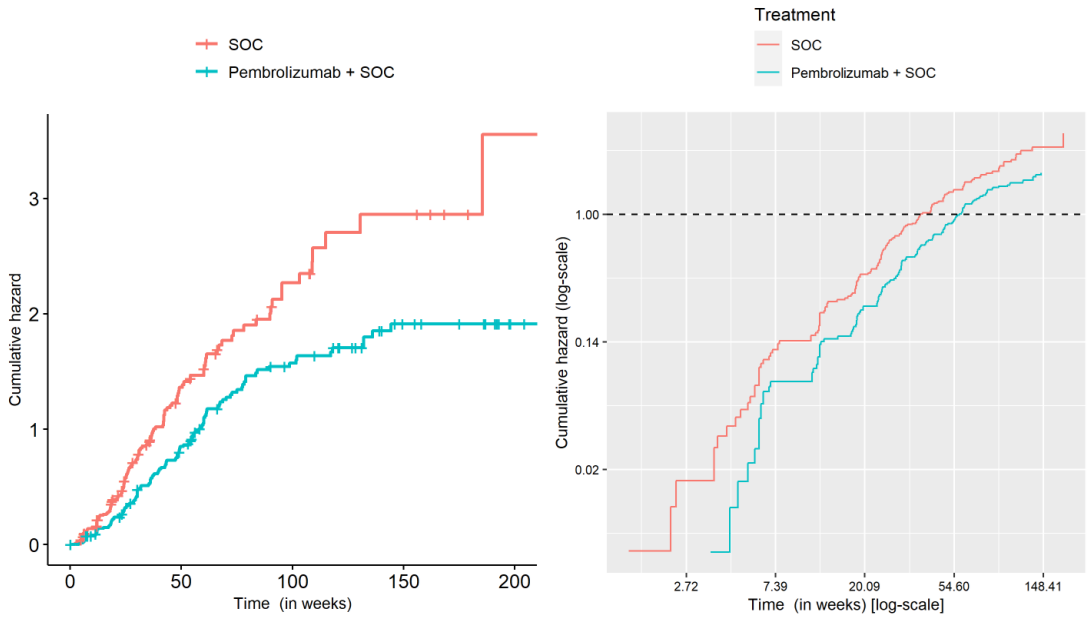
Figure 14. Cumulative hazard of BICR-assessed PFS over time between the intervention and comparator



Key: BICR, blinded independent central review; PFS, progression-free survival; SOC, standard of care

Trastuzumab plus chemotherapy (SoC)

The best fitting parametric model for the SoC arm based on goodness-of-fit statistics (Table 7) is log-logistic, closely followed by log-normal.

As with IA2, the one-piece log-normal extrapolation is used as the base-case in the model as it provides good fit to the data and a lower long-term prediction of PFS that minimises the crossing of the PFS and OS curves. This was also the curve selected by the EAG.

Table 7. Statistical fit of parametric and spline models for PFS (trastuzumab plus chemotherapy)

Model	AIC	BIC
Parametric		
Exponential	1549.180	1552.478
Weibull	1548.351	1554.948
Log-normal	1527.689	1534.286

Log-logistic	1525.386	1531.983
Gompertz	1549.799	1556.396
GenGamma	1529.595	1539.490
Spline		
Hazards, 1 knot	1529.0	1538.9
Hazards, 2 knots	1528.3	1541.5
Hazards, 3 knots	1530.2	1546.7
Odds, 1 knot	1527.4	1537.3
Odds, 2 knots	1529.0	1542.2
Odds, 3 knots	1529.7	1546.2
Normal, 1 knot	1529.4	1539.3
Normal, 2 knots	1528.3	1541.5
Normal, 3 knots	1528.9	1545.4
***Key**: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival*		

Pembrolizumab with trastuzumab plus chemotherapy

Based on statistical fit of parametric PFS extrapolation models, log-logistic is the best-fitting curve based on AIC/BIC, followed by log-normal and generalized gamma (Table 8).

As with IA2, the independently fitted log-normal parametric curve is used as the base case for the intervention arm as it provides a good fit to the trial data and more accurately predicts long-term PFS that reduces the crossing of PFS and OS curves. This was also the curve selected by the EAG.

Table 8. Statistical fit of parametric and spline models for PFS (pembrolizumab with trastuzumab plus chemotherapy)

Model	AIC	BIC
Parametric		
Exponential	1637.655	1640.964
Weibull	1639.190	1645.807
Log-normal	1608.200	1614.817
Log-logistic	1607.011	1613.627
Gompertz	1632.000	1638.616
Generalized Gamma	1607.099	1617.024

Spline		
Hazards, 1 knot	1606.2	1616.1
Hazards, 2 knots	1602.0	1615.2
Hazards, 3 knots	1601.6	1618.2
Odds, 1 knot	1604.8	1614.8
Odds, 2 knots	1603.4	1616.6
Odds, 3 knots	1602.4	1619.0
Normal, 1 knot	1608.3	1618.2
Normal, 2 knots	1602.7	1615.9
Normal, 3 knots	1601.0	1617.6
Abbreviations: *AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival*		

Time-to-treatment discontinuation

The model was updated with time-on-treatment (ToT) data from the IA3 analysis for all drug components separately. As with IA2, KM data was used directly in the model due to the relative completeness of the ToT data. In line with the committee's preference, a treatment cap was removed for trastuzumab in both arms. KM data for all CPS≥1 patients from the non-Asia region is presented for each drug below, Figure 15 to Figure 20.

Figure 15. ToT KM data for pembrolizumab

Figure 16. ToT KM data for trastuzumab

Figure 17. ToT KM data for capecitabine (CAPOX)

Figure 18. ToT KM data for oxaliplatin (CAPOX)

Figure 19. ToT KM data for 5-FU (FP)

Figure 20. ToT KM data for cisplatin (FP)

Summary of clinical parameters used in the model

For the key clinical parameters used in the economic model, the settings used in the IA3 base case analysis are presented in Table 9.

Table 9. Summary of approach to clinical parameters used in the updated model (IA3)

Clinical parameter	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy
OS	Independent fit, 2-knot odds spline	Independent fit, Weibull
PFS	Independent fit, Lognormal	Independent fit, Lognormal
ToT	KM data	KM data
Key: *KM, Kaplan Meier; OS, overall survival; PFS, progression free survival; ToT, time-on-treatment* *Note: all survival data is informed by the non-Asia region population expressing CPS≥1*		

Health-related quality of life

The committee concluded that the linear mixed effects regression model, which accounts for repeated measures, is more appropriate than using a descriptive analysis. Utility values based on the IA3 data were derived using the linear mixed effects regression model and are presented in Table 10 below. These are used in the revised base case analysis.

Table 10. Time-to-death utilities from KEYNOTE-811 (IA3)

Time-to-death (days)	N	Mean	SE
Non-Asia region			
<30	[redacted]	[redacted]	[redacted]

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30 to 180	[redacted]	[redacted]	[redacted]
180 to 360	[redacted]	[redacted]	[redacted]
≥ 360	[redacted]	[redacted]	[redacted]
Abbreviations: N, number of participants with non-missing score; SE, standard error *Source: MK3475_prot811_PEM_EQ5D_Report_v3.0 (Table 118)*			

Summary of model updates

To incorporate IA3 data, the following model inputs were updated:

- OS data inputs
- PFS data inputs
- ToT data inputs
- Utility data inputs (linear mixed effects regression model values)
- Adverse event data
- Relative dose intensity data
- Subsequent treatment data (however base case settings aligned with EAG clinical practice scenario)

Regarding administration costs, the committee concluded that the scenario analysis with updated costs for trastuzumab administration provided by the NHS England CDF clinical lead is appropriate for decision-making. However, the company does not have visibility of the methods for updating this in the model so incorporation of this model setting should be completed by the EAG ahead of the second committee meeting.

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Summary of updated base case results

The results (using the pembrolizumab net price) of the company base case using data from IA3 of KEYNOTE-811 and the committee's preferred assumptions are presented in Table 11. The scenario with updated costs for trastuzumab administration provided by the NHS England CDF clinical lead has not been implemented due to lack of visibility of the model method.

Table 11. Base case results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Trastuzumab plus chemotherapy	[redacted]	1.49	[redacted]	-	-	-	-
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	2.72	[redacted]	[redacted]	1.224	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
**inclusive of x1.2 QALY weight*

The scenario where PD-L1 testing costs are applied to the intervention arm alone is presented in Table 12.

Pembrolizumab with trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma [ID3742]

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Table 12. Scenario analysis results including cost of PD-L1 test in intervention arm (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Trastuzumab plus chemotherapy	[redacted]	1.49	[redacted]	-	-	-	-
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	2.72	[redacted]	[redacted]	1.224	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years **inclusive of x1.2 QALY weight*							

References

1. Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial. Lancet. 2023.
2. Data on File: Market research regarding biomarker testing in UK oncology centres

Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer. A Single Technology Appraisal
Third addendum: EAG critique of the company's response to the draft guidance document

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Date completed 15/01/2024

1. Introduction

In November 2023, the National Institute for Health and Care Excellence invited stakeholders to comment on the Draft Guidance Document (DGD) for the appraisal of pembrolizumab with trastuzumab and chemotherapy for untreated human epidermal growth factor receptor 2 (HER2)-positive advanced gastric or gastro-oesophageal junction (GOJ) cancer.[1] The DGD stated that "*the committee could not identify the most plausible incremental cost-effectiveness ratio because overall survival extrapolations based on interim analysis 3 were not available*," and it requested updated modelling incorporating data from interim analysis 3 (IA3) of the KEYNOTE-811 randomised clinical trial (RCT).[1] The company's response to the DGD included a presentation of these IA3 data and an updated economic model including updated data from IA3 for: overall survival (OS); progression-free survival (PFS); time on treatment (ToT); utility values; adverse events (AEs); relative dose intensities (RDIs) and subsequent treatments.[2] The company has also presented a scenario analysis exploring the impact of incorporating the cost of programmed death-ligand-1 (PD-L1) testing in the cost-effectiveness analysis as the committee stated that they preferred to include costs for PD-L1 testing in the economic analysis.

This addendum provides a critique of the additional evidence submitted by the company in response to the DGD including the company's updated cost-effectiveness analyses. Section 2 provides a summary of the company's response and the EAG's critique of these points; whilst Section 3 presents a fuller discussion on particular issues. Section 4 provides a brief description of the changes in the updated model submitted by the company. Section 5 presents the methods for additional exploratory analyses undertaken by the EAG. Section 6 presents the results of additional exploratory analyses undertaken by the EAG. This addendum should be read in conjunction with the EAG report and previous addenda provided prior to the first committee meeting.[3-5]

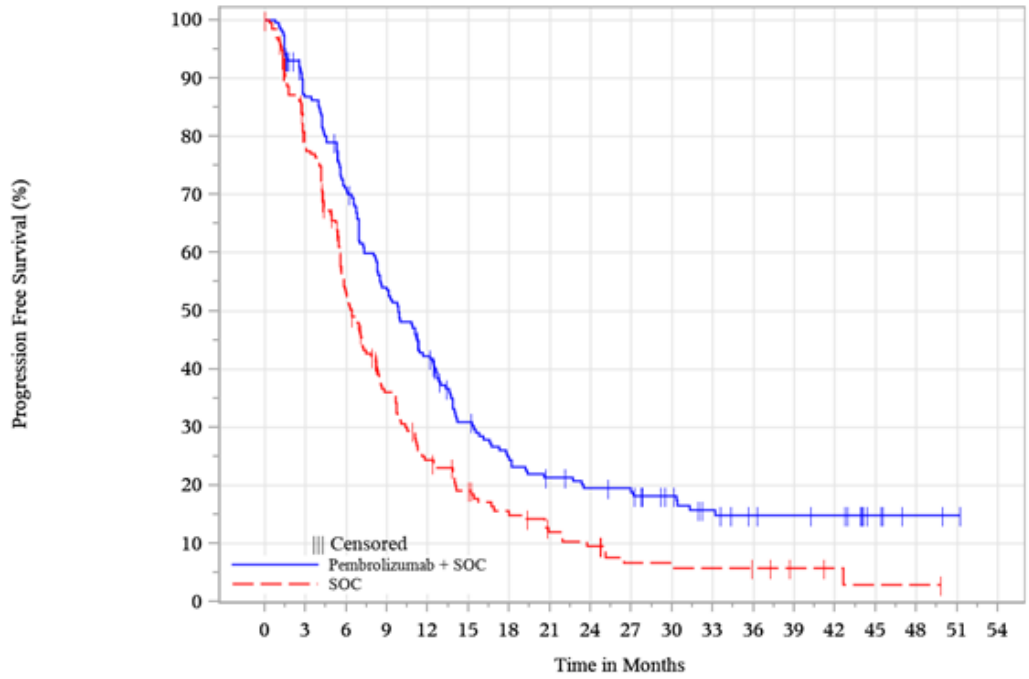
All results presented in this document include the Patient Access Scheme (PAS) discount for pembrolizumab. This remains unchanged from the discount offered at the time of the original company submission (CS).[6] The impact of including confidential discount for other drugs included in the analysis is explored in a confidential appendix.

2. Summary of company's TE response and EAG comments

The interim analysis 3 data are based on data-cut of 29th March 2023.[2] The company reports that for the PD-L1 combined positive score (CPS) ≥1 population the median duration of follow up was 20 months in the pembrolizumab plus standard of care (SoC) group and 18.2 months in the SoC group. In the pembrolizumab plus SoC group and the SoC group, 80.9% and 88.8% of participants discontinued respectively.[2] The most common reason for discontinuation was due to disease progression.

Within the PD-L1 CPS ≥1 non-Asia region subgroup, the estimated hazard ratio (HR) for PFS comparing pembrolizumab plus SoC with SoC alone was 0.64 with 95% CI [0.51, 0.80] and p<0.0001.[2] The Kaplan-Meier curves of PFS for this subgroup is reproduced in Figure 1. The EAG notes that the results for PFS reported in the original CS from interim analysis 2 (IA2) had a slightly lower HR (0.62 with 95% CI [0.49, 0.78] CS Section B2.6.1 Table 14, and CS Clarification response A15).[7]

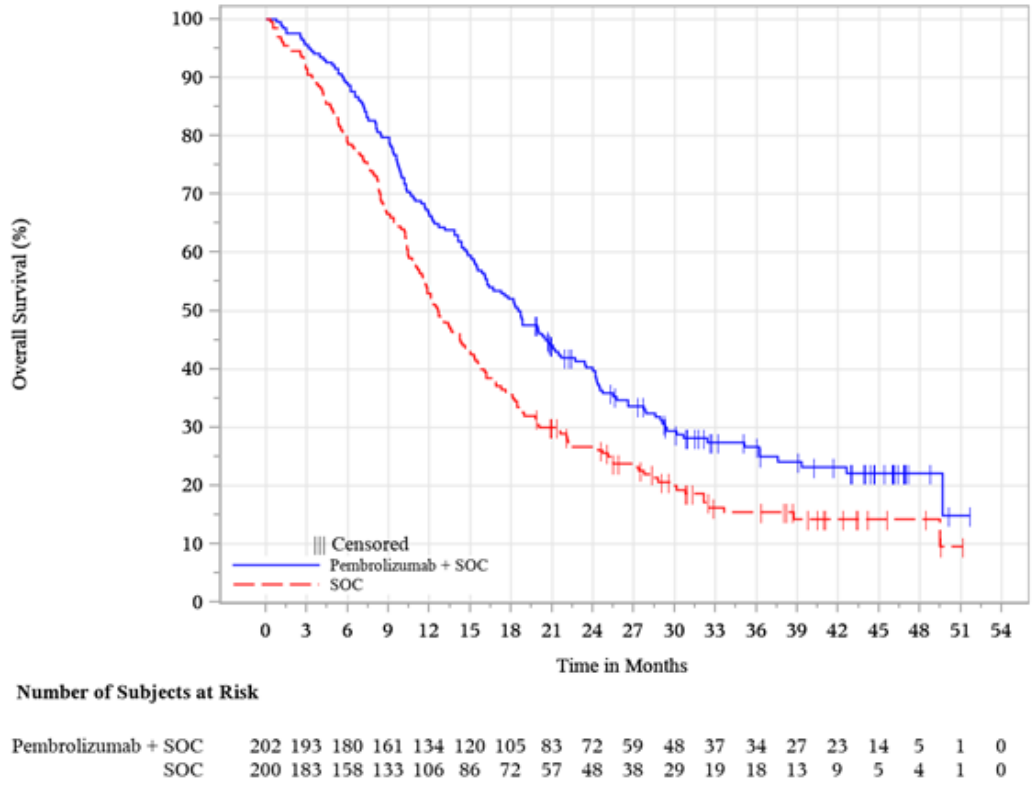
Figure 1: Kaplan-Meier estimates of PFS for the CPS ≥1 non-Asia region subgroup based on IA3 (reproduced from Figure 1 of company response to DGD)[2]



Within the PD-L1 CPS ≥1 non-Asia region subgroup, the HR for OS comparing pembrolizumab plus SoC with SoC alone was 0.70 with 95% CI [0.56, 0.87] and p=0.0007.[2] The Kaplan-Meier curves of OS for this subgroup is reproduced in Figure 2. The EAG notes that the results for OS reported in the original CS from IA2 had a slightly lower HR (0.67 with 95% CI[0.52, 0.85]; CS Section B2.6.1 Table 16 and CS Clarification response A15).[7]

The company also presents updated information on ToT in their response to the DGD, but the EAG has not reproduced these data here and so refers the committee to Figures 15 to 18 of the company's DGD response.[2]

Figure 2: Kaplan-Meier estimates of OS for the CPS ≥1 non-Asia region subgroup based on IA3 (reproduced from Figure 2 of company response to DGD)[2]



The updated time-to-death utilities from KEYNOTE-811 based on IA3 using the linear mixed effect regression model is reported in Table 1. The EAG notes that values in Table 1 are close to those reported for patients without grade 3+ adverse events from the linear mixed effects model when using the IA2 data cut (see EAG report, Table 21).[3] The value in the model for the utility decrement applied in those having grade 3+ adverse events has also been updated from [redacted] to [redacted].

Table 1: Time-to-death utilities from KEYNOTE-811 (IA3)[2]

Time-to-death (days)	N	Mean	SE
Non-Asia region			
<30	[redacted]	[redacted]	[redacted]
30 to 180	[redacted]	[redacted]	[redacted]
180 to 360	[redacted]	[redacted]	[redacted]
≥ 360	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of participants with non-missing score; SE, standard error.

The main points discussed in the company's DGD response and the EAG's comments are summarised in Table 2. Where further critique was considered necessary, this is provided in Section 3.

Table 2: Summary of company's DGD response and EAG comments

Key issue	Headline points in company's DGD response	EAG comments
Updated OS extrapolation using IA3	• The company has provided updated OS models fitted to the data from the latest data cut (IA3) as requested by the committee.[2] • The data presented are those for the non-Asia cohort with PD-L1 CPS of 1 or more which is in-line with the committee's stated preference in the DGD. • The company's approach has been broadly similar to the approach taken in the analysis presented after technical engagement (TE) with the company fitting both standard parametric survival models and flexible spline models independently to each arm of the KEYNOTE-811 study. • The company preferred to adopt the 2-knot odds spline model for the intervention arm (pembrolizumab plus SoC). • The company preferred to adopt the Weibull model for the SoC arm (trastuzumab plus chemotherapy). • These were the same functional forms as selected by the company in their response to TE, however, the parameters for the fitted models differ from those used previously as they have been fitted to the new data cut (IA3).	The EAG prefers to adopt the 1-knot hazards spline for the intervention arm and the 1-knot normal spline for the SoC arm. Whilst these are the same functional forms as selected by the EAG at the time of the first committee meeting, these curves have been selected by the EAG after considering all of the curves fitted to the new data cut and the EAG considers that these updated curves provide the most plausible extrapolation. The EAG has also capped the hazards in the intervention arm so that they do not exceed those modelled in the SoC arm at any time point, but this has minimal impact as this does not become an issue until ~10 years when only a small minority of patients are predicted to survive (~2%). A further discussion of the EAG's reasons for preferring these models for extrapolating OS is provided in Section 3.

Key issue	Headline points in company's DGD response	EAG comments
Updated PFS extrapolation using IA3	• The company has provided updated PFS curves fitted to the data from the latest data cut (IA3) for the non-Asia cohort with PD-L1 CPS score of 1 or more, as requested by the committee.[2] • The company's approach has been broadly similar to the approach taken in the analysis presented after TE with the company fitting both standard parametric survival curves and spline models independently to each arm of the KEYNOTE-811 study. • The company preferred to adopt log-normal models fitted independently to each arm. • These were the same functional forms as selected by the EAG at the time of the first committee meeting, however, the parameters for the fitted curves differ from those used previously as they have been fitted to the new data cut (IA3).	The EAG agrees with the company's choice of curve for PFS using the updated data from IA3.
Updated time on treatment (ToT) data using IA3	• The company has updated the ToT data in the model to use the latest data cut (IA3).[2] • As these data are mature, the Kaplan-Meier data for ToT are used directly without any need for extrapolation.	The EAG agrees with the company's decision to use the ToT data from IA3 without extrapolation and to remove the cap on duration of treatment with trastuzumab.

Key issue	Headline points in company's DGD response	EAG comments
	• The company has also implemented the committee's stated preference in the DGD that ToT for trastuzumab is not capped at 35 cycles.	
Utility values updated using IA3	• The company has updated its estimates of utility from KEYNOTE 811 using data from the latest data cut (IA3).[2] • It has also adopted the committee's stated preference in the DGD for using the utility values from the linear mixed effects regression model. • The utility values are applied in the updated modelling using a time-to-death approach rather than a progression-based approach, and this is consistent with the committee's stated preference in the DGD	The EAG accepts the company's updated approach as it is consistent with the EAG's preferences at the time of the last committee meeting. It has verified that the model has been updated with the new data from IA3 as presented in Table 1. The EAG notes that the utility value for grade 3+ adverse events has also been updated ([redacted] to [redacted]), but this is not explicitly described in the company's DGD response. The company has not presented analyses showing the impact of each individual change made in the updated modelling, but the EAG believes that applying the new utility values in isolation would have had minimal impact on the ICER.
Updated AEs using IA3	• The company has updated its inclusion of AEs within the model using data from IA3.[2] • This involved updating multiple model inputs including: the number of AEs of each type; the events per person; the duration of events; and the duration of patient exposure. • In addition, the AE of decreased appetite was replaced with an AE of 'neuropathy peripheral' which was included in addition	The EAG notes that none of data used by the company to update the AEs to reflect the IA3 data cut were summarised in their response to the DGD. The EAG was able to identify all the changes made by the company within the model by visual inspection of the two model versions and by copying data across until the two versions gave identical results. The EAG did not have time to tabulate all of the updates to the model for review by the committee. In addition, there

Key issue	Headline points in company's DGD response	EAG comments
	to a previously included AE of 'peripheral sensory neuropathy'.	was no updated clinical study report (CSR) provided against which the EAG would have been able to check the data included in the model, so the EAG has had to take these data changes at face value. However, as the update had minimal impact on the ICER, the EAG does not consider that these issues are likely to be associated with significant risk of bias.
Updated RDIs using IA3	• The company has updated the data on RDIs to use the data from IA3.[2] • No further details are provided by the company in their response to the DGD.	The EAG's critique of this issue is essentially the same as that provided for the AEs. The company has not presented the updated data and no updated CSR has been provided to allow the EAG to verify the data. Therefore, the EAG had to visually inspect the model to determine the changes and has had to accept the updates to the model at face value. However, as the update had minimal impact on the ICER, the EAG does not consider that these issues are likely to be associated with significant risk of bias.
Updated subsequent therapies using IA3	• The company has updated the data on subsequent treatment to use the data from IA3.[2] • The company has aligned its approach with the EAG's base case at appraisal committee meeting 1 (ACM1) in which it preferred to assume that only paclitaxel and docetaxel are used as subsequent treatments. • No further details are provided by the company in their response to the DGD.	The EAG's critique of this issue is essentially the same as that provided for the AEs and RDIs, in that the EAG has had to identify the changes manually and accept the updates to the model at face value. However, the majority of the data changes to capture subsequent therapies at IA3 do not affect the base case scenario which includes only paclitaxel and docetaxel. The EAG did note a change in the dosage of weekly paclitaxel when given as monotherapy (down to 80mg from 90mg) but this had minimal

Key issue	Headline points in company's DGD response	EAG comments
		impact on the ICER. Therefore, the EAG does not consider that these updates are likely to be associated with significant risk of bias.
Administration costs	• The company acknowledges the committee's preference in the DGD for using the administration costs based on the advice from the cancer drugs fund (CDF) Lead, which were provided as additional EAG scenarios prior to ACM1 (see EAG report second addendum).[5] • However, the company was unable to replicate these because NICE had not shared with the company the version of the EAG's model that included these scenarios.	The EAG has been able to adapt the company's updated model to include the scenarios which capture the administration costs based on the advice from the CDF Lead. These have been incorporated in the EAG's base case (see Section 5) as the committee stated in the DGD that these assumptions were preferred.
PD-L1 testing	• The company argues that the vast majority of centres (77% to 92%) conduct parallel testing for HER2 and PD-L1 status in order to facilitate rapid access to nivolumab with chemotherapy in patients who are HER2 negative.[2] The company therefore prefers not to include any additional costs for PD-L1 testing in HER2-positive patients because those patients will already have been tested if parallel testing is used for nivolumab. • However, the company has reported results for a scenario analysis in which all patients are tested sequentially (i.e., first for HER2 status and then for PD-L1 status).[2]	The company's submitted model included costs for PD-L1 tests in both arms for its base case analysis. The EAG was able to replicate the results for the company's sequential testing scenario, presented in Table 12 of the company's DGD response, by setting the PD-L1 testing costs to zero for the SoC arm. The EAG is satisfied with the company's implementation of this scenario analysis. This is described and discussed further in Section 3.2

Abbreviations: EAG, external assessment group; CDF, cancer drugs fund; CPS, combined positive score; DGD, draft guidance document; IA3 interim analysis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PL-L1 programmed death-ligand-1; PFS, progression free survival; RDIs, relative dose intensities; TE, technical engagement.

3. EAG's critique on remaining key issues

The EAG has already made brief comments in Table 2 on the updated model inputs for PFS, ToT, utility values, AEs, RDIs and subsequent treatments. The EAG does not consider further discussion of these issues to be necessary, given that there is agreement on the modelling of PFS and the other data sources have minimal impact on the ICER. The EAG provides a fuller critique below of the company's choice of curves for OS.

3.1 Extrapolation of OS using updated IA3 data

The company considered independently fitted models are preferred to jointly fitted models when extrapolating OS. The decision was based on believing the proportional hazards (PH) assumption may not be valid after assessing the PH assumption based on clinical argument of the validity, the Schoenfeld residual plot, and the log-cumulative hazard plot. The models explored include standard parametric models and flexible spline models.

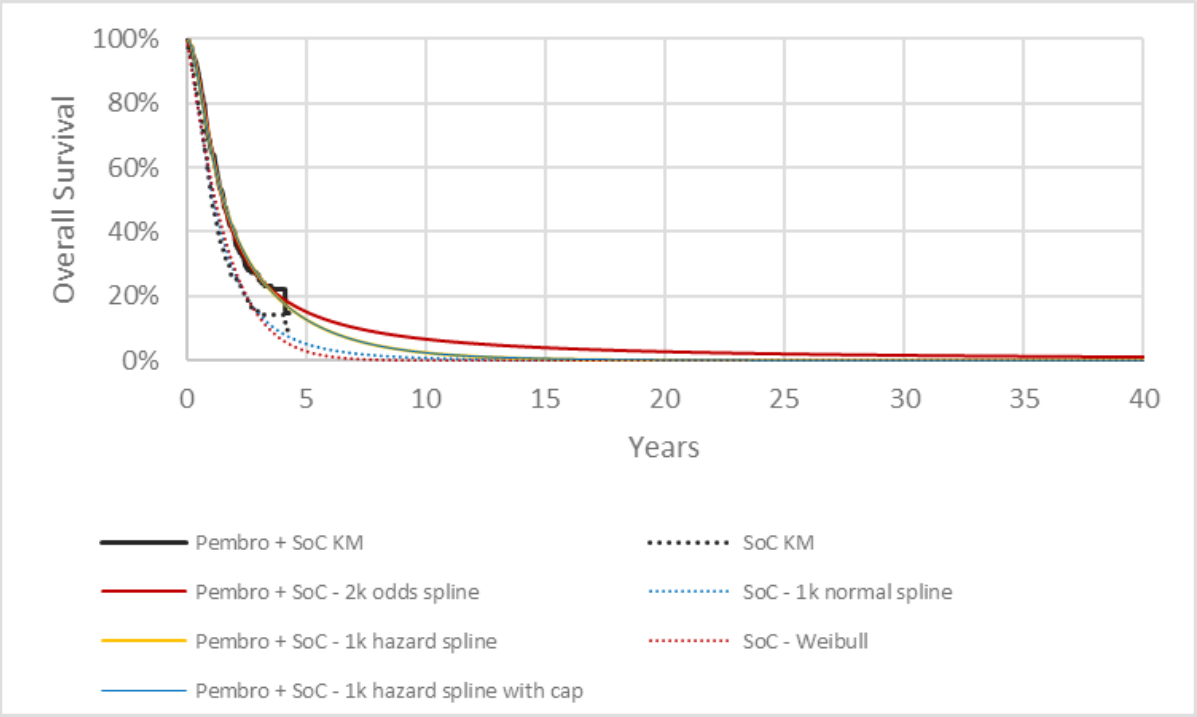
For the pembrolizumab plus SoC arm, the company selects the 2-knot odds spline model as the base case to extrapolate OS as with IA2.[2] The company highlights that this model "*predicts higher survival estimates at later timepoints than are seen in current clinical practice i.e., 15% at 5 years and 7% at 10 years*" and argues that the combination of pembrolizumab and SoC "*represents a step change in the treatment paradigm for these patients, and together with the established pattern of survival tails seen with pembrolizumab use in other cancers, this lends support to the plausibility of higher 5-year and 10-year survival estimates*".[2]

The company also states that 11 clinical experts were asked to choose between the company's base case (2-knot odds spline model) and EAG's base case (1-knot hazard spline model) for pembrolizumab plus SoC in validation interviews. Nine experts chose the company's base case as the more plausible model and two experts were uncertain.[2]

For the SoC arm, the company selects the Weibull model as the base case to extrapolate OS as with IA2.[2] The company states that their clinical experts believe that patients who survive to 5 years while treating with the current SoC are very exceptional and the Weibull model aligns more closely with their expectations than the EAG's base case. The company also states that 11 clinical experts were asked to choose between the company's base case (Weibull model) and EAG's base case (1-knot normal spline model) for SoC in validation interviews. Nine experts chose the company's base case as the more plausible model, one expert chose the EAG's base case, and one expert was indifferent between the two model choices.[2]

The EAG agrees with the company to use the independently fitted modelling approach to extrapolate OS. However, the EAG disagrees with the model choice for both the pembrolizumab plus SoC arm and the SoC arm. The EAG's base case model for pembrolizumab plus SoC arm is the 1-knot hazard spline model and for SoC is the 1-knot normal spline model (see Figure 3).

Figure 3: Overall survival extrapolation (company's base case vs. EAG's base case)



Note: red solid line and red dotted line present the company's base case model for pembrolizumab plus SoC and SoC, respectively. Blue solid line (which overlaps with yellow solid line) and blue dotted line present the EAG's base case model for pembrolizumab plus SoC and SoC, respectively.

The EAG acknowledges the plausibility of a long-term survival benefit at 5 and 10 years for patients receiving pembrolizumab plus SoC and that the survival probability may be small at 5 years for patients receiving SoC. These views align with the clinical opinion received by the company and EAG previously (see Table 3).

The EAG notes that the company's base case model for the pembrolizumab plus SoC arm (2-knot odds spline) predicts 3% and 1% survival probability at 20-year and 40-year, respectively. Given that the cohort starting age in the economic model is 60 and the condition of this cohort, the EAG questions the plausibility of having 3% alive at 80 years old and 1% still alive at 100 years old.

Table 3: OS long-term plausibility informed by clinical expert opinion (adapted from the EAG report Table 25)[3]

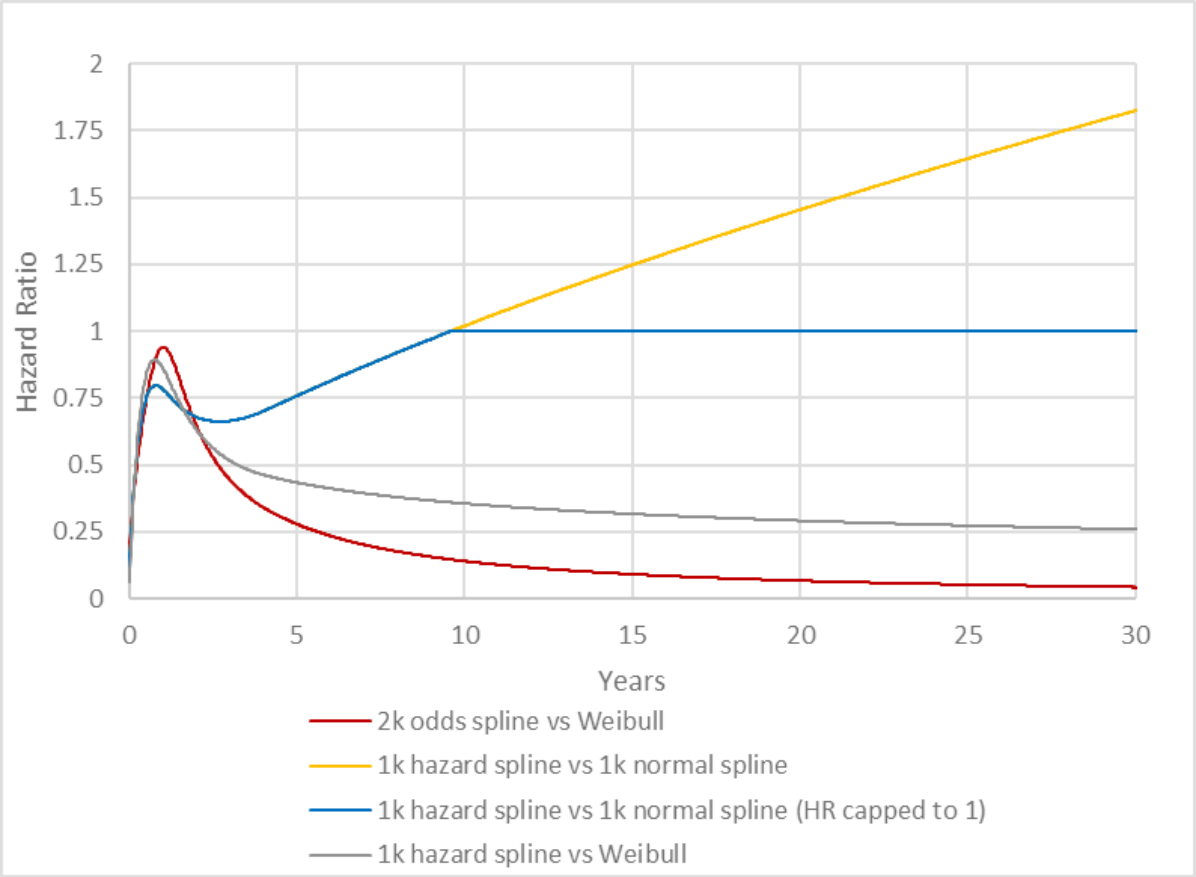
Intervention arm	**Expected survival probability**				**Predicted survival probability**	
Timepoint	**Company's expert 1**	**Company's expert 2**	**EAG's expert 1**	**EAG's expert 2**	**Company's post DGD base case (2k odds spline)[2]**	**EAG's base case (1k hazard spline)**
5 years	NA	NA	5-10%	0%	15%	13%
10 years	NA	NA	1%	0%	7%	2%
20 years	NE	NE	NE	NE	3%	0.1%
40 years	NE	NE	NE	NE	1%	0%
Control arm	**Expected survival probability**				**Predicted survival probability**	
Timepoint	**Company's expert 1**	**Company's expert 2**	**EAG's expert 1**	**EAG's expert 2**	**Company's post DGD base case (Weibull)[2]**	**EAG's base case (1k normal spline)**
5 years	5%	2-5%	≤5%	0%	3%	5%
10 years	2%	0-1%	0%	0%	0%	0.8%
20 years	NE	NE	NE	NE	0%	0.1%
40 years	NE	NE	NE	NE	0%	0%

Abbreviations: NA, not applicable; NE, not evaluated; k, knot.

The EAG plotted the HR between pembrolizumab plus SoC and SoC using the company's base case and the EAG's base case in Figure 4. The EAG notes that the company's base case (2-knot odds spline for pembrolizumab plus SoC and Weibull for SoC) leads to a continuously decreasing HR and pembrolizumab plus SoC becomes more effective in the longer term. Because the majority of patients had progressed by year 4, but the HR continues to decline after this time, the EAG determines the trend of HR based on the company's base case model choice for the two arms is not plausible. A similar trend of HR is also observed when using the EAG's base case for pembrolizumab plus SoC (1-knot hazard spline model) and the company's base case for SoC (Weibull model).

The EAG notes that after approximately 10 years the EAG's base case models (1-knot hazard spline for pembrolizumab plus SoC and 1-knot normal spline for SoC) predict that the risk of death was greater for those who had received pembrolizumab plus SoC than for those had received SoC (as the HR is above unity). The EAG deemed this is unlikely to be plausible. Hence, the EAG has assumed in its base case that the 1-knot hazard spline model for pembrolizumab plus SoC and the 1-knot normal spline model for SoC would be used until the HR exceeds unity and capped at unity afterwards. The EAG notes that the extrapolation with and without capping are almost identical due to only a small number of patients (~2%) are still alive at 10 years, where the capping is applied (see Figure 3).

Figure 4: Displaying the HRs for pembrolizumab plus SoC and SoC for OS using company's and EAG's model choice



3.2 Inclusion of PD-L1 testing costs

The company has included the same PD-L1 testing costs in both arms in its base case on the basis that PD-L1 testing is occurring at the same time as HER2 testing (i.e. in parallel) and therefore HER2-positive patients will receive this test regardless of whether pembrolizumab is recommended.

In the company's scenario analysis exploring sequential testing (i.e., PD-L1 testing occurs after HER2 test results are known), patients testing positive for HER2 would not currently need a PD-L1 test as they are not eligible for nivolumab, but they would need a PD-L1 test if pembrolizumab were to be recommended. Therefore, additional costs are incurred for the HER2-positive patients and these are apportioned over the patients eligible for pembrolizumab. The company's scenario analysis assumes a unit cost for PD-L1 testing of £53. It uses the population of the KEYNOTE-811 study to estimate the proportion of HER2-positive patients who have a CPS score of 1 or more (85.1%) making them eligible for pembrolizumab. This gives a cost for PD-L1 testing of £62.28 (=£53/0.851) for each HER2 positive patient identified as eligible for pembrolizumab.

The EAG agrees with the company that if HER2 and PD-L1 testing are currently being conducted at the same time (i.e., in parallel) to facilitate timely access to nivolumab in HER2-negative patients, then there will be no additional cost associated with requiring PD-L1 testing for access to pembrolizumab in HER-positive patients. If parallel testing is only occurring in a proportion of centres, with sequential testing occurring in the remaining centres, then the additional cost of PD-L1 testing will lie somewhere between the cost applied in the company's base case and the cost applied in its sequential testing scenario analysis (i.e. £0 to £62.28).

The EAG has assumed 100% sequential testing in its base case as the DGD concludes that PD-L1 testing cost should be included but does not clearly state what proportion of testing can be assumed to be occurring in parallel in current practice. The EAG has also provided a scenario analysis exploring the company's position, i.e. that the vast majority of patients are currently offered PD-L1 testing before their HER2 status is known. The EAG has used a figure of 92% having parallel testing as this is the higher of the two figures provided by the company and therefore provides a lower limit for the incremental costs of PD-L1 testing.

4. Summary of the updated economic analysis presented by the company

The company's updated base case analysis is consistent with the committee's preferences stated in the DGD with two exceptions: it assumes the same costs for PD-L1 testing in both arms meaning that pembrolizumab is not associated with any additional costs of PD-L1 testing; and it does not incorporate the committee's preferred administration costs based on the advice from the CDF Lead. The ICER for the company's updated base case is £[redacted] per QALY when applying a QALY weighting of 1.2 (see Table 4).

The company also provides a scenario analysis in which PD-L1 testing is restricted to the intervention arm (i.e. assuming 100% sequential testing) and this provides an ICER of £[redacted] per QALY when applying a QALY weighting of 1.2 (see Table 4). This demonstrates that the ICER is not particularly sensitive to the inclusion of PD-L1 testing costs for the pembrolizumab arm only.

Table 4: Company's base case and scenario analyses presented in its response to the DGD

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company updated base case after ACM1[a]						
SoC[*]	[redacted]	[redacted]				
Intervention[**]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company scenario analysis including PD-L1 testing costs for HER-2 positive patients only in the intervention (pembrolizumab plus chemotherapy) arm						
SoC[*]	[redacted]	[redacted]				
Intervention[**]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] *Includes PD-L1 testing costs for HER2 positive patients in both arms equally (i.e. 100% parallel testing) which is equivalent to assuming no additional costs associated for PD-L1 testing for pembrolizumab*

Abbreviations:ACM1, first appraisal committee meeting; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-year.

[*] *SoC: Trastuzumab plus chemotherapy*

[**] *Intervention: Pembrolizumab with SoC*

[†] *EAG additional scenario analyses use the EAG's preferred base case as their starting point.*

As previously stated, for the model changes related to AEs, RDIs and sequential therapies, the EAG was only able to validate the updates to the company's base case by making visual inspections of the two versions of the model and copying across any identified data changes until the results agreed. This was done using the EAG's preferred base case at the time of ACM1 as a starting point. By doing this, the EAG was able to verify that none of the changes related to AEs, RDIs or sequential therapies had a large impact on the ICER. The EAG is therefore not concerned that any of these updates are likely to have introduced significant bias to the ICER, although it would have preferred to have had all of the updated model inputs tabulated by the company and access to an IA3 updated CSR to verify the inputs.

5. Methods of the EAG's additional exploratory analyses

The EAG has incorporated all of the company's updates to reflect the new data analysis from IA3, however, it has selected different OS models to extrapolate OS in both arms (see Section 3). In addition, the EAG has included the committee's preferred administration costs, which were based on the advice from the CDF Lead, and has included PD-L1 testing costs assuming that testing is sequential in all centres (i.e., PD-L1 tests are ordered after HER2-postive status is confirmed). The EAG has applied all of these changes individually using to the company's updated base case and has also presented an ICER combining all of these changes which represents its updated base case.

The EAG has also presented an exploratory scenario analysis assuming that the vast majority of centres (92%) currently employ parallel testing (i.e., HER2 and PD-L2 status assessed at the same time) to facilitate timely access to nivolumab in HER2-negative patients. The EAG has also explored scenario analyses in which it varies the administration of pembrolizumab from 3-weekly (as assumed in the base case) to 6-weekly. These scenarios were previously described in the second addendum,[5] and are repeated here for completeness as the DGD does not appear to provide any information on the committee's preferences for the proportion of pembrolizumab administrations that occur 6-weekly rather than 3-weekly.

6. Results of the EAG's additional exploratory analyses

The results in Table 5 show that the key driver of the difference in the ICER between the EAG's updated base case and the company's updated base case is the choice of parametric curves for extrapolation of OS. The other areas of difference between the company's updated base case and the EAG's updated base case have minimal impact on the ICER. When discussing the ICERs, this addendum refers to the ICERs when applying the 1.2 QALY multiplier applied as all of the scenarios presented in Table 5 are compatible with a proportionate QALY shortfall of between 0.85 and 0.95. The EAG's updated deterministic base case ICER is £[redacted] per QALY. This is higher than the company's deterministic ICER of £[redacted] per QALY.

The EAG has run the probabilistic sensitivity analysis (PSA) for both the company and the EAG's updated base case scenarios (see Table 5). It can be seen that whilst there is reasonable agreement for the incremental costs between the deterministic and PSA results, the incremental QALYs are slightly higher when using the PSA in both cases, leading to slightly reduced ICERs of £[redacted] and £[redacted] and for the EAG and company updated base case scenarios respectively.

The EAG scenario analyses exploring the impact of assuming 6-weekly administration for pembrolizumab demonstrate that this has a small impact on the ICER for both the company and the

EAG's preferred base case scenarios (see Table 6). The EAG scenario analysis exploring the impact of assuming that a high priority of centres currently uses parallel testing for PD-L1 and HER2 status shows that the impact on the ICER of this assumption is minimal (see Table 6).

Table 5: Results of the EAG's sensitivity analyses and the EAG's updated base case [a]

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company updated base case after ACM1						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company updated base case after ACM1 - probabilistic						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG SA 1: Company updated base case after ACM1 with CDF lead administration costs						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG SA 2: Company updated base case after ACM1 with PD-L1 testing only in the pembrolizumab arm (100% sequential testing)						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG SA 3: Company updated base case after ACM1 with EAG choice of OS survival curves						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG SA 4: Company updated base case after ACM1 with EAG choice of OS survival curves including capping HR <1						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG updated base case after ACM1 – combines SA1, SA2 and SA4						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG updated base case after ACM1 – combines SA1, SA2 and SA4 - Probabilistic						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] *Deterministic unless otherwise indicated*

Abbreviations: ACM1, first appraisal committee meeting; CDF, Cancer Drugs Fund; EAG, external assessment group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life-year; SA, sensitivity analysis.

* *SoC: Trastuzumab plus chemotherapy*

** *Intervention: Pembrolizumab with SoC*

Table 6: Scenario analyses exploring impact of 6-weekly administration of pembrolizumab and alternative assumptions regarding PD-L1 testing (deterministic)

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company updated base case after ACM1 with 6-weekly pembrolizumab						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's updated base case after ACM1 with 6-weekly pembrolizumab						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG updated base case with 92% of current centres using parallel testing for HER2 and PD-L1 status						
SoC*	[redacted]	[redacted]				
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM1, first appraisal committee meeting; EAG, external assessment group; HER2, human epidermal growth factor receptor 2; ICER, incremental cost-effectiveness ratio; PD-L1, of programmed death-ligand-1; QALYs, quality-adjusted life-year

* *SoC: Trastuzumab plus chemotherapy*

** *Intervention: Pembrolizumab with SoC*

7. Discussion

The EAG and the company's updated base case analyses differ mainly due to different opinions regarding the most plausible models to extrapolate OS. The EAG considers that its chosen models are more plausible because the company's preferred OS model predicts survival rates of 7% and 3% at 10 and 20 years for patients treated with pembrolizumab with SoC. The EAG considers this to be out of step with the advice received from their clinical experts on expected survival at 10 years. In addition, the EAG notes that the company's preferred survival models predict a continuously decreasing HR in the long-term indicating that pembrolizumab plus SoC becomes more effective at preventing death relative to SoC in the longer term, which again the EAG considers lacks face validity. In contrast, the EAG's preferred models predict reducing effectiveness for pembrolizumab in the long-term, which the EAG considers to be more realistic. However, the EAG has capped the hazards for death in the pembrolizumab with SoC arm to ensure that they are never higher than for SoC alone.

The EAG's preferred base case ICER is £[redacted] per QALY when using the deterministic model and [redacted] per QALY when using the probabilistic analysis (and applying the 1.2 QALY weighting). These are higher than the ICERs provided by the company's preferred base case scenario of £[redacted] per QALY and £[redacted] per QALY for the deterministic and probabilistic analyses, respectively (applying the 1.2 QALY weighting).

The EAG acknowledges that there is currently variability between centres in their approach to PD-L1 testing and its base case scenario may be pessimistic if a high proportion of centres are currently testing PD-L1 status at the same time as HER2 status, as the company claims. However, its scenario analysis suggests that any bias is likely to be small.

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