Single Technology Appraisal

Pembrolizumab with chemotherapy for treating HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab with chemotherapy for treating HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

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 chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024.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)

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

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:	Irina Voicechovskaja Gemma Gooud

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	**Marketing Authorisation update in GOJ adenocarcinoma subgroup: MSD considers it is imperative that the GOJ population currently reimbursed under TA737 (based on KEYNOTE-590) maintains funding despite the repositioning of this population to a different subsection within section 4.1 of the SmPC for pembrolizumab. Cost-**

	effectiveness has already been demonstrated in the GOJ CPS ≥10 population during the NICE appraisal which led to publication of TA737. DG consultation document section 3.2 (pages 6-7) states: "*The committee noted that NICE's technology appraisal guidance on pembrolizumab with platinum and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer recommends pembrolizumab plus doublet chemotherapy as an option for treating oesophageal or GOJ adenocarcinoma in people whose tumours express PD-L1 with a CPS of 10 or more, but that the indication in the marketing authorisation for GOJ adenocarcinoma has changed since that guidance was published. This means that this evaluation will replace that guidance for people with GOJ adenocarcinoma".* Following receipt of CHMP Opinion for KEYNOTE-859, MSD had communicated to NICE the changes to the SmPC in section 4.1, as detailed below (a copy of the communication sent to NICE in October 2023 has been uploaded to NICE docs with the MSD's response to DG consultation document). In summary, the population covered by the previously approved indication in patients with HER-2 negative gastroesophageal junction (GEJ) adenocarcinoma which was restricted to patients whose tumours express PD L1 with a CPS ≥10 (study KEYNOTE-590; TA737) overlapped with the HER-2 negative gastroesophageal junction (GEJ) adenocarcinoma indication covered by the current indication (study KEYNOTE-859, ongoing appraisal ID4030). Consequently, during the regulatory process, a decision was taken to remove the HER-2 negative GEJ adenocarcinoma population from the oesophageal carcinoma (based on KEYNOTE-590) indication statement in section 4.1 of the SmPC and include it in the gastric cancer (based on KEYNOTE-859) indication (i.e., in adults whose tumours express PD-L1 with a CPS ≥1): *New indication (based on KEYNOTE-859):* *<u>Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma</u>* *KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1.* *Amended indication (based on KEYNOTE-590):* *<u>Oesophageal carcinoma</u>* *KEYTRUDA, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus* ***~~or HER2-negative gastroesophageal junction adenocarcinoma,~~*** *in adults whose tumours express PD-L1 with a CPS ≥ 10 (see section 5.1).* The evidence submitted to NICE in September 2023 as part of the ID4030 appraisal based on the KEYNOTE-859 data is aligned with the new gastric/gastro-oesophageal junction adenocarcinoma indication in the CPS ≥1 population. MSD's position is that in the event that NICE is unable to make a positive recommendation in line with the full population covered by the decision problem in ID4030, **it would not be**

	necessary or appropriate for any change to be made to the existing TA737 recommendation. Clinical and cost-effectiveness has already been demonstrated in the GOJ CPS ≥10 population during the NICE appraisal which led to publication of TA737. Removal of the GOJ population from the current TA737 recommendation would effectively represent removing a treatment option which has been demonstrated to be a cost-effective use of NHS resources. The KEYNOTE-590 data which informed the appraisal which led to publication of TA737 remains valid. The change in the oesophageal carcinoma indication statement in the pembrolizumab SmPC was proposed to avoid duplicating reference to the GOJ population in both oesophageal and gastric indication statements in the SmPC (i.e. overlapping indication statements). To confirm, this was not caused by new safety or efficacy data from the KEYNOTE-590 trial data. In addition, there is no change to the evidence base, clinical pathway or economic case that could lead to a material effect on the recommendation. During the EMA regulatory assessment of KEYNOTE-859, MSD provided supporting evidence demonstrating consistency between the KEYNOTE-859 and KEYNOTE-590 trials which led to a positive regulatory approval and oesophageal cancer indication wording amendment, please see the CHMP assessment conclusion (1) below: *"There was an overlap of the currently applied indication and the previously approved indication in patients with HER-2 negative gastroesophageal junction (GEJ) adenocarcinoma (EMEA/H/C/003820/II/0097) which was restricted to patients whose tumours express PD L1 with a CPS ≥10 (study KEYNOTE-590). The HER-2 negative GEJ adenocarcinoma indication was therefore removed from the oesophageal carcinoma indication in section 4.1 of the SmPC and included in the gastric cancer KEYNOTE-859 indication (i.e., in adults whose tumours express PD-L1 with a CPS ≥1). KEYNOTE-859 enrolled a larger and broader group of participants that was more representative of the subgroup of patients with GEJ adenocarcinoma, including 334 participants with GEJ adenocarcinoma (21.2% of ITT population) as compared to 91 participants (12.1% of ITT population) in KEYNOTE-590."* Clinical efficacy in thePD-L1 CPS ≥10 GOJ subpopulation in KEYNOTE-859 is supportive of the efficacy in the currently reimbursed population covered by KEYNOTE-590. In KEYNOTE-859 CPS ≥10 GOJ subpopulation, OS HR [redacted]); PFS HR [redacted]). MSD considers that the updated base case in the CPS ≥1 population (please see section 5 of this response) supports NICE making a positive recommendation in line with the full population covered by the decision problem in ID4030. This would mean that the CPS 1-10 GOJ population (currently not covered by TA737), would be covered by the new recommendation based on KN-859, as well as the already reimbursed CPS≥10 GOJ population currently covered by TA737. **In this scenario, to avoid duplication in GOJ indications recommendations, MSD would support the TA737 recommendation be amended in line with the above licence change following publication of positive technology appraisal guidance for the ID4030 appraisal**.
2	**Clinical effectiveness data and updated cost-effectiveness analyses are provided based on longer-term follow-up from the KEYNOTE-859 trial.**

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

	DG consultation document, Section 3.3 (page 8) states: *"The committee was aware that longer-term follow up of KEYNOTE-859 (data cut August 2023) had become available, but the data had not been critiqued by the EAG or presented to the committee. This was because it was not available at the time of the company submission, or at the clarification stage, and this evaluation had proceeded without an additional technical engagement step".* The longer-term follow-up data from the KEYNOTE-859 trial is now presented with this response from MSD to the DG consultation document. A summary of the clinical effectiveness data from the analysis is presented in Section 1 of the Appendix. Additionally, MSD has updated the cost-effectiveness analysis with this data. The survival model selection process is outlined in Sections 3 and 4 of the Appendix for the CPS≥1 and CPS≥5 populations, respectively. The updated cost-effectiveness results are presented in Table 13 of the Appendix for the CPS≥1 population (pembrolizumab plus doublet chemotherapy versus doublet chemotherapy) and the revised base case ICER in this population is [redacted] (including the pembrolizumab CAA price). Cost-effectiveness results have also been provided for the CPS≥5 population (pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy) in Table 16 of the Appendix and the ICER in this population is [redacted] (including list prices).
3	**Network meta analyses using time-varying hazard ratios and updated cost-effectiveness analyses are provided because the proportional hazards assumption does not hold for OS in the CPS≥5 population.** DG consultation document, Section 3.4 states: *"The company agreed with the EAG that using time-varying hazard ratios would have been more appropriate. The committee agreed that using time-varying hazard ratios would be its preferred method…".* Updated NMA results in the CPS≥5 population, based on the longer-term follow-up from KEYNOTE-859 and using time-varying hazard ratios, are now presented in Section 2 of the Appendix. MSD has provided updated cost-effectiveness analysis for the CPS≥5 population (pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy) based on this analysis. The survival model selection process is outlined in Section 4 of the Appendix. The cost-effectiveness results for this population are presented in Table 16 of the Appendix and the ICER is [redacted] (including list prices).
4	**Treatment effect waning is included in the revised base case for the CPS≥1 population, as per committee preferences.** DG consultation document, Section 3.7 states: *"…for the 10 to 15% of people who have a complete response, treatment effect waning would not be expected. But, for people who have not had a response within 3 to 6 months, treatment effect waning would be expected as they would have moved on to less clinically effective follow-on treatments. The committee concluded that it was appropriate to apply treatment effect waning for pembrolizumab. It agreed that treatment effect waning starting either 5 years or 7 years after starting treatment and reducing to the same as the comparator after 2 years, were both plausible*". Based on the trial data for pembrolizumab plus doublet chemotherapy and doublet chemotherapy from KEYNOTE-859, there is no clear evidence to indicate a treatment

	waning effect, as the KM curves for PFS and OS separated early and remained separated throughout the evaluation period in favour of pembrolizumab plus doublet chemotherapy (see Figure 1 in the Appendix). Additionally, Figure 5 in the Appendix shows how the HR changes over the KEYNOTE-859 trial period and suggests that the long-term benefits of pembrolizumab are stable after approximately [redacted] of treatment. The 95% CI [redacted]; this is likely due to the small number of patients left at risk in the trial. Acknowledging the NICE committee's preference for a treatment waning effect to be applied, MSD has updated the cost-effectiveness analysis in the CPS≥1 population to include a gradual treatment waning effect starting 5 years following discontinuation of pembrolizumab (i.e. 7 years since treatment initiation) in [redacted]; this excludes the [redacted] on pembrolizumab plus doublet chemotherapy who had a complete response in KEYNOTE-859. The cycle-specific hazard for pembrolizumab gradually becomes equal to that in the doublet chemotherapy arm over the subsequent 2 years. MSD also presents scenarios reflecting a gradual treatment waning effect starting 4 years following discontinuation of pembrolizumab (i.e. 6 years since treatment initiation) and staring 3 years following discontinuation of pembrolizumab (i.e. 5 years since treatment initiation). The cost-effectiveness results of these scenarios are presented in **Table 15** of the Appendix and the ICERs (including the pembrolizumab CAA price) are [redacted] (revised base case including a treatment waning effect beginning 7 years after starting treatment), [redacted] (scenario including a treatment waning effect beginning 6 years after starting treatment) and [redacted] (including a treatment waning effect beginning 5 years after starting treatment). For the CPS≥5 population (pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy), treatment effect waning is not included in the base case analysis as the committee's preferences on treatment effect waning are unclear when the comparator is nivolumab plus doublet chemotherapy. Secondly, if the treatment effects wane to the doublet chemotherapy arm and OS for doublet chemotherapy is based on the same FP model as pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy, the instantaneous hazards in the FP OS curve for doublet chemotherapy [redacted].
5	**A severity weighing of 1.2 is included in the revised base case for the CPS≥1 population, as per committee preferences.** DG consultation document, Section 3.10 states: "*the committee concluded that, for the CPS of 1 or more subgroup, a severity weight of 1.2 should be applied to the QALYs*". MSD has updated the cost-effectiveness analysis in the CPS≥1 population to include a severity modifier of 1.2. The cost-effectiveness results are presented in Table 13 of the Appendix and the revised base case ICER is [redacted] (including the pembrolizumab CAA price).

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

	MSD maintains that committee should consider the extent of unmet health need when assessing the cost-effectiveness of pembrolizumab plus doublet chemotherapy. As mentioned throughout the CS, treatment options for patients with advanced HER2 negative GC and GOJ adenocarcinoma are limited: although NICE's TA857 recommends nivolumab in combination with platinum- and fluoropyrimidine-based chemotherapy as a first-line treatment option, this is only recommended for those patients whose tumours express PD-L1 with a CPS≥5. Overall, there have been no innovative treatments for patients expressing a CPS<5, with doublet chemotherapy regimens remaining the only available treatment option. This appraisal aims to offer the first IO treatment option for patients with GC and GOJ adenocarcinoma expressing a CPS≥1, thereby addressing the existing unmet need.
6	**A cost-minimisation analysis is presented for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy.** DG consultation document, Section 3.11 states: *"The committee was satisfied that pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy were similarly effective (see section 3.4) and tolerated (see section 3.5). For the modelling, the committee stated that this meant that it was reasonable to consider that the QALYs were the same for the 2 treatments and to compare only the costs. So the committee stated that its preference would be for the company to present a cost-minimisation analysis for this subgroup".* This analysis is now presented with MSD's response to the DG consultation document. Results are presented in Table 18 of the Appendix over a lifetime time horizon and a 2-year time horizon. These results do not represent the true cost to the NHS as they are based on list prices; patient access scheme discounts are in place for pembrolizumab and nivolumab and the discount for nivolumab is unknown to MSD. The results of the cost-utility analysis should be used for decision making when nivolumab plus doublet chemotherapy is the comparator as they are based on trial evidence and characterise the uncertainty in the NMA via variance-covariance matrices. These results are reported in Section 5.
7	**Pembrolizumab 200mg was given Q3W in the KEYNOTE-859 trial and this is reflected in the economic analysis. The pembrolizumab label also permits pembrolizumab 400mg to be given Q6W. Thus, the administrative burden of pembrolizumab to the patient and provider is expected to be less than nivolumab which is given 240mg Q2W or 360mg Q3W.**

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.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

- 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 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.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

MSD response to the Draft guidance document

Appendix

March 2024

File name	Version	Contains confidential information	Date
ID4030 MSD response to the Draft guidance document [REDACTED]	1	No	26 March 2024

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

1. **Longer-term follow-up data from KEYNOTE-859 (data cut-off August 2023)**

Primary efficacy endpoint longer term follow up post-hoc analysis – Database cut 22 August 2023

Following the submission of ID4030 the results of post-hoc analysis of the KEYNOTE-859 trial, conducted for publication purposes, has become available to MSD UK. This provides longer-term follow-up data on OS and PFS, with data cut-off on 22 August 2023, (10 additional months of follow-up [defined as time from randomisation to database cut-off date] beyond data from the first interim analysis [IA1] of KEYNOTE-859 which had informed the original submission to NICE). Additional statistical analyses at this data cut would not be powered to show statistically significant differences This appendix presents the results of longer-term OS and PFS follow-up data for PD-L1 CPS≥1 and CPS ≥5 populations. Updated cost-effectiveness results using survival extrapolations which provide the best fit to the longer-term data are also provided.

Overall survival in participants whose tumour express PD-L1 CPS ≥1: Longer term follow-up based on post-hoc analysis

As of the data cut-off date (22 August 2023) for longer term follow-up post-hoc analysis CPS ≥1 population, the median duration of follow up (defined as the date of randomisation until the date of death, date of last contact, or the database cut-off date if the participant is still alive) was [redacted] months ([redacted] months) in the pembrolizumab plus chemotherapy group and [redacted] months ([redacted] months) in the chemotherapy group.

Pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS when compared with chemotherapy alone.

- The OS HR was [redacted], which is less than the p-value crossing boundary of 0.020556 for statistical significance) [redacted] of pembrolizumab plus chemotherapy, representing a [redacted] reduction in the risk of death.
- The median OS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.
- By KM estimation, the OS rates at 12, 18, 24, and 30 months were [redacted] in the pembrolizumab plus chemotherapy group compared with the chemotherapy group.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

- The KM curves for OS separated early and remained separated throughout the evaluation period in favour of the pembrolizumab plus chemotherapy group.

Table 1. Analysis of Overall Survival (ITT Population with CPS ≥1) long term post-hoc data cut

	Pembrolizumab + Chemotherapy		Chemotherapy	
	[redacted]		[redacted]	
Number of Events (%)	[redacted]		[redacted]	
Kaplan-Meier Estimates (months)[a]				
Median (95% CI)	[redacted]		[redacted]	
[Q1, Q3]	[redacted]		[redacted]	
Person-months	[redacted]		[redacted]	
Event Rate / 100 Person-months	[redacted]		[redacted]	
vs Chemotherapy				
Hazard Ratio (95% CI)[b]	[redacted]			
p-value[c]	[redacted]			
OS Rate at month 6 (%) (95% CI)	[redacted]		[redacted]	
OS Rate at month 12 (%) (95% CI)	[redacted]		[redacted]	
OS Rate at month 18 (%) (95% CI)	[redacted]		[redacted]	
OS Rate at month 24 (%) (95% CI)	[redacted]		[redacted]	
OS Rate at month 30 (%) (95% CI)	[redacted]		[redacted]	

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 Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
c One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cut-off Date: 22AUG2023

Figure 1. Kaplan-Meier Plot of Overall Survival (ITT Population with CPS ≥1) long term post-hoc analysis

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Progression free survival in participants whose tumour express PD-L1 CPS ≥1: Longer term follow up based on post-hoc analysis.

Pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in PFS when compared with chemotherapy alone based on BICR assessment per RECIST 1.1.

- The PFS HR was [redacted], which is less than the *p-value* crossing boundary of 0.025 for statistical significance) in favour of pembrolizumab plus chemotherapy, representing [redacted] in the risk of disease progression or death.
- The median PFS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.
- By KM estimation, the PFS rates at 6, 12, 18, 24, and 30 months were [redacted] in the pembrolizumab plus chemotherapy group compared with the chemotherapy group.
- The KM curves for PFS separated early and remained separated throughout the evaluation period in favour of pembrolizumab plus chemotherapy group.

Table 2. Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥1) long term follow up post hoc analysis

	Pembrolizumab + Chemotherapy	Chemotherapy
	[redacted]	[redacted]
Number of Events (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Documented progression	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
Person-months	[redacted]	[redacted]
Event Rate / 100 Person-months	[redacted]	[redacted]
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	[redacted]	

p-value[c]	[redacted]	
PFS Rate at month 6 (%) (95% CI)	[redacted]	[redacted]
PFS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
PFS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
PFS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]
PFS Rate at month 30 (%) (95% CI)	[redacted]	[redacted]

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 Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
c One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cutoff Date: 22AUG2023

Figure 2. Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥1) long term follow up post hoc analysis

Overall survival in participants whose tumour express PD-L1 CPS ≥5: Longer term follow-up based on post-hoc analysis

Pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS when compared with chemotherapy alone.

- The OS HR was [redacted], which is less than the p-value crossing boundary of 0.020556 for statistical significance) [redacted] of pembrolizumab plus chemotherapy, representing a [redacted] reduction in the risk of death.
- The median OS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

- By KM estimation, the OS rates at 12, 18, 24, and 30 months were [redacted] in the pembrolizumab plus chemotherapy group compared with the chemotherapy group.

- The KM curves for OS separated early and remained separated throughout the evaluation period in favour of the pembrolizumab plus chemotherapy group.

Table 3. Analysis of Overall Survival (ITT Population with CPS ≥5) longer term post-hoc data cut

	Pembrolizumab + Chemotherapy	Chemotherapy
	[redacted]	[redacted]
Number of Events (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
Person-months	[redacted]	[redacted]
Event Rate / 100 Person-months	[redacted]	[redacted]
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
OS Rate at month 6 (%) (95% CI)	[redacted]	[redacted]
OS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
OS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
OS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]
OS Rate at month 30 (%) (95% CI)	[redacted]	[redacted]

[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 Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
[c] One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cutoff Date: 22AUG2023

Figure 3. Kaplan-Meier Plot of Overall Survival (ITT Population with CPS ≥5) long term follow up post hoc analysis

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Progression free survival in participants whose tumour express PD-L1 CPS ≥5: Long term follow up based on post-hoc data cut.

Pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in PFS when compared with chemotherapy alone based on BICR assessment per RECIST 1.1.

- The PFS HR was [redacted], which is less than the *p-value* crossing boundary of 0.025 for statistical significance) in favour of pembrolizumab plus chemotherapy, representing [redacted] in the risk of disease progression or death.
- The median PFS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]9) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.
- By KM estimation, the PFS rates at 6, 12, 18, 24, and 30 months were [redacted] in the pembrolizumab plus chemotherapy group compared with the chemotherapy group.
- The KM curves for PFS separated early and remained separated throughout the evaluation period in favour of pembrolizumab plus chemotherapy group.

Table 4. Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥5) long term follow up post hoc analysis

	Pembrolizumab + Chemotherapy	Chemotherapy
	[redacted]	[redacted]
Number of Events (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
Person-months	[redacted]	[redacted]
Event Rate / 100 Person-months	[redacted]	[redacted]
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
PFSIRC Rate at month 6 (%) (95% CI)	[redacted]	[redacted]
PFSIRC Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
PFSIRC Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
PFSIRC Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

PFSIRC Rate at month 30 (%) (95% CI)	[redacted]	[redacted]

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 Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
c One-sided p-value based on log-rank test stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World) and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP.
Western Europe includes France, Germany, Spain, Italy, United Kingdom, Ireland, Switzerland, Czech Republic, Denmark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.
Database Cutoff Date: 22AUG2023

Figure 4. Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS ≥5) long term follow up post hoc analysis

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Time dependent hazard ratio for overall survival in participants whose tumour express PD-L1 CPS ≥1: Longer term follow-up based on post-hoc analysis

Figure 5 shows how the HR changes over the KEYNOTE-859 trial period and suggests that the long-term benefits of pembrolizumab are stable after approximately [redacted] of treatment. The 95% CI [redacted]; this is likely due to the small number of patients left at risk in the trial. The corresponding number of patients at risk are provided in Figure 1.

Figure 5. Time dependent HR for OS (ITT population with CPS≥1)

[redacted]

2. NMA results in the CPS≥5 population

The NMA is not relevant for the comparison with doublet chemotherapy in the CPS ≥1 population as this is informed directly from the KEYNOTE-859 trial data. For the PD-L1 CPS ≥5 population based on long term follow-up data cut, KM curves, log cumulative hazard plots and the Schoenfeld residuals test are presented below. Using this, MSD has reassessed the results of proportional hazards test for the PD-L1 CPS ≥5 population; based on the visual inspection of the KM curves, log cumulative hazard plots and Schoenfeld residuals test result, MSD also concludes that the proportional hazards assumption for OS is violated in PD-L1 CPS ≥5 population [(p=0.0153) and KM curves cross before six months].

The survival curves implemented in the economic model using a time varying approach are discussed in more detail in Section 4.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Overall survival in PD-L1 CPS ≥5

The evidence network informing the time-varying analysis of OS comprised two trials (KEYNOTE-859 and CheckMate-649) assessing three interventions. According to the model selection process, the best fitting model was the first-order fractional polynomial (P1=1, P2=0.5, scale and 2nd shape). Results of the fixed-effects time-varying analysis comparing pembrolizumab plus chemotherapy with competing interventions are presented below (Table 5, Figure 14, Figure 15).

Results of proportional hazards tests are provided below:

Figure 6 KEYNOTE-859, PD-L1 CPS ≥ 5, OS, KM

Source: KM plotted from KEYNOTE-859 CSR August 2023 data cut-off

Figure 7 KEYNOTE-859, PD-L1 CPS ≥ 5, OS, Schoenfeld residuals

Figure 8 KEYNOTE-859, PD-L1 CPS ≥ 5, OS, Log Cumulative hazard

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 9 KEYNOTE-859, PD-L1 CPS ≥ 5, OS, smoothed curve

Figure 10 CheckMate-649, PD-L1 CPS ≥ 5, OS, KM

Figure 11 CheckMate-649, PD-L1 CPS ≥ 5, OS, Schoenfeld residuals

Figure 12 CheckMate-649, PD-L1 CPS ≥ 5, OS, Log Cumulative hazard

Figure 13 CheckMate-649, PD-L1 CPS ≥ 5, OS, smoothed hazard

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Table 5. DIC of competing survival models, overall survival

Distribution	Scenario	Treatment effect	Deviance	pD	DIC
Gompertz	**P1=1, P2=0.5**	**scale, 2nd shape**	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=0	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=1	scale, 1st shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=1	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=0	scale, 1st shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=0.5	scale, 1st shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=0.5	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=0.5	scale, 1st shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=1	scale, 1st shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=1	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=-0.5	scale, 1st shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=-0.5	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=0	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=0	scale, 1st shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=-1	scale, 1st shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1, P2=-1	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=-0.5	scale, 1st shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=-0.5	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=-1	scale, 1st shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0, P2=-1	scale, 2nd shape	[redacted]	[redacted]	[redacted]
Gompertz	P1=1	scale, 1st shape	[redacted]	[redacted]	[redacted]
Weibull	P1=0	scale, 1st shape	[redacted]	[redacted]	[redacted]
Note: Best fitting model (lowest DIC in bold)					

Figure 14. Results for the time-varying analysis of overall survival; hazard ratios of PEMBRO + FP/PLT versus comparators

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 15. Results for the time-varying analysis of overall survival; modelled survival curves

Under the best-fitting time-varying NMA model for overall survival in the PD-L1 CPS ≥ 5 population (p1 p0.5 with treatment effects on scale and 2nd shape), the point estimate of the hazard ratio for pembrolizumab in combination with chemotherapy versus nivolumab in combination with chemotherapy decreased over time from [redacted] (95% CrI: [redacted]) at [redacted] months to [redacted] (95% CrI: [redacted]) at [redacted] months. [redacted]. Strong conclusions regarding the relative efficacy of pembrolizumab in combination with chemotherapy versus nivolumab in combination with chemotherapy as well as the change in efficacy over time are limited.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Table 6. Results of the fixed effect fractional polynomial network meta-analysis for overall survival; presented as hazard ratios over time for pembrolizumab + chemotherapy versus comparators

PEMBRO + FP/PLT versus	Time-varying HR (95% CrI)										
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months
FP/PLT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO + FP/PLT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: model presented is P1=1, P2=0.5, scale and 2nd shape, fixed effect; All bolded values are statistically significant at the 0.05 significance level; Abbreviations: CrI – credible interval; HR – hazard ratio

Progression free survival in PD-L1 CPS ≥5

The evidence network informing the NMA of PFS consisted of two RCTs (KEYNOTE-859 and CheckMate-649)**.** All analyses were conducted using a fixed-effects model given that there was insufficient evidence available (only one study per connection in the network of evidence) to estimate the between-study heterogeneity required to run random-effects models.

Constant HR NMA results and time-varying HR NMA results are presented for PFS as it is unclear if PH holds for PFS and the same functional type of distribution for OS and PFS is preferred (by definition OS is included in PFS and therefore, the hazard function is expected to behave in a similar way). Section 4 discusses the survival models applied in the economic analysis in more detail.

Constant HR NMA results

Results of the constant HR NMA are presented in Table 7. Treatment with pembrolizumab + chemotherapy performed similarly when compared to nivolumab + chemotherapy (HR, 95% CrI: [redacted]), and the difference between treatments was not statistically meaningful.

Table 7 Results of fixed-effects NMA of PFS based on constant HRs

Chemotherapy	[redacted]	[redacted]
[redacted]	**Nivolumab + chemotherapy**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + chemotherapy**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 3.41; Deviance: 1.41

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Time-varying HRs NMA results

Analyses assuming time-varying HRs were conducted. Treatment with pembrolizumab + chemotherapy led to a statistically meaningful improvement in PFS when compared to chemotherapy alone at all timepoints (i.e., between 3 and 54 months). Although not statistically significant at any time point, the hazard ratio for pembrolizumab + chemotherapy decreased relative to nivolumab + chemotherapy over the course of follow-up.

The evidence network informing the time-varying analysis of PFS comprised two trials assessing three interventions. According to the model selection process, the best fitting model was the second-order fractional polynomial (P1=0, P2=0.5, scale and 2nd shape). Results of the fixed-effects time-varying analysis comparing pembrolizumab + chemotherapy with competing interventions are provided below (Table 8, Figure 24, Figure 25).

Results of proportional hazards tests are presented below:

Figure 16: KEYNOTE-859, PD-L1 CPS ≥ 5, PFS, KM

Source: KM plotted from KEYNOTE-859 CSR August 2023 data cut-off

Figure 17: KEYNOTE-859, PD-L1 CPS ≥ 5, PFS, Schoenfeld residuals

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 18: KEYNOTE-859, PD-L1 CPS ≥ 5, PFS, Log Cumulative hazard

Figure 19: KEYNOTE-859, PD-L1 CPS ≥ 5, PFS, smoothed curve

Figure 20: CheckMate-649, PD-L1 CPS ≥ 5, PFS, KM

Source: KM plotted from CheckMate-649 Janjigian 2023 using estimated IPD

Figure 21: CheckMate-649, PD-L1 CPS ≥ 5, PFS, Schoenfeld residuals

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 22: CheckMate-649, PD-L1 CPS ≥ 5, PFS, Log Cumulative hazard

Figure 23: CheckMate-649, PD-L1 CPS ≥ 5, PFS, smoothed curve

Table 8. DIC of competing survival models, progression free survival

Distribution	Scenario	Treatment effect	Deviance	pD	DIC
Weibull	**P1=0, P2=0.5**	**scale, 2nd shape**			
Weibull	P1=0, P2=0.5	scale, 1st shape			
Weibull	P1=0, P2=0	scale, 1st shape			
Weibull	P1=0, P2=0	scale, 2nd shape			
Gompertz	P1=1, P2=-1	scale, 1st shape			
Gompertz	P1=1, P2=-1	scale, 2nd shape			
Gompertz	P1=1, P2=-0.5	scale, 1st shape			
Gompertz	P1=1, P2=-0.5	scale, 2nd shape			
Gompertz	P1=1, P2=0	scale, 2nd shape			
Weibull	P1=0, P2=-0.5	scale, 1st shape			
Weibull	P1=0, P2=1	scale, 1st shape			
Gompertz	P1=1, P2=0	scale, 1st shape			
Weibull	P1=0, P2=1	scale, 2nd shape			
Weibull	P1=0, P2=-0.5	scale, 2nd shape			
Gompertz	P1=1, P2=0.5	scale, 2nd shape			
Gompertz	P1=1, P2=0.5	scale, 1st shape			
Weibull	P1=0, P2=-1	scale, 1st shape			
Weibull	P1=0, P2=-1	scale, 2nd shape			
Gompertz	P1=1, P2=1	scale, 1st shape			
Gompertz	P1=1, P2=1	scale, 2nd shape			
Gompertz	P1=1	scale, 1st shape			
Weibull	P1=0	scale, 1st shape			

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 24. Results for the time-varying analysis of progression free survival; hazard ratios of PEMBRO + FP/PLT versus comparators

Figure 25. Results for the time-varying analysis of progression free survival; modelled survival curves

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Table 9. Results of the fixed effect fractional polynomial network meta-analysis for progression free survival; presented as hazard ratios over time for PEMBRO + FP/PLT versus comparators

Pembrolizumab + chemotherapy versus	Time-varying HR (95% CrI)										
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months	54 months
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Cells shaded in grey indicate estimates based on model extrapolations; model presented is P1=0, P2=0.5, scale and 2nd shape, fixed effect; All bolded values are statistically significant at the 0.05 significance level; Abbreviations: CrI – credible interval; HR – hazard ratio

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

3. Survival model selection in the CPS≥1 population

Goodness-of-fit statistics using the AIC are provided in Table 10. Generally, the best statistically fitting parametric curve for both outcomes and treatment arms is the log-logistic, followed by the generalised gamma. The best statistically fitting spline curve for each outcome and treatment arm varies.

Figure 26 and Figure 27 overlay the KM data from the LT FU data on the standard parametric curves for OS. Generally, all curves overestimated survival between Years 1 and 3, then underestimated survival thereafter. Figure 28 and Figure 29 overlay the KM data from the LT FU data on the spline curves for OS. The splines models using 2 knots or 3 knots provided a better visual fit to the KM data than the parametric models and were investigated further.

Table 10. Goodness-of-fit statistics for OS and PFS in the CPS≥1 population using LT FU data

Model	OS		PFS	
	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy
Parametric				
Exponential	5556.2	5747.4	4588.2	4493.1
Weibull	5557.9	5734.1	4580.7	4487.8
Log-logistic	**5505.9**	**5689.8**	4466.3	**4379.2**
Lognormal	5523.5	5736.2	4473.3	4408.4
Gompertz	5545.7	5749.3	4506.5	4480.5

Gamma	5555.2	5724.3	4589.4	4471.2
Generalised gamma	5522.5	5711.5	**4462.6**	4409.8
Spline				
1k hazards	5,517.1	5,712.3	4437.4	4400.5
2k hazards	**5,495.3**	5,690.3	4421.2	4360.6
3k hazards	5,497.6	5,675.0	4421.5	4353.2
1k odds	5,507.3	5,683.8	4442.2	4381.2
2k odds	5,495.9	5,679.4	4425.1	4369.0
3k odds	5,498.1	**5,674.8**	4418.4	**4351.0**
1k normal	5,520.6	5,701.1	4461.9	4407.7
2k normal	5,497.2	5,685.6	4424.2	4372.4
3k normal	5,498.7	5,675.9	**4417.5**	4351.6
Lowest AIC values in bold Abbreviations: AIC, Akaike's Information Criterion; CPS, combined positive score; k, knots; LT FU, longer-term follow-up; OS, overall survival; PFS, progression free survival				

Figure 26. OS parametric extrapolations for pembrolizumab plus doublet chemotherapy in the in the CPS≥1 population using LTFU data

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 27. OS parametric extrapolations for doublet chemotherapy in the in the CPS≥1 population using LTFU data

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 28. OS spline extrapolations for pembrolizumab plus doublet chemotherapy in the in the CPS≥1 population using LTFU data

Figure 29. OS spline extrapolations for doublet chemotherapy in the in the CPS≥1 population using LTFU data

The best statistically fitting spline curves are summarised in Table 11. When these curves are chosen, PFS crosses OS in both treatment arms (Figure 30 and Figure 31). Thus, curves involving minimal PFS and OS crossing, with good visual fit and statistical fit, were preferred for the base case analysis. Subsequently, the 3k odds model was chosen for OS in both treatment arms and the 2k hazards model was chosen for PFS in both treatment arms (also summarised in Table 11). For illustrations of the base case curves, see Figure 32 to Figure 35.

Table 11. Preferred extrapolations in the CPS≥1 population using the LT FU data

Outcome	Treatment arm	Best statistical fit according to AIC	Base case
OS	Pembrolizumab	2k hazards	3k odds*
	Chemotherapy	3k odds	3k odds
PFS	Pembrolizumab	3k normal	2k hazards^
	Chemotherapy	3k odds	2k hazards^

*A difference in the AIC of less than 3 is considered negligible: 5,495.3 for 2k hazards versus 5,498.1 for 3k odds; curves of the same type are preferred for both treatment arms when possible

^3k spline models result in more OS crossing than the 2k and 1k spline models. The 2k hazards model had the best statistical fit of 2k and 1k splines in both treatment arms

Abbreviations: AIC, Akaike's Information Criterion; CPS, combined positive score; LT FU, longer-term follow-up; OS, overall survival; PFS, progression free survival

Figure 30. Best statistically fitting spline curves for pembrolizumab plus doublet chemotherapy in the in the CPS≥1 population using LTFU data

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 31. Best statistically fitting spline curves for doublet chemotherapy in the in the CPS≥1 population using LTFU data

Figure 32. Base case curves for pembrolizumab plus doublet chemotherapy in the CPS≥1 population using LTFU data

Figure 33. Base case curves for doublet chemotherapy in the CPS≥1 population using LTFU data

Figure 34. Base case OS curves in the CPS≥1 population using LTFU data

Figure 35. Base case PFS curves in the CPS≥1 population using LTFU data

4. **Survival model selection in the CPS≥5 population**

According to the NMA model selection process, described in Section 2, the best fitting OS model was the first-order fractional polynomial (FP) (P1=1, P2=0.5, scale and 2nd shape). This model is used to inform the base case analysis in the CPS≥5 population. The second and third best fitting FP curves for OS are also included as options in the economic model (these curves can be selected in the "FP NMA" worksheet).

The resulting OS curves for pembrolizumab with doublet chemotherapy and nivolumab plus doublet chemotherapy, without adjustments for general population mortality, are illustrated in Figure 36. After approximately [redacted] in the economic model, these survival curves are capped to ensure that the conditional probability of survival does not exceed that of the general population in any model cycle. Following this adjustment, survival in the economic model continues to fall (Figure 37).

As immunotherapies act on the patient's immune system rather than directly on the tumour, the immune system will continue to recognise the cancer cells after treatment is stopped, which leads to durable responses and prolonged survival in some patients. Thus, a plateau in the survival curves and mortality comparable to general population mortality in some patients is plausible (Figure 36, Figure *37*). In the control arms of the KEYNOTE-859 and CheckMate 649 trials, some patients received immunotherapies as a subsequent treatment, which would explain the plateau in the survival curve for chemotherapy. Subsequent treatment data are reported among all randomised subjects (ITT population) for CheckMate 649; in the control arm 8.1% (2) of patients received a subsequent immunotherapy. This is similar to the proportion in KEYNOTE-859 (9.1% of patients in the control arm of the ITT population received a subsequent immunotherapy) (1).

MSD acknowledges the [redacted] and therefore provides cost-effectiveness results deterministically and probabilistically.

Figure 36. OS curves resulting from the best fitting FP model

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 37. OS extrapolations in the CPS≥5 population adjusted for general population mortality

According to the Schoenfeld residuals tests, PH may hold for PFS (P>0.05, Figure 17 and Figure 21). According to the log-cumulative hazard plot (Figure 18 and Figure 22) and smoothed hazard plot (Figure 19 and Figure 23), PH may not hold for PFS as the curves in the hazard plot separate after a few months and the smoothed hazard curves cross. Additionally, the PH tests are underpowered to detect violations as the null hypothesis is that PH holds. For these reasons, and for consistency with the OS approach, the best fitting FP model, the second-order FP (P1=0, P2=0.5, scale and 2nd shape) is used to inform PFS in the base case analysis.

A scenario analysis using a single-HR approach is also provided. When the single-hazard ratio approach is taken for PFS, the HR for nivolumab plus doublet chemotherapy versus pembrolizumab plus doublet chemotherapy estimated from the NMA ([redacted]) is applied to the pembrolizumab plus doublet chemotherapy PFS curve to estimate the PFS curve for nivolumab plus doublet chemotherapy. As the HR is [redacted], the PFS curves for nivolumab plus doublet chemotherapy and pembrolizumab plus doublet chemotherapy will be [redacted].

Goodness-of-fit statistics (AIC) for each PFS model are provided in Table 12. The best statistically fitting parametric curve is the generalised gamma. Figure 38 overlays the KM LT FU data on the parametric curves for PFS. The only parametric model which provides a good visual fit to the end of the KM data is the Gompertz. The best statistically fitting spline curve is the 3k normal, this model also provides the best visual fit to the KM data (Figure 39).

The 3k normal has a better visual fit to the KM data between Years 1 and 2 than the Gompertz and is the most conservative option of the two (Figure 40 and Figure 41). When the 3k normal PFS curve is compared to the OS curve, the PFS and OS curves appear to converge towards

Month 48 then diverge slightly thereafter (Figure 41). This does not occur when the PFS curve is informed by the best fitting FP NMA model (Figure 42) and further supports the base case approach

Table 12. Goodness-of-fit statistics for PFS in the CPS≥*5* population using LT FU data

Model	Pembrolizumab plus doublet chemotherapy
Parametric	
Exponential	2798.2
Weibull	2788.8
Log-logistic	2719.5
Lognormal	2718.9
Gompertz	2732.8
Gamma	2797.4
Generalised gamma	**2703.6**
Spline	
1k hazards	2688.4
2k hazards	2684.0
3k hazards	2684.5
1k odds	2692.9
2k odds	2686.2
3k odds	2683.7
1k normal	2701.5
2k normal	2684.4
3k normal	**2682.3**

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Lowest AIC values in bold
Abbreviations: AIC, Akaike's Information Criterion; CPS, combined positive score; k, knots; LT FU, longer-term follow-up; PFS, progression free survival

Figure 38. PFS parametric extrapolations for pembrolizumab plus doublet chemotherapy in the in the CPS≥5 population using LTFU data

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Figure 39. PFS spline extrapolations for pembrolizumab plus doublet chemotherapy in the CPS≥5 population using LTFU data

Figure 40. Extrapolations for pembrolizumab plus doublet chemotherapy in the CPS≥5 population using LTFU data (PFS: Gompertz)

Figure 41. Extrapolations for pembrolizumab plus doublet chemotherapy in the CPS≥5 population using LTFU data (PFS: 3k normal)

Figure 42. Best fitting FP extrapolations for pembrolizumab plus doublet chemotherapy in the CPS≥5 population using LTFU data

5. Revised base case results

MSD presents revised cost-effectiveness results in the CPS≥1 population incorporating the following changes:

- In response to DG consultation document, Section 3.3, longer-term follow-up data is used to inform OS, PFS and ToT

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

- In response to DG consultation document, Section 3.7, a gradual treatment waning effect 5 years following discontinuation of pembrolizumab (7 years since treatment initiation) is applied to [redacted] of patients

- In response to DG consultation document, Section 3.10, a severity weighting of 1.2 is applied to QALYs.

MSD's revised base case results are presented in Table 13, alongside previous base case results. Probabilistic results are presented in Table 14. Cost-effectiveness results exploring different treatment waning assumptions are presented in Table 15.

Table 13. Base case results in the CPS≥1 population (including the pembrolizumab CAA price).

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Original company base case (including corrections at the clarification stage and a severity modifier of 1.7)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (including a severity modifier of 1.2)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case in response to the DG consultation document (including a severity modifier of 1.2)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*QALYs excluding a severity modifier of reported in brackets. Abbreviations: CAA, commercial access agreement; CPS, combined positive score; DG, draft guidance; EAG, Evidence Assessment Group; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Table 14. Probabilistic base case results in the CPS≥1 population (including the pembrolizumab CAA price)

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Revised company base case in response to the DG consultation document (including a severity modifier of 1.2)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*QALYs including a severity modifier of 1.2. Abbreviations: CAA, commercial access agreement; CPS, combined positive score; DG, draft guidance; EAG, Evidence Assessment Group; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years. Note: results based on 2,000 simulations.							

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Table 15. Cost-effectiveness results in the CPS≥1 population, varying treatment waning assumptions (including the pembrolizumab CAA price)

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Treatment waning effect 7 years after starting treatment (revised base case)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning effect 6 years after starting treatment (scenario analysis)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment waning effect 5 years after starting treatment (scenario analysis)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*QALYs excluding a severity modifier of reported in brackets.

Abbreviations: CAA, commercial access agreement; CPS, combined positive score; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

MSD presents cost-effectiveness results in the CPS≥5 population incorporating the following:

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

- In response to DG consultation document, Section 3.3, longer-term follow-up data is used to inform OS, PFS and ToT
- In response to DG consultation document, Section 3.4, time-varying HRs are used to estimate OS because proportional hazards do not hold in the network.

MSD's results are presented in Table 16. This is the first time cost-effectiveness results have been provided in the CPS≥5 population. Results of a scenario using a single-HR approach for PFS (3k normal spline model) are presented in Table 17.

Table 16. Cost-effectiveness results in the CPS≥5 population (including list prices)

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Including a severity modifier of 1.0

Abbreviations: CPS, combined positive score; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic							
Note: probabilistic results based on 5,000 simulations.							

Table 17. Cost-effectiveness results in the CPS≥5 population using a single-HR approach for PFS (including list prices)

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
* Including a severity modifier of 1.0 Abbreviations: CPS, combined positive score; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

6. Cost-minimisation

Cost-minimisation results are provided in the CPS≥5 population over 30 years (equivalent to a lifetime time horizon) and 2 years (in clinical practice, immunotherapy treatment is usually given for a maximum of 35 treatment cycles [Q3W x 35 = 105 weeks] or a maximum duration of 2 years [104 weeks]).

To achieve a cost-minimisation, the QALYs are made equal in both treatment arms ([redacted]) by assuming the treatments have the same PFS, OS and adverse event incidence. The pembrolizumab arm is used to inform the nivolumab arm. All unit costs in the cost-minimisation reflect those in the initial CS.

ToT data was recorded in the KEYNOTE-859 trial for all drug components separately and the longer-term follow-up data is mature. Thus, KM data is directly used in the economic model to inform study treatment costs for all treatments without parametric extrapolation. Additionally, doublet chemotherapy treatment is capped at 6 treatment cycles. These approaches to model ToT were also employed in the initial CS, except the most recent data cut is used here.

Results of the cost-minimisation are reported in Table 18. These results do not represent the true cost to the NHS as they are based on list prices; patient access scheme discounts are in place for pembrolizumab and nivolumab and the discount for nivolumab is unknown to MSD.

Table 18. Cost-minimisation results in the CPS≥5 population (including list prices)

Treatment	Acquisition	Administration *	Disease management	Adverse events	Progression	Subsequent treatment	End of life	Total costs
30-year time horizon (discounted at 3.5% per year)								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year time horizon (undiscounted)								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Administration costs differ as the backbone chemotherapy was taken from KEYNOTE-859 for pembrolizumab and from CheckMate 649 for nivolumab, and different chemotherapies have different infusion times and administration costs								

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Tuesday 26 March 2024. Please submit via NICE Docs.

References:

1. European Medicines Agency (EMA) CfMPfHUC. EMA/506795/2023 Committee for Medicinal Products for Human Use (CHMP) Assessment report 2023 [Available from: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0135-epar-assessment-report-variation_en.pdf.
2. European Medicines Agency (EMA). EMA/556100/2021 Committee for Medicinal Products for Human Use (CHMP) Assessment report, OPDIVO International non-proprietary name: nivolumab Procedure No. MEA/H/C/003985/II/0096. 16 September 2021 16 September 2021.

Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]

April 2024

MDS identified a programming error where the ratio of nivolumab Q2W:Q3W was being double counted when it came to calculating administration costs. As a result, the administration costs associated with nivolumab in MSD's ACD response were underestimated (reproduced in Table 1 and Table 2). Corrected results are provided

Table 3 and Table 4.

Table 1. Cost-effectiveness results in the CPS≥5 population (including list prices) – ACD response

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic (5,000 simulations)							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Including a severity modifier of 1.0

Abbreviations: CPS, combined positive score; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 2. Cost-minimisation results in the CPS≥5 population (including list prices) – ACD response

Treatment	Acquisition	Administration	Disease management	Adverse events	Progression	Subsequent treatment	End of life	Total costs
30-year time horizon (discounted at 3.5% per year)								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year time horizon (undiscounted)								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3. Cost-effectiveness results in the CPS≥5 population (including list prices) – corrected

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Deterministic							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probabilistic (5,000 simulations)							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Including a severity modifier of 1.0

Abbreviations: CPS, combined positive score; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 4. Cost-minimisation results in the CPS≥5 population (including list prices) – corrected

Treatment	Acquisition	Administration	Disease management	Adverse events	Progression	Subsequent treatment	End of life	Total costs
30-year time horizon (discounted at 3.5% per year)								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year time horizon (undiscounted)								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Response to the

Appraisal Consultation Document

Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma

ID4030

Bristol-Myers Squibb Pharmaceuticals

March 2023

Contents

1. Has all the relevant evidence been taken into account?

BMS do not believe that all relevant evidence has been taken into account, as no analysis has been provided demonstrating a comparison of pembrolizumab versus chemotherapy in patients with PD-L1 CPS ≥1 and <5.

Pembrolizumab versus chemotherapy in PD-L1 CPS ≥1 and <5

The appraisal consultation document (ACD)[1] states that:

- Nivolumab plus doublet chemotherapy is the comparator for people whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more.
- Doublet chemotherapy would be the relevant comparator for people whose tumours express PD-L1 with a CPS between 1 and 4, because in clinical practice these people do not currently have access to immunotherapy.

BMS agrees with this conclusion from the committee. The inference from this conclusion is that the population of interest for a comparison of pembrolizumab with doublet chemotherapy should be considered to be patients whose tumours express PD-L1 CPS ≥1 and <5.

Despite this, all analyses provided in the company submission and EAG report reflect a comparison of pembrolizumab against doublet chemotherapy in patients whose tumours express PD-L1 CPS ≥1.[2] This comparison includes patients with tumours expressing PD-L1 CPS ≥5 (i.e. patients likely to experience additional benefit from immuno-oncology therapies), where the primary comparator would be nivolumab plus doublet chemotherapy. Given that PD-L1 CPS indicates the potential benefit of pembrolizumab treatment, analyses including patients whose tumours express PD-L1 CPS ≥5 may overestimate the comparative effectiveness of pembrolizumab over chemotherapy.

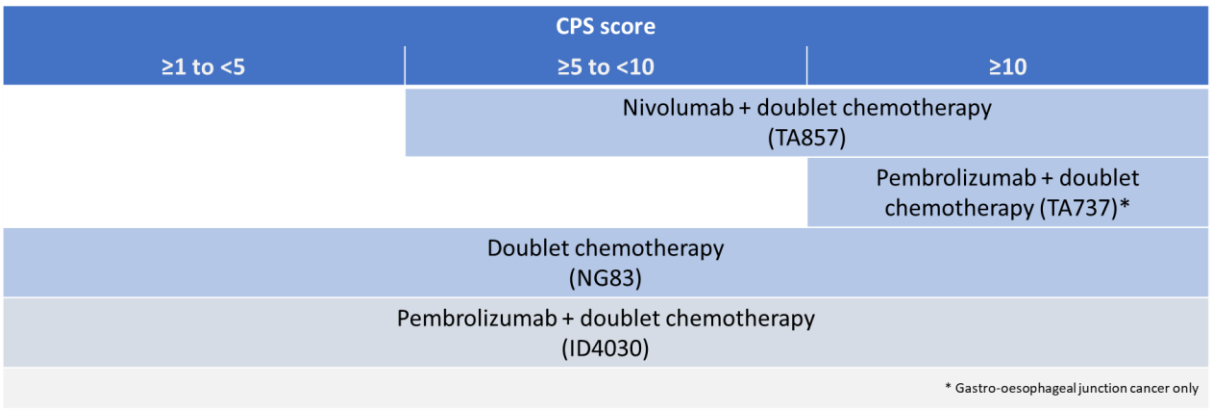

Figure 1. First-line treatment options for patients with HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma

There is significant similarity between TA865 and the current appraisal, primarily that only a subset of the population would be considered suitable for chemotherapy alone. During TA865 (Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma)[3], the EAG concluded that pembrolizumab should be a comparator for the PD-L1 tumour cell (TC) ≥1% and CPS ≥10 population and requested that a separate analysis for nivolumab versus chemotherapy should be conducted for the PD-L1 TC ≥1% and CPS <10 population.[4] This analysis was provided at technical engagement and demonstrated that survival outcomes were impacted in this subgroup analysis but the comparison remained cost-effective at a willingness to pay threshold of £30,000/QALY.[4]

This subgroup analysis remains highly relevant to the decision problem, particularly as it has the potential to be more impactful for KEYNOTE-859 and the comparison of pembrolizumab plus doublet chemotherapy versus doublet chemotherapy alone. Figure 2 provides a subgroup analysis of CheckMate 649, which included a similar patient group to KEYNOTE-859 where key differences were that CheckMate 649 also included people with unknown HER2 status and oesophageal adenocarcinoma; however, it is not anticipated that this would impact on comparative outcomes based on subgroup analyses.[5] Within the doublet chemotherapy arm, survival outcomes remained relatively similar when stratified by CPS. However, outcomes in the nivolumab plus chemotherapy arm were more impacted by CPS stratification, particularly in the PD-L1 CPS ≥1 (overall survival HR 0·77 [99·3% CI 0·64–0·92]; p<0·0001) and <5 subgroup (overall survival HR 0·94 [95% CI 0·78–1·13];

p=0·0107).[5] As can be seen in Figure 3 (CPS ≥1 and <5) and Figure 4 (CPS ≥1), a similar impact was observed in the KEYNOTE-859 trial, which is likely to impact on cost-effectiveness of pembrolizumab. Therefore, conclusions on the cost-effectiveness of pembrolizumab should be assessed considering separate subgroups (specifically CPS ≥1 and <5) to address uncertainty.

Figure 2. CheckMate 649 overall survival stratified by CPS subgroup[6]

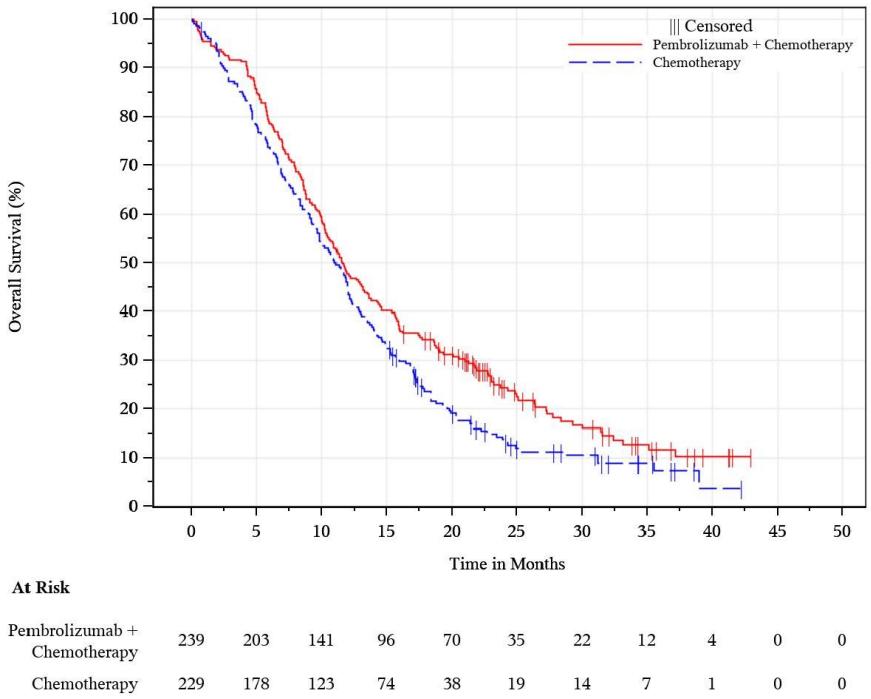

Figure 3. KEYNOTE-859 overall survival CPS ≥1 to <5[7]

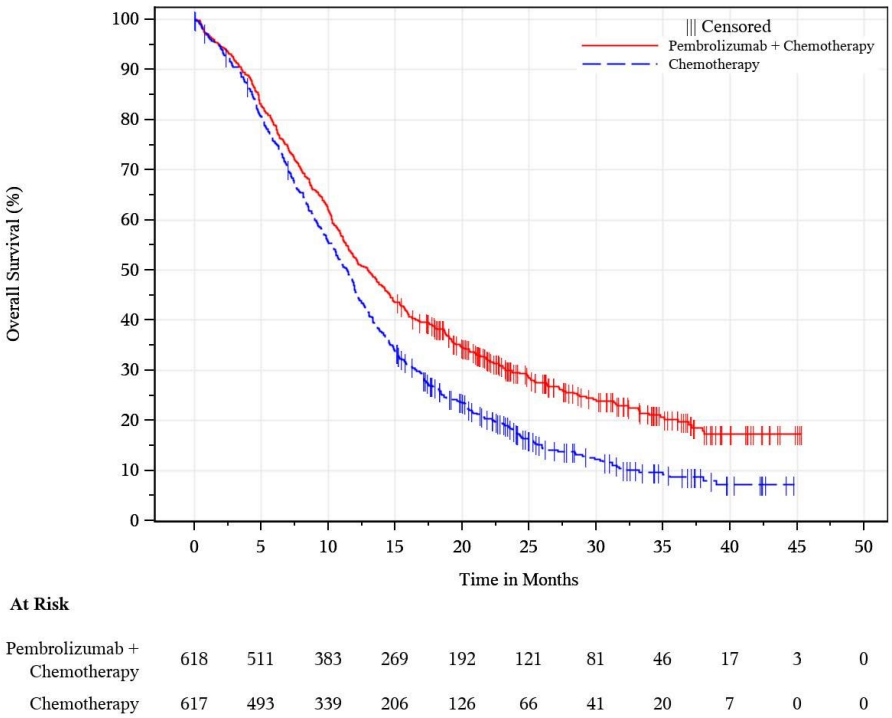

Figure 4. KEYNOTE-859 overall survival CPS ≥1[7]

2. Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

BMS disagrees with two key interpretations of the evidence:

- Use of KEYNOTE-859 PD-L1 CPS≥10 data to inform the comparison of nivolumab versus pembrolizumab in the PD-L1 CPS≥5 population.
- Application of treatment waning starting at 5 years or 7 years.

Use of CPS≥10 data to inform a cost-effectiveness analysis of the CPS≥5 subgroup

BMS agree with the concerns expressed by the committee and the EAG pertaining to the ITC included within the company submission,[1,2] although BMS has not had opportunity to fully assess the ITC and provide critique, particularly in the PD-L1 CPS ≥5 subgroup. Further, BMS agrees with the conclusion from the committee that pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy are similarly effective at treating HER2-negative advanced gastric or GOJ adenocarcinoma in people whose tumours express PD-L1 with a CPS of 5 or more.[1]

However, it is not appropriate to use data from the PD-L1 CPS ≥10 subgroup as a proxy to inform the PD-L1 CPS ≥5 subgroup, as used within the company submission and EAG base case analysis.[2] Although the relative effectiveness measures for nivolumab versus pembrolizumab may be comparable between these subgroups, absolute outcomes will vary substantially for immunotherapies between the PD-L1 CPS ≥10 subgroup and the PD-L1 CPS ≥5 subgroup. This is illustrated in Table 1, where it is demonstrated that median overall survival (OS) is 15.7 months in the pembrolizumab PD-L1 CPS ≥10 subgroup and 14.0 months in the PD-L1 CPS ≥5 subgroup, while remaining relatively similar in the chemotherapy arm (11.8 months and 11.5 months respectively).[7] Further, Figure 5 and Figure 6 demonstrate how these differences in the hazard profile evolve over time and vary between the

CPS subgroups for overall survival. Similarly, disparities in progression-free survival outcomes are observed between CPS subgroups.

As a result, cost-effectiveness outcomes in one CPS subgroup may not be reflective of outcomes in another CPS subgroup. Modelled patients may spend more time within the pre-progressed state in one CPS subgroup or may spend more time on treatment, impacting on accrual of costs and utilities.

Hence, the company base case analysis in the PD-L1 CPS ≥10 subgroup should be considered to reflect the PD-L1 CPS ≥10 subgroup only. Further, BMS advocate that if further cost-effectiveness analyses using the CPS ≥5 subgroup are not undertaken, the company submission should be considered to reflect a restricted population of the overall nivolumab-eligible patient group.

Table 1. KEYNOTE-859 overall survival by CPS subgroup[7]

	PD-L1 CPS ≥5		PD-L1 CPS ≥10	
	Pembro +chemo	**Chemo**	**Pembro +chemo**	**Chemo**
N	379	388	279	272
Number of events (%)	269 (71.0)	325 (83.8)	188 (67.4)	226 (83.1)
Median OS (95% CI), months	14.0 (12.1, 15.4)	11.5 (10.3, 12.5)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
HR (95% CI)	0.70 (0.60, 0.82)		0.65 (0.53, 0.79)	
p-Value	<0.0001		<0.0001	

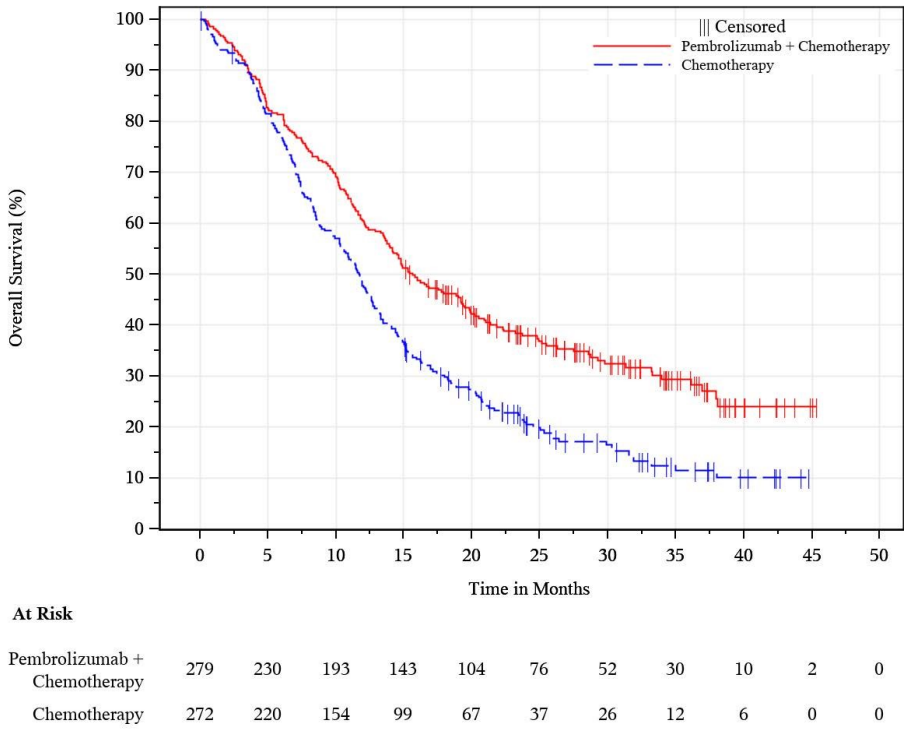

Figure 5. KEYNOTE-859 overall survival CPS ≥10[7]

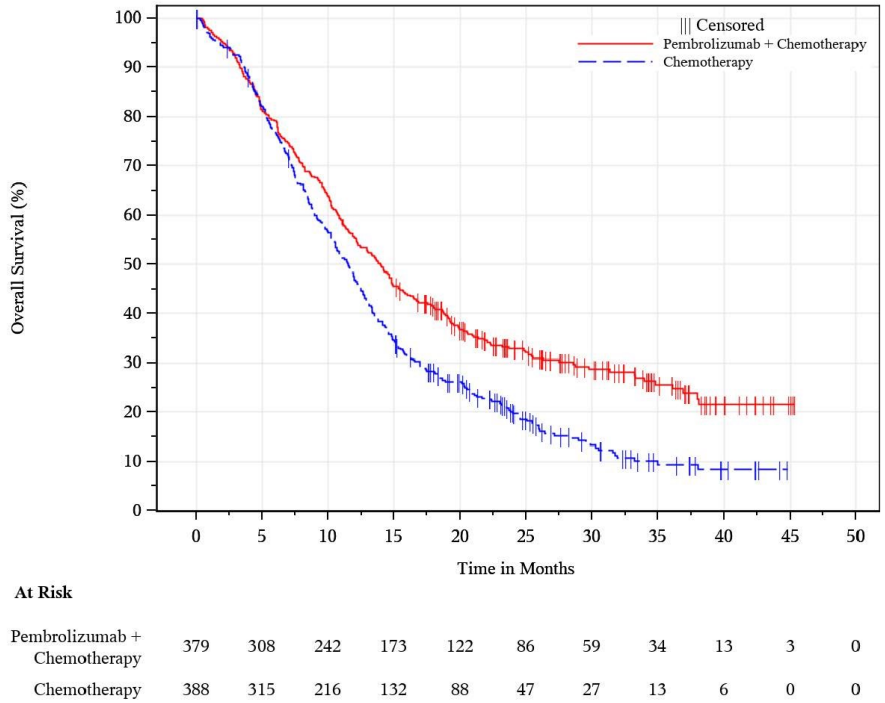

Figure 6. KEYNOTE-859 overall survival CPS ≥5[7]

Treatment waning

The appraisal consultation document notes:[1]

- Available clinical trial follow-up data for pembrolizumab is for less than 5 years.
- The company provided a scenario that applied gradual treatment effect waning 7 years after starting pembrolizumab plus doublet chemotherapy, that reduced to the same as the comparator arm over the next 2 years.
- The EAG preferred to apply gradual treatment effect waning 5 years after starting treatment that reduced to the same as the comparator arm over the next 2 years.

Based on this evidence, the committee preferred the model to include gradual treatment effect waning that reduces to the same as the comparator arm over 2 years and, in the absence of data to demonstrate otherwise, the committee agreed it was plausible that this may start 5 or 7 years after starting treatment.[1]

However, this recommendation is not based on a consideration of the plausibility of long-term outcomes. By contrast, within TA857[8], the committee considered the ICERs resulting from scenarios with 5- or 6.5-year treatment waning assumptions, applied as an immediate switch to chemotherapy mortality hazard, were potentially plausible but were still uncertain.[9] As a result, NICE decision making required scenarios reflecting both assumptions and reflecting the degree of uncertainty,[9] so that an ICER well below £50,000 per QALY was needed to be considered cost-effective.[10]

Therefore, BMS advocates that future analyses for this appraisal reflect treatment waning at five years. In the absence of evidence to the contrary, this would enable transparency and comparability between appraisals.

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

BMS has highlighted several issues that should be assessed in order to provide fully considered guidance to the NICE.

However, BMS agree with the committee conclusion that pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy were similarly effective and tolerated. This aligns with the view of the clinical experts at the appraisal committee meeting, that nivolumab and pembrolizumab have comparable efficacy and tolerability. Further, this is supported by the ITCs contained within the company submission, which demonstrated that there is no statistically significant benefit between nivolumab and pembrolizumab.

Further, BMS note that the committee agreed that current NICE methods for health technology evaluation should be followed, concluding that the severity modifier should be applied over end-of-life criteria.[1] BMS agree with the committee decision and highlight that this is made clear within the NICE health technology evaluations manual.[11] As such, use of end-of-life criteria for the current appraisal would be inappropriate and could encourage use in future appraisals.

4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Impact of testing availability

Although use of nivolumab and pembrolizumab are both dependent on CPS testing, these therapies require a validated test which could be either the Dako PD-L1 IHC 28-8 pharmDx assay or the Dako PD-L1 IHC 22C3 pharmDx assay. As noted by clinical experts during the appraisal committee meeting, PD-L1 testing capabilities

vary between treatment centres and while some centres are able to undertake both CPS tests, many have access to only one assay. The experts stated that comparing pembrolizumab with nivolumab across CPS subgroups can be difficult because of different PD-L1 testing methods used in clinical practice. Further, there is a lack of robust concordance data that would allow a meaningful comparison of outputs from the two tests. While the KEYNOTE-859 and CHECKMATE-649 trials used the two respective tests, NICE guidance recommends that any validated test may be used; however, there remains a large amount of uncertainty regarding CPS testing pathways and variability in choice of assay across the country due to resource limitations, lack of awareness and different clinical opinions. Several clinical experts contacted by BMS are able to use either test to initiate use of nivolumab or pembrolizumab. However, BMS are aware that clinicians and treatment centres may require that pembrolizumab and nivolumab initiation requires the test used during clinical trial, which may restrict access to effective therapies due to testing limitations.

In centres where both assays are available, there are limitations around testing that can be undertaken. Clinical experts at the appraisal committee meeting noted that clinicians would ideally prefer to undertake parallel testing using both tests to streamline access to the preferred immunotherapy. However, many NHS trusts advise against parallel testing due to burden on pathology departments. Sequential testing could delay treatment initiation in a patient group, which is especially important in this population with advanced disease since any delay in initiating treatment may impact their long-term outcomes.

As a result, if NICE subsequently recommends use of pembrolizumab, BMS advocates that any recommendation supports this complex testing setting, emphasising clinician judgement and enabling swift access to immunotherapies for as many patients as possible. BMS would further suggest recommendation wording that reflects that access to nivolumab and pembrolizumab may be impacted by clinical judgement, test availability and/or timing to facilitate optimal patient outcomes.

Unmet need for patients diagnosed with advanced cancer

BMS agree with the committee conclusions that symptoms of gastric or GOJ cancer can have a considerable impact on quality of life and that life expectancy with the condition is poor. The committee also noted that this may particularly be the case for younger adults who tend to be diagnosed when their cancer is more advanced. These patients diagnosed when their cancer is more advanced have will fewer effective treatment options, which significantly impact their prognosis and long-term outcomes.

5. References

1. National Institute for Health and Care Excellence. Draft guidance consultation – Pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma. 2024.
2. National Institute for Health and Care Excellence. Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]. Committee Papers. 2024.
3. National Institute for Health and Care Excellence. TA865. Nivolumab with fluoropyrimidine- and platinum-based chemotherapy for untreated unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma. 2023. Available from: www.nice.org.uk/guidance/ta865 [accessed 18/03/2024].
4. National Institute for Health and Care Excellence. TA865. Nivolumab in combination for untreated advanced unresectable recurrent or metastatic oesophageal squamous cell carcinoma cancer. Committee Papers 2022. Available from: www.nice.org.uk/guidance/ta865/documents/committee-papers [accessed 18/03/2024].
5. European Medicines Agency. Assessment report. Opdivo. Procedure No. EMEA/H/C/003985/II/0096 2021. Available from: https://www.ema.europa.eu/en/documents/variation-report/opdivo-h-c-003985-ii-0096-epar-assessment-report-variation_en.pdf [accessed 26/03/2024].
6. Bristol-Myers Squibb Pharmaceuticals. CheckMate 649 data on file. 2024.
7. European Medicines Agency. Assessment report. Keytruda. Procedure No. EMEA/H/C/003820/II/0135 2023. Available from: https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0135-epar-assessment-report-variation_en.pdf [accessed 18/03/2024].
8. National Institute for Health and Care Excellence. TA857. Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. 2023. Available from: www.nice.org.uk/guidance/ta857.
9. National Institute for Health and Care Excellence. Final appraisal document. Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma 2022. Available from: www.nice.org.uk/guidance/ta857/documents/final-appraisal-determination-document [accessed 18/03/2024].
10. National Institute for Health and Care Excellence. Pembrolizumab with chemotherapy for treating HER2-negative advanced gastric or gastro-oesophageal junction adenocarcinoma [ID4030]. Committee slides. 2024.
11. National Institute for Health and Care Excellence. NICE process and methods [PMG36]. NICE health technology evaluations: the manual. 2023. Available from: www.nice.org.uk/process/pmg36/ [accessed 18/03/2024].

Pembrolizumab with chemotherapy for treating HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma
ID4030

cPAS results for MSD response to DG

KSR – Maiwenn Al

Results and scenarios CPS≥1

MSD has presented revised cost-effectiveness results in the CPS≥1 population incorporating the following changes:

- In response to DG consultation document, Section 3.3, longer-term follow-up data is used to inform OS, PFS and ToT
- In response to DG consultation document, Section 3.7, a gradual treatment waning effect 5 years following discontinuation of pembrolizumab (7 years since treatment initiation) is applied to [redacted] of patients
- In response to DG consultation document, Section 3.10, a severity weighting of 1.2 is applied to QALYs.

MSD's revised base case results are presented in Table 1, alongside previous base case results and the results when applying cPAS prices to the MSD revised base case.
[redacted] (see company response Table 14 and 15).

It can be seen that, based on the long term follow-up data now included, a higher gain in life years and QALYs is expected. The company's scenario analyses on time of start of treatment waning show that the impact of assuming the waning starts at 5 versus 7 years from treatment initiation is quite minimal.

Table 1 Base case results in the CPS≥1 population (including the pembrolizumab CAA price).

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Original company base case (including corrections at the clarification stage and a severity modifier of 1.7)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case (including a severity modifier of 1.2)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised company base case in response to the DG consultation document (including a severity modifier of 1.2)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Revised company base case in response to the DG consultation document (including a severity modifier of 1.2), using confidential prices where applicable for all drugs in the model							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*QALYs excluding a severity modifier reported in brackets. Abbreviations: CAA, commercial access agreement; CPS, combined positive score; DG, draft guidance; EAG, Evidence Assessment Group; ICER, incremental cost effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.							

Additional scenarios EAG

The EAG explored a few extra scenarios, similar to those explored for the original submission. The two most relevant alternatives to the 3-knot odds spline that was used for the base case are the 3-knot hazard and the 2-knot hazard spline. Table 1.2 shows the results with list prices, [redacted] When comparing the company scenarios for treatment waning to the additional EAG scenarios, it is clear that the impact of assuming waning only for patients without a complete response is very small.

Table 2 EAG scenarios in the CPS≥1 population

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Revised company base case in response to the DG consultation document (including a severity modifier of 1.2)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 knot hazard spline for OS							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 knot hazard spline for OS							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No treatment waning							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
100% waning at 7 years							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
100% waning at 5 years							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*QALYs excluding a severity modifier reported in brackets.
Abbreviations: CPS, combined positive score; DG, draft guidance; ICER, incremental cost effectiveness ratio; LYG, life years gained; OS = Overall survival; QALYs, quality-adjusted life years.

Results and scenarios CPS≥5

MSD has further presented cost-effectiveness results in the CPS≥5 population incorporating the following:

- In response to DG consultation document, Section 3.3, longer-term follow-up data is used to inform OS, PFS and ToT
- In response to DG consultation document, Section 3.4, time-varying HRs are used to estimate OS because proportional hazards do not hold in the network.

MSD's results are presented in Table 1.3. This is the first time cost-effectiveness results have been provided in the CPS≥5 population, in the previous reports the comparison of pembrolizumab versus nivolumab was made for the CPS≥10 population.

The company considered various functional forms for the hazards in the treatment groups, and the model with the best goodness-of-fit was selected as base case. In Table 5 the EAG also presents the cost-effectiveness results if the second or third best fit are applied instead.

Results of a scenario using a single-HR approach for PFS (3k normal spline model) are presented in Table 3, showing that the impact of using a fixed HR or a time-dependent HR for PFS is minimal.

Table 3. Cost-effectiveness results in the CPS≥5 population

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company base case, using list prices							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case with confidential prices							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* Including a severity modifier of 1.0
Abbreviations: CPS = combined positive score; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.

Table 4. Cost-effectiveness results (CPS≥5) using a single-HR approach for PFS

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company scenario single HR, using list prices							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company scenario single HR with confidential prices							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
* Including a severity modifier of 1.0 Abbreviations: CPS = combined positive score; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.							

Table 5 Cost-effectiveness results (CPS≥5) using various fractional polynomial functions for the HR

Treatment	Total Costs	Total LYG	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Company base case with confidential prices							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario second best fit time-dependent hazard ratios							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario third best fit time-dependent hazard ratios							
Nivolumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
* Including a severity modifier of 1.0 Abbreviations: CPS = combined positive score; ICER = incremental cost effectiveness ratio; LYG = life years gained; HR = hazard ratio; QALYs = quality-adjusted life years.							

Cost-minimisation

Cost-minimisation results were provided in the CPS≥5 population over a time horizon of 30 years (equivalent to a lifetime time horizon) and 2 years (in clinical practice, immunotherapy treatment is usually given for a maximum of 35 treatment cycles [Q3W x 35 = 105 weeks] or a maximum duration of 2 years [104 weeks]).

To achieve a cost-minimisation, the QALYs were made equal in both treatment arms ([redacted]) by assuming the treatments have the same PFS, OS and adverse event incidence. The pembrolizumab

arm was used to inform the nivolumab arm. All unit costs in the cost-minimisation reflect those in the initial CS.

ToT data was recorded in the KEYNOTE-859 trial for all drug components separately and the longer-term follow-up data is mature. Thus, KM data was directly used in the economic model to inform study treatment costs for all treatments without parametric extrapolation. Additionally, doublet chemotherapy treatment was capped at 6 treatment cycles. These approaches to model ToT were also employed in the initial CS, except the most recent data cut is used here.

Results of the cost-minimisation are reported in Table 6, both based on list prices for nivolumab and pembrolizumab and on confidential discounts (cPAS).

Table 6. Cost-minimisation results in the CPS≥5 population

Treatment	Acquisition	Administration*	Disease management	Adverse events	Progression	Subsequent treatment	End of life	Total costs
30-year time horizon (discounted at 3.5% per year) with list prices								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30-year time horizon (discounted at 3.5% per year) with confidential prices								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year time horizon (undiscounted) with list prices								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-year time horizon (undiscounted) with confidential prices								
Pembrolizumab plus doublet chemotherapy (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab plus doublet chemotherapy (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental costs (1-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*Administration costs differ as the backbone chemotherapy was taken from KEYNOTE-859 for pembrolizumab and from CheckMate 649 for nivolumab, and different chemotherapies have different infusion times and administration costs								

Network meta-analyses using time-varying hazard ratios

EAG comments:
Previously, the EAG pointed out the issue in the company submission: the rejection of the proportional hazards assumption for overall survival (OS) in patients with PD-L1 CPS ≥5 in the KEYNOTE-859 trial was inconsistent with the approach used by the company for the base-case analysis of network meta-analysis (NMA) where constant hazard ratios were presented. The company agreed with EAG that using time-varying hazard ratios would have been more appropriate.

Therefore, the company has addressed this issue. The company has now conducted the updated network meta-analysis (NMA) for OS data in the PD-L1 CPS≥5 population by using the time varying NMA approach (fractional polynomial NMA approach), because there was evidence to reject proportional hazards assumption for OS in the PD-L1 CPS≥5 population of the KEYNOTE-859 trial.

Due to the rejection of the proportional hazards assumption for OS in patients with PD-L1 CPS ≥5 of the KEYNOTE-859 trial, the EAG considered the time-varying NMA analysis approach to be appropriate for OS in the PD-L1 CPS≥5 population. The updated NMA results for the PD-L1 CPS≥5 population were based on longer-term follow-up data from the KEYNOTE-859 trial.

The updated NMA results using time-varying hazard ratios showed that there were no statistically significant differences in OS between patients receiving pembrolizumab with chemotherapy and those patients receiving nivolumab with chemotherapy among patients with PD-L1 CPS ≥5 across all time points (between [redacted] months and [redacted] months).