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

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Contents:

The following documents are made available to stakeholders:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission summary** from MSD
   a. **Company summary of information for patients (SIP)**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Together OG Support Group*

4. **Expert personal perspectives** from
   a. Ceri Steele, patient advocate – patient expert, nominated by OG Support
   b. Dave Chuter, support group chair - patient expert, nominated by OG Support (*see item 3a)

5. **External Assessment Report** prepared by KSR Ltd.

6. **External Assessment Report – factual accuracy check**

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

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

Document B

Company evidence submission

September 2023

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ID4030 MSD submission document B [REDACTED]	V3	No	19/01/2024

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Tables and figures

Tables

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Abbreviations

Abbreviation/acronym	Definition
AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike information criterion
APaT	All participants as treated
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BSA	Body surface area
CAA	Commercial access agreement
CAPOX	Capecitabine and oxaliplatin
CC	Complications and comorbidities
CG	Clinical guideline
CI	Confidence interval
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CPS	Combined positive score
CR	Complete response
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
DCO	Data cut-off
DOR	Duration of response
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic market information tool
EOL	End of life
ESMO	European Society for Medical Oncology
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FP	Cisplatin and 5-fluorouracil
GC	Gastric cancer
GHS	Global health status
GOJ	Gastroesophageal junction
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IO	Immunotherapy
ITT	Intention-to-treat

IV	Intravenous
KM	Kaplan Meier
LY	Life year
MSD	Merck Sharp & Dohme Corp., Whitehouse Station, NJ, USA
MSI	Microsatellite instability
MUGA	Multiple-gated acquisition
NA	Not applicable
NHB	Net health benefit
NHSCII	NHS Cost Inflation Index
NMA	Network meta-analysis
NMB	Net monetary benefit
ONS	Office National Statistics
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PD	Progressive Disease
PD-L1	programmed cell death ligand 1
PF	Progression free
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcome(s)
PSA	Probabilistic sensitivity analysis
PSS	Personal and social services
PSSRU	Personal social services research unit
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality-adjusted life year
QoL	Quality-of-life
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
ToT	Time on treatment
TSD	Technical support document
WTP	Willingness-to-pay
XP	Capecitabine and cisplatin

B.1 Decision problem, description of the technology and clinical care pathway

Summary of the decision problem, technology, and clinical care pathway

- The submission covers the technology's anticipated marketing authorisation for this indication. The relevant comparators for both gastric (GC) and gastro-oesophageal junction (GOJ) adenocarcinoma have been identified based on international guidelines and clinical expert consultation and are representative of the clinical practice in England.
- Pembrolizumab is a humanized monoclonal antibody which binds to the programmed death-ligand 1 (PD-L1) receptor that is involved in the control of T-cell immune responses, thereby potentiating an immune response to tumour cells.
- Many patients with GC or GOJ adenocarcinoma are diagnosed when their disease is at an advanced stage, owing to the vagueness of, or even lack of, symptoms, as well as limited awareness of symptoms and their relevance to possible underlying cancer.
- This submission aims to address the persisting unmet need in this population and would represent the first immuno-oncology treatment option for patients with unresectable advanced metastatic HER2 negative GC and GOJ adenocarcinoma whose tumours express CPS≥1. For patients with CPS≥5, the proposed new technology would offer an additional immuno-oncology treatment option thereby broadening the available treatment options for clinicians to use for these patients.
- No equality considerations are anticipated.

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with previously untreated HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma	Patients with locally advanced unresectable or metastatic HER-2 negative gastric or gastroesophageal junction adenocarcinoma whose tumours express CPS≥1.	In line with the anticipated GB MHRA marketing authorisation population wording.
Intervention	Pembrolizumab with chemotherapy	As per final scope	-
Comparator(s)	• Chemotherapy only, which includes: ○ doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin • For people with untreated HER2 negative advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS of 5 or more: ○ Nivolumab with platinum- and fluoropyrimidine-based chemotherapy	Mainly as per final scope. A comparison between pembrolizumab CPS ≥1 and nivolumab CPS ≥5 is not currently feasible.	KEYNOTE-859 trial results provide direct evidence between: • pembrolizumab plus CAPOX or FP vs. CAPOX or FP Based on previous appraisals in this setting, ESMO guidelines and clinical opinion received, doublet chemotherapy regimens are considered to be clinically equivalent. An indirect comparison between nivolumab in CPS ≥5 and pembrolizumab in CPS ≥1 is not currently feasible. Differences exist between the respective trial multiplicity analysis strategies in KEYNOTE-859 and CheckMate-649. In KEYNOTE-859, CPS ≥1 and CPS ≥10 cuts were prespecified and adjusted for type 1 error, however CheckMate-649 trial had a prespecified CPS ≥5 cut for the primary outcome measure. Therefore, the analysis for pembrolizumab in CPS ≥5 is not considered to be statistically

			appropriate. Instead, a comparison between pembrolizumab and nivolumab in CPS ≥1 and CPS ≥10 has been undertaken and results are presented in this submission section B.2.9.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	As per final scope	-
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Subgroups by PD-L1 status • Subgroups by tumour location	As per final scope	KEYNOTE-859 trial included a small proportion of patients with GOJ and it was a pre-specified subgroup in the trial, however it was not powered to be tested. Results for this subgroup of patients is included within the subgroup analysis section B.2.7.

B.1.2 Description of the technology being evaluated

Table 2 Technology being evaluated

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) is a monoclonal antibody (mAb) of the IgG4/kappa isotype designed to exert dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2 which appear on antigen-presenting or tumour cells. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour immunity (1)
Marketing authorisation/CE mark status	Pembrolizumab currently has a marketing authorisation (MA) covering the following indications: **Melanoma:** • the treatment of advanced (unresectable or metastatic) melanoma in adults. • the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. **Non-small cell lung carcinoma** • the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations. • the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults. • the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda. **Classical Hodgkin lymphoma** • the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. **Urothelial carcinoma** • the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. • the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for

	cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10. **Head and neck squamous cell carcinoma** • the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. • the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. **Renal Cell Carcinoma** • the first-line treatment of advanced renal cell carcinoma in adults. • in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults • for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions **Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers:** *Colorectal cancer* • as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings: o first-line treatment of metastatic colorectal cancer. o treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy. *Non-colorectal cancers* • for the treatment of the following MSI-H or dMMR tumours in adults with: o advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation. o unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy. **Oesophageal carcinoma or gastro-oesophageal junction adenocarcinoma** • the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10. **Triple-negative breast cancer** • the treatment of adults with locally advanced, or early-stage triple negative breast cancer at high risk of recurrence.

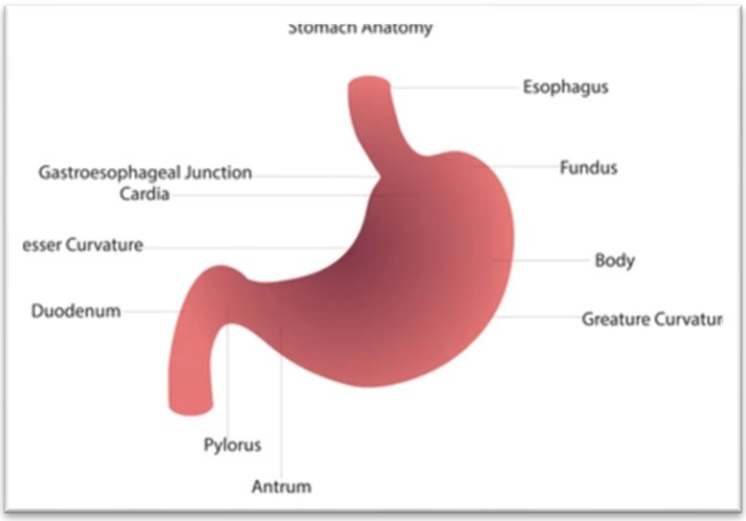
	• the treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease. **Endometrial carcinoma** • the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation. **Cervical cancer** • the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD L1 with a CPS ≥ 1. **Gastric or gastro-oesophageal junction (GOJ) adenocarcinoma** • in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication to which this submission relates: pembrolizumab in combination with fluoropyrimidine and platinum-containing containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER-2 negative gastric or gastroesophageal junction adenocarcinoma whose tumours express CPS≥1.
Method of administration and dosage	Pembrolizumab 200 mg every three weeks (Q3W) or 400 mg every six weeks (Q6W); intravenous (IV) infusion (up to a maximum 35 cycles). Fluoropyrimidine containing chemotherapy: • Capecitabine: 1000 mg/m^2 administered orally twice daily (BID) on Days 1 to 14 Q3W; or, • Fluorouracil (5-FU): 800 mg/m^2 IV administered on Days 1–5 Q3W Platinum containing chemotherapy: • Oxaliplatin: 130 mg/m^2 IV administered on Day 1 Q3W; or, • Cisplatin: 80 mg/m^2 IV administered on Day 1 Q3W
Additional tests or investigations	Not applicable (both HER2 testing and PD-L1 testing are established in the 1L gastric cancer and GOJ adenocarcinoma population).
List price and average cost of a course of treatment	The list price of pembrolizumab is £2,630 per 100 mg vial, the cost of a single administration being £5,260 for Q3W regimen and £10,520 for Q6W regimen.
Patient access scheme (if applicable)	A Commercial Access Agreement (CAA) with a simple discount of [redacted], therefore 200 mg administration of pembrolizumab will cost [redacted].

B.1.3 Health condition and position of the technology in the treatment pathway

Health condition

Gastric cancer (GC) refers to any malignant neoplasm that arises when healthy cells in the lining of the stomach become abnormal and divide sporadically, resulting in formation of a tumour that can metastasise to other regions of the body (2). Although often reported as a single entity, gastric GC can generally be classified into two topographical categories: cardia GC arising in the area of the stomach adjoining the oesophageal-gastric junction, and non-cardia GC arising from more distal regions of the stomach (3). This appraisal covers both parts of the stomach, and we are referring to it as gastric (non-cardia GC) and gastroesophageal junction (cardia GC) (Figure 1).

Figure 1 :Stomach anatomy



Adapted from Cancer Research UK

The GC histological classifications most utilised are those from Nakamura and colleagues, Laurén, and WHO. The Laurén classification is the most commonly used for subgroup analyses in clinical trials. It distinguishes intestinal type, diffuse type, and indeterminate or unclassifiable type which we will be referring to in this submission (4).

Symptoms associated with GC are indigestion (dyspepsia), anorexia (poor appetite) or early satiety, weight loss, and abdominal pain. Dysphagia or regurgitation might occur in proximal gastric cancer or cancers located at the gastroesophageal junction.

Anaemia might be present in bleeding cancers. If symptoms are present at the time of diagnosis, the disease is often advanced and incurable (5). The most common method for diagnosing GC is via a specific type of endoscopy, called gastroscopy (4).

GC is the fifth most common cancer worldwide, and the third leading cause of death with an estimated 768,793 deaths in 2020. Over a million new cases of GC are diagnosed, worldwide, each year (6). Many patients with GC cancers are diagnosed when their disease is at an advanced stage, owing to this vagueness of, or even lack of, symptoms, and lack of understanding symptoms and their relevance to possible underlying cancer. Overall, about 60% of people with GC are not eligible for curative treatment owing to late presentation or co-morbidities (7). Excess mortality from this cancer is high, with approximately 800,000 deaths globally (8).

In the UK, GC accounts for 2% of all new cancer cases, making it a significant ongoing risk to health in the UK, with 6,453 new cases reported every year (2016-2018) (9). GC is almost twice as common in men, with approximately 4,200 cases diagnosed in men, and 2,200 cases in women in England. In the UK, GC is most common in people with Black ethnicity, then White ethnicity, and least common in those with Asian ethnicity (9).

Incidence of GC in the UK is strongly related to age, with the highest incidence in older people. In the UK in 2015-2017, on average each year around half of new cases (51%) were in people aged 75 and over (9).

Dietary factors increase risk; foods preserved by salting, low fruit intake, alcohol consumption and active tobacco smoking are established risk factors (10). GC is linked with Helicobacter pylori (*H.pylori*) which causes around 40% of GC in the UK. *H. pylori* is a bacteria that lives in the mucous which lines the stomach. It spreads through contaminated food and water. For most people, having an *H. pylori* infection will not cause any problems. But in some, *H. pylori* can cause inflammation and stomach ulcers, which can lead to cancer (11). Other factors, such as smoking and diet may increase the risk of *H. pylori* leading to cancer (12).

More than 5% of GC cases in the UK are caused by obesity, defined as having a body mass index (BMI) ≥30. Smoking increases the risk of developing GC by 15%, the risk increases with the number of cigarettes smoked a day (12).

The treatment for GC is largely dependent on the stage at which the cancer is diagnosed. Stage 1 GC is defined as cancer that has not spread to other body parts, structures or distant organs (13). Locally advanced GC are either stage 2 or stage 3 and are defined as cancer that has spread into the tissues around the stomach, but not spread to other organs (14), (15). For stage 1-3 GC, surgical resection of the affected section of the stomach (gastrectomy) is the usual course of treatment (16). However, an extensive nodal spread in patients with locally advanced GC patients means that they may not be eligible for surgery and therefore have an unresectable disease which negatively impacts treatment prognosis (17), (18). Advanced, metastatic cancers are stage 4. Stage 4 GC is unlikely to be cured, however chemotherapy and radiotherapy can slow the cancer spreading, and provide relief from other symptoms (16). In the UK, the percentage of patients diagnosed with stage 4 disease (advanced cancer) increased from 41.6% in 2019/20 to 44.9% in 2020/21 (19).

Treatment pathway

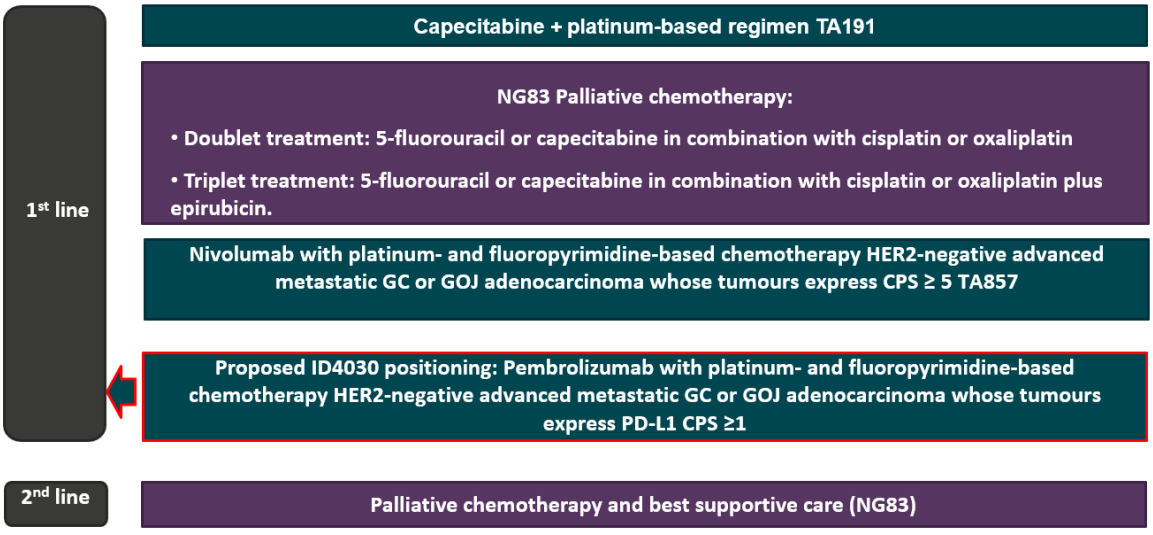
Currently there is no national screening programme for GC in the UK. In England, standard first-line treatment for people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and no significant comorbidities is palliative chemotherapy. NICE's guideline (NG) 83 on oesophago-gastric cancer: assessment and management in adults recommends dual therapy with fluorouracil or capecitabine plus cisplatin or oxaliplatin, or triple therapy with epirubicin (20). NICE’s TA857 guidance recommends nivolumab with platinum- and fluoropyrimidine-based chemotherapy, within its marketing authorisation, as an option for untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more (21). Patients with HER2 negative GOJ adenocarcinoma whose tumours express PD-L1 CPS≥ 10 can be treated with pembrolizumab in combination with fluoropyrimidine chemotherapy (22).

During the TA857 appraisal, clinical experts explained that dual therapy regimens are preferred and that most patients would receive capecitabine and oxaliplatin (CAPOX) (21). This is because oxaliplatin is better tolerated than cisplatin and has a shorter infusion time. Some people may be offered fluorouracil with oxaliplatin and folinic acid (FOLFOX). People receiving FOLFOX treatment are required to attend hospital more regularly (every 2 weeks) than people receiving CAPOX (every 3 weeks).

European Society for Medical Oncology (ESMO) guidelines (23) recommend platinum–fluoropyrimidine doublet chemotherapy as a standard of care in patients with advanced metastatic HER2 negative GC or GOJ. Oxaliplatin and cisplatin are considered to be the most commonly used platinum drugs. ESMO guidelines do not recommend the addition of a taxane to a platinum doublet chemotherapy regimen because it is associated with substantially increased toxicity. For patients whose tumours express PD-L1, ESMO guidelines recommend nivolumab in combination with doublet chemotherapy in patients with a PD-L1 CPS ≥5.

ESMO guidelines and clinical opinion suggest that doublet chemotherapies (cisplatin and oxaliplatin; 5FU and capecitabine) are clinically equivalent (24), (25), (26). Triplet chemotherapy regimens do not have a role in treating HER2 negative metastatic or locally advanced GC or GOJ adenocarcinoma due to increased toxicity and lack of added clinical effect (23).

Figure 2 GC treatment pathway and proposed pembrolizumab positioning



HER2 and PD-L1 testing in GC

NG83, ESMO and NCCN (National Comprehensive Cancer Network) recommend HER2 testing for people with metastatic oesophago-gastric adenocarcinoma (20), (23), (27). HER2 is overexpressed in about 30% of intestinal type gastric cancers, 15% of mixed type tumours, and about 5% of diffuse type. This appraisal focusses on HER2 negative locally advanced unresectable or metastatic GC and GOJ adenocarcinoma population.

The expression of PD-L1 is observed in many malignant tumours and is associated with poor prognosis in patients with GC. ESMO guidelines recommend that HER2 status and PD-L1 CPS should be evaluated in patients with metastatic or locally advanced gastric cancer to tailor first-line treatment in combination with chemotherapy (23). Following publication of NICE guidance TA208 (28), TA737 (22) and TA857 (21), both HER2 and PD-L1 testing respectively have become established routine testing regimens in NHS clinical practice for the population covered by this submission.

Unmet need

There is still an unmet need in patients with advanced metastatic HER2 negative GC and GOJ adenocarcinoma. NICE's TA857 recommends nivolumab in combination with platinum- and fluoropyrimidine-based chemotherapy as a first-line treatment option for HER2 negative advanced gastric, GOJ or oesophageal adenocarcinoma, only for those patients whose tumours express PD-L1 with a CPS ≥5. For patients with PD-L1 CPS<5, there are currently no newer, innovative treatments as doublet chemotherapy regimens remain the only available treatment options. This appraisal aims to offer the first IO treatment option for patients with GC and GOJ adenocarcinoma with CPS ≥ 1, thereby addressing the existing unmet need and broadening the available treatment options for clinicians across all CPS positive GC and GOJ adenocarcinoma patients.

Under NICE's previous methods for evaluating new medicines (29) and based on the poor prognosis associated with locally advanced unresectable or metastatic GC or GOJ adenocarcinoma, pembrolizumab with chemotherapy would have met the end-of-life (EoL) criteria (treatment is for patients with a short life expectancy [less than 24 months] and should extend life by at least 3 months compared to current NHS

treatment) and would therefore have qualified for a higher cost-effectiveness willingness-to-pay (WTP) threshold of £50,000/QALY. It should be noted that all recent appraisals in HER2 negative GC (21) and oesophageal cancer (22), (30) also met NICE's EoL criteria and a higher decision-making threshold was applied.

B.1.4 Equality considerations

MSD does not envisage any equality issues with the use of pembrolizumab in combination with fluoropyrimidine chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER-2 negative GC and GOJ adenocarcinoma.

B.2 Clinical effectiveness

Summary of key clinical effectiveness information

Randomised controlled trial:

- An SLR was conducted (search date of May 2023) with eligibility criteria aligned with the decision problem.
- KEYNOTE–859 is a phase III, randomised, double-blind trial comparing pembrolizumab plus chemotherapy with chemotherapy and placebo as first-line treatment in participants with HER2 negative advanced gastric or gastroesophageal junction adenocarcinoma (NCT 03675737). 1579 participants from 33 countries were randomised, including 42 patients from the UK. 1235 participants in the ITT population had PD-L1 positive tumours defined by CPS ≥1 including 34 UK patients.
- KEYNOTE –859 trial results presented in this submission are based on a data cut from the first interim analysis of this study (IA1) conducted in October 2022.
- This submission is focussed on the results of the PD-L1 CPS≥1 subgroup of patients and for the purpose of HTA. Median duration of follow up was 11.9 months. The results in ITT population and CPS≥10 subgroup have been presented in appendix E.

Network meta-analysis:

- An NMA would be required to compare pembrolizumab plus CAPOX/FP against XP/ FOLFOX in the untreated locally advanced or metastatic GC or GOJ adenocarcinoma patients. A comparison versus nivolumab in combination with doublet chemotherapy is required in patients whose tumours express PD-L1 CPS ≥5.
- The feasibility assessment concluded that an NMA versus doublet chemotherapies of interest was feasible only under the assumption of doublet

chemotherapy equivalence, and the results mirror the KEYNOTE-859 trial results.

- At the time of company submission, an NMA for OS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1 or CPS ≥10. The results show that in participants with PD-L1 CPS ≥1 and CPS ≥10, efficacy of nivolumab in combination with chemotherapy is similar to pembrolizumab in combination with chemotherapy (HR, 95% CrI: 1.00, 0.84-1.19) and (HR, 95% CrI: 0.98, 0.76-1.26) respectively. The difference between treatments was not statistically meaningful.

- An NMA for PFS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1. The results show that pembrolizumab in combination with chemotherapy performed similarly to nivolumab in combination with chemotherapy (HR, 95% CrI: 0.97, 0.80-1.17). The difference between treatments was not statistically meaningful.

- An NMA in participants with PD-L1 CPS ≥5 was not feasible at the time of the evidence submission preparation. KEYNOTE-859 did not have a prespecified cut point of PD-L1 CPS ≥5 as a primary outcome measure so is not considered statistically appropriate. Subgroup analysis data for pembrolizumab in combination with chemotherapy in the PD-L1 CPS ≥5 sub-population was not part of the pre-planned statistical analyses and clinical study report generated and is currently unavailable to support this submission.

Clinical effectiveness conclusions

- Efficacy results show that pembrolizumab plus chemotherapy provide a clinically meaningful improvement in both PFS and OS compared with chemotherapy in previously untreated participants with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma whose tumours express PD-L1 CPS≥1.

- Among participants with PD-L1 CPS ≥1 and CPS ≥10, with previously untreated locally advanced unresectable or metastatic HER2-negative gastric

or GOJ adenocarcinoma, pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR when compared with chemotherapy alone, while maintaining HRQoL.

- In the PD-L1 CPS ≥1 population, the OS HR was 0.74 (95% CI: 0.65, 0.84; p<0.0001, which is less than the p-value crossing boundary of 0.020556 for statistical significance) in favour of pembrolizumab plus chemotherapy, with a 26% reduction in the risk of death.
- The PFS HR was 0.72 (95% CI: 0.63, 0.82; p<0.0001, which is less than the p-value crossing boundary of 0.025 for statistical significance) in favour of pembrolizumab plus chemotherapy, with a 28% reduction in the risk of disease progression and death.

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2 List of relevant clinical effectiveness evidence

A systematic literature review (SLR) was conducted to identify clinical studies relevant to this submission. The SLR was designed to identify randomised controlled trials (RCTs) relating to the efficacy and safety of pembrolizumab in combination with chemotherapy and relevant comparators (as per final scope described in Table 1 in patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma.

The SLR was originally conducted in May 2023. As the manufacturer of the technology being appraised, MSD is aware of all relevant RCTs for pembrolizumab in combination with chemotherapy in this indication.

In total, two RCTs were identified: one trial reporting evidence for the relevant comparators: CheckMate 649 (31) and one reporting evidence for pembrolizumab in combination with chemotherapy: KEYNOTE-859 (32).

Please refer to Table 3 for a summary of the evidence coming from the pivotal clinical trial KEYNOTE-859.

Table 3 Clinical effectiveness evidence

Study	Josep Tabernero, Yung-Jue Bang, Eric Van Cutsem, Charles S Fuchs, Yelena Yuriy Janjigian et al. KEYNOTE-859: a Phase III study of pembrolizumab plus chemotherapy in gastric/gastroesophageal junction adenocarcinoma. Future Oncology 2021 17:22, 2847-2855 (32)
Study design	Phase III Randomised, Double-Blind, Placebo-Controlled Clinical Trial
Population	Human epidermal growth factor receptor 2 (HER2) negative participants with advanced gastric or GOJ adenocarcinoma
Intervention(s)	Pembrolizumab plus either cisplatin plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX)
Comparator(s)	Placebo plus FP or CAPOX
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	• **Overall survival** • **Progression-free survival** • Objective response rate • **Adverse effects of treatment** • **Health related quality of life** Bolded outcomes are included in the economic model
All other reported outcomes	N/A

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Sections B.2.3 – B.2.6 report the KEYNOTE-859 clinical trial design and results

Summary of the methodology of the KEYNOTE-859 study

Trial design, assignment, randomisation, and blinding

KEYNOTE–859 (32) is a randomised, double-blind, placebo-controlled multi-centre phase III trial to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy versus placebo plus chemotherapy as first-line treatment in participants

with HER-2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma.

Participants were stratified by geographic region, PDL1 tumour expression status (CPS <1, ≥1), and combination chemotherapy (FP or CAPOX). The study was double-blind with respect to randomised study intervention (pembrolizumab/placebo). The investigator had 2 choices of combination chemotherapy regimen which must have been chosen prior to randomisation in the study.

Treatment allocation/randomisation occurred centrally using an interactive response technology (IRT) system. There were 2 study intervention arms. Participants were assigned randomly in a 1:1 ratio to pembrolizumab or placebo, respectively. A double-blinding technique was used. Pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject and the investigator who was involved in the treatment or clinical evaluation of the subjects were unaware of the group assignments. The administration of pembrolizumab or placebo treatment was blinded to the subject, study site personnel, and sponsor personnel.

Allocation was stratified by geographic region, histology, and ECOG performance score. Details of the two treatment arms are provided below:

- Combination of pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W) or placebo and either:
    - FP: cisplatin 80 mg/m^2 IV Q3W and 5-FU 800 mg/m^2/day continuous IV infusion on each of days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle)

or

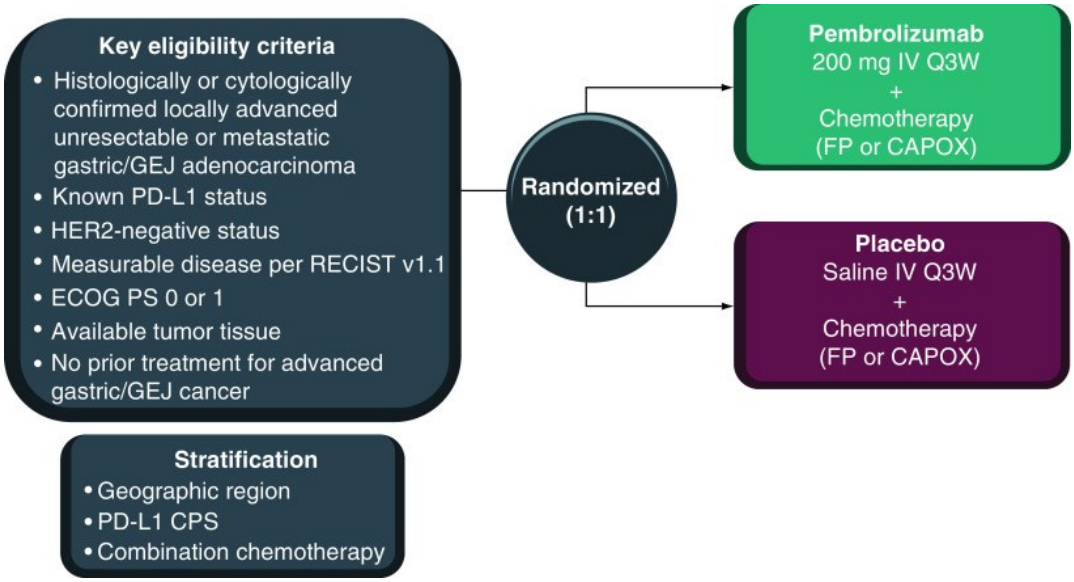
    - CAPOX- Oxaliplatin 130 mg/m² as a 60- to 120- minute IV infusion on Day 1 of each treatment cycle.

Treatment continued until confirmed progressed disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevented further administration of treatment, investigator's decision to withdraw the participant, participant withdrew consent,

pregnancy of the participant, noncompliance with study treatment or procedure requirements, completion of 35 administrations (approximately 2 years) of treatment with pembrolizumab or achievement of a CR, or administrative reasons. No crossover from placebo arm to pembrolizumab arm was allowed.

A schematic of the trial design is provided below in Figure 3.

Figure 3 Schematic of KEYNOTE – 859



Abbreviations: CAPOX: Capecitabine plus oxaliplatin; CPS: Combined positive score; ECOG PS: Eastern Cooperative Oncology Group performance status; FP: 5-Fluorouracil plus cisplatin; GOJ: Gastroesophageal junction; iv.: Intravenously; Q3W: Every 3 weeks.

Eligibility criteria

Inclusion Criteria

- Age ≥18 years.
- Histologically or cytologically confirmed locally advanced unresectable or metastatic gastric or GOJ adenocarcinoma.
- Known PD-L1 status (CPS <1, ≥1).
- HER2 negative cancer.
- Measurable disease per RECIST 1.1 as assessed by investigator.

- Archival tumour tissue sample or newly obtained core or excisional biopsy for PD-L1 expression and MSI biomarker analysis.
- ECOG PS 0 or 1.
- Adequate hematologic function, defined as ANC ≥1500/µl, platelet count ≥100,000/µl and haemoglobin count ≥9.0 g/dl or ≥5.6 mmol/l.
- Adequate renal function, defined as creatinine ≤1.5× ULN or measured or calculated creatinine clearance ≥60 ml/min for those with creatinine levels >1.5× ULN.
- Adequate hepatic function, defined as total bilirubin ≤1.5× ULN or direct bilirubin ≤ULN for those with total bilirubin >1.5× ULN, ALT/AST levels ≤2.5× ULN (≥5× ULN for participants with liver metastasis) and albumin ≥2.5 g/dl.
- Adequate coagulation function, defined as INR ≤1.5× ULN unless the patient is receiving anticoagulant therapy as long as PT or aPTT is within the therapeutic range.
- Willing to use an adequate method of contraception throughout the study and for 120 days after the last dose of pembrolizumab and up to 180 days after the last dose of chemotherapy.
- Negative urine or serum pregnancy test results within 72 h before the first dose of study intervention.
- Written informed consent.

Exclusion Criteria

- Squamous cell or undifferentiated gastric cancer.
- Major surgery, open biopsy or significant traumatic injury within 28 days before randomisation or anticipated need for major surgery during the study treatment period.
- Pre-existing peripheral neuropathy grade >1.

- Any prior therapy for locally advanced or metastatic gastric or GOJ cancer.
- Prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent or with any other agent directed to stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX40, CD137).
- Prior radiotherapy within 2 weeks of study intervention.
- Systemic anticancer therapy, including investigational agents, ≤4 weeks before randomisation.
- History of live vaccine within 30 days before the first dose of study intervention.
- Known additional malignancy that is progressing or has required active treatment within the past 5 years (except for BCC or SCC of the skin or for carcinoma in situ [e.g., breast carcinoma, cervical cancer in situ] that has undergone potentially curative treatment).
- Active autoimmune disease that has necessitated systemic treatment (other than replacement therapy) in the past 2 years or history of solid organ/allogeneic stem cell transplant.
- Diagnosis of immunodeficiency, receiving chronic systemic steroid therapy (>10 mg daily prednisone equivalent) or receiving any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
- History or current evidence of any condition, therapy or laboratory abnormality that might confound the study results or interfere with study participation.
- Active infection necessitating systemic therapy.
- Active CNS metastases and/or carcinomatous meningitis.
- Known psychiatric or substance abuse disorder that would interfere with cooperation with study requirements.

- Pregnant or breastfeeding or expecting to conceive within the projected study duration.
- Known severe hypersensitivity (grade ≥3) to any of the study drugs or their excipients.
- Known history of HIV, HBV or HCV infection.
- Known history of active tuberculosis.
- History of non-infectious pneumonitis treated with steroids or current pneumonitis.

Settings and locations where the data were collected

The KEYNOTE-859 study was conducted at 215 centres in 33 countries: Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, France, Germany, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, New Zealand, Peru, Poland, Russia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, and United States. 42 participants from 3 UK centres participated in the KEYNOTE-859 trial.

Trial drugs and concomitant medications

Study medications used in this trial are outlined below (Table 4).

Table 4 Trial Treatments

Group Name	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regiment / Treatment Period	Use
Pembrolizumab	Vial	25 mg/mL vial 100 mg vial	200 mg on Day 1 of each cycle	IV Infusion	Q3W up to 35 cycles	Test product
Placebo	Solution for infusion	N/A	On Day 1 of each cycle	IV Infusion	Q3W up to 35 cycles	Placebo
FP Backbone Chemotherapy						
Cisplatin	Ampule	1 mg/mL vial 20 mg vial or 50 mg vial	80 mg/m^2 on Day 1 of each cycle	IV Infusion	Q3W up to 35 cycles *	Comparator regimen and combination agent

5-FU	Ampule	25 mg/mL vial 50 mg/mL vial	800 mg/m^2/day continuous on Days 1 to 5 of each cycle (120 hours, or per local standard)	IV Infusion	Q3W up to 35 cycles	Comparator regimen and combination agent
CAPOX Backbone Chemotherapy						
Oxaliplatin	Ampule	5 mg/mL vial 50 mg vial or 100 mg vial	130 mg/m^2 on Day 1 of each cycle	IV Infusion	Q3W up to 35 cycles *	Comparator regimen and combination agent
Capecitabine	Tablet	150 mg tablet 500 mg tablet	1000 mg/m^2	Oral	Twice daily on Days 1 to 14 of each cycle (Q3W)	Comparator regimen and combination agent

5-FU=5-fluorouracil; CAPOX=capecitabine and oxaliplatin; EEA=European Economic Area; FP=cisplatin and 5-fluorouracil; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational medicinal product/auxiliary medicinal product; Q3W=every 3 weeks

The classification of IMP and NIMP/AxMP is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the classification/definition of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

** Duration of cisplatin or oxaliplatin treatment may be capped at 6 cycles as per local country guidelines. Treatment with 5-FU/capecitabine may continue per protocol. Investigator decision regarding the type of backbone chemotherapy (FP or CAPOX) should be determined prior to randomisation.*

Participants should continue on the type of backbone chemotherapy chosen prior to randomisation throughout the study. Exceptions may be permitted after consultation with the Sponsor.

In this protocol, placebo for pembrolizumab is diluent alone (normal saline and/or dextrose); diluent is used for blinding purposes and does not contain active ingredients. Participants who are randomised to placebo are not allowed to crossover to pembrolizumab treatment.

Note: The unit dose strength of chemotherapy may vary depending on the source. The table captures the current available unit dose strengths but could vary depending on availability.

Trial treatment for cycle 1 should have begun within 3 days of randomisation. All trial treatments were administered on an outpatient basis. For 5-FU continuous infusion, use of a portable infusion pump was preferred; however, hospitalisation was acceptable if that was the standard procedure for the local site.

Study treatment in both arms begun on Day 1 of each 3-week dosing cycle.

Treatments were administered in the following order:

- Pembrolizumab or placebo infusion was administered first, followed by the cisplatin and 5-FU infusions. Administration of chemotherapy should have followed 1 to 2 days after pembrolizumab/placebo as needed per local standard

of care. Treatment continued with pembrolizumab plus chemotherapy or placebo plus chemotherapy until documented confirmed PD, unacceptable AE(s), intercurrent illness that prevented further administration of treatment, investigator's decision to discontinue treatment, subject withdrew consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject received 35 administrations (approximately 2 years) of study medication, or administrative reasons requiring cessation of treatment. Regardless of clinical benefit, subjects only received 35 administrations (approximately 2 years) with pembrolizumab. Pembrolizumab 200-mg fixed dose was administered as a 30-minute IV infusion Q3W.

- Placebo was normal saline solution prepared by the local pharmacist. Placebo was dosed and administered by blinded qualified trial site personnel in the same manner as pembrolizumab.

- Cisplatin 80 mg/m^2 was administered as a 60- or 120-minute IV infusion (or per site's standard practice) Q3W on Day 1 of each treatment cycle and after pembrolizumab/placebo administration. Duration of cisplatin treatment was capped at 6 doses.

- 5-FU was administered as a continuous IV infusion of 800 mg/m^2/day on each of Days 1 to 5 Q3W or per local standard for 5-FU administration duration as long as total dose of 4000 mg/m^2 per 3-week cycle was followed. 5-FU was administered after pembrolizumab/placebo administration. Duration of 5-FU treatment did not exceed 35 cycles.

- Oxaliplatin 130 mg/m^2 was administered as a 60- to 120-minute IV infusion or per the site's standard practice on Day 1 of each treatment cycle.

- Capecitabine was administered orally as a 1000 mg/m^2 dose twice daily from Day 1 to Day 14 of each treatment cycle.

Outcomes assessed

Primary outcomes

- Overall Survival (OS)

OS is defined as the time from randomisation to death due to any cause.

Other outcomes

Secondary outcomes

- Progression-free survival (PFS) per RECIST 1.1 assessed by BICR

PFS is defined as the time from randomisation to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

- Objective Response Rate (ORR) per RECIST 1.1 by BICR

OR is defined as a CR or a PR.

- Duration of Response (DOR) per RECIST 1.1 by BICR

For participants who demonstrated CR or PR, DOR is defined as the time from first or PR) to subsequent disease progression or death from any cause, whichever occurs first.

Exploratory outcomes

- PFS per RECIST 1.1 assessed by investigator
- PFS using modified RECIST 1.1 for immune-based therapeutics (iRECIST) by investigator
- ORR per RECIST 1.1 by investigator
- ORR using modified RECIST 1.1 for immune-based therapeutics (iRECIST) by investigator

Safety outcomes

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events, laboratory values, and vital signs.

Patient-reported Outcome (PRO) Endpoints

The PRO endpoints include results from the EORTC QLQ-C30, EORTC QLQ-STO22, and EQ-5D-5L questionnaires.

Key PRO outcomes:

Mean change from baseline

- The mean score changes from baseline as measured by the EORTC QLQ-C30 global health status/quality of life scale.
- The mean score changes from baseline for QLQ-C30 physical functioning scale.
- The mean score changes from baseline for QLQ-C30 role functioning scale.
- The mean score changes from baseline for QLQ-C30 symptom sub-scales/items.
- The mean score changes from baseline for all QLQ-STO22 sub-scales/items.
- The mean score changes from baseline for EQ-5D-5L VAS.

B 2.3.2 Comparative summary of the trial methodology

A summary of the trial methodology is present below in Table 5

Table 5 Summary of trial methodology

Study name	Josep Tabernero, Yung-Jue Bang, Eric Van Cutsem, Charles S Fuchs, Yelena Yuriy Janjigian et al. KEYNOTE-859: a Phase III study of pembrolizumab plus chemotherapy in gastric/gastroesophageal junction adenocarcinoma. Future Oncology 2021 17:22, 2847-2855 (32)
Trial design	Phase III Randomised, Double-Blind, Placebo-Controlled Clinical Trial
Eligibility criteria for participants	Patients with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma. • an ECOG PS of 0 or 1; • no active central nervous system metastases and/or carcinomatous meningitis; and • no active infection or autoimmune disease that required systemic therapy.
Settings and locations where the data were collected	Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, France, Germany, Guatemala, Hong Kong, Hungary, Ireland, Israel,

	Italy, Japan, Mexico, New Zealand, Peru, Poland, Russia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, UK, Ukraine, USA. Patients from 4 UK centres were included in the study.
Trial drugs	Pembrolizumab plus FP or CAPOX Q3W, up to 35 cycles* Placebo plus FP or CAPOX Q3W, up to 35 cycles
Primary outcomes	OS
Other outcomes used in the economic model/specified in the scope	PFS, OR, DOR, safety (adverse events of treatment) and PROs (health-related quality of life)
Pre-planned subgroups	• Age category: (<65 versus ≥65 years) • Sex: (female versus male) • Race: (Asian versus non-Asian) • Stratification factors: (Section 6.3.2) • MSI status: (MSI-H versus non-MSI-H) • ECOG status: (0 versus 1) • Disease status (locally advanced versus metastatic) • Primary location (stomach versus GOJ) • Histologic subtype (diffuse versus indeterminate versus intestinal)
FP: cisplatin and 5-fluorouracil; CAPOX: capecitabine and oxaliplatin; OS: overall survival; PFS: progression free survival **patients who completed 35 cycles of pembrolizumab treatment or who achieved a complete response but progressed after discontinuation of treatment could initiate a second course of pembrolizumab treatment in the KEYNOTE-859 trial, for up to 17 cycles. Please refer to section 3.3.3 for more details and the results.*	

Pre-planned subgroups

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect for OS, PFS and ORR (with a nominal 95% CI) was estimated and plotted within each category of each subgroup. The following are examples of classification variables:

- Age category: (<65 versus ≥65 years)
- Sex: (female versus male)
- Race: (Asian versus non-Asian)
- MSI status: (MSI-H versus non MSI-H)
- ECOG status: (0 versus 1)
- Disease status (locally advanced versus metastatic)

- Primary location (stomach versus GOJ)
- Histologic subtype (diffuse versus indeterminate versus intestinal)
- Stratification factors (i.e. geographic region; PD-L1 tumour expression (CPS <1, ≥1); combination chemotherapy (FP, CAPOX)

Baseline characteristics of trial participants

The baseline characteristics were generally reflective for this population with previously untreated, HER2 negative, advanced gastric or GOJ adenocarcinoma based on clinical expert feedback and were generally well balanced between the 2 intervention groups.

Most participants were male, <65 years old, and had an ECOG performance status of 1, had adenocarcinoma of the stomach (78.7%), had tumour PD-L1 status of CPS ≥1 (78.2%), and were on a CAPOX regimen (86.3%) Table 6**Error! Reference source not found.**.

The baseline characteristics in the participants with PD-L1 CPS ≥1 were generally consistent with all participants baseline characteristics and those with CPS ≥10 (reported in Appendix E).

Table 6 Participant Characteristics (ITT Population with CPS≥1)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n (%)		n	(%)	n (%)	
Participants in population	618		617		1,235	
Sex						
Male	422	(68.3)	448	(72.6)	870	(70.4)
Female	196	(31.7)	169	(27.4)	365	(29.6)
Age Category 1 (Years)						
< 65	377	(61.0)	364	(59.0)	741	(60.0)
≥ 65	241	(39.0)	253	(41.0)	494	(40.0)
Mean	59.8		60.5		60.1	
SD	11.8		11.6		11.7	
Median	62.0		63.0		62.0	
Range	24 to 86		25 to 85		24 to 86	
Age Category 2 (Years)						
< 65	377	(61.0)	364	(59.0)	741	(60.0)
≥ 65 to <75	195	(31.6)	203	(32.9)	398	(32.2)

≥ 75 to <85	44	(7.1)	49	(7.9)	93	(7.5)
≥ 85	2	(0.3)	1	(0.2)	3	(0.2)
Age Category 3 (Years)						
18-39	42	(6.8)	34	(5.5)	76	(6.2)
40-49	70	(11.3)	75	(12.2)	145	(11.7)
50-59	150	(24.3)	141	(22.9)	291	(23.6)
60-69	236	(38.2)	230	(37.3)	466	(37.7)
70-79	110	(17.8)	121	(19.6)	231	(18.7)
≥80	10	(1.6)	16	(2.6)	26	(2.1)
Race						
American Indian Or Alaska Native	24	(3.9)	29	(4.7)	53	(4.3)
Asian	206	(33.3)	203	(32.9)	409	(33.1)
Black Or African American	7	(1.1)	9	(1.5)	16	(1.3)
Multiple	32	(5.2)	25	(4.1)	57	(4.6)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	1	(0.2)	2	(0.2)
White	342	(55.3)	343	(55.6)	685	(55.5)
Missing	6	(1.0)	7	(1.1)	13	(1.1)
Ethnicity						
Hispanic Or Latino	135	(21.8)	124	(20.1)	259	(21.0)
Not Hispanic Or Latino	461	(74.6)	480	(77.8)	941	(76.2)
Not Reported	12	(1.9)	11	(1.8)	23	(1.9)
Unknown	7	(1.1)	2	(0.3)	9	(0.7)
Missing	3	(0.5)	0	(0.0)	3	(0.2)
Geographic Region for Randomisation						
Western Europe/Israel/North America/Australia	166	(26.9)	166	(26.9)	332	(26.9)
Asia	201	(32.5)	200	(32.4)	401	(32.5)
Rest of the World	251	(40.6)	251	(40.7)	502	(40.6)
Combination Chemotherapy for Randomisation						
CAPOX	528	(85.4)	528	(85.6)	1,056	(85.5)
FP	90	(14.6)	89	(14.4)	179	(14.5)
PD-L1 Status for Randomisation						
CPS ≥ 1	618	(100.0)	616	(99.8)	1,234	(99.9)
CPS < 1	0	(0.0)	1	(0.2)	1	(0.1)
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS ≥ 10	279	(45.1)	272	(44.1)	551	(44.6)
CPS < 10	337	(54.5)	345	(55.9)	682	(55.2)
Missing	2	(0.3)	0	(0.0)	2	(0.2)
MSI Status						
MSI-High	34	(5.5)	29	(4.7)	63	(5.1)
non-MSI-High	454	(73.5)	471	(76.3)	925	(74.9)
Missing	130	(21.0)	117	(19.0)	247	(20.0)
ECOG Performance Scale						
0	223	(36.1)	228	(37.0)	451	(36.5)
1	395	(63.9)	389	(63.0)	784	(63.5)
Primary Location						
Adenocarcinoma of the gastroesophageal junction	123	(19.9)	164	(26.6)	287	(23.2)

Adenocarcinoma of the stomach	494	(79.9)	453	(73.4)	947	(76.7)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Overall Stage						
IIA	0	(0.0)	1	(0.2)	1	(0.1)
IIB	0	(0.0)	2	(0.3)	2	(0.2)
IIIA	2	(0.3)	7	(1.1)	9	(0.7)
IIIB	10	(1.6)	7	(1.1)	17	(1.4)
IIIC	9	(1.5)	5	(0.8)	14	(1.1)
IV	596	(96.4)	595	(96.4)	1,191	(96.4)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Disease Status						
Locally advanced	26	(4.2)	24	(3.9)	50	(4.0)
Metastatic	591	(95.6)	593	(96.1)	1,184	(95.9)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Histological Subtype (Lauren classification)						
Diffuse	236	(38.2)	220	(35.7)	456	(36.9)
Intestinal	239	(38.7)	215	(34.8)	454	(36.8)
Indeterminate	141	(22.8)	182	(29.5)	323	(26.2)
Unknown	1	(0.2)	0	(0.0)	1	(0.1)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Number of Metastasis						
0-2	345	(55.8)	329	(53.3)	674	(54.6)
≥3	272	(44.0)	288	(46.7)	560	(45.3)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Tumour Burden						
≥ Median	308	(49.8)	285	(46.2)	593	(48.0)
< Median	277	(44.8)	299	(48.5)	576	(46.6)
Missing	33	(5.3)	33	(5.3)	66	(5.3)
Liver Metastases						
Yes	258	(41.7)	253	(41.0)	511	(41.4)
No	359	(58.1)	364	(59.0)	723	(58.5)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Prior Gastrectomy/Esophagectomy						
Yes	109	(17.6)	105	(17.0)	214	(17.3)
No	506	(81.9)	508	(82.3)	1,014	(82.1)
Missing	3	(0.5)	4	(0.6)	7	(0.6)

CAPOX: Backbone chemotherapy oxaliplatin + capecitabine. FP: Backbone chemotherapy cisplatin + 5-FU.
Database Cutoff Date: 03 October 2022

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical analysis and definition of study groups in the KEYNOTE-859 study

This section reports the relevant statistical methodology of KEYNOTE-859 (32)

Objectives, hypotheses, and endpoints

Table 7 KEYNOTE-859 study objectives, hypotheses, and endpoints

Objectives/Hypothesis	Endpoint(s)
Primary	
Objective: To compare the OS of the participants following administration of pembrolizumab versus placebo when each is combined with chemotherapy **Hypothesis (H1):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in participants with PD-L1 CPS ≥10 **Hypothesis (H2):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in participants with PD-L1 positive tumours defined by CPS ≥1 **Hypothesis (H3):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for OS, in all participants	OS: The time from randomisation to death due to any cause
Secondary	
Objective: To compare the PFS per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy **Hypothesis (H4):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in participants with PD-L1 positive tumours defined by CPS ≥10 **Hypothesis (H5):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in participants with PD-L1 positive tumours defined by CPS ≥1 **Hypothesis (H6):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for PFS, in all participants	PFS: The time from randomisation to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: To compare the ORR per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy **Hypothesis (H7):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in participants with PD-L1 positive tumours defined by CPS ≥10 **Hypothesis (H8):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in participants with PD-L1 positive tumours defined by CPS ≥1 **Hypothesis (H9):** Pembrolizumab plus chemotherapy is superior to placebo plus chemotherapy for ORR, in all participants	OR: CR or PR
Objective: To describe the DOR per RECIST 1.1, as assessed by BICR, following administration of pembrolizumab versus placebo when each is combined with chemotherapy in participants with PD-L1 CPS ≥10, PD-L1 CPS ≥1, and in all participants	DOR: The time from first response (CR or PR) to subsequent disease progression, or death from any cause, whichever occurs first
Objective: To evaluate the safety and tolerability of pembrolizumab plus chemotherapy versus placebo plus chemotherapy	AEs Study intervention discontinuation due to AEs
Tertiary/Exploratory	

Objective: To compare the changes from baseline in health-related quality-of-life assessments, using the EORTC QLQ-C30 and the EORTC QLQ-STO22, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	EORTC QLQ-C30 scores EORTC QLQ-STO22 scores
Objective: To characterize utilities, using the EQ-5D™, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	EuroQoL EQ-5D-5L scores
To compare PFS and ORR using modified RECIST 1.1 for iRECIST, as assessed by the investigator, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	PFS using iRECIST OR using iRECIST
Objective: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments	Germline genetic variation, genetic (DNA) mutations from tumour, tumour and blood RNA variation, proteomics and IHC, and other biomarkers

Analysis populations

Efficacy analysis population

The Intention-to-Treat (ITT) population (hereafter referenced as all participants), which consisted of all 1579 randomised participants, whether treatment was administered, served as the population for primary efficacy analysis of OS, PFS, ORR, and DOR. The ITT populations with PD-L1 positive tumours defined by CPS ≥1 and CPS ≥10 (hereafter referenced as PD-L1 CPS ≥1 and CPS ≥10 populations) consisted of 1235 and 551 participants, respectively.

Safety analysis population

Safety analyses were based on all participants as treated (APaT) population, which included all 1572 randomised participants who received at least 1 dose of study intervention according to the study intervention they received.

Patient-reported Outcome Analysis Population

PRO analyses for the EORTC-QLQ-C30, EORTC-QLQ-STO22, and EQ-5D-5L questionnaires were based on the PRO FAS population, which included all 1543 (EORTC-QLQ-C30 and EQ-5D-5L) and 1528 (EORTC-QLQ-STO22) randomised

participants who had at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of study intervention.

Statistical methods

Table 8 Summary of KEYNOTE-859 study statistical methods

Study Design Overview	Phase 3, randomised, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-859) (32)
Treatment Assignment	Participants were randomised in a 1:1 ratio to the experimental group and the control group.
Analysis Populations	Efficacy: ITT Safety: APaT PRO: FAS
Primary Endpoint	OS
Key Secondary Endpoints	PFS per RECIST 1.1 assessed by BICR OR per RECIST 1.1 assessed by BICR
Statistical Methods for Key Efficacy Analyses	The hypotheses on PFS and OS were evaluated by comparing the experimental group to the control group using a stratified Log-rank test. The hazard ratio (HR) was estimated using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method. The stratified Miettinen and Nurminen (M&N) method with sample size weights was used for analysis of ORR (33).
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs were provided for between-treatment differences in the percentage of participants with events, these analyses were performed using the M&N method (33).
Interim Analyses	One interim analysis was planned in this study. Results were reviewed by an external DMC. **Interim Analysis:** Timing: scheduled to be performed after ~ 403 OS events have occurred in CPS ≥10 participants AND ~ 12 months after last participant randomised. If there were fewer than 1187 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number was reached, whichever occurred first. Primary purpose: the final efficacy analysis for ORR and PFS endpoints and the interim analysis for OS in CPS ≥10, in CPS ≥1 and in all participants. **Final analysis:** Timing: scheduled to be performed after ~ 463 OS events have occurred in CPS ≥10 participants and ~ 23 months after last participant randomised. If there were fewer than 1358 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number was reached, whichever occured first. Primary purpose: the final efficacy analysis for OS in CPS ≥10, in CPS ≥1, in all participants.

Multiplicity	The overall type I error over the primary and secondary hypotheses was strongly controlled at 2.5% (1-sided) An initial alpha of 1.7% were assigned to OS in CPS ≥10 participants (H1) and 0.8% to OS in all participants (H3). By using the graphical approach of Mauer and Bretz, if one hypothesis is rejected, the alpha will be shifted to other hypotheses (34).
Sample Size and Power	The overall sample size of the study (ie, all participants) was ~ 1579. The sample size for CPS ≥10 was projected to be ~551 based on a prevalence rate of ~ 35% of the CPS ≥10 participants among all participants. The sample size of CPS ≥1 participants was projected to be ~ 1235 based on a prevalence rate of ~ 78% of the CPS ≥1 participants among all participants. The number of all participants randomised drive the completion of enrolment. There will be ~ 463 OS events in CPS ≥10 participants at the OS final analysis (expected ~54 months). With 463 OS events, the study has ~ 87% power for detecting an AHR of 0.73 in CPS ≥10 participants (H1) at an initially assigned 0.017 (1-sided) significance level. There will be ~ 1057 OS events in CPS ≥1 participants at the OS final analysis. With 1057 OS events, the study has ~ 90% power for detecting an AHR=0.81 in CPS ≥1 participants at the final analysis with an (1-sided) significance level of 0.017 (alpha=0.017 can be passed from H1 to H2 if H1 is rejected). It is estimated that there will be ~ 1358 OS events in all participants at the OS final analysis. With 1358 OS events, the study has ~ 84% power for detecting an AHR=0.83 in all participants at the final analysis with an initially assigned 0.008 (1- sided) significance level.
Data management, patient withdrawals	Subjects may withdraw from the trial at any time for any reason. If a subject withdrew from the trial, h/she no longer received treatment or was followed at scheduled protocol visits. A subject was withdrawn from the trial if: The subject or subject's legally acceptable representative withdrew consent from the trial. The subject was lost to follow-up Subjects who withdrew from treatment prior to completion of the trial were encouraged to continue to be followed for all remaining study visits. When a subject withdrew from participation in the trial, all applicable activities scheduled for the End of Treatment visit were performed at the time of discontinuation.

Table 9 Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method [a]	Analysis Population	Missing Data Approach
Primary Endpoint			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	Censored at the last known alive date
Key Secondary Endpoints			

PFS per RECIST 1.1 by BICR	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	Primary censoring rule Sensitivity analysis 1 Sensitivity analysis 2 (More details are provided in Table 10, Censoring Rules for Primary and Sensitivity Analyses of PFS)
ORR per RECIST 1.1 by BICR	Test and Estimation: Stratified M&N method with sample size weight	ITT (CPS ≥10, CPS ≥1, and all participants)	Participants without assessments are considered no responders and conservatively included in the denominator

BICR=blinded independent central review; CPS=combined positive score; ITT=Intention to Treat; M&N=Miettinen and Nurminen; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours

a. Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomisation (Protocol Section 6.3.2) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.

The non-parametric Kaplan Meier (KM) method was used to estimate the PFS and OS rates over time in each treatment group. The hypotheses of treatment differences in PFS and OS were assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate the magnitude of the treatment difference (HR) between the treatment groups. The stratification factors used for the randomisation were applied to both the stratified log-rank test and the stratified Cox model.

Since PD was assessed periodically, PD could occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD was documented. For the primary analysis, for the subjects who have PD, the true date of PD was approximated by the date of the first assessment at which PD was objectively documented per RECIST 1.1 by investigator. Death was always considered as a confirmed PD event. Subjects who did not experience a PFS event were censored at the last disease assessment.

To evaluate the robustness of the PFS endpoint per RECIST 1.1 by investigator, two sensitivity analyses with different sets of censoring rules were performed for comparison of PFS per RECIST 1.1 by investigator. The first sensitivity analysis followed the intention-to-treat principle. That is, PDs/deaths were counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second

sensitivity analysis considered discontinuation of treatment due to reasons other than complete response or initiation of new anti-cancer treatment, whichever occurred later, to be a PD event for subjects without documented PD or death. If a subject met multiple criteria for censoring, the censoring criterion that occurred earliest was applied. The censoring rules for primary and sensitivity analyses are summarised in Table 10.

Subjects in the placebo plus chemotherapy arm were expected to discontinue treatment earlier compared with subjects in the pembrolizumab plus chemotherapy arm and may have switched to another anti PD-1 treatment following the verification of PD by the central imaging vendor.

Table 10 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study intervention or completed study intervention
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD=progressive disease; PFS=progression-free survival			

The proportional hazards assumption on PFS was examined using both graphical and analytical methods if warranted.

One interim analysis was permitted to be performed in this study based on projection of enrolment and the purpose of each analysis are summarised in Table 11.

Table 11 Summary of Interim and Final Analyses Strategy for Efficacy

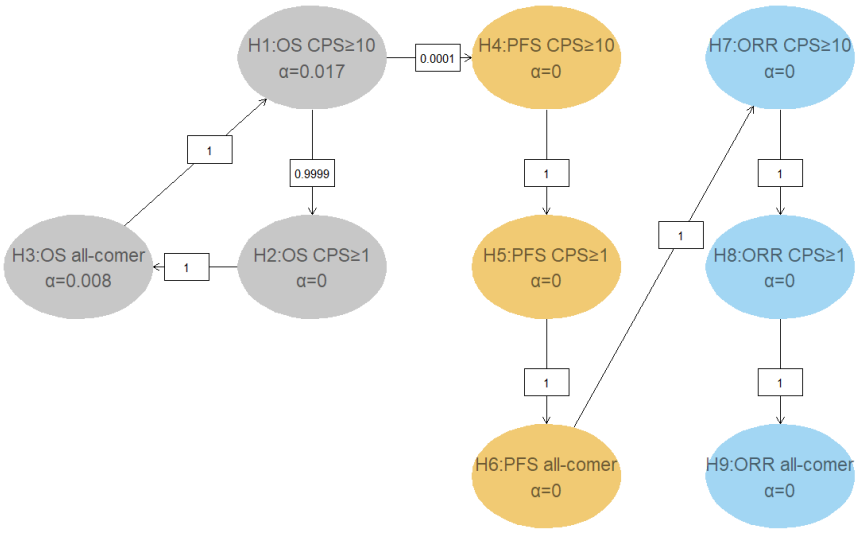
Analyses	Timing	Estimated Months After First Participant Randomised	Primary Purpose of Analysis
Interim Analysis	~ 403 OS events have occurred in CPS ≥10 participants AND ~ 12 months after the last participant has been randomised. If there are fewer than ~1187 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number is reached, whichever occurs first. This is the final analysis of PFS and ORR.	~ 43 months	Efficacy analysis for ORR, PFS, and OS in CPS ≥10, in CPS ≥1, and in all participants.
Final Analysis	~ 463 OS events have occurred in CPS ≥10 participants AND ~ 23 months after the last participant has been randomised. If there are fewer than ~1358 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number is reached, whichever occurs first.	~ 54 months	Efficacy analysis for OS in CPS ≥10, in CPS ≥1, in all participants.
CPS=combined positive score; ORR=objective response rate; OS=overall survival; PFS=progression-free survival			

Multiplicity strategy for PFS, OS and ORR

The study used the graphical method of Maurer and Bretz (34) to provide strong multiplicity control for multiple hypotheses as well as interim analysis. According to this approach, study hypotheses might be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 4 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for re-allocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses. The boundaries provided in this section are calculated based on the estimated number of events at each analysis, and the actual boundaries were

determined from the actual number of events observed at the time of the analyses, using the spending functions specified. Details of multiplicity strategy for the primary and key secondary endpoints are provided in Appendix D.

Figure 4 Maurer and Bretz multiplicity strategy approach used for hypothesis testing in KEYNOTE-859



CPS1=combined positive score ≥1; ORR=objective response rate; OS=overall survival; PFS=progression-free Survival

B 2.4.2 Subgroup Analyses

The estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints were estimated and plotted within each category considered.

Please refer to Section 2.7 for details on statistical tests used in the primary analysis of the subgroups and results.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality Assessment of KEYNOTE-859 was conducted using the Cochrane risk of bias tool. Based on this analysis, the study was determined to be at 'low risk' across all six key domains. The complete quality assessment is included in Appendix D1.4.

B.2.6 Clinical effectiveness results of the relevant studies

Summary of key RCT clinical effectiveness results

- Among participants with PD-L1 CPS ≥1, with previously untreated locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma, pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR when compared with chemotherapy alone, while maintaining HRQoL. This is also true for the results seen in the CPS ≥10 subgroup (see Appendix E).
- The results reported below are for the PD-L1 CPS ≥1 population.
- More complete responses were observed, and the responses were more durable with pembrolizumab plus chemotherapy when compared with chemotherapy alone.
- The OS HR was 0.74 (95% CI: 0.65, 0.84; p<0.0001, which is less than the p-value crossing boundary of 0.020556 for statistical significance) in favour of pembrolizumab plus chemotherapy, representing a statistically significant 26% reduction in the risk of death.
- The median OS was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (13.0 months vs 11.4 months, respectively).
- The PFS HR was 0.72 (95% CI: 0.63, 0.82; p<0.0001, which is less than the p-value crossing boundary of 0.025 for statistical significance) in favour of

pembrolizumab plus chemotherapy, representing a statistically significant 28% reduction in the risk of disease progression and death.

- The median PFS was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (6.9 months vs 5.6 months, respectively).
- The confirmed ORR was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (52.1% vs 42.6%), reflecting a clinically meaningful and statistically significant difference of 9.5% (95% CI: 3.9, 15.0; p=0.00041, which is less than the p-value crossing boundary of 0.025 for statistical significance).
- The median DOR was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (8.3 months vs 5.6 months). The percentage of participants with extended DOR remained higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group at ≥6 months (60.2% vs 47.2%) and ≥24 months (30.0% vs 11.1%).
- Pembrolizumab plus chemotherapy was generally consistent with the individual safety profiles of either chemotherapy regimen alone or pembrolizumab monotherapy. No new safety concerns were identified.

B 2.6.1. KEYNOTE-859 results

Results are presented from the KEYNOTE-859 study, based on the interim analysis 1 (IA1), which had a data cut-off date of 3 October 2022. The trial SOPs for study conduct, monitoring, and oversight during the pandemic were continuously followed and a risk-based approach to assess and mitigate impact on study conduct was employed. Efficacy analyses were conducted using the ITT population. The median duration of follow-up in the PD-L1 CPS ≥1 population was 11.9 months (range: 0.1 to 45.9 months).

The study enrolment period was divided into 2 periods: Global portion of the study and the China mainland extension. After enrolment of the Global portion of the study was completed, the study remained open to enrolment in China mainland until the target number of participants were enrolled to meet local regulatory requirements. The China mainland extension portion was merged into the Global portion of the study and this merged population was used for primary analyses.

The focus of this submission is the PD-L1 positive subgroup of patients (defined as CPS≥1) in line with the population covered by the anticipated marketing authorisation. PD-L1 status was a pre-specified subgroup that was employed as a stratification factor. The majority of participants enrolled in KEYNOTE-859 had tumours with CPS ≥1 (1235 [78.2 %]) including 618 and 617 participants from the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.

Results in both the full ITT population and the subgroup of patients with CPS≥10 are provided in an Appendix E.

Interim analysis 1 – data-cut 3 October 2022

The IA was planned to be performed when approximately 403 OS events occurred in participants whose tumours express PD-L1 with CPS ≥10 and approximately 12 months after the last participant had been randomised.

The primary efficacy endpoints were analysed in the ITT, CPS ≥10 and CPS ≥1 populations, and the hypotheses on PFS and OS were evaluated by comparing the experimental group to the control group using a stratified log-rank test. The HR was estimated using a stratified Cox regression model with Efron's tie handling method. Event rates over time were estimated within each treatment group using the Kaplan-Meier (KM) method.

A total of 1235 participants with PD-L1 CPS≥1 were randomised across 215 global study sites in 33 countries. 42 patients were recruited across 3 sites in the UK. A total of 1235 randomised participants received at least 1 dose of study medication (pembrolizumab plus chemotherapy: 618; chemotherapy: 617). The participant flow and subject disposition from KEYNOTE-859 are provided in Appendix D.

Primary efficacy endpoints: clinical outcome measures included within the health economic model

At IA1, KEYNOTE-859 efficacy results showed that pembrolizumab plus chemotherapy provided a clinically meaningful improvement in both PFS and OS compared with chemotherapy in previously untreated participants with locally advanced unresectable or metastatic HER2 negative gastric or GOJ adenocarcinoma. As of the data cut-off date (3 October 2022) for IA1 CPS≥1 population, the median duration of follow up was 13.0 months (0.2 to 45.9 months) in the pembrolizumab plus chemotherapy group and 11.5 months (0.1 to 45.5 months) in the chemotherapy group.

Overall survival in participants whose tumour express PD-L1 CPS ≥1

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

- The OS HR was 0.74 (95% CI: 0.65, 0.84; p<0.0001, which is less than the p-value crossing boundary of 0.020556 for statistical significance) in favour of pembrolizumab plus chemotherapy, representing a statistically significant 26% reduction in the risk of death.

- The median OS was 13.0 months (95% CI: 11.6, 14.2) and 11.4 months (95% CI: 10.5, 12.0) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.

- By KM estimation, the OS rates at 12, 18, 24, and 30 months were higher 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, with the pembrolizumab plus chemotherapy group reaching a plateau at approximately 39 months, suggesting clinically meaningful long-term benefit with pembrolizumab plus chemotherapy.

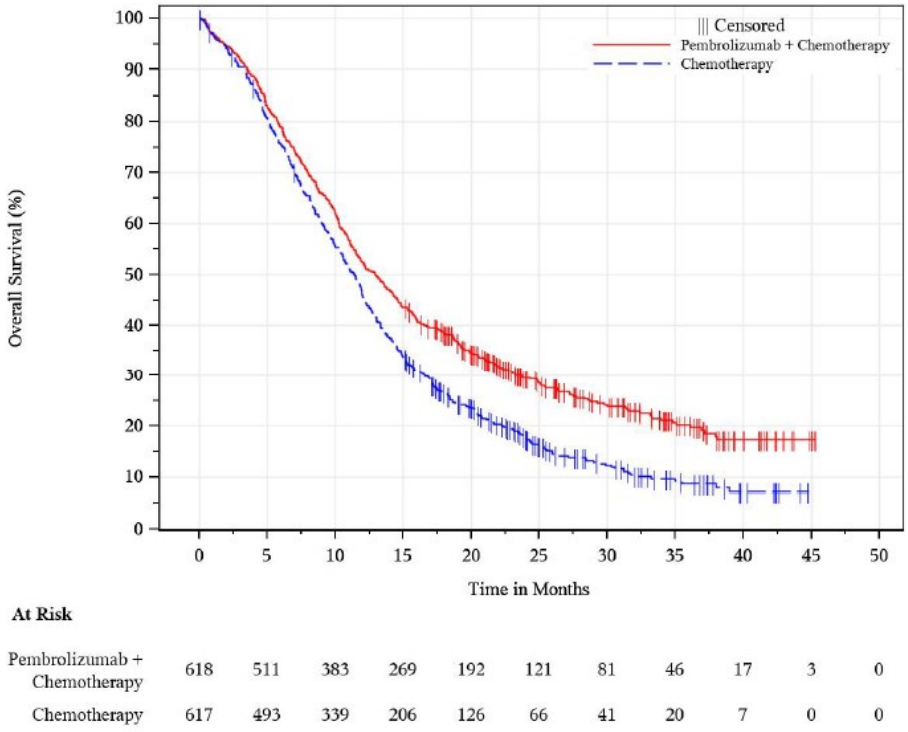
- Improvement in OS with pembrolizumab plus chemotherapy was generally consistent across all subgroups analysed and with the PD-L1 CPS ≥1 population.

Table 12 Analysis of Overall Survival (ITT Population with CPS≥1)

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Number of Events (%)	464 (75.1)	526 (85.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)
[Q1, Q3]	[6.9, 28.7]	[6.2, 18.6]
Person-months	9644.5	8008.1
Event Rate / 100 Person-months	4.8	6.6
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.74 (0.65, 0.84)	
p-value[c]	<0.0001	
OS Rate at month 6 (%) (95% CI)	79.0 (75.5, 82.0)	75.7 (72.1, 78.9)
OS Rate at month 12 (%) (95% CI)	52.4 (48.4, 56.3)	45.7 (41.7, 49.6)
OS Rate at month 18 (%) (95% CI)	38.4 (34.6, 42.3)	26.6 (23.2, 30.2)
OS Rate at month 24 (%) (95% CI)	29.6 (25.9, 33.3)	17.7 (14.7, 21.0)
OS Rate at month 30 (%) (95% CI)	23.9 (20.3, 27.6)	12.3 (9.6, 15.4)

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: 03 October 2022

Figure 5 Kaplan-Meier Plot of Overall Survival (ITT Population with CPS≥1)



Secondary efficacy endpoints: clinical outcome measures included within the health economic model

Progression free survival in participants whose tumour express PD-L1 CPS ≥1

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 0.72 (95% CI: 0.63, 0.82; $p<0.0001$, which is less than the *p-value* crossing boundary of 0.025 for statistical significance) in favour of pembrolizumab plus chemotherapy, representing a statistically significant 28% reduction in the risk of disease progression or death.

- The median PFS was 6.9 months (95% CI: 6.0, 7.2) and 5.6 months (95% CI: 5.4, 5.7) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.

- By KM estimation, the PFS rates at 6, 12, 18, 24, and 30 months were higher 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.

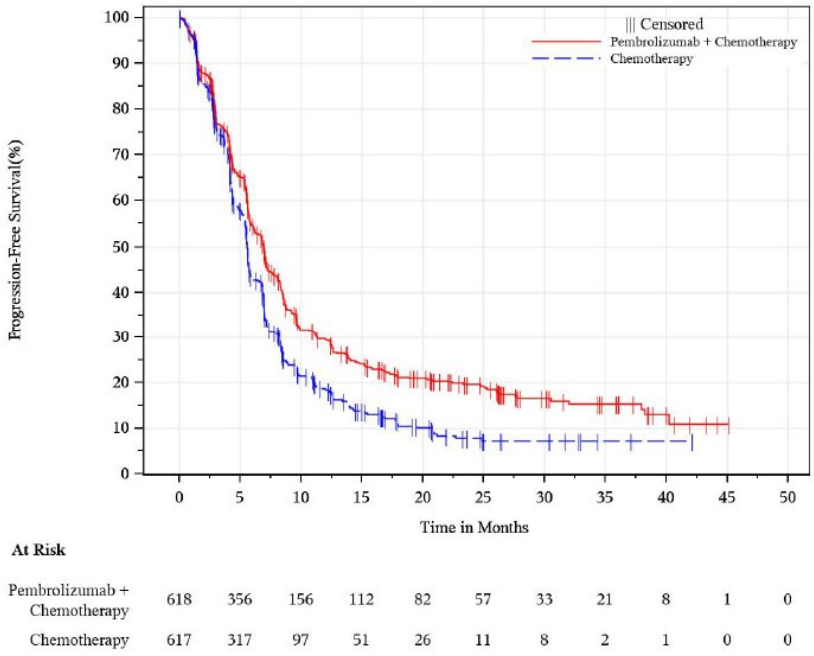
- Improvement in PFS with pembrolizumab plus chemotherapy was generally consistent across all subgroups analysed and with the PD-L1 CPS ≥1 population.

Table 13 Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS≥1)

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Number of Events (%)	443 (71.7)	483 (78.3)
Death	91 (14.7)	92 (14.9)
Documented progression	352 (57.0)	391 (63.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)
[Q1, Q3]	[3.9, 14.0]	[3.2, 8.6]
Person-months	5538.1	3987.5
Event Rate / 100 Person-months	8.0	12.1
vs Chemotherapy		
Hazard Ratio (95% CI)[b]	0.72 (0.63, 0.82)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	54.4 (50.1, 58.4)	43.4 (39.3, 47.5)
PFS Rate at month 12 (%) (95% CI)	29.4 (25.5, 33.3)	18.4 (15.1, 21.9)
PFS Rate at month 18 (%) (95% CI)	21.2 (17.7, 24.9)	10.4 (7.7, 13.6)
PFS Rate at month 24 (%) (95% CI)	19.5 (16.1, 23.2)	7.9 (5.3, 11.0)
PFS Rate at month 30 (%) (95% CI)	16.6 (13.2, 20.3)	7.3 (4.7, 10.5)

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: 03 October 2022

Figure 6 Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS≥1)



Objective response rate in participants whose tumour express PD-L1 CPS ≥1

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

- The confirmed ORR was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (52.1% [95% CI: 48.1, 56.1] vs 42.6% [95% CI: 38.7, 46.6]), reflecting a clinically meaningful and statistically significant difference of 9.5% (95% CI: 3.9, 15.0; *p*=0.00041, which is less than the *p-value* crossing boundary of 0.025 for statistical significance).

- The CR and PR rates were higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (9.9% vs 5.8% and 42.2% vs 36.8%, respectively).

- Improvement in ORR with pembrolizumab plus chemotherapy was generally consistent across all subgroups analysed and with thePD-L1 CPS ≥1 population.

Table 14 Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS≥1)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + Chemotherapy vs. Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	618	322	52.1 (48.1, 56.1)	9.5 (3.9, 15.0)	0.00041
Chemotherapy	617	263	42.6 (38.7, 46.6)		

a Based on Miettinen & Nurminen method 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 i s consistent with the 'Europe' region defined in the protocol for stratification.
b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded Independent Central Review.
Database Cut-off Date: 03 October 2022

Table 15 Summary of Best Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS≥1)

	Pembrolizumab + Chemotherapy			Chemotherapy		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Participants in Population	618			617		
Complete Response (CR)	61	9.9	(7.6, 12.5)	36	5.8	(4.1, 8.0)
Partial Response (PR)	261	42.2	(38.3, 46.2)	227	36.8	(33.0, 40.7)
Overall Response (CR+PR)	**322**	**52.1**	**(48.1, 56.1)**	**263**	**42.6**	**(38.7, 46.6)**
Stable Disease (SD)	194	31.4	(27.7, 35.2)	243	39.4	(35.5, 43.4)
Disease Control (CR+PR+SD)	**516**	**83.5**	**(80.3, 86.3)**	**506**	**82.0**	**(78.7, 85.0)**
Progressive Disease (PD)	54	8.7	(6.6, 11.2)	64	10.4	(8.1, 13.1)
Not Evaluable (NE)	5	0.8	(0.3, 1.9)	12	1.9	(1.0, 3.4)
No Assessment	43	7.0	(5.1, 9.3)	35	5.7	(4.0, 7.8)

Responses are based on BICR assessment per RECIST 1.1. BICR = Blinded independent central review.
Stable disease includes both SD and Non-CR/Non-PD and NED.
NED: No lesions were identified at baseline assessment and there remained no lesions at post baseline assessment(s).
NE: post-baseline assessment(s) available however not being evaluable.
No Assessment: no post-baseline assessment available for response evaluation.
Database Cut-off Date: 03 October 2022

Duration of response in participants whose tumour express PD-L1 CPS ≥1

Pembrolizumab plus chemotherapy resulted in a longer DOR when compared with chemotherapy alone based on BICR assessment per RECIST 1.1.

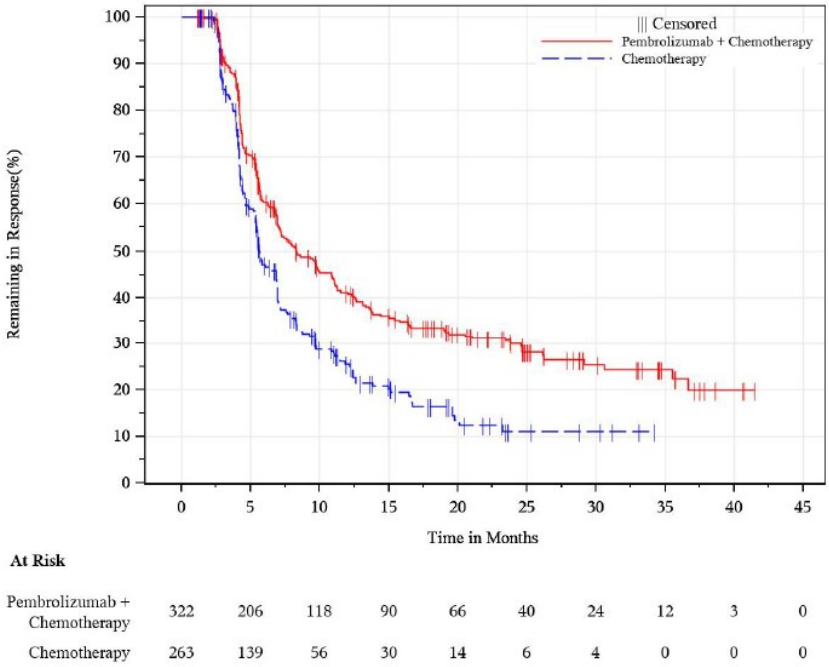
- The median DOR was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (8.3 months vs 5.6 months).
- By KM estimation, the percentage of responders with extended DOR remained higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group at ≥6 months (60.2% vs 47.2%) and ≥24 months (30.0% vs 11.1%).
- The KM curves for DOR separated early and remained separated throughout the evaluation period in favour of the pembrolizumab plus chemotherapy group.
- The median TTR was 1.5 in both intervention groups.

Table 16 Summary of Time to Response and Duration of Response Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response (Participants with CPS≥1)

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Number of participants with response [a]	322	263
Time to Response (months)		
Mean (SD)	2.1 (1.6)	2.0 (1.3)
Median (Range)	1.5 (1.0-15.2)	1.5 (1.1-13.6)
Response Duration [b] (months)		
Median (Range)	8.3 (1.2+ - 41.5+)	5.6 (1.3+ - 34.2+)
Number (%b) of Participants with Extended Response Duration:		
≥6 months	170 (60.2)	106 (47.2)
≥12 months	106 (41.2)	44 (25.6)
≥18 months	76 (33.6)	20 (16.3)
≥24 months	49 (30.0)	6 (11.1)
≥30 months	24 (25.5)	4 (11.1)

[a] Includes participants with complete response or partial response
[b] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment. BICR = Blinded independent central review.
Database Cutoff Date: 03 October 2022

Figure 7 Kaplan-Meier Plot of Duration of Response Based on BICR Assessment per RECIST 1.1 in Participants with a Confirmed Response (Participants with CPS≥1)



Exploratory endpoints

Patient reported outcomes Compliance Rate and Completion Rate – IA1 October 2022 data-cut

Based on criteria for compliance and completion rates prespecified in the statistical analysis plan, Week 18 was selected as the time point for analysing changes from baseline for the EQ-5D-5L.

- In the PRO FAS population, at baseline, completion and compliance rates for the EQ-5D-5L were the same in both intervention groups (97.2% vs 97.8% for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively). At Week 18, the completion rates were 64.1% vs 64.7% and the compliance rates were 82.5% vs 85.7% in the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.

- In the PRO FAS population, baseline EQ-5D-5L VAS scores were similar in both intervention groups. At Week 18, the LS mean change in EQ-5D-5L VAS was similar in both intervention groups (Table 17).

Table 17 Analysis of Change from Baseline in EQ-5D-5L VAS to Week 18 (PRO FAS Population with CPS≥1)

Treatment	Baseline		Week 18		Change from Baseline to Week 18	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)a
Pembrolizumab + Chemotherapy	587	75.21 (17.86)	387	75.83 (16.30)	603	-0.91 (-2.50, 0.68)
Chemotherapy	591	74.87 (18.55)	391	75.44 (17.30)	604	-1.21 (-2.79, 0.38)

Pairwise Comparison	Difference in LS Means [a] (95% CI)	p-Value[a]
Pembrolizumab + Chemotherapy vs. Chemotherapy	0.30 (-1.78, 2.38)	0.7772

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factors (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, Den mark and Hungary, which is consistent with the 'Europe' region defined in the protocol for stratification.
For baseline and Week 18, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Two-sided p-value is based on t test.
Database Cut-off Date: 03 October 2022

B.2.7 Subgroup analysis

Subgroup analyses were pre-specified in the KEYNOTE-859 study protocol to determine whether the treatment effect was consistent across subgroups. The estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints were estimated and plotted within each category of the following classification variables:

- Geographic region (Global Cohort only)
    - Europe/Israel/North America/Australia
    - Asia
    - Rest of the World (including South America)
- Disease status (ECOG 0 versus ECOG 1)
- Chemotherapy regimen (FP or CAPOX)

The results of subgroup analyses for the ITT and CPS≥10 populations are presented in Appendix E.

OS by Subgroup: IA1 October 2022 data-cut

The improvement in OS for pembrolizumab plus chemotherapy compared with chemotherapy in all subjects (based on the October 2022 data-cut) was consistent across the majority of subgroups and sub-populations analysed (Appendix E). Subgroup analyses of OS for the ITT and CPS≥10 population are presented in Appendix E.

PFS by Subgroup: IA1 October 2022 data-cut

The improvement in PFS for pembrolizumab plus chemotherapy compared with chemotherapy (based on the October 2022 data-cut) was observed across all subgroups and sub-populations analysed (Appendix E.) Subgroup analyses of PFS for the ITT and CPS≥10 population are presented in Appendix E.

B.2.8 Meta-analysis

Based on the SLR results, there is only one phase III randomised, controlled trial of pembrolizumab with chemotherapy compared with a relevant comparator, in our specific population of interest (patients with patients with locally advanced or metastatic HER2 negative GC or GOJ adenocarcinoma): KEYNOTE-859. Therefore, it was not possible to conduct a meta-analysis. Please refer to Appendix D for full details of the methodology used for the SLR.

B.2.9 Indirect and mixed treatment comparisons

Summary of key NMA results:

- An NMA would be required to compare pembrolizumab plus CAPOX/FP against XP/ FOLFOX in the untreated locally advanced or metastatic GC or GOJ adenocarcinoma patients. A comparison versus nivolumab in combination with doublet chemotherapy is required in patients whose tumours express PD-L1 CPS ≥5.

- The feasibility assessment concluded that an NMA versus doublet chemotherapies of interest was feasible only under the assumption of doublet

chemotherapy equivalence, and the results mirror the KEYNOTE-859 trial results.

- The trials included in the NMA were identified via the SLR described previously.
- At the time of company submission, an NMA for OS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1 or CPS ≥10. The results show that in participants with PD-L1 CPS ≥1 and CPS ≥10, efficacy of nivolumab in combination with chemotherapy is similar to pembrolizumab in combination with chemotherapy (HR, 95% [redacted]) and (HR, 95% CrI: [redacted]) respectively. The difference between treatments was not statistically meaningful.
- An NMA for PFS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1. The results show that pembrolizumab in combination with chemotherapy performed similarly to nivolumab in combination with chemotherapy (HR, 95% CrI: [redacted]). The difference between treatments was not statistically meaningful.
- An NMA in participants with PD-L1 CPS ≥5 was not undertaken at the time of the evidence submission preparation, since KEYNOTE-859 did not have PD-L1 CPS ≥5 as a prespecified cut point. Further, differences exist between the respective trial multiplicity analysis strategies in KEYNOTE-859 and CheckMate-649. In KEYNOTE-859, CPS ≥1 and CPS ≥10 cuts were prespecified and adjusted for type 1 error however CheckMate-649 trial had a prespecified CPS ≥5 cut for the primary outcome measure. Therefore, the NMA comparison of pembrolizumab in CPS ≥5 may not be statistically appropriate.

In the KEYNOTE-859 study, pembrolizumab in combination with CAPOX or FP has only been directly compared to placebo plus CAPOX or FP in patients with metastatic or locally advanced unresectable HER2-negative GC or GOJ adenocarcinoma. An indirect treatment comparison would be needed to obtain estimates of the relative

efficacy and safety of pembrolizumab + CAPOX/FP versus other regimens relevant to the UK context, including XP and FOLFOX (in participants regardless of PD-L1 CPS status) and nivolumab with chemotherapy (in patients whose tumours express PD-L1 CPS ≥5). A feasibility assessment was undertaken accordingly.

Further details are provided in the following sections.

B 2.9.1 Summary of trials identified following systematic literature review (SLR)

Trials which are relevant for the generation of comparative effectiveness data were identified through the SLR and are presented in Table 18. An overview of the patients' characteristics in all included studies is provided in Appendix D.

Table 18 Summary of the trials of relevance identified through the SLR

Trial	Population	Outcome, assessment
KEYNOTE-859	PD-L1 CPS ≥1	OS
	PD-L1 CPS ≥1	PFS
	PD-L1 CPS ≥10	OS
CheckMate-649	PD-L1 CPS ≥1	OS
	PD-L1 CPS ≥1	PFS
	PD-L1 CPS ≥10	OS

Feasibility assessment

Chemotherapy regimens

For the purposes of this submission, it was of interest to compare the relative efficacy of pembrolizumab + chemotherapy to specific relevant alternative interventions in distinct populations, as outlined in Table 19. For each population, the feasibility of conducting an NMA comparing the relative efficacy of pembrolizumab + chemotherapy versus the population-specific comparators of interest was evaluated.

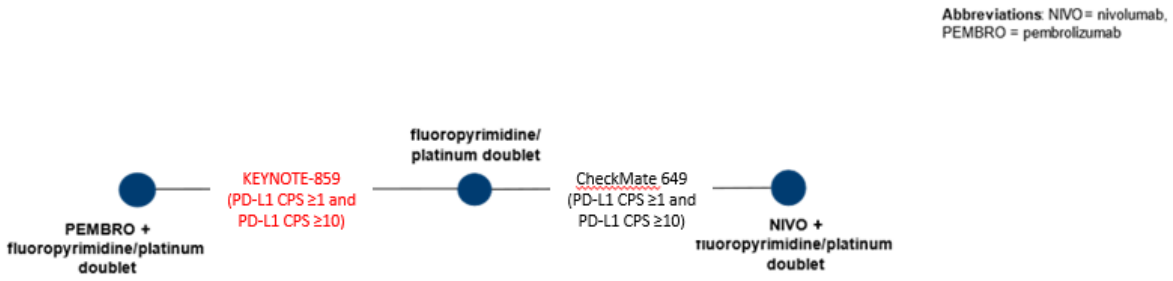
Table 19 Specific indirect comparisons of interest as per NICE final scope

Population	Comparator

Untreated HER2-negative advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with PD-L1 CPS ≥1	Fluorouracil + oxaliplatin: (FOLFOX) Capecitabine + oxaliplatin (CAPOX) Cisplatin + fluorouracil (FP) Cisplatin + capecitabine (XP)
Untreated HER2-negative advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with PD-L1 CPS ≥5	Nivolumab with platinum- and fluoropyrimidine-based chemotherapy

A summary of the feasibility of conducting an NMA of pembrolizumab versus relevant treatments in untreated HER 2-negative advanced or metastatic GC or GOJ adenocarcinoma irrespective of PD-L1 expression status is provided in **Error! Reference source not found.**. A comparison of pembrolizumab plus chemotherapy versus CAPOX and FP can be directly informed from the KEYNOTE-859 study. Comparisons to other specific conventional care chemotherapy regimens used in the UK (XP/FOLFOX) were not feasible as no common comparators were available to form a connected network of RCTs between these treatments and pembrolizumab plus chemotherapy. Based on the widely accepted assumption of clinical equivalence between doublet chemotherapies (as verified by clinical experts consulted), the comparative efficacy of pembrolizumab plus chemotherapy versus XP/FOLFOX is expected to be similar to results seen in KEYNOTE-859.

Figure 8 Illustration of connected network in PD-L1 CPS ≥1 and CPS ≥10



Comparison with Nivolumab + chemotherapy

Both RCTs (KEYNOTE – 859 (32) and CheckMate 649 (31)) identified through the SLR were included in the feasibility assessment. A comparison between pembrolizumab + CAPOX/FP from KEYNOTE-859 and nivolumab + CAPOX/FOLFOX from CheckMate-649 is of interest for the locally advanced metastatic GC or GOJ adenocarcinoma population with CPS ≥5. An NMA in participants with PD-L1 CPS ≥5

was not undertaken at the time of the evidence submission preparation, since KEYNOTE-859 did not have PD-L1 CPS ≥5 as a prespecified cut point. Further, differences exist between the respective trial multiplicity analysis strategies in KEYNOTE-859 and CheckMate-649. In KEYNOTE-859, CPS ≥1 and CPS ≥10 cuts were prespecified and adjusted for type 1 error however CheckMate-649 trial had a prespecified CPS ≥5 cut for the primary outcome measure. Therefore, the NMA comparison of pembrolizumab in CPS ≥5 may not be statistically appropriate. Instead, a feasibility assessment was conducted for an indirect comparison in the CPS ≥1 and CPS ≥10 populations, which is summarised in Table 20.

Table 20 Feasibility of indirect comparison of pembrolizumab + chemotherapy to each comparator relevant to untreated HER2-negative advanced or metastatic GC or GOJ adenocarcinoma with PD-L1 CPS ≥1 and CPS ≥10

Population	Treatment	Comparison feasible for OS?	Comparison feasible for PFS?	Rationale
PD-L1 CPS ≥ 1	Nivolumab with platinum and fluoropyrimidine-based chemotherapy	Yes	Yes	Indirect path via combined platinum doublets
PD-L1 CPS ≥ 10	Nivolumab with platinum- and fluoropyrimidine-based chemotherapy	Yes	No	Indirect path via combined platinum doublets. For CheckMate-649, only a hazard ratio for OS is reported in this population.

NMA results versus nivolumab with chemotherapy

The evidence network informing the NMA of OS and PFS consisted of two RCTs (KEYNOTE-859 and CheckMate-649). Since the proportional hazards tests were consistent with the proportional hazards assumption (see Appendix D), the NMA was conducted assuming constant HRs. Additional NMA methods were also explored (time-varying HRs) with results provided in appendix D. All analyses for OS and PFS 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.

Untreated HER2-negative advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with PD-L1 CPS ≥1

Overall survival

Results of the constant HR NMA for OS in patients with PD-L1 CPS ≥1 are presented in Table 21**Error! Reference source not found.**. Treatment with pembrolizumab plus chemotherapy performed similarly when compared to nivolumab plus chemotherapy (HR, 95% CrI: [redacted]), with no statistically meaningful difference between the treatments.

Table 21 Results of fixed-effects NMA of OS based on constant HRs PD-L1 CPS ≥1 population

Chemotherapy	**1.35 (1.20, 1.52)**	[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

Progression-free survival

Results of the constant HR NMA for PFS in patients with PD-L1 CPS ≥1 are presented in Table 22. Treatment with pembrolizumab plus chemotherapy performed similarly when compared to nivolumab plus chemotherapy (HR, 95% CrI: [redacted]), and the difference between treatments was not statistically meaningful.

Table 22 Results of fixed-effects NMA of PFS based on constant HRs PD-L1 CPS ≥1 population

Chemotherapy	**1.35 (1.18, 1.54)**	[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: 3.36; Deviance: 1.37

Untreated HER2-negative advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma with PD-L1 CPS ≥10

Overall survival

Results of the constant HR NMA in patients in patients with PD-L1 CPS ≥10 are presented in Table 23. Treatment with pembrolizumab with chemotherapy performed similarly when compared to nivolumab with chemotherapy (HR, 95% CrI: [redacted]), and there was not a statistically meaningful difference between treatments.

Table 23 Results of fixed-effects NMA of OS based on constant HRs (PD-L1 CPS ≥10 population)

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: 3.38; Deviance: 1.38

Progression free survival results in PD-L1 CPS ≥10 population are not available due to a lack of reported CheckMate-649 results in this subgroup of patients.

Uncertainties in the indirect and mixed treatment comparisons

The SLR identified two RCTs evaluating the efficacy or safety of interventions of interest for the UK setting in patients with HER2- locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma. Each trial allowed for administration of a mix of fluoropyrimidine and platinum doublet agents, either alone or in combination with pembrolizumab (KEYNOTE-859) or nivolumab (CheckMate-649) The two RCTs were sufficiently similar in study design, sample size, and ECOG performance status (PS) of 0-1. By treating the conventional chemotherapy arms of each study as equivalent, it was deemed feasible to compare pembrolizumab + chemotherapy versus nivolumab + chemotherapy in a network meta-analysis.

KEYNOTE-859, evaluated CAPOX or FP either with or without pembrolizumab and CheckMate-649 evaluated CAPOX or FOLFOX either with or without nivolumab. Due to the differences in pooled chemotherapy arms between the two RCTs, the trials did not form a connected network via a single common comparator. Based on clinical opinion and ESMO guidelines, the specific fluoropyrimidine and platinum doublets

were considered equivalent, and the fluoropyrimidine and platinum arms from both trials were pooled into a single node to form a connected evidence network.

Because pembrolizumab and nivolumab modulate PD-1/PD-L1 pathways, PD-L1 expression is an important relative treatment effect modifier in both KEYNOTE-859 and CheckMate-649.

One key difference between studies limiting the indirect comparisons was the difference in the primary analysis populations. In KEYNOTE-859, CPS ≥1 and CPS ≥10 cuts were prespecified and adjusted for type 1 error however CheckMate-649 trial had a prespecified CPS ≥5 cut for the primary outcome measure. Therefore, the NMA comparison of pembrolizumab in CPS ≥5 may not be statistically appropriate. An NMA in participants with PD-L1 CPS ≥5 was not undertaken at the time of the evidence submission preparation, since KEYNOTE-859 did not have PD-L1 CPS ≥5 as a prespecified cut point.

To mitigate these differences, alternative scenarios (CPS ≥1 and CPS ≥10) were explored and analyses were only conducted when data from comparable populations were available from each study.

In the PD-L1 CPS ≥1 population, pembrolizumab + chemotherapy performed similarly to nivolumab + chemotherapy under a constant hazard ratio assumption for both OS and PFS. In the PD-L1 CPS ≥10 population, pembrolizumab + chemotherapy performed similarly to nivolumab + chemotherapy under a constant hazard ratio assumption for OS; PFS data in this subgroup were not reported in CheckMate-649.

Finally, the NMA was limited by the available data; with only one study informing each comparison, random-effects NMA was not feasible and the fixed-effects analysis results are predicated on an assumption of minimal between-study heterogeneity. In all, results of the NMA suggested that treatment with pembrolizumab + chemotherapy performed similarly in OS and PFS when compared to nivolumab + chemotherapy in locally advanced or metastatic HER-2 negative GC or GOJ adenocarcinoma, irrespective of PD-L1 status.

B.2.10 Adverse reactions

Summary of adverse events information

- The proportion of participants who experienced AEs, drug-related AEs, Grade 3 to 5 AEs, SAEs, drug-related SAEs, discontinuation due to drug-related SAEs, and discontinuations due to SAEs were similar between treatment groups.
- The proportion of participants who experienced drug-related Grade 3 to 5 AEs was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group.
- The number of reported deaths due to drug-related AEs was lower in the pembrolizumab plus chemotherapy group (8 participants [1.3%]) compared with the chemotherapy group (16 participants [2.6%]).
- There were no trends identified in the overall incidences of the AEs by backbone therapy, age, ECOG status, sex, geographic region, and race.
- AEs were consistent with the established safety profile of pembrolizumab and the chemotherapy, and no new safety concerns were identified.

The primary safety analyses of IA1 were based on data from the All Participants as Treated (APaT) population of 1572 participants (ITT population) of whom 1231 participants were with CPS $\geq$1 as of the cut-off date of 3 October 2022. In all tables, individuals are counted only once for a specific AE term by the worst severity recorded.

Please refer to Appendix F for information related to the following:

- Drug-related AEs
- Grade 3-5 AEs
- Serious AEs
- Death to AEs

- Discontinuation due to AEs
- AEs of special interest.

The median exposure to study drug was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (9.1 vs 7 months) (Table 24). The mean exposure and mean number of cycles received was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group. Participants in the pembrolizumab plus chemotherapy group (26.7%) remained on treatment for ≥12 months compared with the chemotherapy group (15.1%). The rate of drug-related AEs was similar between the groups (Table 25).

Table 24 Summary of Drug Exposure Participants with CPS≥1 (All-Participants-as-Treated Population)

	Pembrolizumab + Chemotherapy	Chemotherapy	Total
	(N=615)	(N=616)	(N=1231)
Study Days on Therapy (months)			
n	615	616	1231
Mean (SD)	9.1 (7.8)	7.0 (5.7)	8.0 (6.9)
Median	6.5	5.6	5.8
Range	0.0 to 33.7	0.0 to 29.7	0.0 to 33.7
Number of Cycles			
n	615	616	1231
Mean (SD)	12.6 (10.5)	9.8 (7.6)	11.2 (9.3)
Median	9.0	8.0	8.0
Range	1.0 to 35.0	1.0 to 35.0	1.0 to 35.0
Database Cut-off Date: 03 October 2022			

In the pembrolizumab plus chemotherapy group, more participants had a duration of exposure of ≥3, ≥6, ≥12 months compared with participants in the chemotherapy group.

Table 25 Exposure by Duration Participants with CPS≥1 (All-Participants-as-Treated Population)

Duration of Exposure	Pembrolizumab + Chemotherapy			Chemotherapy		
	(N=615)			(N=616)		
	n	(%)	Person-months	n	(%)	Person-months
> 0 m	615	(100.0)	5,613.5	616	(100.0)	4,283.0
≥ 1 m	563	(91.5)	5,591.8	569	(92.4)	4,262.4

≥ 3 m	477	(77.6)	5,421.5	459	(74.5)	4,042.8
≥ 6 m	322	(52.4)	4,706.5	280	(45.5)	3,220.4
≥ 12 m	164	(26.7)	3,369.3	93	(15.1)	1,672.7
≥ 18 m	109	(17.7)	2,554.4	40	(6.5)	896.4
Each participant is counted once on each applicable duration category row. *Duration of exposure is the time from the first dose date to the last dose date.* *Database Cutoff Date: 03OCT2022*						

Table 26 Estimated Median and Mean Time on Treatment Participants with CPS≥1 (All-Participants-as-Treated Population)

Treatment	N	Number of Events (%)	Estimated Median (95% CI) Time in months	Estimated Mean (SE) Time in months	95% CI of Estimated Mean Time in months
Pembrolizumab + Chemotherapy	615	581 (94.5)	6.47 (5.75, 6.93)	9.4 (0.3)	(8.7, 10.0)
Chemotherapy	616	599 (97.2)	5.55 (5.32, 5.95)	7.1 (0.2)	(6.6, 7.5)
Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method *Time on Treatment is defined as the time from the date of initial dose until the date of last dose* *Number of Events is defined as number of participants who had discontinued or completed primary study treatment at the database cutoff date* *Database Cutoff Date: 03OCT2022*					

Adverse events

The observed AEs in the pembrolizumab plus chemotherapy group were generally consistent with the known safety profiles of either chemotherapy regimen alone or pembrolizumab monotherapy. No new safety concerns were identified.

The incidences of AEs were generally similar in the pembrolizumab plus chemotherapy group and the chemotherapy group for most AE categories. Notably, generally similar proportions of participants in both intervention groups experienced drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, and drug-related SAEs.

The incidences of AEs resulting in treatment discontinuations and treatment interruptions were generally similar in the pembrolizumab plus chemotherapy group and the chemotherapy group.

The number of participants with AEs resulting in death was similar between the pembrolizumab plus chemotherapy (53 [8.6%] participants) and chemotherapy group

(50 [8.1 %] participants). Overall, 8 participants (1.3%) died due to drug-related AEs in the pembrolizumab plus chemotherapy group and 16 participants (2.3%) died due to drug-related AEs in the chemotherapy group. Based on medical review, the AEs and resulting fatal outcomes were likely related to underlying disease or other comorbidities. No new safety concerns were identified for pembrolizumab.

As expected, a higher proportion of participants experienced AEOSIs in the pembrolizumab plus chemotherapy group than in the chemotherapy group. Observed AEOSIs in the study were generally reversible and manageable with standard therapeutic and supportive care strategies. Most AEOSIs were nonserious and Grade 2 or 3 in severity. A total of two participants died due to an AEOSI of pneumonitis, including 1 participant in the pembrolizumab plus chemotherapy group and 1 participant in the chemotherapy group.

The most frequently reported AEOSIs in the pembrolizumab plus chemotherapy group were infusion reactions, hypothyroidism, hyperthyroidism, colitis and pneumonitis, while the most frequently reported AEOSI in the chemotherapy group was infusion reactions. Most AEOSIs were Grade 1 or 2 in severity and managed by standard treatments, as appropriate. The infusion reactions observed in both groups may be likely attributed to chemotherapy and trastuzumab. Overall, the severity, outcome, and manageability of the AEOSI events in the pembrolizumab plus chemotherapy group were generally consistent with those previously reported for pembrolizumab monotherapy or for the chemotherapy.

Table 27 Adverse Event Summary Participants with CPS≥1 (All-Participants-as-Treated Population)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Participants in population	615		616	
with one or more adverse events	607	(98.7)	602	(97.7)
with no adverse event	8	(1.3)	14	(2.3)
with drug-related[a] adverse events	586	(95.3)	575	(93.3)
with toxicity grade 3-5 adverse events	464	(75.4)	418	(67.9)
with toxicity grade 3-5 drug-related adverse events	366	(59.5)	306	(49.7)
with serious adverse events	293	(47.6)	244	(39.6)
with serious drug-related adverse events	156	(25.4)	116	(18.8)
with dose modification[b] due to an adverse event	533	(86.7)	510	(82.8)
who died	53	(8.6)	50	(8.1)

who died due to a drug-related adverse event	8	(1.3)	16	(2.6)
discontinued due to an adverse event	205	(33.3)	167	(27.1)
discontinued pembrolizumab/placebo	99	(16.1)	73	(11.9)
discontinued any chemotherapy	187	(30.4)	164	(26.6)
discontinued all drugs	57	(9.3)	54	(8.8)
discontinued due to a drug-related adverse event	161	(26.2)	129	(20.9)
discontinued pembrolizumab/placebo	57	(9.3)	35	(5.7)
discontinued any chemotherapy	147	(23.9)	127	(20.6)
discontinued all drugs	27	(4.4)	25	(4.1)
discontinued due to a serious adverse event	89	(14.5)	71	(11.5)
discontinued pembrolizumab/placebo	80	(13.0)	65	(10.6)
discontinued any chemotherapy	71	(11.5)	68	(11.0)
discontinued all drugs	48	(7.8)	50	(8.1)
discontinued due to a serious drug-related adverse event	47	(7.6)	34	(5.5)
discontinued pembrolizumab/placebo	41	(6.7)	28	(4.5)
discontinued any chemotherapy	35	(5.7)	33	(5.4)
discontinued all drugs	21	(3.4)	22	(3.6)

a Determined by the investigator to be related to the drug.
b Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
MedDRA V25.0 preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 03OCT2022

B.2.11 Ongoing studies

The KEYNOTE-859 study is ongoing, with an estimated study completion date of September 2024. There are no other ongoing clinical trials for pembrolizumab in this indication other than KEYNOTE-859.

B.2.12 Interpretation of clinical effectiveness and safety evidence

The KEYNOTE-859 trial demonstrates that pembrolizumab plus chemotherapy provides a statistically significant and clinically meaningful improvement in OS, PFS, and ORR when compared with chemotherapy alone, while maintaining HRQoL, in participants with previously untreated locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma expressing PD-L1 at CPS ≥1. This finding is also consistent in an all-comer (ITT) population as well as the CPS ≥10 subgroup (see Appendix E). More complete responses were observed, and the responses were more durable with pembrolizumab plus chemotherapy when compared with chemotherapy alone.

The safety results from KEYNOTE-859 showed the combination of pembrolizumab plus chemotherapy is comparable with chemotherapy alone and reflective of AEs expected for chemotherapy and pembrolizumab. Thus, pembrolizumab plus chemotherapy aims to offer the first IO treatment option for patients in with GC and GOJ adenocarcinoma, with CPS ≥ 1, thereby addressing the existing unmet need and broadening the available treatment options for clinicians across all GC and GOJ adenocarcinoma patients.

Efficacy

Among participants with PD-L1 CPS ≥1 with previously untreated locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma, pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS when compared with chemotherapy alone. The results in all participants (ITT population) and the CPS≥10 subgroup are consistent with these findings and are reported in appendix E.

- In the PD-L1 CPS ≥1 population, the OS HR was 0.74 (95% CI: 0.65, 0.84; *p*<0.0001, which is less than the *p-value* crossing boundary of 0.020556 for statistical significance) in favour of pembrolizumab plus chemotherapy, representing a statistically significant 26% reduction in the risk of death.

- The median OS was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (13.0 months vs 11.4 months, respectively).

Among participants with PD-L1 CPS ≥1 with previously untreated locally advanced unresectable or metastatic HER2-negative gastric or GOJ adenocarcinoma, pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in PFS and ORR when compared with chemotherapy alone. Pembrolizumab plus chemotherapy provided a longer DOR when compared with chemotherapy alone. The results in all participants (ITT population) and the CPS≥10 subgroup are consistent with these finding and are reported in appendix E.

- The PFS HR was 0.72 (95% CI: 0.63, 0.82; p<0.0001, which is less than the p-value crossing boundary of 0.025 for statistical significance) in favour of pembrolizumab plus chemotherapy, representing a statistically significant 28% reduction in the risk of disease progression and death. The median PFS was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (6.9 months vs 5.6 months, respectively).

- The confirmed ORR was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (52.1% vs 42.6%), reflecting a clinically meaningful and statistically significant difference of 9.5% (95% CI: 3.9, 15.0; p=0.00041, which is less than the p-value crossing boundary of 0.025 for statistical significance).

- The median DOR among responders in the PD-L1 CPS ≥1 population was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (8.3 months vs 5.6 months). The percentage of participants with extended DOR remained higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group at ≥6 months (60.2% vs 47.2%) and ≥24 months (30.0% vs 11.1%).

Safety

The safety profile of pembrolizumab in combination plus chemotherapy:

- Is generally consistent with the individual profiles of either chemotherapy regimen alone or pembrolizumab monotherapy. No new safety concerns were identified.

- Has a tolerable and manageable safety profile. AEs are generally managed by standard clinical practice as applicable for pembrolizumab monotherapy, or chemotherapy.

- Showed no new indication-specific immune-mediated AEs.

Patient-reported Outcomes Results Summary

HRQoL, as evaluated by the EORTC-QLQ C30, the EORTC-QLQ STO22, and the EuroQoL EQ-5D-5L scores, was maintained in the pembrolizumab plus chemotherapy group compared with the chemotherapy group in the PRO FAS and PD-L1 CPS ≥1 population. No scales or scores worsened in the pembrolizumab plus chemotherapy group.

NMA results summary

An NMA would be required to compare pembrolizumab plus CAPOX/FP against XP/ FOLFOX in the untreated locally advanced or metastatic GC or GOJ adenocarcinoma patients. A comparison versus nivolumab in combination with doublet chemotherapy is required in patients whose tumours express PD-L1 CPS ≥5.

The feasibility assessment concluded that an NMA versus doublet chemotherapies of interest was feasible only under the assumption of doublet chemotherapy equivalence, and the results mirror the KEYNOTE-859 trial results.

At the time of company submission, an NMA for OS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1 or CPS ≥10. The results show that in participants with PD-L1 CPS ≥1 and CPS ≥10 efficacy of nivolumab in combination with chemotherapy is similar to pembrolizumab in combination with chemotherapy (HR, 95% CrI: [redacted]) and (HR, 95% CrI: [redacted]) respectively. The difference between treatments was not statistically meaningful.

An NMA for PFS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1. The results show that pembrolizumab in combination with chemotherapy performed similarly to nivolumab in combination with chemotherapy (HR, 95% CrI: [redacted]). The difference between treatments was not statistically meaningful.

An NMA in participants with PD-L1 CPS ≥5 was not undertaken at the time of the evidence submission preparation, since KEYNOTE-859 did not have PD-L1 CPS ≥5 as a prespecified cut point. Therefore, the NMA comparison of pembrolizumab in CPS ≥5 may not be statistically appropriate.

Internal validity

KEYNOTE-859 is a robust, multi-centre, randomised, double-blind, placebo-controlled phase III trial of pembrolizumab and chemotherapy versus chemotherapy alone in patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ who have not received prior therapy. Prior to randomisation, eligible subjects were first stratified by, geographic region, chemotherapy regimen and PD-L1 status.

The primary endpoint was to compare OS and PFS (per RECIST 1.1 as assessed by BICR) in subjects treated with pembrolizumab and chemotherapy versus chemotherapy. OS is a clinically relevant endpoint, that was directly referenced in the final scope for this appraisal and the decision problem. This selected endpoint is consistent with that used in studies of other therapeutic agents in the population of locally advanced unresectable or metastatic GC or GOJ adenocarcinoma. The definition of progression when evaluating the secondary endpoint -PFS in KEYNOTE-859, followed an established response evaluation criterion (RECIST 1.1), in line with European Guidance (35).

HRQoL was explored under exploratory endpoints in the KEYNOTE-859 study, with changes from baseline in patients treated with pembrolizumab and chemotherapy compared to chemotherapy recorded using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC QLQ-C30 and EORTC QLQ-ST022.

KEYNOTE-859 is a double-blind study, with study sponsor, investigator and participant not aware of the treatment administered. This ensures the absence of bias in study results and the credibility of study conclusions.

External validity

KEYNOTE-859 is a global study conducted in 215 centres in 33 countries, including 3 sites in the UK. Of the patients participating in the study, 42 were enrolled at sites in the UK.

Baseline characteristics of patients enrolled in KEYNOTE-859 were as expected for patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma. Most patients were male, <65 years old, and had an ECOG

performance status of 1. The majority of participants had adenocarcinoma of the stomach (78.7%), had tumour PD-L1 status of CPS ≥1 (78.2%), and were on a CAPOX regimen (86.3%). The treatment arms were generally well balanced by all baseline characteristics.

The observed safety profile of pembrolizumab and chemotherapy in KEYNOTE-859 reflects the known safety profiles of the components i.e. generally well-tolerated. The types and severity of adverse events observed in the pembrolizumab and chemotherapy group were generally consistent with the established pembrolizumab safety profile. No new safety signal was identified.

Part of this study was conducted during the COVID-19 pandemic. The trial SOPs for study conduct, monitoring, and oversight during the pandemic were continuously followed and a risk-based approach to assess and mitigate impact on study conduct was employed. The impact of the COVID-19 pandemic has not been captured in the KEYNOTE–859 results.

B.3 Cost effectiveness

Summary of key cost effectiveness information

Objective:

- To estimate the cost-effectiveness of adding pembrolizumab to doublet chemotherapy for patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma, expressing a CPS≥1.
- To estimate the cost-effectiveness of pembrolizumab plus doublet chemotherapy compared with nivolumab plus doublet chemotherapy for patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma. As data does not currently permit a comparison in patients expressing a CPS≥5, cost-effectiveness was instead assessed in patients expressing a CPS≥10.

Model structure:

- Partitioned survival analysis structure, with three key health states: progression free, progressed disease and death.
- This structure enables the primary (OS) and secondary endpoints (PFS) of the KEYNOTE-859 trial to be utilised.

Model inputs:

Patient population inputs:

- Aligned with the KEYNOTE-859 trial, which clinical experts considered to be broadly generalisable to patients in the NHS.

Clinical efficacy inputs:

- The KEYNOTE-859 trial was the primary source of evidence for the efficacy and safety of pembrolizumab plus doublet chemotherapy compared to doublet chemotherapy treatment.

- An NMA was required to compare pembrolizumab plus doublet chemotherapy with nivolumab plus doublet chemotherapy; this was feasible for OS in patients expressing a CPS≥10.
- Survival curve fitting was carried out in line with NICE DSU guidelines.
- Statistical goodness-of-fit, visual plausibility and clinical plausibility of the predicted survival were used to select the base case parametric survival curves.

Utility inputs:

- Given the paucity of utility data in the published literature within HER2 negative GC, utility data from the KEYNOTE-859 trial were used to inform the economic analysis.
- In the KEYNOTE-859 trial, the EuroQoL EQ-5D-5L questionnaire was completed by patients. Utility values from the KEYNOTE-859 trial were calculated by mapping the 5L descriptive system onto the 3L value set.
- A time-to-death approach for estimating utility was employed to address the potential limitations of the health state approach.
- AE disutility values were applied as a one-off QALY loss in the first model cycle to account for different AE profiles.

Costs and resource use inputs:

- Drug costs and unit costs of tests and services were obtained from NICE approved sources.
- Resource use estimates were sought from the literature identified in the SLR and previous NICE appraisals.
- Clinical expert opinion was obtained to validate resource use estimates.

Base-case results and sensitivity analyses:

- The ICER for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy in the CPS≥1 population is [redacted]. This ICER includes a severity modifier of [redacted] and the pembrolizumab CAA price.
- The ICER for pembrolizumab plus doublet chemotherapy versus nivolumab doublet chemotherapy in the CPS≥10 population is [redacted]. This ICER includes a severity modifier of [redacted] and the pembrolizumab list price.
- Extensive sensitivity analyses have been conducted, including probabilistic analyses, deterministic one-way sensitivity analyses and pessimistic scenarios.
- ICERs are generally robust to alternative assumptions in both comparisons. The exception is the ICER for pembrolizumab plus doublet chemotherapy versus nivolumab doublet chemotherapy in the CPS≥10 population, which is sensitive to the OS HR.

Cost effectiveness conclusions:

- The results show that pembrolizumab plus doublet chemotherapy would be considered cost-effective compared to doublet chemotherapy in the CPS≥1 population as the ICER is [redacted] the WTP threshold of £30,000 per QALY.
- The CAA discount associated with nivolumab is unknown; therefore, pembrolizumab plus doublet chemotherapy may be considered cost-effective compared to nivolumab plus doublet chemotherapy in the CPS≥10 population after CAA is taken into consideration.
- A key strength of pembrolizumab is that the label permits pembrolizumab 400mg to be given Q6W. Therefore, 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.

B.3.1 Published cost-effectiveness studies

In line with the NICE health technology evaluations manual of process and methods, a systematic literature review (SLR) was conducted to identify relevant cost-effectiveness studies from published literature. The search was conducted in April 2023.(36)

Cost-effectiveness studies evaluating pembrolizumab with doublet chemotherapy compared with doublet chemotherapy alone in the specified population were not identified. Three previous NICE appraisals in similar populations were identified by the review. Table 28 summarises the populations covered by these appraisals while Table 29 summarises their cost-effectiveness results. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

Table 28. Summary of populations in previous related NICE TAs

HTA	HER2 status	Tumour location			CPS expression
		Oesophageal	GOJ	Gastric	
ID4030 (current)	Negative	No	Yes	Yes	≥1
TA857	Negative	Yes	Yes	Yes	≥5
TA737	Negative	Yes	Yes	No	≥10
TA208	Positive	No	Yes	Yes	NA

Abbreviations: CPS, combined positive score; GOJ, gastroesophageal; HER2, human epidermal growth factor receptor 2; HTA, health technology assessment; NA, not applicable.

TA857 appraised nivolumab with doublet chemotherapy for patients with untreated HER2 negative advanced gastric, GOJ or oesophageal cancer expressing a CPS≥5.(21) This appraisal is considered to be the most relevant of those identified as it aligns with this submission's population regarding HER2 status and largely regarding tumour location. Many assumptions in the TA857 appraisal were informed by the NICE appraisal of trastuzumab for untreated HER2 positive metastatic gastric and GOJ cancer (TA208).(28) TA208 is considered less relevant to this appraisal as it focuses on patients who are HER2 positive.

In Table 29, recommendations according to CPS expression are also provided. This summary shows that there have been no innovative treatments for patients expressing

a CPS<5 and doublet chemotherapy regimens remain the only available treatment options. 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 and broadening the available treatment options for clinicians when treating GC and GOJ adenocarcinoma patients.

Table 29. Summary of cost-effectiveness results in previous related NICE TAs

Study	Year	Comparator	Summary of model	QALYs	Costs	ICER (per QALY gained)
TA208	2010	Triplet chemotherapy (ECX, ECF or EOX)	Markov with three health states*	Total QALYs, ERG: HCX 1.097 to 1.192 HCF 0.994 to 1.084	Total costs, ERG: HCX £28,464 to £29,761† HCF £27,629 to £28,636†	Committee agreed the ICER for the IHC3 subgroup was between £45,000 and £50,000 using the ERG analyses†
TA737	2021	Doublet chemotherapy (CAPOX or FP)	Partitioned survival with three health states	Total QALYs redacted Company inc. QALYs 0.92 ERG inc. QALYs 0.76	Total costs redacted. Company inc. costs £26,213 ERG inc. costs £26,192‡	Company base case £28,651 ERG base case £34,330%‡
TA857	2023	Doublet chemotherapy (XELOX or FOLFOX)	Partitioned survival with three health states§	Redacted	Redacted	After the third committee meeting the company updated its commercial arrangement and submitted updated results which led to ICERs below £50,000

Abbreviations: ECX, epirubicin in combination with cisplatin and capecitabine; ECF, epirubicin in combination with cisplatin and 5-FU; EOX, epirubicin in combination with oxaliplatin and capecitabine; ERG, Evidence Review Group; CAPOX/XELOX, oxaliplatin and capecitabine; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FP, cisplatin and fluorouracil; HCF, trastuzumab in combination with cisplatin and 5-FU; HCX, trastuzumab in combination with cisplatin and capecitabine; ICER, incremental cost-effectiveness ratio; ICH3, positive immunohistochemistry score of 3 (to determine HER2 positivity); OS, overall survival; PFS, progression free survival; QALYs, quality-adjusted life years.
*This structure would be interpreted as a partitioned survival model as health state occupancy was determined by PFS and OS curves
†The company did not submit a PAS
‡ Results include the CAA discount for pembrolizumab
§ In the company's original submission, the model was a semi-Markov model with 4 states: pre-progression, progressed disease, long-term remission, and death. After consultation, the company presented a partitioned survival model, which the committee concluded was appropriate.

B.3.2 Economic analysis

3.2.1 Patient population

The base case patient population included in the economic analysis is patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma, expressing a CPS≥1. This aligns with the anticipated licensed population in the UK. The patient population included in the economic analysis also reflects a pre-defined subgroup investigated in the KEYNOTE-859 trial. Patients were stratified by CPS <1 and ≥1 in the KEYNOTE-859 trial.

The NICE final scope(37) asks for subgroups to be considered by PD-L1 status and tumour location, if evidence allows:

- **PD-L1 status**. Cost-effectiveness results are also estimated for patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma, expressing a CPS≥10. Although treatment allocation/randomisation were not stratified according to CPS≥10 in the KEYNOTE-859 trial, CPS≥10 was pre-specified in the sample size and power calculations for hypothesis testing. Subgroup results from the KEYNOTE-859 trial suggest cost-effectiveness results will differ between patients expressing CPS≥1 and CPS≥10 (OS HRs [95% CIs] of 0.74 [0.65 to 0.84] and 0.65 [0.53 to 0.79], respectively). Furthermore, as detailed in Section B.3.2.2, the comparators in the NICE final scope vary depending on a patient's CPS level.

- **Tumour location**. Cost-effectiveness results are not estimated according to tumour location for a number of reasons. Firstly, based on current NICE recommendations (TA857, TA208, TA737), treatments do not depend on tumour location. Secondly, clinical experts consulted by MSD explained how the definition of GOJ is subjective and varies between clinics and clinical trials. Thirdly, patients in KEYNOTE-859 with untreated HER2 negative advanced gastric adenocarcinoma, expressing a CPS≥1, had similar results to those patients with untreated HER2 negative advanced GOJ adenocarcinoma, expressing a CPS≥1 (OS HRs [95% CIs] of 0.73 [0.63 to 0.84] and 0.71 [0.55 to 0.93], respectively – See Appendix E).

The baseline patient characteristics in the economic model reflect the baseline characteristics of patients enrolled into the KEYNOTE-859 trial, as detailed in Table 30. Clinical experts consulted by MSD reviewed the baseline patient characteristics in the KEYNOTE-859 trial and noted that patients in the trial are a few years younger than those treated in clinical practice, but this would not invalidate our results. Similarly, the TA857 committee concluded that there is no evidence that treatment would be less effective in older people and treatment should be based on patient fitness and comorbidities, regardless of age. To determine if the cost-effectiveness results are sensitive to baseline patient characteristics, these inputs are varied in one-way sensitivity analysis; the impact of age on the results was found to be minimal.

Table 30. Baseline patient characteristics included in the economic model

Baseline patient characteristic	CPS≥1	CPS≥10
Age, years	60.1	60.7
Proportion of females	29.6%	27.8%
Weight, kg	66.3	66.7
BSA, m^2	1.7	1.7
Abbreviations: BSA, body surface area; CPS, combined positive score. Source: Tables 12 and 18 of the HTA Disposition and Demographics Report		

3.2.2 Intervention technology and comparators

The modelled intervention is pembrolizumab plus doublet chemotherapy.

There are two relevant comparators:

1. doublet chemotherapy for all patients expressing a CPS≥1 and,
2. in patients expressing CPS≥5, nivolumab plus doublet chemotherapy.

Thus, the modelled comparator depends on the patient's CPS level.

Cost-effectiveness results for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy are presented for the full anticipated licensed indication (i.e., patients expressing a CPS≥1). MSD acknowledges that the patient population receiving doublet chemotherapy in NHS practice could be narrower than this (i.e.,

patients expressing a CPS<5). To help address this uncertainty, CPS 1 to 9 results for pembrolizumab plus doublet chemotherapy vs doublet chemotherapy from the KEYNOTE-859 trial are presented and discussed (see Section 3.3.1.2).

As noted in Section B.2.9, CPS≥5 was not a prespecified cut-off in the KEYNOTE-859 trial and subgroup data for the CPS≥5 population of KEYNOTE-859 is not currently available. Consequently, an NMA at CPS≥5 was infeasible and cost-effectiveness results for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy are presented for patients expressing CPS ≥10, which was prespecified and had subgroup data available, making an NMA feasible.

In the KEYNOTE-859 trial, pembrolizumab 200mg or placebo was given intravenously (IV) every 3 weeks (Q3W) in combination with investigator's choice of doublet chemotherapy:

- FP (continuous infusion of 5-fluorouracil [800 mg/m2/day on days 1–5 of each cycle] + iv. cisplatin [80 mg/m2] Q3W); or,
- CAPOX (oral capecitabine [1000 mg/m2 twice daily on days 1–14 of each cycle] + iv. oxaliplatin [130 mg/m2 on day 1 of each cycle] Q3W).

In the base case, the proportion of patients receiving each type of doublet chemotherapy regimen are informed by KEYNOTE-859 for pembrolizumab plus doublet chemotherapy and doublet chemotherapy, and CheckMate 649 for nivolumab plus doublet chemotherapy (Table 31).

Clinical expert opinion indicated that the majority of NHS patients receive the CAPOX regimen. However, if patients experience swallowing difficulties, capecitabine would be substituted with fluorouracil (FOLFOX or FP). Also, if patients are at risk of neuropathy, oxaliplatin would be substituted with cisplatin (FP or XP), but this does not occur often. Clinical experts also noted that the choice of doublet chemotherapy would not depend on CPS level or the IO it was given in combination with. Furthermore, the recommendation wording in TA737 and TA857 does not specify specific doublet chemotherapy regimens (IO with platinum and fluoropyrimidine-based

chemotherapy). A scenario analysis explores the doublet chemotherapy proportions provided by the clinical experts (Table 32).

Table 31. Proportion of patients receiving each doublet chemotherapy regimen (base case analysis: trial data)

Doublet chemotherapy regimen	Treatment arm			
	Pembrolizumab plus doublet chemotherapy		Doublet chemotherapy	Nivolumab plus doublet chemotherapy
Population	CPS≥1	CPS≥10	CPS≥1	CPS≥10*
CAPOX/XELOX	85.4%	86.7%	85.6%	51%
FP	14.6%	13.3%	14.4%	-
FOLFOX	-	-	-	49%
XP	-	-	-	-

Abbreviations: CAPOX/XELOX, oxaliplatin and capecitabine; CPS, combined positive score; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FP, cisplatin and fluorouracil; XP, capecitabine and cisplatin
Source: Tables 26 and 45 of the HTA HECON Baseline and Efficacy Report
*Data from patients in CheckMate 649 expressing CPS≥5 used as a proxy in the absence of data from patients expressing CPS≥10

Table 32. Proportion of patients receiving each doublet chemotherapy regimen (scenario analysis: NHS practice)

Doublet chemotherapy regimen	Proportion applied in scenario analysis
CAPOX/XELOX	70%
FP	-
FOLFOX	25%
XP	5%
Total	100%

Abbreviations: CAPOX/XELOX, oxaliplatin and capecitabine; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FP, cisplatin and fluorouracil; XP, capecitabine and cisplatin

In the CheckMate 649 trial, the administration schedule of nivolumab depended on the doublet chemotherapy given in combination.(31) Nivolumab 240mg was given every 2 weeks (Q2W) in combination with FOLFOX and nivolumab 360mg was given Q3W in combination with XELOX (known more commonly as CAPOX). In the economic model, the same dependency is assumed.

As noted above, pembrolizumab 200mg was given Q3W in the KEYNOTE-859 trial. The pembrolizumab label also permits pembrolizumab 400mg to be given every 6 weeks (Q6W). Administration using this alternative dosing regimen (Q6W) is modelled in a scenario analysis.

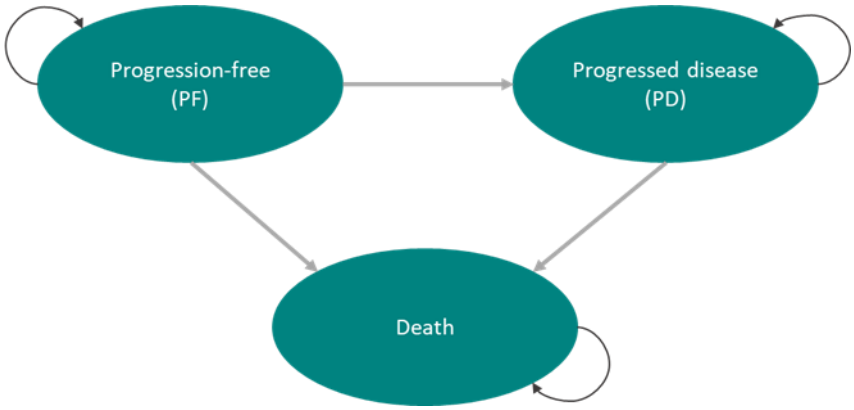
For details on the duration of treatment (and treatment stopping rules), see Section B.3.3.3. For details on drug acquisition and administration costs, see Section B.3.5.1.

3.2.3 Model structure

As noted in Section B.3.1, cost-effectiveness studies evaluating pembrolizumab plus doublet chemotherapy in the specified population were not identified. Thus, a *de novo* economic model was developed in Microsoft Excel to compare the expected health outcomes (LYs and QALYs) and costs of treating a patient with pembrolizumab plus doublet chemotherapy versus comparator treatments. The type of economic evaluation in the economic model is a cost-utility analysis using an NHS and PSS perspective.

The economic model is based on a partitioned survival analysis structure, with three key health states: progression free, progressed disease and death. These health states are mutually exclusive (i.e., patients can only reside in one health state). A partitioned survival model was preferred to a Markov model as a partitioned survival structure supports the inclusion of OS and PFS data available from the KEYNOTE-859 trial. Partitioned survival models are routinely appraised by NICE in oncology submissions and have been accepted by NICE in previous advanced gastric, GOJ and oesophageal cancer submissions (TA208(28), TA737(22), TA857(21), TA707(38), TA865(30)). Figure 9 provides an overview of the model structure.

Figure 9. Model structure



All patients enter the economic model in the progression free health state and are assumed to be treated with pembrolizumab plus doublet chemotherapy or a comparator treatment. The proportion of patients in the progression free health state is represented by the PFS curve at that point in time. When moving to the next model cycle, patients may remain progression free and continue first line treatment, remain progression free and discontinue first line treatment, progress (where they may receive subsequent treatment) or die. The proportion of patients receiving first line treatment is represented by the ToT curve at that point in time.

The progressed disease state consists of patients who are alive but have progressed. Subsequent treatments are included in the model as a one-off cost upon progression. The proportion of patients in the progressed disease health state at any point in time is calculated as the difference between the PFS and OS curves. When moving to the next model cycle, progressed patients cannot return to the progression free health state, they may remain progressed or die. Death is an absorbing health state.

For the two study arms of pembrolizumab plus doublet chemotherapy and doublet chemotherapy, parametric curves for PFS, OS and ToT were fitted using patient-level data from the KEYNOTE-859 trial; methods for deriving these curves are provided in Section B.3.3. Hazard ratios (HRs) for other relevant comparators (nivolumab plus doublet chemotherapy) are derived from an NMA; also described in Section B.3.3. NMA methodology and results have been described previously in Section B.2.9. As OS and PFS were modelled independently, a cap was used to prevent PFS from exceeding OS, to prevent illogical (negative) state occupancy of the progressed

disease health state, and the illogical conclusion that a patient could be progression-free but not alive

The model cycle length is set to one week. Weekly cycles were considered appropriate because it enables the model to more easily reflect the timings of drug administrations associated with pembrolizumab plus doublet chemotherapy and comparators. Weekly cycles further capture a realistic minimum time during which progressions and treatments can change in UK clinical practice. No half-cycle correction was applied in the base case as the cycle length is short enough to allow robust estimates of benefits and costs to be calculated.

The time horizon in the model is set to 30 years (1,566 weekly cycles) and considered to cover a lifetime time horizon. Based on a starting age of 60.1 years in the CPS≥1 population, patients would be 90.1 years old at the end of the time horizon. In the economic model, 100% of patients have died at the end of the 30-year time horizon (99.9% in the previous cycle). Shorter time horizons are explored in scenario analysis.

As per the NICE reference case, the annual discount rate in the model was set to 3.5% for costs and QALYs and an annual discount rate of 1.5% for costs and QALYs was explored in scenario analysis.(36) Table 33 below compares the key features of the economic analysis in this appraisal with TA857.

Table 33. Features of the economic analysis

Factor	Previous evaluations	Current evaluation	
	TA857	Chosen values	Justification
Time horizon	Lifetime (up to 50 years)	Lifetime (up to 30 years)	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.
Treatment waning effect	In the CheckMate 649 trial, nivolumab was continued for a maximum of 24 months, even if their cancer had not progressed at this time. The economic analysis also included this 24-month stopping rule. No treatment effect waning was applied in the company's base case analysis as there was no evidence of treatment effect waning in the CheckMate 649 trial which had long follow-up (49.5 months). The company also referred to the long-term benefits of nivolumab in other indications (melanoma and NSCLC). The committee noted that both the company and ERG had provided treatment waning scenarios. In these scenarios the risk of death in the nivolumab plus XELOX arm became the same as the XELOX arm at 6.5 years in the company's scenario and 5 years in the ERG's model. The committee concluded that nivolumab's treatment effect may not last for a person's lifetime after treatment is stopped. Although treatment waning is uncertain, it would take both the company's and ERG's scenarios on treatment waning into account in its decision making.	In the base case analysis, no treatment waning effect is assumed. A scenario analysis is presented which explores the impact of a gradual treatment waning effect 7 years from the start of pembrolizumab treatment (5 years from the end of pembrolizumab treatment), where the cycle-specific hazard for the pembrolizumab arm gradually becomes equal to that in the comparator arm over the subsequent 2 years.	Based on the independent estimation of survival curves for the intervention and comparator arms, the length of the follow-up period and the immunotherapy precedent, there is no clear evidence to indicate a treatment waning. Given that treatment waning has been considered a key area of uncertainty in previous appraisals which include a treatment stopping rule, scenario analysis is considered worthwhile to assess the impact of the uncertainty.

Factor	Previous evaluations	Current evaluation	
	TA857	Chosen values	Justification
Source of utilities	In the CheckMate 649 trial, the EuroQoL EQ-5D-3L questionnaire was administered. Each EQ-5D-3L questionnaire was converted to utility using the UK EQ-5D-3L tariff. A PFS utility, PD utility and time-to-death utility applied 6 months before death were derived from the CheckMate 649 trial. The committee concluded that these utility values were appropriate. These values are academic in confidence.	Utility values are derived from the EQ-5D-5L data collected from patients in the KEYNOTE-859 trial. This data has been mapped onto the 3L value set. Utility values are estimated according to progression status and time to death.	Given that the NICE methods manual states a preference for using utility data collected from the relevant clinical trial to inform cost-utility analysis, and the paucity of utility data in the published literature within HER2 negative GC, utility data from the KEYNOTE-859 trial are used to inform the economic analysis.
Source of costs	Intervention and comparator costs sourced from eMIT where possible. Otherwise, as per TA208 (either from the newer version of sources or inflated using PSSRU indices)	Unit costs of tests and services are sourced from the National Schedule of NHS Costs or the Unit Costs of Health and Social Care. Drug costs are sourced from the UK BNF for branded products and the eMIT for generic products. All other costs sourced from the literature were inflated to a 2021/22 cost year as necessary using the NHSCII pay and prices indices. Resource use will be informed by the literature, previous NICE appraisals such as TA857, or clinical expert opinion.	These sources align with those specified in the NICE methods manual. Using the cost and resource use data accepted in TA857, where appropriate, will promote consistent decision making.

Factor	Previous evaluations	Current evaluation	
	TA857	**Chosen values**	**Justification**
Source of clinical effectiveness	Nivolumab efficacy and XELOX/FOLFOX efficacy were derived from the survival outcomes of the CheckMate 649 trial. An NMA was performed to estimate HRs of PFS and OS for other comparators (CF and CX).	Pembrolizumab efficacy and FP/CAPOX efficacy are derived from the survival outcomes of the KEYNOTE-859 trial. An NMA was performed to estimate HRs of PFS and OS for other comparators in the NICE final scope (nivolumab plus doublet chemotherapy).	The KEYNOTE-859 trial is the pivotal trial used to support the marketing authorisation for this indication. ESMO guidelines, previous NICE appraisals in GC and clinical opinion suggest that doublet chemotherapies are clinically equivalent. An NMA is required to estimate relative effectiveness against nivolumab plus doublet chemotherapy.
Abbreviations: BNF, British National Formulary; CAPOX, oxaliplatin and capecitabine; CX, cisplatin and capecitabine; eMIT, electronic market information tool; ESMO, European Society for Medical Oncology; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FP, cisplatin and fluorouracil; GC, gastric cancer; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NHSCII, NHS Cost Inflation Index; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressed disease; PFS, progression free survival; PSSRU: personal social services research unit; UK, United Kingdom; XP, capecitabine and cisplatin			

B.3.3 Clinical parameters and variables

The primary outcome in the KEYNOTE-859 trial is OS; defined as the time from randomisation to death due to any cause. PFS is a secondary outcome in the KEYNOTE-859 trial; defined as the time from randomisation to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

As noted in Section 2.6.1, pembrolizumab with doublet chemotherapy showed a statistically significant and clinically meaningful improvement in the trial's primary endpoint of OS versus chemotherapy alone in the ITT, CPS≥1 and CPS≥10 populations at the pre-specified IA1 conducted by an independent Data Monitoring Committee. PD-L1 status was a pre-specified subgroup in the trial that was employed as a stratification factor. Statistically significant and clinically meaningful improvements in PFS and ORR were also observed in the ITT, CPS≥1 and CPS≥10 populations; all hypotheses were met. As such, IA1 is deemed the final analysis for statistical analysis. The trial will continue until the final number of events specified in the protocol are reached and this data will be published at a later date for publication purposes.

The PFS and OS KM data from the KEYNOTE-859 trial were used to estimate survival curves for pembrolizumab plus doublet chemotherapy and doublet chemotherapy in the economic model. The most recent data-cut off was used (first pre-specified interim analysis [IA1], with data cut-off 03 October 2022). To estimate survival curves for nivolumab plus doublet chemotherapy in the CPS≥10 population, the HR for nivolumab plus doublet chemotherapy versus pembrolizumab plus doublet chemotherapy estimated from the NMA ([redacted] for OS) was applied to the pembrolizumab plus doublet chemotherapy survival curve. As explained in Section B.2.9, the NMA was conducted assuming constant HRs as the proportional hazards (PH) assumption was defensible.

For the economic model, survival curve fitting was carried out in line with NICE DSU guidelines. Whilst acknowledging that NICE DSU TSD 14 outlines that the reliance on the PH assumption is reduced when IPD are available, the PH assumption was tested

to indicate whether it may be preferable to separately fitted models to each arm, or jointly fitted models with treatment group as a covariate.(39)

Statistical goodness-of-fit statistics based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), visual inspection (comparing fitted parametric curves to the observed KM plots during the trial follow-up period), and clinical plausibility of the predicted survival (versus external data where available and/or clinical expert opinion) were used to select the base case parametric survival curves. The standard survival distributions (Exponential, Gamma, Generalised Gamma, Gompertz, Log-logistic, Log-normal, Weibull) were all assessed. Spline modelling was also investigated.

There was no obvious visual change in the hazards of both the intervention and comparator curves therefore a “two-piece” approach was not further considered.

3.3.1 Overall survival (OS)

3.3.1.1 CPS≥1

First the PH assumption between pembrolizumab plus doublet chemotherapy and doublet chemotherapy was assessed followed by survival extrapolation and validation.

Proportional hazard assessment (OS, CPS≥1)

The PH assumption, i.e., that hazards are proportional over time implying that the effect of a risk factor is constant over time, was evaluated for pembrolizumab plus doublet chemotherapy versus chemotherapy.

MSD considers the PH assumption may not be valid for the comparison of pembrolizumab plus doublet chemotherapy and doublet chemotherapy in patients expressing CPS≥1 during the trial period. This is based on a number of factors, as described below.

Based on the log cumulative hazard plot and log-log plot (Figure 10), there is evidence that hazards may not be proportional at the start of the trial as the curves overlap. Also, the flattening of the curves between weeks 150 and 200 suggests a change in the hazard, but this is likely due to the small number of patients left at risk in the trial.

Based on the Schoenfeld Residuals plot (Figure 11), there is some divergence from zero during the latter part of the curve. Also, the test was found to be significant (p=0.0248), providing additional evidence that the PH assumption may not be valid.

Figure 10. OS CPS≥1 cumulative hazard plot and log-log plot

Figure 11. OS CPS≥1 Schoenfeld Residuals plot

In summary, there is evidence to reject the PH assumption between pembrolizumab plus doublet chemotherapy and doublet chemotherapy during the trial period in patients expressing CPS≥1. There is a clinical argument that the PH assumption may not be valid for IO versus chemotherapy comparisons.

Jointly fitted models (OS, CPS≥1)

Separately fitted models are preferred to jointly fitted models as they provide better visual fit to the KM data and more plausible long-term extrapolations. Furthermore, jointly fitted survival models rely on the PH assumption, which may not be valid. For these reasons, this section focuses on separately fitted models. Jointly fitted models are provided in Appendix M.

Separately fitted models (OS, CPS≥1)

AIC and BIC statistics are presented in Table 34. Of the parametric models, the lognormal provided the best statistical fit in both treatment arms.

For pembrolizumab plus doublet chemotherapy, the best statistically fitting parametric models (lognormal and log-logistic) show good visual alignment to the KM data (Figure 12) and smoothed hazard plot (Figure 15).

For doublet chemotherapy, the best statistically fitting parametric model (lognormal) overestimates the tail of the KM data (Figure 13). Based on visual inspection of the smoothed hazard plot the log-logistic could be preferred as more time is spent within the 95% confidence interval (Figure 14).

Smoothed hazard plots for the best fitting splines are presented in Figure 16 for pembrolizumab plus doublet chemotherapy and Figure 17 for doublet chemotherapy. The model that has been selected as the base case for the pembrolizumab plus doublet chemotherapy arm is the 2-knot hazards spline model. An initial statistical and visual inspection reveals that this curve fits the KM data very well, better than the separately fitted parametric survival models (Figure 18).

A separately fitted 2-knot hazards spline model was also selected as the base case model for the doublet chemotherapy arm (Figure 19). The 2-knot hazard spline model provides both good statistical fit and visual fit to the trial data and was selected above the odds scale spline model for these reasons.

Table 34. OS goodness of fit statistics CPS≥1 (separately fitted models)

Model	Pembrolizumab plus doublet chemotherapy		Doublet chemotherapy	
	AIC	BIC	AIC	BIC
Standard parametric				
Exponential	5109.9	5114.1	5464.7	5469.1
Weibull	5105.6	5114.5	5430.8	5439.6
Log-logistic	5094.0	5102.9	5468.0	5476.8
Lognormal	**5076.0**	**5084.8**	**5421.5**	**5430.3**
Gompertz	5111.2	5120.1	5457.4	5466.3
Gamma	5100.9	5109.8	5424.5	5433.3
Generalised gamma	5087.6	5100.9	5424.6	5437.9
Spline				
1k hazard	5086.9	5100.2	5427.1	5440.3
2k hazard	**5071.3**	**5089.0**	5409.8	5427.5
3k hazard	5073.5	5095.7	**5408.5**	5431.6

1k odds	5077.9	5091.2	5408.6	**5421.9**
2k odds	5072.2	5089.9	5410.3	5428.0
3k odds	5074.0	5096.2	5409.8	5432.0
1k normal	5084.7	5098.0	5415.6	5428.9
2k normal	5073.1	5090.8	5414.6	5432.3
3k normal	5074.1	5096.3	5410.8	5433.0
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; OS, overall survival				

Figure 12. OS CPS≥1 pembrolizumab plus doublet chemotherapy (separately fitted)

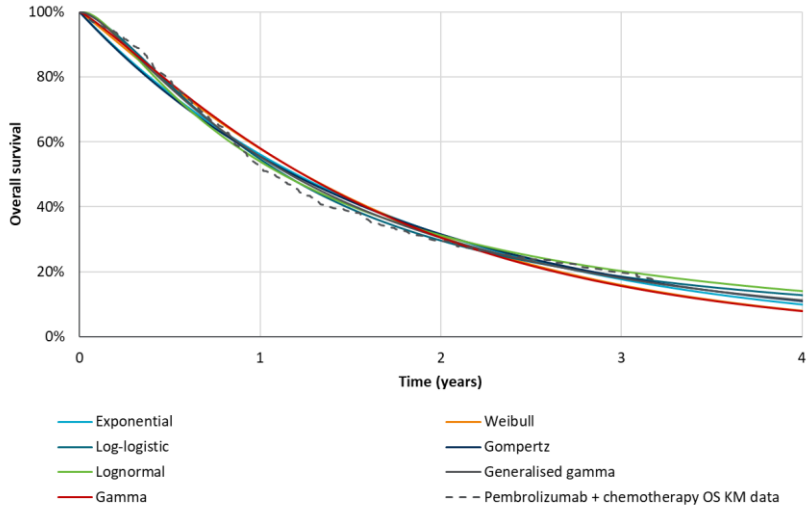


Figure 13. OS CPS≥1 doublet chemotherapy (separately fitted)

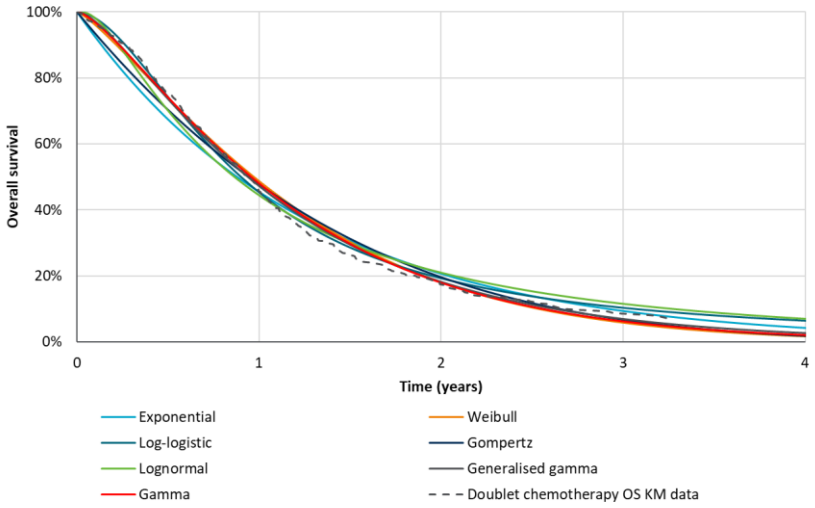


Figure 14. OS CPS≥1 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards

Figure 15. OS CPS≥1 doublet chemotherapy (separately fitted) smoothed hazards

Figure 16. OS CPS≥1 spline curve hazard profile pembrolizumab plus doublet chemotherapy (separately fitted)

Figure 17. OS CPS≥1 spline curve hazard profile doublet chemotherapy (separately fitted)

Figure 18. OS CPS≥1 2-knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)

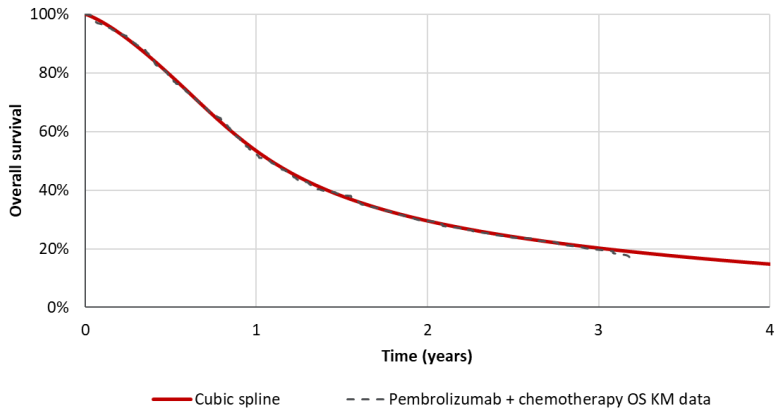
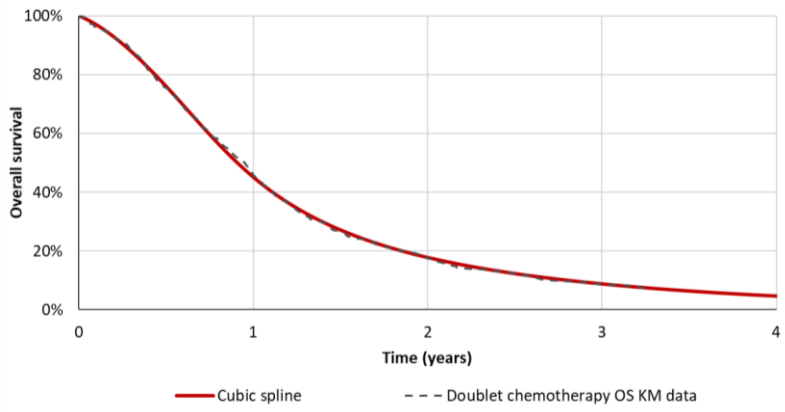


Figure 19. OS CPS≥1 2-knot hazard spline doublet chemotherapy (separately fitted)



Internal and external validation (OS, CPS≥1)

Fitted data was internally validated by comparing median OS in weeks and months for observed KEYNOTE-859 data and modelled KEYNOTE-859 data. OS curve fittings for pembrolizumab plus doublet chemotherapy and doublet chemotherapy fit the observed data well with minimal discrepancies as evidenced in Table 35. Survival rate validation at different timepoints (6, 12, 18, 24, 30, 36, and 60 months) are also reported in Appendix N. These tables report trial data versus selected parametric and spline survival models at each time point, and demonstrate the intervention provides higher survival rates compared to the comparator across all selected parametric and spline models selected.

Table 35. OS internal validation of fitted model (CPS≥1)

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	56.4	56.0	13.0	12.9
Doublet chemotherapy	49.6	47.0	11.4	10.8
Abbreviations: CPS, combined positive score; OS, overall survival				

Clinical experts consulted by MSD were unaware of any external data sources that could be used to validate the survival outcomes predicted from the economic model, apart from CheckMate 649. Based on their experience, the experts provided the proportion of patients they would expect to be alive on doublet chemotherapy at 2, 5 and 10 years (Table 36). Following this, the experts were shown extrapolations over 10 years and considered the separately fitted lognormal curve to be too optimistic. Extrapolations using the separately fitted gamma and spline 2-knot hazards were considered most plausible.

Table 36. OS rates for doublet chemotherapy provided by the clinical experts in NHS practice (CPS≥1)

Year	Expert A	Expert B	Expert C
2	≤20%	<20%	15%
5	<5%	3 to 4%	<1%
10	0%	0%	0%
Abbreviations: CPS, combined positive score; OS, overall survival.			

As for pembrolizumab plus doublet chemotherapy, the experts were unable to provide OS rates at different timepoints as they have no experience using pembrolizumab plus doublet chemotherapy for the indication being appraised. To generate a discussion around the relative treatment effect, the KM data for doublet chemotherapy was presented alongside the extrapolations for pembrolizumab plus doublet chemotherapy (up to 10 years). The experts agreed the distance between the survival curves would increase over time and a plateau in the pembrolizumab plus doublet chemotherapy curve would be likely. The experts also agreed the separately fitted 2-knot hazard spline model was a reasonable extrapolation for the base case analysis.

3.3.1.2 CPS≥5

As explained in Section B.2.9, an NMA at CPS≥5 was infeasible and cost-effectiveness results for pembrolizumab plus doublet chemotherapy versus nivolumab

plus doublet chemotherapy are presented for patients expressing CPS ≥10, which was prespecified and had subgroup data available, making an NMA feasible. To address the current uncertainty in patients expressing CPS≥5, related clinical effectiveness evidence is compared.

NICE TA857 considered results from CheckMate 649 in patients who expressed CPS≥1 and CPS≥5. The Opvido EMA EPAR assessment report contains OS results from CheckMate 649 at additional CPS levels, summarised in Table 37.(40)

Although NICE TA857 recommends nivolumab plus doublet chemotherapy as a suitable treatment option for patients expressing a CPS≥5, the data presented in the EMA EPAR confirms that nivolumab plus doublet chemotherapy showed no statistically significant difference compared to doublet chemotherapy at a CPS level of 5 to 9.

In KEYNOTE-859, pembrolizumab plus doublet chemotherapy showed a statistically significant difference compared to doublet chemotherapy at CPS levels of 1 to 9. The point estimate of this HR is also lower than those from CheckMate 649 at CPS levels of 1 to 4 and 5 to 9 (0.83 versus 0.97 and 0.92, respectively).

For these reasons, MSD would expect pembrolizumab plus doublet chemotherapy to be an effective option versus nivolumab plus doublet chemotherapy in the CPS ≥5 population.

Table 37. CPS≥1 supplementary data: KEYNOTE-859 versus CheckMate 649

CPS	KEYNOTE-859 (N=1,579)		CheckMate 649 (N=1,518)	
	n	OS HR (IO vs chemo)	n	OS HR (IO vs chemo)
1 to 4	NA		341 (22.5%)	0.97 (0.76 to 1.24)
5 to 9			187 (12.1%)	0.92 (0.66 to 1.28)
1 to 9	682 (43.2%)	0.83 (0.70 to 0.98)	NA	
Abbreviations: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; IO, immunotherapy; NA, not applicable; OS, overall survival n= number of patients with specified CPS				

3.3.1.3 CPS≥10

Herein, the NMA is briefly described followed by survival extrapolations for pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy including validation.

Proportional hazards assessment (OS, CPS≥10)

As noted in DSU TSD 14, there is often a reliance on summary statistics when there are multiple comparators which have been examined in separate RCTs, which lends itself to PH modelling.(39) Under this approach a HR is applied to a base survival curve to compare an experimental treatment to a control so that all treatments can be compared to a common comparator. Where one HR is applied to the entire modelled period, the PH assumption must be made – that is, the treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape.

PH assessments related to the NMA have been presented previously in Section B.2.9 and the results justify the approach of applying a single HR which assumes PH.

Separately fitted models (OS, CPS≥10)

For pembrolizumab plus doublet chemotherapy, the log-logistic and log-normal models provide the best fit for standard parametric curves based on AIC/BIC statistics (Table 38). These models also have the best visual alignment among the parametric survival models to the KM data (Figure 20) and smoothed hazard plot (Figure 21).

An initial statistical and visual inspection also reveals that the spline models fit the hazard data very well, better than other separately fitted parametric survival models. The model that has been selected as the base case for the pembrolizumab plus doublet chemotherapy arm is a 2-knot odds spline model.

In the absence of an NMA for PFS in this population, the HR resulting from the NMA for OS ([redacted] for nivolumab plus doublet chemotherapy versus pembrolizumab plus doublet chemotherapy) is used as a proxy and applied to the OS curve for pembrolizumab plus doublet chemotherapy to generate the OS curve for nivolumab plus doublet chemotherapy.

Table 38. OS goodness of fit statistics CPS≥10 (separately fitted)

Model	Pembrolizumab plus doublet chemotherapy	
	AIC	BIC
Standard parametric		
Exponential	2158.6	2162.2
Weibull	2159.7	2167.0
Log-logistic	**2147.7**	**2154.9**
Lognormal	2147.7	2155.0
Gompertz	2159.6	2166.8
Gamma	2158.4	2165.6
Generalised gamma	2149.5	2160.4
Spline		
1k hazard	2,149.5	2,160.4
2k hazard	2,149.5	2,164.0
3k hazard	2,149.3	2,167.5
1k odds	**2,148.4**	**2,159.3**
2k odds	2,149.9	2,164.4
3k odds	2,149.4	2,167.5
1k normal	2,149.3	2,160.2
2k normal	2,149.5	2,164.0
3k normal	2,149.3	2,167.5
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; OS, overall survival		

Figure 20. OS CPS≥10 pembrolizumab plus doublet chemotherapy (separately fitted)

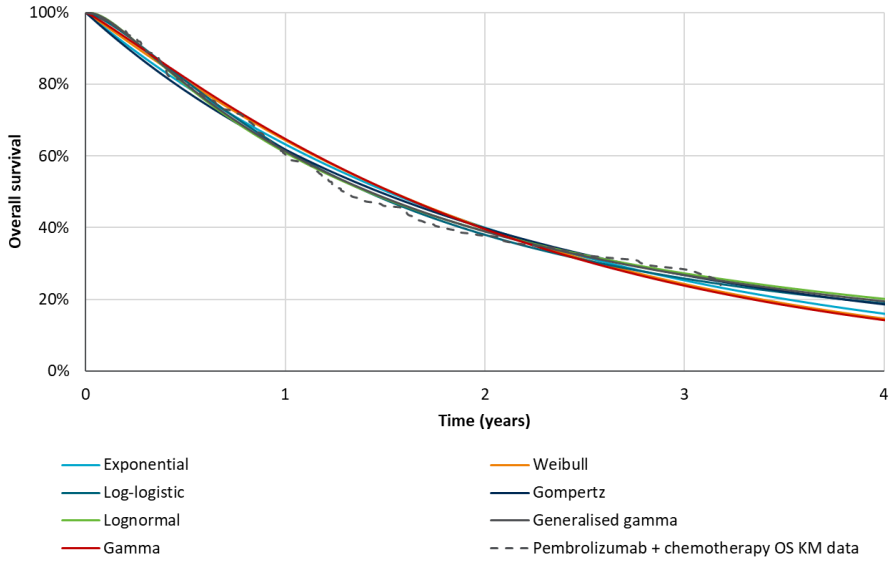


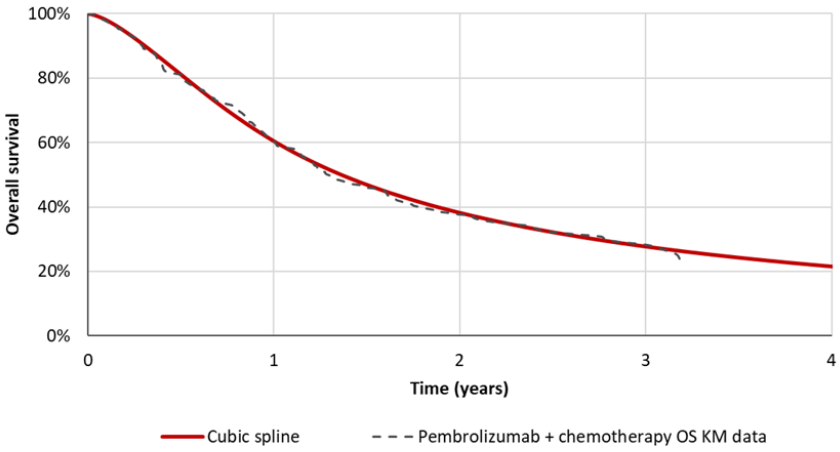
Figure 21. OS CPS≥10 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards

[redacted]

Figure 22. OS CPS≥10 spline curve hazard profile pembrolizumab plus doublet chemotherapy (separately fitted)

[redacted]

Figure 23. OS CPS≥10 2-knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)



Internal and external validation (OS, CPS≥10)

Fitted data was internally validated by comparing median OS in weeks and months for observed KEYNOTE-859 data and modelled KEYNOTE-859 data. OS curve fittings for pembrolizumab plus doublet chemotherapy fit the observed data well with minimal discrepancies as evidenced in Table 39. Survival rate validation at different timepoints (6, 12, 18, 24, 30, 36, and 60 months) are also reported in Appendix N.

Table 39. OS internal validation of fitted model (CPS≥10)

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	67.1	72.0	15.4	16.6
Abbreviations: CPS, combined positive score; OS, overall survival				

As per clinical expert validation for the CPS≥1 population, clinical experts were shown extrapolations for pembrolizumab plus doublet chemotherapy (up to 10 years) alongside KM data for doublet chemotherapy. The experts agreed that curves like the Weibull are too pessimistic and curves like the separately fitted 2-knot odds spline model are more plausible.

3.3.1.4 Treatment waning

Based on the independent estimation of survival curves for the intervention and comparator arms, there is no clear evidence to indicate a treatment waning effect. A treatment waning effect was also absent from the base case analysis in TA857 as there was no evidence of a treatment waning effect in the CheckMate 649 trial. Additionally, when clinical experts described the expected long-term shape of the pembrolizumab plus doublet chemotherapy OS curve relative to the doublet chemotherapy OS curve, they stated the curves would diverge over time and never meet. For these reasons, no treatment waning effect is assumed in the base case analysis.

For completeness, a scenario analysis is presented for the comparison with doublet chemotherapy in which a gradual treatment waning effect five years following discontinuation of pembrolizumab (seven years since treatment initiation) is applied. The cycle-specific hazard for pembrolizumab gradually becomes equal to that in the doublet chemotherapy arm over the subsequent two years. With additional follow-up observed in IO trials, the ongoing benefit of IO following cessation of treatment is further supported, and the waning timepoints in this scenario should be viewed as conservative.(41-44)

For the comparison with nivolumab plus doublet chemotherapy, no waning scenario analysis is presented as the impact would be common to both treatment arms, given the comparable biological mechanisms of action and stopping rules. Undertaking a

scenario in this comparison would also require additional assumptions regarding the survival that the treatment effect wanes to.

3.3.2 Progression free survival (PFS)

3.3.2.1 CPS≥1

First the PH assumption between pembrolizumab plus doublet chemotherapy and doublet chemotherapy was assessed followed by survival extrapolation and validation.

Proportional hazards assessment

The PH assumption was evaluated for pembrolizumab plus doublet chemotherapy versus chemotherapy. MSD considers the PH assumption valid for this comparison in patients expressing CPS≥1 during the trial period. This is based on a number of factors, as described below.

Based on the log cumulative hazard plot and log-log plot (Figure 24), the curves overlap at the start of the trial, this is then followed by clear separation. The flattening of the curves from week 100 suggests a change in the hazard, but this is likely due to the small number of patients left at risk in the trial.

Based on the Schoenfeld Residuals plot (Figure 25), the plot does not vary significantly from zero. Also, the test was found to not be significant (p=0.2072), providing evidence that the PH assumption is valid.

Figure 24. PFS CPS≥1 cumulative hazard plot and log-log plot

Figure 25. PFS CPS≥1 Schoenfeld Residuals plot

Jointly fitted models

Jointly fitted models are provided in Appendix M.

Separately fitted models

Of the parametric models, the lognormal model provided the best fit in both treatment arms based on AIC/BIC statistics (Table 40).

For pembrolizumab plus doublet chemotherapy, none of the parametric models have good visual alignment to the KM data (Figure 26) or smoothed hazard plot (Figure 28).

For doublet chemotherapy, the best statistically fitting parametric model (lognormal) had good visual alignment to the KM data (Figure 27) and one of the better visual fits in the smoothed hazard plot (Figure 28).

Figure 30 illustrates the smoothed hazard fit of all separately fitted spline models with pembrolizumab plus doublet chemotherapy data. After visual inspection, the 1-knot model on the hazard scale showed best statistical fit and minimal OS crossing and was as selected as the base case (Figure 31). For the same reason, the 1-knot model on the hazard scale was also chosen as the base case for doublet chemotherapy (Figure 32).

Table 40. PFS goodness of fit statistics CPS≥1 (separately fitted)

Model	Pembrolizumab plus doublet chemotherapy		Doublet chemotherapy	
	AIC	BIC	AIC	BIC
Standard parametric				
Exponential	4428.1	4432.5	4426.9	4431.3
Weibull	4429.1	4437.9	4409.3	4418.1
Log-logistic	4342.2	4351.0	4356.6	4365.4
Lognormal	**4337.9**	**4346.7**	**4330.9**	**4339.7**

Gompertz	4388.1	4397.0	4427.4	4436.3
Gamma	4429.3	4438.2	4391.3	4400.2
Generalised gamma	4338.2	4351.5	4355.1	4368.4
Spline				
1k hazard	4319.9	4333.2	4351.1	4364.3
2k hazard	4306.0	**4323.7**	4319.9	4337.6
3k hazard	4306.3	4328.4	4312.9	4335.0
1k odds	4322.5	4335.8	4332.6	4345.9
2k odds	4309.3	4327.0	4326.2	4343.9
3k odds	4303.1	4325.2	4310.5	**4332.7**
1k normal	4338.1	4351.4	4351.6	4364.9
2k normal	4308.4	4326.1	4329.3	4347.0
3k normal	**4302.2**	4324.4	**4311.1**	4333.2
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; PFS, progression free survival				

Figure 26. PFS CPS≥1 pembrolizumab plus doublet chemotherapy (separately fitted)

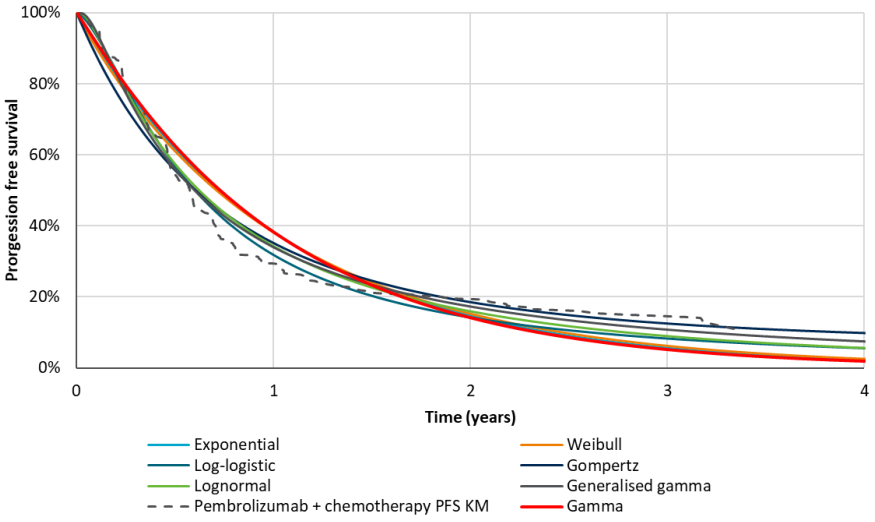


Figure 27. PFS CPS≥1 doublet chemotherapy (separately fitted)

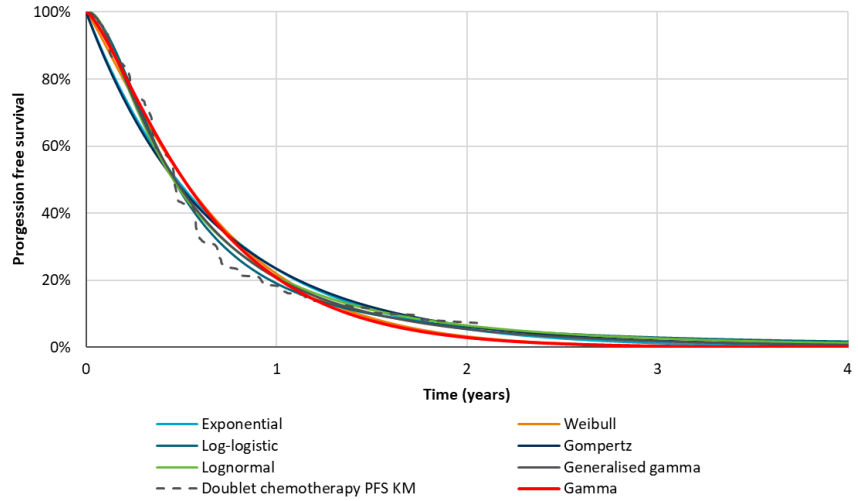


Figure 28. PFS CPS≥1 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards

[redacted]

Figure 29. PFS CPS≥1 doublet chemotherapy (separately fitted) smoothed hazards

[redacted]

Figure 30. PFS CPS≥1 spline curve hazard profile pembrolizumab plus doublet chemotherapy (separately fitted)

[redacted]

Figure 31. PFS CPS≥1 1 knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)

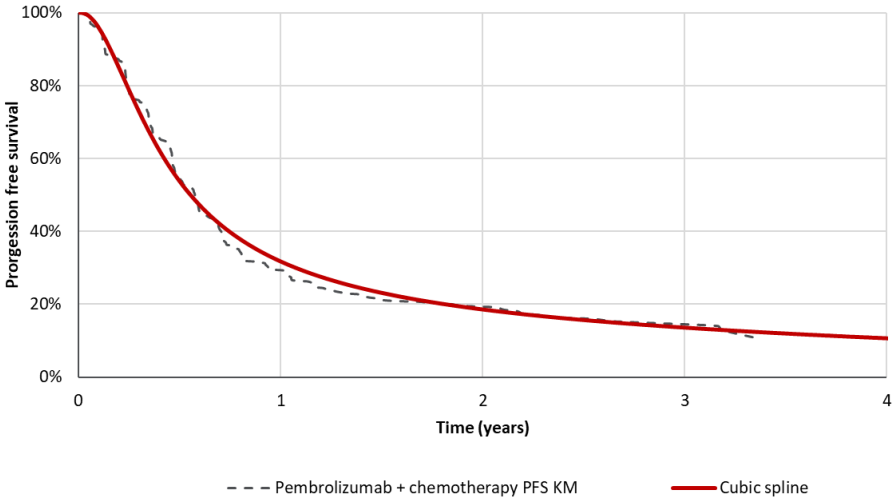
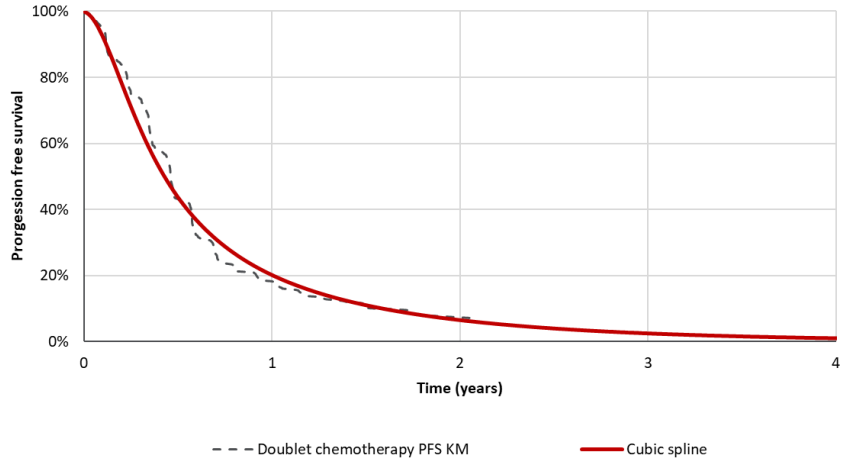


Figure 32. PFS CPS≥1 1 knot hazard spline doublet chemotherapy (separately fitted)



Internal and external validation (PFS, CPS≥1)

Fitted data was internally validated by comparing median PFS in weeks and months for observed KEYNOTE-859 data and modelled KEYNOTE-859 data. PFS curve fittings for pembrolizumab plus doublet chemotherapy and doublet chemotherapy fit the observed data well with minimal discrepancies, as evidenced in Table 41. Survival rate validation at different timepoints (6, 12, 18, 24, 30, 36, and 60 months) are also reported in Appendix N.

Table 41. PFS internal validation of fitted model (CPS≥1)

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	30.0	28.0	6.9	6.4
Doublet chemotherapy	24.1	22.0	5.6	5.1
Abbreviations: CPS, combined positive score; PFS, progression free survival				

Clinical experts consulted by MSD were unaware of any external data sources that could be used to validate the survival outcomes predicted from the economic model, apart from CheckMate 649. Based on their experience, the experts provided the proportion of patients they would expect to be progression free on doublet chemotherapy at 2 and 5 years (Table 42). The experts also noted that their estimates at 5 years would apply at 4 years. Following this, the experts were shown extrapolations over 10 years. The experts found it difficult to distinguish between the curves, but noted that some extrapolations like the lognormal overpredicted survival from Year 2 and extrapolations closer to the gamma would be more reflective of long-term PFS.

Table 42. PFS rates for doublet chemotherapy provided by the clinical experts in NHS practice (CPS≥1)

Year	Expert A	Expert B	Expert C
2	10%	<10%	<10%
5	≤1%	≤1%	0%
Abbreviations: CPS, combined positive score; PFS, progression free survival.			

3.3.2.2 CPS≥10

Herein, the NMA is briefly described followed by survival extrapolations for pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy including validation.

Proportional hazards assessment

See Section 3.3.1.3.

Separately fitted models

For pembrolizumab plus doublet chemotherapy, the generalised gamma model provides the best fit parametric fit based on AIC/BIC statistics (Table 43). However, none of the parametric models have good visual alignment to the KM data (Figure 33) or smoothed hazard plot (Figure 34).

An initial statistical and visual inspection reveals that the spline models fit the data better than other separately fitted parametric survival models. The spline model that has been selected as a base case for the pembrolizumab plus doublet chemotherapy arm is a 1-knot odds model as it shows the best long-term fit and minimal OS crossing (Figure 36).

To generate the PFS curve for nivolumab plus doublet chemotherapy, a HR of [redacted] for nivolumab plus doublet chemotherapy versus pembrolizumab plus doublet chemotherapy is assumed and applied to the PFS curve for pembrolizumab plus doublet chemotherapy.

Table 43. PFS goodness of fit statistics CPS≥10 (separately fitted)

Model	Pembrolizumab plus doublet chemotherapy	
	AIC	**BIC**
Standard parametric		
Exponential	1984.2	1987.8
Weibull	1983.7	1991.0
Log-logistic	1945.0	1952.2
Lognormal	1947.5	1954.8
Gompertz	1960.2	1967.4
Gamma	1986.0	1993.3
Generalised gamma	**1940.3**	**1951.2**
Spline		

1k hazard	1932.9	1943.8
2k hazard	1929.1	1943.6
3k hazard	1929.6	1947.8
1k odds	1934.9	1945.8
2k odds	1930.1	1944.6
3k odds	1927.9	1946.1
1k normal	1939.8	1950.7
2k normal	1929.0	**1943.5**
3k normal	**1927.0**	1945.2
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; CPS, combined positive score; PFS, progression free survival		

Figure 33. PFS CPS≥10 pembrolizumab plus doublet chemotherapy (separately fitted)

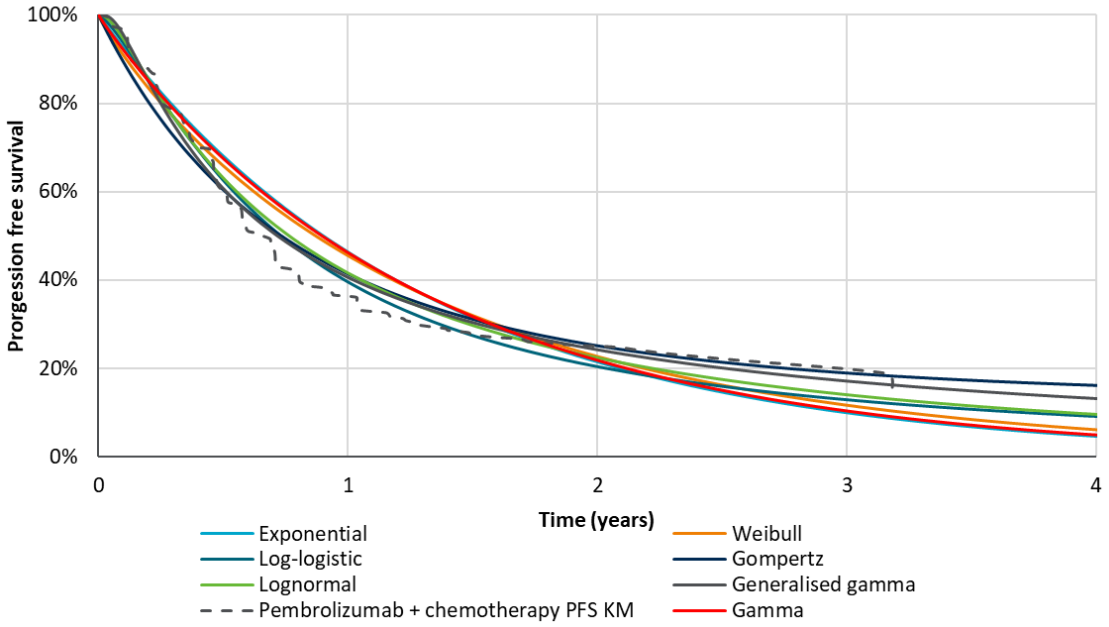


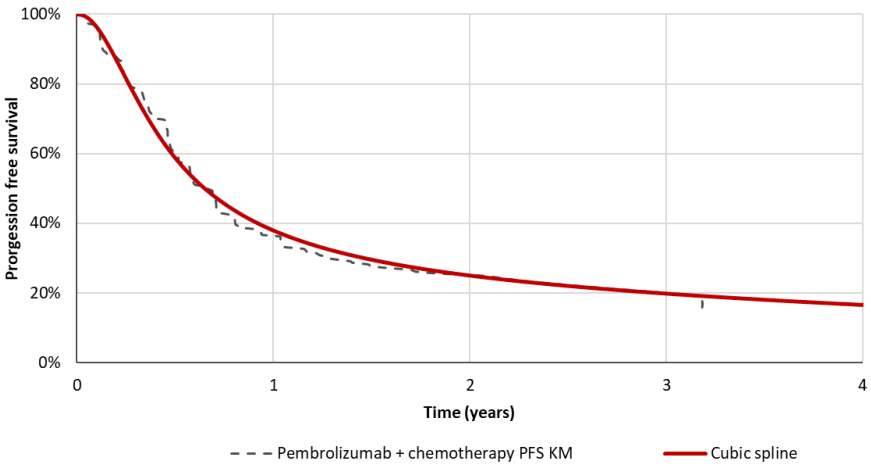
Figure 34. PFS CPS≥10 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards

[redacted]

Figure 35. PFS CPS≥10 spline curve hazard profile pembrolizumab plus doublet chemotherapy (separately fitted)

[redacted]

Figure 36. PFS CPS≥10 1 knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)



Internal and external validation (PFS, CPS≥10)

Fitted data was internally validated by comparing median PFS in weeks and months for observed KEYNOTE-859 data and modelled KEYNOTE-859 data. PFS curve fittings for pembrolizumab plus doublet chemotherapy fit the observed data well with minimal discrepancies as evidenced in Table 44. Survival rate validation at different timepoints (6, 12, 18, 24, 30, 36, and 60 months) are also reported in Appendix N.

Table 44. PFS internal validation of fitted model (CPS≥10)

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	35.1	34.0	8.1	7.8
Abbreviations: CPS, combined positive score; PFS, progression free survival				

3.3.2.2 Treatment waning

Treatment waning is not considered for the PFS estimates due to the maturity of the trial data and because most patients will have progressed before any treatment waning effect might begin, hence any potential waning effect is reflected in the extrapolated curves. For a further discussion of treatment waning, see Section 3.3.1.4.

3.3.3 Time on treatment (ToT)

ToT data was recorded in the KEYNOTE-859 trial for all drug components separately. The ToT data is relatively mature for all treatments, with most patients having discontinued from the treatments in both arms at data cut-off (less than 5% remain on-treatment for all drugs). Hence KM data (in combination with maximum treatment durations) is directly used in the model to inform study treatment costs for all treatments without parametric extrapolation. These curves are provided in Figure 37, Figure 38 and Figure 39. In scenario analysis, the best fitting parametric models are explored.

Given that ToT is not an included endpoint in the NMA, it is assumed nivolumab has the same ToT as pembrolizumab (i.e., a HR of 1). Also, no publicly available ToT KM curves could be identified in patients expressing CPS≥10 from the CheckMate 649 trial. As FOLFOX was an option in CheckMate 649 and not KEYNOTE-859, the oxaliplatin component of CAPOX and 5-FU component of FP is used to inform ToT on FOLFOX.

Figure 37. ToT pembrolizumab plus doublet chemotherapy CPS≥1

Figure 38. ToT doublet chemotherapy CPS≥1

Figure 39. ToT pembrolizumab plus doublet chemotherapy CPS≥10

3.3.3.1 Treatment stopping rules

Pembrolizumab and nivolumab

In the KEYNOTE-859 trial, pembrolizumab was continued until confirmed disease progression, unacceptable toxicity, investigator or patient decision to withdraw from the study, noncompliance with treatment or trial procedures, or completion of 35 cycles of treatment (200mg Q3W) (approximately 2 years). Following this, no patient exceeded 35 cycles of treatment, and the mean number of pembrolizumab cycles received was [redacted] and [redacted] in the populations expressing CPS≥1 and ≥10, respectively. As KM data is used directly to inform the pembrolizumab ToT, no additional stopping rule is imposed on pembrolizumab in the economic model.

NHS representatives have previously explained to NICE committees that the NHS can implement a stopping rule of 2 years (TA858, TA857). A 2-year stopping rule can result in fewer than 35 cycles of treatment if patients miss an administration. From a clinical perspective, 35 cycles is likely to be easier to monitor and allows a full course of treatment to be provided if a cycle of treatment is missed. To reflect both scenarios, a 2-year stopping rule is applied to pembrolizumab and nivolumab in scenario analysis.

MSD also notes that patients who completed 35 cycles of pembrolizumab treatment or who achieved a complete response but progressed after discontinuation of treatment could initiate a second course of pembrolizumab treatment in the KEYNOTE-859 trial, for up to 17 cycles. [redacted] These patients contribute to OS estimates, not PFS or ToT estimates. MSD is therefore satisfied that these patients are not having any meaningful contribution to the benefits or costs of pembrolizumab in the economic model. Furthermore, second courses would not be offered in clinical practice based on the draft SmPC.

Doublet chemotherapy

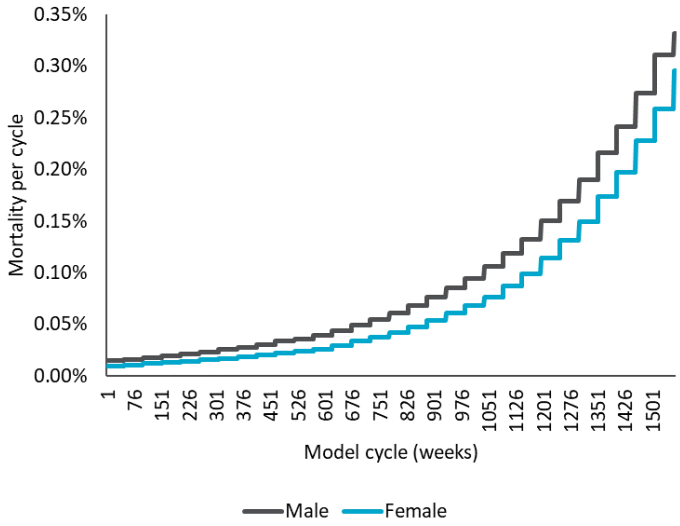
In the KEYNOTE-859 trial, cisplatin or oxaliplatin treatment may be capped at 6 cycles per local standard. In NHS clinical practice, cisplatin and oxaliplatin are capped at 6 cycles, and clinical experts consulted by MSD confirmed that this treatment cap applies to all components of the regimen. One clinical expert also noted that some centres may cap at 8 cycles (approximately 6 months) when treating fit patients, but this is rare. Therefore, all regimens in the model (CAPOX, FP and FOLFOX) are subject to a maximum treatment duration of 6 cycles in the base case, without adjustment for efficacy. The impact of removing the cap is explored in scenario analysis.

3.3.4 General population mortality

The economic model utilises mortality data from the UK national life tables collected and sourced from the ONS.(45) The 2017-2019 life tables from the ONS were used as the primary source for general population mortality as they do not account for the effects of the recent COVID-19 pandemic.

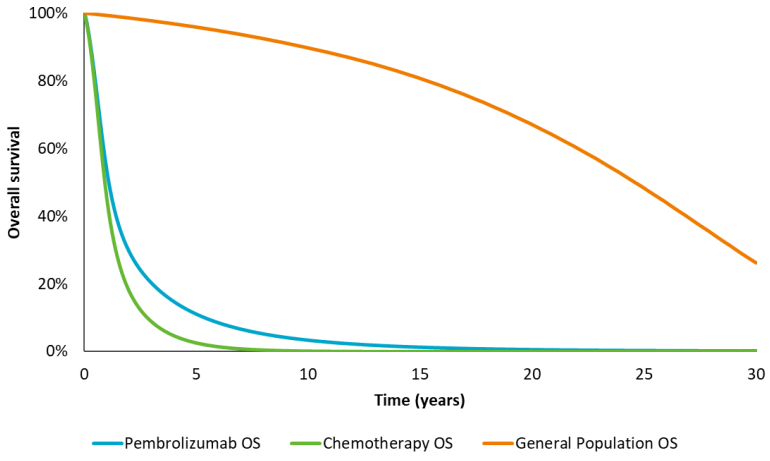
General population mortality was calculated for each model cycle, based on the starting proportion of male and female patients (for baseline characteristics, see Table 21). The resulting mortality per cycle is illustrated in Figure 40.

Figure 40. General population mortality per cycle



OS estimates are capped by ensuring that the conditional probability of survival for the intervention or comparator does not exceed that of the general population in any model cycle. For PFS no adjustment for general population mortality is made directly to the PFS extrapolation, except that the model ensures that the PFS curve does not cross the OS curve once it has been adjusted to account for general population mortality. In the base case analysis, this cap for general population mortality was not needed (Figure 41).

Figure 41. General population mortality versus extrapolations (CPS≥1 population)



3.3.5 Survival analysis summary

The extrapolations applied in the base case analysis are summarised in Table 45 and illustrated in Figure 42, Figure 43, Figure 45 and Figure 46 for the CPS≥1 population,

and Figure 44, Figure 47 and Figure 48 for the CPS≥10 population. Results using the next best fitting curves (statistically and/or visually) are provided in scenario analysis (see Section 3.11.3). The economic model includes all aforementioned curves as executable options.

Table 45. Summary of base case extrapolations

Treatment	OS	PFS	ToT
CPS≥1			
Pembrolizumab plus doublet chemotherapy	Independent spline 2 knot hazards	Independent spline 1 knot hazards	KM
Doublet chemotherapy	Independent spline 2 knot hazards	Independent spline 1 knot hazards	KM
CPS≥10			
Pembrolizumab plus doublet chemotherapy	Independent spline 2 knot odds	Independent spline 1 knot hazards	KM
Nivolumab plus doublet chemotherapy	HR of [redacted] applied to pembrolizumab plus doublet chemotherapy based on the NMA results	HR of [redacted] applied to pembrolizumab plus doublet chemotherapy based on the NMA results for OS	Assumed equal to pembrolizumab plus doublet chemotherapy (HR=1)
Abbreviations: CPS, combined positive score; HR, hazard ratio; KM, Kaplan Meier; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; ToT, time-on-treatment			

Figure 42. Survival curves: pembrolizumab plus doublet chemotherapy CPS≥1

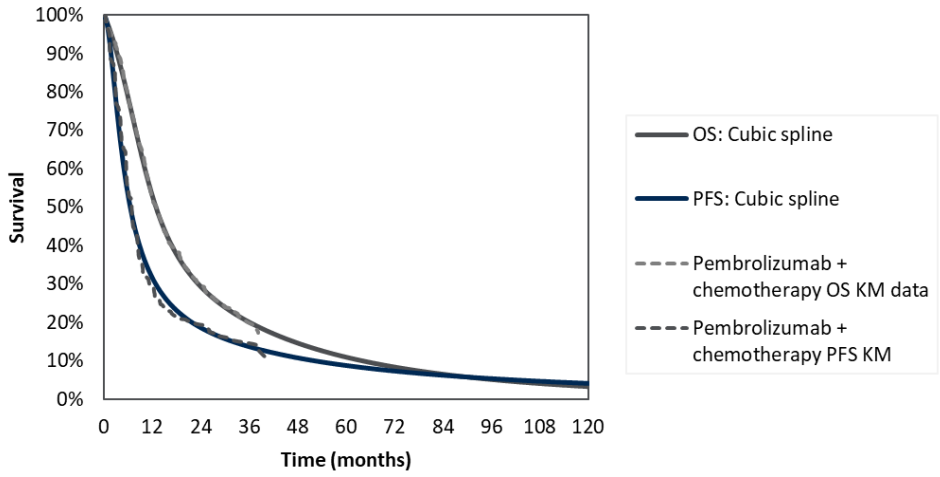


Figure 43. Survival curves: doublet chemotherapy CPS≥1

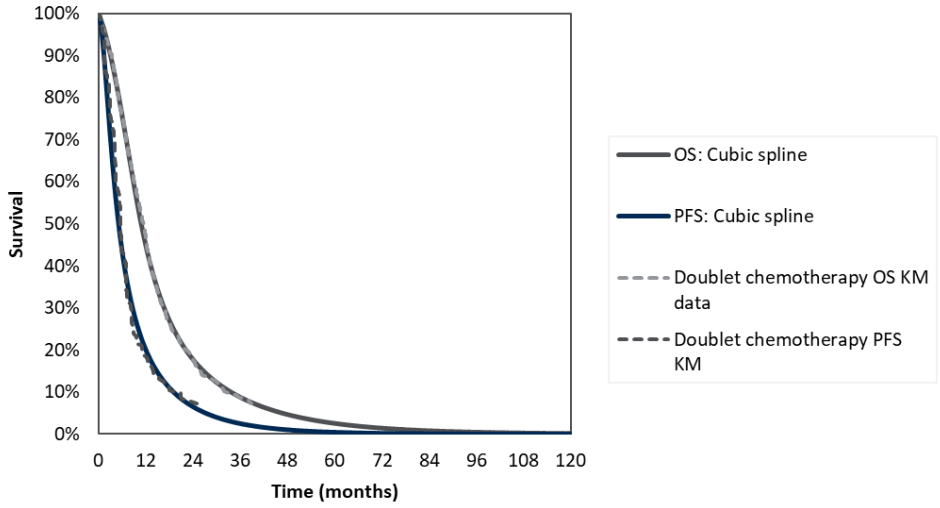


Figure 44. Survival curves: pembrolizumab plus doublet chemotherapy CPS≥10

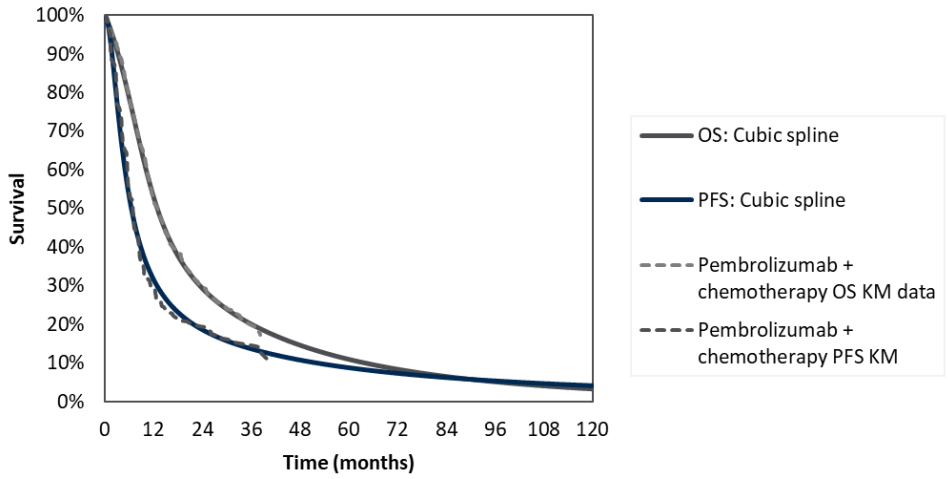


Figure 45. OS curves: CPS≥1

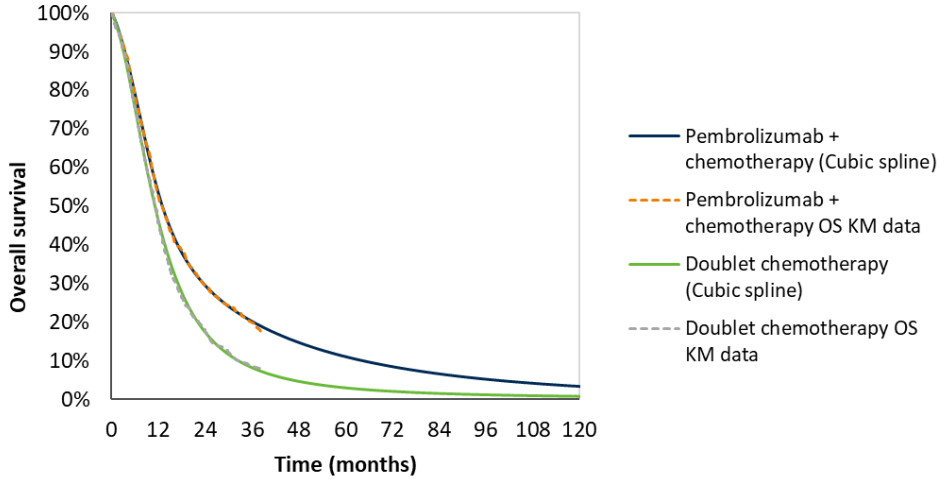


Figure 46. PFS curves: CPS≥1

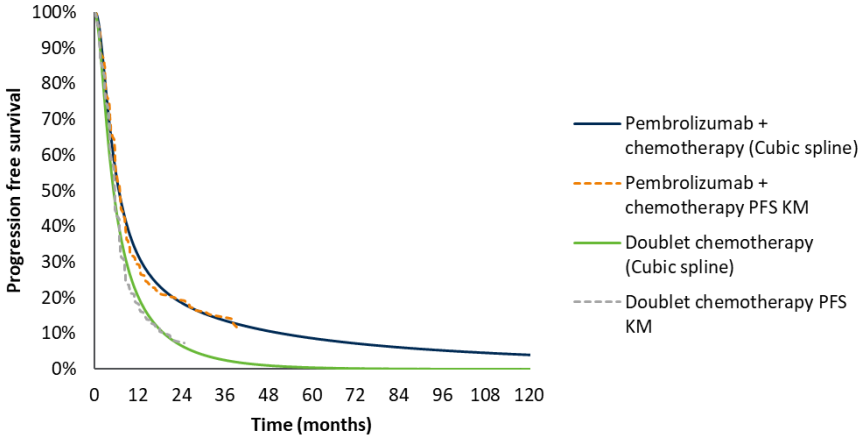


Figure 47. OS curves: CPS≥10

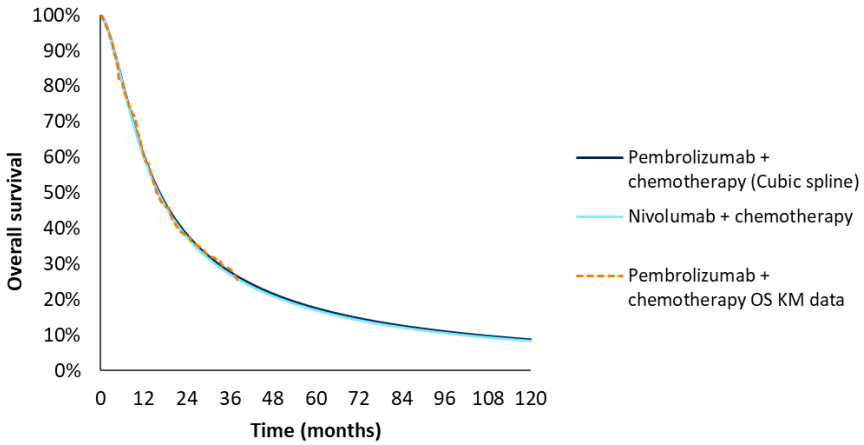
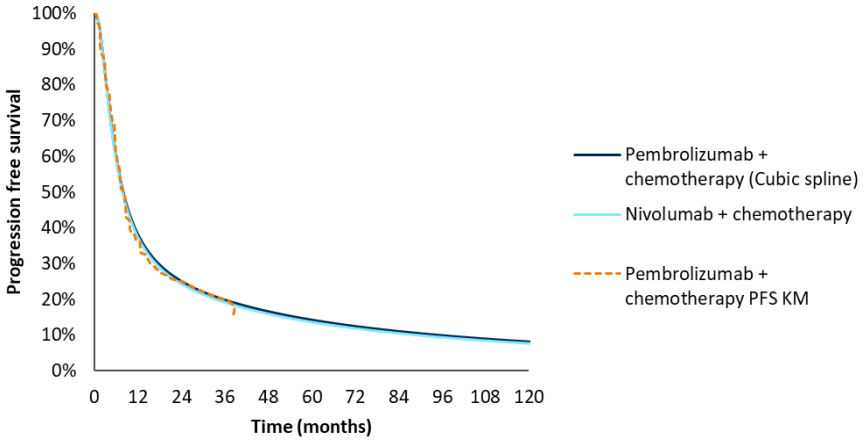


Figure 48. PFS curves: CPS≥10



3.3.6 Adverse events

The safety results of the KEYNOTE-859 trial are presented in detail in Section B.2.10. The economic model includes treatment-related Grade 3+ AEs occurring in ≥3% of patients receiving either treatment.

As per TA857, decreased neutrophil count and decreased platelet count are not included in the economic model as they are laboratory type events which have minimal treatment cost and quality of life impacts, and are distinct from symptoms or disease temporally associated with the use of a medicinal product (whether or not considered related to the medicinal product). The KEYNOTE-859 CSR also referred to decreased neutrophil count and decreased platelet count as investigations rather than disorders or conditions.

Table 46 provides the treatment-specific incidence rates applied in the economic model. The incidence rates were obtained from the ITT populations in the KEYNOTE-859 trial and CheckMate 649 trials as AE incidence rates and types are not dependent on CPS level. The difference in AE profiles between pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy may be driven largely by the backbone chemotherapy received in the trials. In scenario analysis, incidence rates in the pembrolizumab arm are used to inform the nivolumab arm.

Table 46. Treatment-specific AE data

AE	Pembrolizumab plus doublet chemotherapy (N=785)	Doublet chemotherapy (N=787)	Nivolumab plus doublet

					chemotherapy (N=782)	
	Number of events	**Incidence rate**	**Number of events**	**Incidence rate**	**Number of events**	**Incidence rate**
Anaemia	69	7.5%	59	7.5%	47	6.0%
Neutropenia	82	9.9%	78	9.9%	118	15.1%
Diarrhoea	51	5.1%	40	5.1%	35	4.5%
Vomiting	39	4.3%	34	4.3%	17	2.2%
Fatigue	29	4.3%	34	4.3%	30	3.8%
Nausea	28	3.9%	31	3.9%	20	2.6%
Hypokalaemia	30	3.0%	24	3.0%	0	0.0%
Palmar-plantar erythrodysaesthesia syndrome	25	3.2%	14	1.8%	11	1.4%
Neuropathy peripheral	10	1.3%	25	3.2%	31	4.0%
Abbreviations: AE, adverse event Source: Table 6 of the HTA HECON Safety report						

B.3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life studies

Health-related quality-of-life data were identified via an SLR described in Appendix H. The search was conducted in April 2023. Amongst the 59 included studies in this SLR, seven reported utility values among patients with untreated locally advanced unresectable gastric or GOJ cancer. None of the seven studies reported utility values according to progression status or time-to-death; thus, none were deemed appropriate for inclusion in the economic model.

In the SLR for economic evaluations, described in Appendix G, utility values were also extracted from studies conducting cost-utility analysis. Of the included studies in this SLR, ten studies conducting cost-utility analysis reported utility data according to progression status. HER2 status of the study participants was poorly reported in these studies. Nevertheless, the mean progression free utility ranged from 0.740 to 0.836 and the mean progressed disease utility ranged from 0.577 to 0.600.

The SLR for economic evaluations also included seven HTAs; one of these reported unredacted utility values. This HTA was the appraisal of trastuzumab for the treatment

of HER2 positive metastatic gastric cancer (NICE TA208).(28) For the progression free health state in this submission, the baseline utility value was 0.7292 (which increased daily by 0.000142 PFS). For progressed disease health state, the utility value was 0.577 and this was taken from the NICE appraisal of sunitinib for the treatment of gastrointestinal stromal tumours (TA179).(46)

The NICE methods for health technology assessment manual states a preference for using utility data collected from the relevant clinical trial to inform cost-utility analysis.(36) Given the paucity of published utility data specifically concerning the HER2 negative patient population, utility data taken directly from the KEYNOTE-859 trial are used to inform the economic model. This data is described in the following subsections.

3.4.2 Health-related quality-of-life data from clinical trials

3.4.2.1 Data collection and mapping

In the KEYNOTE-859 trial, the EuroQoL EQ-5D-5L questionnaire was administered by trained site personnel and completed by patients. The questionnaire was administered prior to dosing at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, and every 2 cycles thereafter (e.g., Cycle 7, Cycle 9, etc.), at the Treatment Discontinuation Visit, and at the 30-day Safety Follow-up Visit. A visit window of ± 7 days was applied to patient reported outcome (PRO) visit assessments.

Patients were compliant at completing the EQ-5D-5L questionnaire at each treatment visit; compliance ranged from [redacted] (Table 47).

Table 47. Compliance percentages for EQ-5D-5L by treatment visit

Treatment visit	Compliance (% of patients who completed the PRO questionnaire among those who are expected to complete the questionnaire at this time point)	
	CPS≥1	CPS≥10
Baseline	[redacted]	[redacted]
Week 3	[redacted]	[redacted]
Week 6	[redacted]	[redacted]
Week 9	[redacted]	[redacted]
Week 12	[redacted]	[redacted]
Week 18	[redacted]	[redacted]
Week 24	[redacted]	[redacted]
Week 30	[redacted]	[redacted]

Week 36	[redacted]	[redacted]
Week 42	[redacted]	[redacted]
Week 48	[redacted]	[redacted]
Week 54	[redacted]	[redacted]
Week 60	[redacted]	[redacted]
Week 66	[redacted]	[redacted]
Week 72	[redacted]	[redacted]
Week 78	[redacted]	[redacted]
Week 84	[redacted]	[redacted]
Week 90	[redacted]	[redacted]
Week 96	[redacted]	[redacted]
Week 102	[redacted]	[redacted]
Abbreviations: CPS, combined positive score; PRO, patient reported outcome Source: Tables 14.2-93 and 14.2-94 of the CSR		

All utility analyses from the KEYNOTE-859 trial were conducted descriptively, without adjustment for repeated measurements, which may have occurred if a trial patient completed multiple EQ-5D assessments while experiencing the same health state (e.g., progression free). Adjustments for repeated measurements were deemed inappropriate as they effectively down-weight values for subjects with multiple measurements, relative to those with a single measurement. These adjustments generally assume that the number of measures available per subject is not correlated with the value of the measure of interest. When such correlation is present, biased estimates of the sample mean can result.(47)

Aligning with NICE health technology evaluations manual of process and methods, utility values were calculated by mapping the 5L descriptive system onto the 3L value set. The mapping function developed by the NICE DSU was used to perform this mapping.(48)

Using the utility analyses from the KEYNOTE-859 trial, two methods of assigning utilities are considered in the economic model:

1. by time-to-death, where a utility value is given to patients depending on how long the patient is expected to live (see Section B.3.4.2.2) – base case.

2. by health state, where a utility value is given to progression free patients and progressed patients (see Section B.3.4.2.3) – scenario analysis.

The economic model also includes the option to include or exclude disutility values for AEs (see Section B.3.4.3).

Section B.3.4.4 further summarises the methods applied in the base case analysis.

3.4.2.2 Utility values according to time to death

The time-to-death approach was developed by Batty *et al.* 2011(49) and Hatswell *et al.* 2014(50) who found that disease progression may not fully capture all predictive factors of patient utility and that time-to-death provides a good fit to patient data. The evidence presented in these publications was informed by advanced melanoma patients, but the generalisability to other cancers has been accepted, for example in NICE's recent appraisal in advanced renal cell carcinoma (TA858).(51)

Furthermore, due to the post-progression data collection schedule in the KEYNOTE-859 trial, there would be a maximum of two assessments in those with progressed disease:

1. Treatment Discontinuation Visit
2. 30-day Safety Follow-up Visit.

With the limited collection of assessments with progressed disease, utility for this health state may only reflect quality of life in proximity to the progression event rather than the entirety of progressed disease. As noted in the following subsection, [redacted] and are informed by relatively fewer records and patients than progression free. The time-to-death approach mitigates against this bias, by categorising utility valuations according to time-to-death (regardless of whether death arises from a progression free or progressive disease state) rather than by progression status.

The following time intervals represent the standard set of pre-specified time intervals used across MSD trials; no other time intervals were pre-specified:

- 360 or more days to death
- 180 to 359 days to death
- 30 to 179 days to death
- Less than 30 days to death

Another time-to-death category was “unknown”. Trial patients who had not died at database cut off (censored OS) were included in the “unknown” category if the time from assessment date to OS censor date was less than 360 days. If the difference in the OS censor date and their most recent EQ-5D assessment was greater or equal to 360 days, it was included in the ‘≥360 days’ category. The EQ-5D assessment during baseline or before treatment start date is not included in the analysis.

The number of patients included in the “unknown” category is provided in Table 48. The proportion of patients in the “unknown” category is low in both arms and notably lower in the doublet chemotherapy arm than the pembrolizumab plus doublet chemotherapy arm.

Based on the censoring rules above, there is potential for patients classified as “unknown” to live longest and for their utility values to be similar to or higher than the utility values in the ‘≥360 days’ category (if there is a link between time-to-death and utilities, which seems to be the case in this dataset). If so, it could be that the utilities using the time-to-death approach are underestimated; more so in the treatment arm with more “unknown” utility assessments (pembrolizumab plus doublet chemotherapy).

Table 48. Number of trial patients with an unknown time-to-death category

Population	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy
CPS≥1	[redacted]	[redacted]
CPS≥10	[redacted]	[redacted]
Abbreviations: CPS, combined positive score Source: Tables 85 and 129 of the HTA HECON PRO report		

The resulting time-to-death utility values analysed from the KEYNOTE-859 trial data and included in the economic model are presented in Table 49. As per the health state utility data, the treatment-specific data in Table 49 is based on treatment arm and therefore includes patients on- and off-treatment in the treatment arm they were randomised to.

MSD acknowledges that the time-to-death intervals do not fully align with the model cycle length used. This discrepancy is expected to have a negligible impact on the

cost-effectiveness results as the weekly cycles in the economic model limit the discrepancy to a few days.

Table 49. KEYNOTE-859 Health Utility Scores by Time from EQ-5D Assessment Date to Death (mapped to EQ-5D-3L)

Time from EQ-5D Ass. Date to Death (days)	Pembrolizumab plus doublet chemotherapy*						Doublet chemotherapy						Pooled					
	n	m	Mean	SE	LB 95% CI	UB 95% CI	n	M	Mean	SE	LB 95% CI	UB 95% CI	n	m	Mean	SE	LB 95 % CI	UB 95 % CI
CPS≥1																		
≥360	[redacted]																	
180 to 359	[redacted]																	
30 to 179	[redacted]																	
<30	[redacted]																	
CPS≥10																		
≥360	[redacted]																	
180 to 359	[redacted]																	
30 to 179	[redacted]																	
<30	[redacted]																	

Abbreviations: CI, confidence interval; CPS, combined positive score; LB, lower bound; SE, standard error; UB, upper bound
*Nivolumab plus doublet chemotherapy utility assumed to equal pembrolizumab plus doublet chemotherapy
n=number of participants
m=number of records
Source: Tables 85 and 129 of the HTA HECON PRO report

3.4.2.3 Utility values according to health state

The EQ-5D utility scores according to health state use post-baseline EQ-5D assessments. The following criteria were used to determine the health state the assessment related to:

- Progression free: A post-baseline EQ-5D assessment is considered to be completed during the progression free state (based on BICR) if (a) it was completed prior to the date of the first documented disease progression if progression occurred, or (b) if it was completed prior to the censoring date of progression-free survival if no progression.

- Progressed disease: The EQ-5D assessment, which was assessed at or after the date of the first documented disease progression is considered to be completed during the progressive state.

- Unknown: EQ-5D assessments that were completed after the censoring date of progression-free survival if no progression occurred are included in a "unknown" category and not used to inform the economic model.

The resulting health state utility values analysed from the KEYNOTE-859 trial data and included in the economic model are presented in Table 50. The treatment-specific data in Table 50 is based on treatment arm and therefore includes patients on- and off-treatment in the treatment arm they were randomised to.

Table 50 also shows the number of records and number of patients contributing to each health state utility value; relatively fewer records and patients are available for the progressed disease health state (approximately 50% of the number of records and 25% of the number of patients for whom values were collected for the progression free heath state), which suggests the progressed disease utility value could be unreliable. Compared to the range of utility data captured in the SLR, the progressed disease utility values from the KEYNOTE-859 trial [redacted] ([redacted] versus 0.577 to 0.600).

Table 50. KEYNOTE-859 Health Utility Scores by Health State Based on BICR Assessment (mapped to EQ-5D-3L)

Treatment	Progression free						Progressed disease					
	n	m	Mean	SE	LB 95% CI	UB 95% CI	n	m	Mean	SE	LB 95% CI	UB 95% CI
CPS≥1												
Pembrolizumab plus doublet chemotherapy	[redacted]											
Doublet chemotherapy	[redacted]											
Pooled	[redacted]											
CPS≥10												
Pembrolizumab plus doublet chemotherapy*	[redacted]											
Doublet chemotherapy	[redacted]											
Pooled	[redacted]											

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; LB, lower bound; SE, standard error; UB, upper bound
*Nivolumab plus doublet chemotherapy utility data assumed to equal pembrolizumab plus doublet chemotherapy
n=number of participants
m=number of records
Source: Tables 52, 63, 96 and 107 of the HTA HECON PRO report

The number of patients included in the “unknown” category is provided in Table 51. These proportions are relatively low in both treatment arms.

Table 51. Number of trial patients with an unknown health state

Population	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy
CPS≥1	[redacted]	[redacted]
CPS≥10	[redacted]	[redacted]
Abbreviations: CPS, combined positive score Source: Tables 52, 63, 96 and 107 of the HTA HECON PRO report		

3.4.3 Adverse events

As noted in Section 3.3.6, the economic model considers treatment-related Grade 3+ AEs occurring in ≥3% of patients receiving either treatment. To account for differences in AE profiles between treatments, two methods of assigning AE disutilities are considered appropriate in the economic model:

1. Pooled health state utility values or time-to-death utility values including AE disutility values – base case.

2. Treatment-specific health state utility values or time-to-death utility values excluding AE disutility values (including AE disutility values could double-count the impact of AEs) – scenario analysis.

For the base case, the estimated disutility associated with Grade 3+ AEs is based on analyses of the KEYNOTE-859 trial data. In the “During AE” assessments in these analyses, the EQ-5D questionnaire was completed on or after the date of AE onset and on or prior to the date of AE resolution. The EQ-5D assessment during baseline or before treatment start date is not included. The disutility can then be calculated as the difference between the “During Grade 3+ AE” utility value and the “without Grade 3+ AE” utility value. In consequence, the disutility analysis considers AE grade, but not the type of AE (e.g., anaemia or nausea). For completeness, a scenario was included in the economic model to employ the sources used in the TA857 submission, which did differentiate disutility by the type of AE. The disutility values due to AEs included as options in the economic model are summarised in Table 52.

To account for the impact of AEs on HRQoL a one-off QALY loss is applied in the first cycle. To calculate the one-off QALY loss, the disutility values in Table 52 are

combined with the treatment-specific probabilities of experiencing each AE (see Section B.3.3.6) and the mean duration of each AE (Table 53).

Table 52. Disutility values due to AEs included in the economic model

AE	Disutility			Source	Disutility	Source (TA857)
	CPS≥1		CPS≥10			
	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy	Pembrolizumab plus doublet chemotherapy*			
Anaemia	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.11500	Swinburn *et al.* 2010
Neutropenia	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.08973	Nafees *et al.* 2008
Diarrhoea	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.04680	Doyle *et al.* 2008
Vomiting	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.10300	Swinburn *et al.* 2010
Fatigue	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.11900	Lloyd *et al.* 2006
Nausea	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.10300	Swinburn *et al.* 2010
Hypokalaemia	[redacted]	[redacted]	[redacted]	KEYNOTE-859	0.00000	Assumption
Palmar-plantar erythron dysaesthesia syndrome	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.04320	Nafees *et al.* 2008
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	KEYNOTE-859	-0.21600	Tabberer *et al.* 2006

Abbreviations: AE, adverse event; CPS, combined positive score
Source: Tables 68 and 112 of the HTA HECON PRO report
*Nivolumab plus doublet chemotherapy disutility assumed to equal pembrolizumab plus doublet chemotherapy

Table 53. Adverse event durations obtained from KEYNOTE-859 (ITT population)

AE	Pembrolizumab plus doublet chemotherapy*	Doublet chemotherapy
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]
Abbreviations: AE, adverse event; CPS, combined positive score Source: Table 6 of the HTA HECON Safety report *Nivolumab plus doublet chemotherapy AE durations assumed to equal pembrolizumab plus doublet chemotherapy		

3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values used in the base case analysis are summarised in Table 54. A wide range of scenarios using alternative assumptions are also explored (see Section B.3.11.3).

Table 54. Summary of utility values for cost-effectiveness analysis

Treatment arm	State	Mean utility	Reference in CS	Justification
CPS≥1				
Pembrolizumab plus doublet chemotherapy	≥360 days to death	[redacted]	Section B.3.4.2.3	Time-to-death method addresses the issue with the data collection schedule (small number of PD assessments). AE disutility values are applied as a one-off QALY loss in the first model cycle to account for different AE profiles. Time-to-death utility values and AE disutility values are obtained from the KEYNOTE-859 trial to reduce heterogeneity.
	180 to 359 days to death	[redacted]		
	30 to 179 days to death	[redacted]		
	<30 days to death			
	One-off QALYs loss	[redacted]	Section B.3.4.3	
Doublet chemotherapy	≥360 days to death	[redacted]	Section B.3.4.2.3	
	180 to 359 days to death	[redacted]		
	30 to 179 days to death	[redacted]		
	<30 days to death			
	One-off QALYs loss	[redacted]	Section B.3.4.3	
CPS≥10				
	≥360 days to death	[redacted]		

Treatment arm	State	Mean utility	Reference in CS	Justification
Pembrolizumab plus doublet chemotherapy	180 to 359 days to death	[redacted]	Section B.3.4.2.3	Time-to-death method addresses the issue with the data collection schedule (small number of PD assessments). AE disutility values are applied as a one-off QALY loss in the first model cycle to account for different AE profiles. Time-to-death utility values and AE disutility values are obtained from the KEYNOTE-859 trial to reduce heterogeneity.
	30 to 179 days to death	[redacted]		
	<30 days to death			
	One-off QALYs loss	[redacted]	Section B.3.4.3	
Nivolumab plus doublet chemotherapy	≥360 days to death	[redacted]*	Section B.3.4.2.3	
	180 to 359 days to death	[redacted]*		
	30 to 179 days to death	[redacted]*		
	<30 days to death	[redacted]*		
	One-off QALY loss	[redacted]	Section B.3.4.3	
Abbreviations: AE, adverse event; CPS, combined positive score; CS, company submission; NA, not applicable; PD, progressed disease; SE standard error. *Nivolumab plus doublet chemotherapy utility assumed to equal pembrolizumab plus doublet chemotherapy				

3.4.5 General population adjustments

The general population baseline utility was first determined using the algorithm by NICE DSU, based on the starting patient age and proportion of female patients (for baseline characteristics, see Table 30).(52) Following this, the baseline general population utility is 0.8434 and 0.8401 in patients expressing CPS≥1 and CPS≥10, respectively.

None of the utility values according to health state exceed the baseline general population utility, [redacted]. Given that it lacks face validity for a patient with advanced gastric or GOJ adenocarcinoma to have a higher quality of life than someone in the general population, this utility value was capped at the general population utility.

In addition, the equivalent general population utility was estimated at each model cycle to enable utilities to be adjusted for an ageing population, as suggested in NICE TSD 12.(53)

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Cost and healthcare resource use inputs included in the economic model comprise of:

- Intervention and comparator costs
    - Acquisition costs
    - Administration costs
- Health-state costs (disease management costs)
- Adverse-event costs
- Subsequent treatment costs
- Miscellaneous costs
    - Progression costs
    - End-of-life care costs

Relevant healthcare resource use data for England were identified via an SLR described in Appendix I. Two studies included in this SLR reported healthcare resource use data from the UK (Guest *et al.* 2006 and Gomez-Ulloa *et al*. 2020).(54, 55). The healthcare resource use data included in the TA857 was also considered relevant. The healthcare resource use data from these sources are discussed further in Section B.3.5.2.

As for unit costs, tests and services are sourced from the National Schedule of NHS Costs or the Unit Costs of Health and Social Care.(56, 57) Drug costs are sourced from the UK British National Formulary (BNF) for branded products and the Department of Health and Social Care Drugs and pharmaceutical electronic market information tool (eMIT) for generic products.(58, 59) All other costs sourced from the literature were inflated to a 2021/22 cost year as necessary using the NHS Cost Inflation Index (NHSCII) pay and prices indices.

3.5.1 Intervention and comparators' costs

3.5.1.1 Drug acquisition costs

Table 55 presents the drug acquisition costs included in the economic model. The list price of pembrolizumab 25 mg/mL concentrate solution is £2,630.00 per 4mL vial,

leading to a cost per 200mg dose of £5,260.00. As discussed in Section B.1.2, a commercial access agreement is currently in place for pembrolizumab. MSD is also aware that nivolumab has a commercial access agreement in place. Given that the CAA discounts associated with pembrolizumab and nivolumab are confidential, cost-effectiveness estimates for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy are presented using list prices. Results using the pembrolizumab CAA and assumed nivolumab CAA discounts in 10% increments will be presented as additional information. Cost-effectiveness estimates for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy will be presented using the CAA price for pembrolizumab as the doublet chemotherapy prices available to the NHS are publicly available.

Table 55. Drug acquisition costs: unit costs

Treatment	Unit size	Vials/tablets per pack	Cost per vial/pack	Unit cost	Source
Pembrolizumab	100 mg	1	£2,630.00	£2,630.00	BNF
Capecitabine (CAPOX)	150 mg	60	£6.40	£0.11	eMIT
	500 mg	120	£36.49	£0.30	eMIT
Oxaliplatin (CAPOX)	50 mg	1	£13.49	£13.49	eMIT
	100 mg	1	£24.44	£24.44	eMIT
	200 mg	1	£21.52	£21.52	eMIT
5-FU (FP)	500 mg	1	£3.25	£3.25	eMIT
	1000 mg	1	£3.93	£3.93	eMIT
	2500 mg	1	£4.05	£4.05	eMIT
	5000 mg	1	£10.54	£10.54	eMIT
Cisplatin (FP)	10 mg	1	£2.71	£2.71	eMIT
	50 mg	1	£9.10	£9.10	eMIT
	100 mg	1	£10.97	£10.97	eMIT
Leucovorin (FOLFOX)	50 mg	1	£2.04	£2.04	eMIT
	100 mg	1	£1.10	£1.10	eMIT
	300 mg	1	£30.59	£30.59	eMIT
Oxaliplatin (FOLFOX)	50 mg	1	£13.49	£13.49	eMIT
	100 mg	1	£24.44	£24.44	eMIT
	200 mg	1	£21.52	£21.52	eMIT
5-FU (FOLFOX)	500 mg	1	£3.25	£3.25	eMIT

	1000 mg	1	£3.93	£3.93	eMIT
	2500 mg	1	£4.05	£4.05	eMIT
	5000 mg	1	£10.54	£10.54	eMIT
Nivolumab	40 mg	1	£439.00	£439.00	BNF
	100 mg	1	£1,097.00	£1,097.00	BNF
	120 mg	1	£1,317.00	£1,317.00	BNF
	240 mg	1	£2,633.00	£2,633.00	BNF
Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool Note: eMIT Pharmex data for the period 1 January 2022 to 31 December 2022, for Pharmex products shown as Generic in the period 1 July 2022 to 31 December 2022					

Drug acquisition costs are applied in line with dosing schedules. These dosing schedules are detailed in

Table 56. For pembrolizumab plus doublet chemotherapy and doublet chemotherapy the dosing schedules reflect those used in the KEYNOTE-859 trial. For nivolumab plus doublet chemotherapy, dosing schedules from the CheckMate 649 trial were used.

Based on the dosing type (mg flat dose or mg/m^2 or mg/kg), the drug dose and patient body surface area (BSA) or weight are used to calculate the required number of milligrams per dose for each treatment component. A cost minimising approach ensuring that the lowest cost was used for each required dosage was implemented. This approach was used as the estimation of drug costs in health economic evaluations should account for the distribution in BSA to produce accurate results. Given that patient data was available from the trial baseline patient characteristics this approach was feasible. For treatments with multiple pack options, the pack with the lowest cost per mg was used (employing the assumption that the NHS has access to this “best value” as much as possible) without wastage (with vial sharing). Without vial sharing, the vial combination providing the lowest cost per dose was used.

Also, for IV drugs dosed by patient BSA, wastage costs are included in the base case. This implies that the contents of a vial which is surplus to one patient is discarded and the cost of this surplus is included in the drug acquisition cost. The impact of vials being shared is explored in a scenario analysis, where wastage costs are excluded. It is assumed there are no wastage costs associated with treatments that are administered orally.

Finally, a relative dose intensity (RDI) is applied to all treatments in the base case. The RDI is the percentage of actual versus expected number of dose administrations, defined as the actual number of dose administrations a trial patient received within the protocol regimen, divided by the expected number of dose administrations a trial patient is expected to receive based on the treatment duration. As per TA857, the RDI is applied to the acquisition cost per dose. Incorporating the RDI provides a more accurate estimation of accrued costs in clinical practice; removing the RDI provides an overestimate of cost accrual. In scenario analysis, an RDI of 100% is assumed.

Table 57 summarises the resulting costs per treatment cycle. The proportion of patients on treatment and incurring these costs are discussed in detail in Section B.3.3.3.

Table 56. Drug acquisition costs: dosing schedules

Combination	Treatment	Dose required	Dose units	RDI*	Doses per treatment cycle	Cycle length (weeks)
Pembrolizumab plus doublet chemotherapy	Pembrolizumab Q3W	200	mg	[redacted]	1	3
	Pembrolizumab Q6W	400	mg	[redacted]	1	6
	Capecitabine (CAPOX)	1000	mg/m^2	[redacted]	28	3
	Oxaliplatin (CAPOX)	130	mg/m^2	[redacted]	1	3
	5-FU (FP)	800	mg/m^2	[redacted]	5	3
	Cisplatin (FP)	80	mg/m^2	[redacted]	1	3
Doublet chemotherapy	Capecitabine (CAPOX)	1000	mg/m^2	[redacted]	28	3
	Oxaliplatin (CAPOX)	130	mg/m^2	[redacted]	1	3
	5-FU (FP)	800	mg/m^2	[redacted]	5	3
	Cisplatin (FP)	80	mg/m^2	[redacted]	1	3
Nivolumab plus doublet chemotherapy	Nivolumab Q2W	240	mg	[redacted]	1	2
	Nivolumab Q3W	360	mg	[redacted]	1	3
	Capecitabine (CAPOX)	1000	mg/m^2	[redacted]	28	3
	Oxaliplatin (CAPOX)	130	mg/m^2	[redacted]	1	3
	Leucovorin (FOLFOX)	400	mg/m^2	[redacted]	1	2
	Oxaliplatin (FOLFOX)	85	mg/m^2	[redacted]	1	2
	5-FU (FOLFOX)	2800	mg/m^2	[redacted]	1	2

Abbreviations: Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RDI, relative dose intensity.

*Nivolumab plus doublet chemotherapy RDI assumed to equal pembrolizumab plus doublet chemotherapy As FOLFOX was an option in CheckMate 649 and not KEYNOTE-859, the oxaliplatin component of CAPOX and 5-FU component of FP is used to inform FOLFOX RDI.

Table 57. Drug acquisition costs: costs per treatment cycle

Combination	Treatment	Treatment cost without vial sharing (base case)	Treatment cost with vial sharing (scenario analysis)
Pembrolizumab plus doublet chemotherapy	Pembrolizumab Q3W	£4,997.00	£4,997.00
	Pembrolizumab Q6W	£9,994.00	£9,494.00
	Capecitabine (CAPOX)	£0.93	£0.93
	Oxaliplatin (CAPOX)	£32.91	£22.35
	5-FU (FP)	£3.89	£2.12
	Cisplatin (FP)	£19.47	£14.47
Doublet chemotherapy	Capecitabine (CAPOX)	£0.94	£0.94
	Oxaliplatin (CAPOX)	£33.26	£22.59
	5-FU (FP)	£3.89	£2.12
	Cisplatin (FP)	£19.47	£14.47
Nivolumab plus doublet chemotherapy	Nivolumab Q2W	£2,501.35	£2,501.16
	Nivolumab Q3W	£3,752.50	£3,751.74
	Capecitabine (CAPOX)	£0.93	£0.93
	Oxaliplatin (CAPOX)	£32.91	£22.35
	Leucovorin (FOLFOX)	£7.40	£7.19
	Oxaliplatin (FOLFOX)	£20.23	£14.62
	5-FU (FOLFOX)	£7.78	£7.40

Abbreviations: BSA, body surface area; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks
Note: BSA is 1.7m^2 in the CPS≥1 and CPS≥10 populations

3.5.1.2 Drug administration costs

Drug administration costs included in the economic model, sourced from the National Schedule of NHS Costs 2021/22, are summarised in Table 58.(57)

It is assumed patients receive IV treatment in a hospital setting. For administrations of regimens involving 5-FU (doublet chemotherapy FP comprises of 5-FU and cisplatin and FOLFOX comprises of 5-FU, leucovorin and oxaliplatin), the tariff associated with a prolonged infusion (SB14Z) is employed as 5-FU is administered over 5 days of a 21-day treatment cycle. For administrations involving all other combinations with IV

treatments, the tariff associated with more complex parenteral chemotherapy (SB13Z) is employed.

The oral therapy, capecitabine, can be co-administered with IV therapies (i.e., as part of doublet chemotherapies CAPOX and XP), or taken at home, hence no additional cost to the NHS is assumed to administer it.

The tariff associated with simple parenteral chemotherapy (SB12Z) is considered for pembrolizumab monotherapy and nivolumab monotherapy (i.e., once doublet chemotherapy has stopped). This is because these treatments take 30 minutes to infuse. When these treatments are given in combination with CAPOX or XP, the total infusion time is closer to 2 hours.

Table 58. Drug administration costs

Currency code	Currency description	Unit cost	Treatment
SB12Z	Deliver simple parenteral chemotherapy at first attendance	£287.71	Pembrolizumab monotherapy Nivolumab monotherapy
SB13Z	Deliver more complex parental chemotherapy at first attendance	£354.64	Pembrolizumab with CAPOX Nivolumab with CAPOX CAPOX
SB14Z	Deliver complex chemotherapy including prolonged infusion treatment at first attendance	£474.94	Pembrolizumab with FP Nivolumab with FOLFOX FP FOLFOX
Abbreviations: CAPOX, capecitabine and oxaliplatin; FOLFOX, 5-FU, leucovorin and oxaliplatin; FP, 5-FU and cisplatin; FU, fluorouracil. Note: one-off CVAD pump and installation costs associated are not included as the cost would be common to all treatment arms			

3.5.2 Health-state costs (disease management costs)

Resource use is assumed to be linked to health state rather than treatment arm or time-to-death category.

For the progression free health state, TA857 was used to inform resource use.(21) These resource use estimates reflect those used in the TA208 submission, which were informed by clinical expert opinion.(28) As shown in Table 59, resource use in the progression free health state also depends on whether a patient is on or off chemotherapy treatment.

Table 59. PF health state costs

Healthcare resource	Frequency (per week)	Frequency reference	Unit cost	Unit cost reference
Oncologist consultation (during chemotherapy treatment)	1 per 3 weeks (0.33)	Table 48 of the TA857 CS	£363.83	National Schedule of NHS Costs 2021/22. Outpatient Care. Non-admitted face-to-face attendance, first. WF01B. Consultant led. Service code 370.
Oncologist consultation (after chemotherapy treatment)	1 per 6 weeks (0.17)		£221.48	National Schedule of NHS Costs 2021/22. Outpatient Care. Non-admitted face-to-face attendance, follow-up. WF01A. Consultant led. Service code 370
Cardiac monitoring (MUGA)	1 per 3 months (0.08), 33% MUGA (0.028)		£375.99	National Schedule of NHS Costs 2021/22. MUGA Scan. RN22Z
Cardiac monitoring (echocardiogram)	1 per 3 months (0.08), 67% echocardiogram (0.056)		£130.45	National Schedule of NHS Costs 2021/22. Simple Echocardiogram, 19 years and over. RD51A.
Total cost per week during chemotherapy treatment	**£138.90**			
Total cost per week after chemotherapy treatment	**£54.54**			
Abbreviations: CT, computed tomography; CS, company submission; MUGA, multiple-gated acquisition; NA, not applicable; NHS, National Health Service; PF, progression free.				

For the progressed disease health state, resource use estimates in TA857 were also informed by TA208 (Table 61). These estimates were based on those reported in the NICE clinical guideline for advanced breast cancer (CG81).(60) It is probable that disease management in gastric and GOJ cancer is different to breast cancer and that clinical practice has changed since CG81 was published (2009).

As mentioned earlier, the Gomez-Ulloa *et al.* 2020 study was identified by the SLR.(54) This is a retrospective real-world evidence study of resource use in patients receiving second-line therapy for advanced gastric cancer in the UK (n=62) between January 2013 and July 2015, with a mean follow-up of 6.6 months. This study was deemed to

be of good quality and to provide a more contemporary representation of the current treatment practice in progressed disease than that presented in TA857 and TA208 (Table 60). However, based on the reporting methods, each patient who reported a specific category of care may only be counted once during the 6.6 months of follow-up, which may underestimate the frequency of resource use.

MSD consulted clinical experts to determine which source best reflects NHS practice. All three experts expressed concerns about both estimates. In brief, the frequencies used by TA857/TA208/CG81 were considered too high and align with those seen during palliative care. Moreover, important resources like hospitalisations, outpatient visits and blood and biochemistry test are missing. As for the frequencies reported in Gómez-Ulloa *et al.* 2020, they were considered too low. Also, imaging tests like X-rays, ultrasound and endoscopy are unlikely for the population of interest. The experts also said it was important to distinguish between a patient who is progressed and on treatment (second line plus), as in Gómez-Ulloa, and one who is off treatment. It was then concluded that the overall cost may lie somewhere in between these two sources.

Table 60. PD health state costs (scenario analysis: Gómez-Ulloa *et al.* 2020)

Healthcare resource	Frequency (per year)	Frequency (per week)	Unit cost	Unit cost reference
Hospitalisation/ in-patient stay	0.59	0.01	£2,152	National Schedule of NHS Costs 2021/22. Total HRGs. Weighted average of: • elective • non-elective long stay • non-elective short stay • day case • regular day or night admission.
Emergency room visit	0.21	0.00	£174.10	National Schedule of NHS Costs 2021/22. Emergency Care. Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment. VB03Z. Service code 2.
Outpatient (visit for follow-up)	1.47	0.03	£221.48	National Schedule of NHS Costs 2021/22. Outpatient Care. Non-admitted face-to-face attendance, follow-up. WF01A. Consultant led. Service code 370
Concomitant medication	1.76	0.03	£0.00	Assumption covered by AE management costs
Blood test cost (e.g. blood cell count, liver function, kidney function)	1.79	0.03	£4.70	National Schedule of NHS Costs 2021/22. Directly accessed pathology. Phlebotomy. DAPS08.
Biochemistry test	1.79	0.03	£1.55	National Schedule of NHS Costs 2021/22. Directly accessed pathology Clinical biochemistry. DAPS04
Electrocardiogram	0.41	0.01	£222.62	National Schedule of NHS Costs 2021/22.

				Outpatient procedures. Electrocardiogram Monitoring or Stress Testing. EY51Z. Service code 370.
X-ray	0.29	0.01	£38.28	National Schedule of NHS Costs 2021/22. Directly accessed diagnostic services. Direct Access Plain Film. DAPF.
Ultrasound	0.26	0.01	£58.10	National Schedule of NHS Costs 2021/22. Diagnostic imaging. Direct Access. Ultrasound Scan with duration of less than 20 minutes, without Contrast. RD40Z.
CT scan	1.58	0.03	£128.84	National Schedule of NHS Costs 2021/22. Diagnostic imaging. Computerised Tomography Scan of Three Areas, without Contrast. RD25Z.
Endoscopy	0.15	0.00	£219.95	National Schedule of NHS Costs 2021/22. Outpatient procedures. Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over. FE22Z. Service code 106.
Total cost per week	**£38.23**			
Abbreviations: AE, adverse event; CT, computed tomography; HRG, healthcare resource group; PD, progressed disease; NHS, National Health Service.				

Table 61. PD health state costs (base case: TA857/TA208/CG81)

Healthcare resource	Frequency (per week)	Frequency reference	Unit cost	Unit cost reference
Nurse, home visit	20 minutes per week (1)	Table 49 of the TA857 CS	£17.33	Unit Costs of Health and Social Care 2022. Table 9.3.1: Costs and unit estimations for nurses working in a GP practice nurse (Band 5) Costs.
Clinical nurse specialist	1 hour per week (1)		£52.00	Unit Costs of Health and Social Care 2022. Table 9.3.1: Costs and unit estimations for nurses working in a GP practice nurse (Band 5) Costs.
GP	1 visit per 2 weeks (0.5)		£42.00	Unit Costs of Health and Social Care 2022. Table 9.4.2: Unit costs for a GP. Per surgery consultation lasting 9.22 minutes.
Therapist	1 hour per 2 weeks (0.5)		£50.00	Unit Costs of Health and Social Care 2022. Table 10.3.1: Costs and unit estimations for a community occupational therapist.
Total cost per week	**£115.33**			
Abbreviations: CG, clinical guideline; GP, General Practitioner; PD, progressed disease.				

3.5.3 Adverse event costs

As noted in Section B.3.3.6, the economic model considers treatment-related Grade 3+ AEs occurring in ≥3% of patients receiving either treatment. The unit cost to manage each AE was obtained from the National Schedule of NHS Costs for 2021/22, these costs are summarised in Table 62.(57)

Table 62. Adverse event costs

AE	Unit cost	Currency code and description
Anaemia	£770.29	Non-elective short stay. Weighted average of SA01G-K. In response to ERG criticism in TA737 (weighted average preferred to one code)
Neutropenia	£2,257.20	Total HRGs. Weighted average of SA35A-E
Diarrhoea	£522.09	Non-elective short stay. FD10M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2.

		Consistent with TA857 and TA737.
Vomiting	£522.09	Assumed equal to diarrhoea. Similar assumptions made in TA857 and TA737.
Fatigue	£780.14	Non-elective short stay. SA01G. Aplasia or Other Aplastic Anaemia, with CC Score 8+ Consistent with TA737.
Nausea	£522.09	Assumed equal to diarrhoea. Similar assumptions made in TA857 and TA737.
Hypokalaemia	£753.88	Total HRGs. WJ11Z. Other disorders of immunity.
Palmar-plantar erythrodysaesthesia syndrome	£267.00	WF01B. General Medicine, Non-Admitted Face-to-Face Attendance, First
Neuropathy peripheral	£1,867.70	Total HRGs. Weighted average of AA26C-H.
Abbreviations: AE, adverse event; CC, complications and comorbidities; ERG, Evidence Review Group; HRG, healthcare resource group.		

In the economic model, a one-off cost is applied in the first cycle to account for the cost of managing AEs. This approach is consistent with other NICE appraisals including TA857(21) and TA737(22). To calculate the one-off cost, the unit costs in Table 62 are combined with the treatment-specific probabilities of experience each AE (see Section B.3.3.6). For the one-off cost resulting from the base case analysis, see Table 63.

Table 63. One-off AE cost

One-off AE cost loss*	**Pembrolizumab plus doublet chemotherapy**	**Doublet chemotherapy**	**Nivolumab plus doublet chemotherapy**
	£472	£472	£543
Abbreviations: AE, adverse event; CPS, combined positive score; NA, not applicable; QALY, quality-adjusted life year *AEs are assumed to be independent of CPS level			

3.5.4 Subsequent treatment costs

In the advanced gastric and GOJ pathway, patients can receive subsequent lines of treatment when they progress and/or discontinue their first line of treatment. In the economic model, the impact of subsequent treatments on efficacy is included within OS as some patients received subsequent lines of treatment in the KEYNOTE-859 trial. To cost these benefits, the economic model applies a one-off cost upon progression as a simplifying assumption.

As the KEYNOTE-859 trial is a global trial, patients could receive subsequent treatments that are not offered by the NHS. For example, ramucirumab received a negative recommendation by NICE (TA378).(61) To better understand the treatment pathway in NHS practice, clinical expert opinion was sought on the proportion of patients who would receive subsequent treatments (some may not want to or be fit enough to) and what types of subsequent treatments are offered. These estimates are summarised in Table 64 and used to inform the base case analysis.

To optimise alignment between subsequent treatments which are costed and those which contribute to OS benefit, consideration was given to the appropriateness of conducting a cross-over adjustment type analysis where OS benefits in both treatment arms would be adjusted to better reflect the subsequent treatments received in NHS practice. To retain sufficient sample size, only key non-UK treatments would be removed (e.g., pembrolizumab [non-MSI high in the doublet chemotherapy arm and all in the pembrolizumab plus doublet chemotherapy arm], ramucirumab, ramucirumab plus paclitaxel and nivolumab). Upon further investigation, the impact of such analysis on the ICER is expected to be minimal since:

- [redacted] of patients in the pembrolizumab plus doublet chemotherapy arm received pembrolizumab as a subsequent treatment
- The proportion of patients receiving ramucirumab plus paclitaxel in each treatment arm is similar [redacted]
- The proportion of patients receiving nivolumab in each treatment arm is similar [redacted]
- The QALY gain in the progressed disease health state is [redacted] in the pembrolizumab arm [redacted] than the chemotherapy arm [redacted] and close enough to suggest QALY gains within this health state do not depend on the type of subsequent treatment received.

For these reasons, the analysis was not conducted as it was considered that it would be unnecessarily complex with minimal impact on the ICER, therefore being of limited

value from a decision-making perspective. Instead, more pessimistic OS curves can be explored in scenario analysis to assess the impact of the uncertainty on the ICER.

Table 64. Subsequent treatment distributions (base case: NHS practice)

Inputs	Pembrolizumab plus doublet chemotherapy*	Doublet chemotherapy
Patients that receive a subsequent treatment	70%	
2nd line treatments		Pembrolizumab would be offered to MSI high patients (NICE ID4036), in place of FOLFIRI. Non-MSI high patients receive the same subsequent treatments as the pembrolizumab plus doublet chemotherapy arm, so the proportions of the other subsequent treatments are equivalent in both arms.
FOLFIRI	60%	
Paclitaxel	30%	
Irinotecan	10%	
3rd line treatments		
FOLFIRI	6%	
Paclitaxel	12%	
Lonsurf	12%	
Distributions applied in the economic model		
FOLFIRI	66%	61%
Paclitaxel	42%	42%
Irinotecan	10%	10%
Lonsurf	12%	12%
Pembrolizumab (NICE ID4036)	0%	5%^
*Nivolumab plus doublet chemotherapy subsequent treatment proportions and distributions assumed to equal pembrolizumab plus doublet chemotherapy, in line with clinical expert opinion ^Informed by the proportion of MSI high patients in the trial, which the clinical experts considered generalisable to clinical practice. Pembrolizumab is assumed to displace FOLFIRI in this proportion of patients		

In scenario analysis, the ten most commonly used subsequent treatments in the KEYNOTE-859 trial are used (Table 65). The total proportion exceeds 100% as all subsequent lines are considered. The duration of each subsequent treatment was also taken from KEYNOTE-859. As clinical experts did not expect subsequent treatment proportions, types or durations to depend on CPS level, the ITT population of the KEYNOTE-859 trial was used to inform these inputs.

To estimate the one-off cost of subsequent treatment, a weighted average of the proportion of patients who progressed and received a subsequent treatment, the distribution of subsequent treatments and the acquisition and administration cost of each subsequent treatment is taken. Consistent with first line drug costs, subsequent treatment acquisition costs are sourced from BNF and the eMIT, and administration

costs are sourced from the National Schedule of NHS Costs 2021/22. In the absence of data, RDI was assumed to be 100% for all subsequent treatments.

The resulting one-off costs calculated and applied in the economic model are given in Table 66.

Table 65. Subsequent treatment distributions (scenario analysis: trial data)

Treatment arm	Subsequent treatment											Patients that receive a subsequent treatment
	Pem.	Paclitaxel + ramucirumab	Paclitaxel	Iri.	FOLFIRI	Nivo	Docetaxel	Cap.	Trifluridine/tipiracil	Cap. + oxaliplatin	Total	
Duration of treatment (weeks)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Pem. plus doublet chemo†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Doublet chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Cap, capecitabine; Chemo, chemotherapy; CPS, combined positive score; Iri, irinotecan; Nivo, nivolumab; Pem, pembrolizumab
*Duration is based on the sum of all of the subsequent lines
†Nivolumab plus doublet chemotherapy subsequent treatment distributions assumed to equal pembrolizumab plus doublet chemotherapy
^[redacted]
Source: Table 7 of the HTA HECON Drug Utilization report

Table 66. Subsequent treatment costs (administration and acquisition)

Treatment arm	NHS practice (base case)		Trial data (scenario analysis)	
	List prices	Including CAA price for pembrolizumab	List prices	Including CAA price for pembrolizumab
Pembrolizumab plus doublet chemotherapy*	£16,779	£16,779^	£48,060	[redacted]
Doublet chemotherapy	£35,203	[redacted]	£58,281	[redacted]
Abbreviations: CPS, combined positive score; NHS, National Health Service *Nivolumab plus doublet chemotherapy subsequent treatment costs assumed to equal pembrolizumab plus doublet chemotherapy ^No subsequent usage of pembrolizumab in NHS practice according to clinical experts				

3.5.5 Miscellaneous costs

3.5.5.1 End of life

An end-of-life cost is applied to all patients who die in the model; the cost is applied to those entering the death health state. End-of-life costs are included in the 2022 Unit Costs of Health and Social Care Manual based on research carried out by the Nuffield Trust.(56, 62) These costs cover the care received by patients in their final year. The cancer-specific end-of-life cost reported in 2021/22 prices and applied in the economic model is £13,113.

3.5.5.2 Progression cost

A one-off cost upon progression is applied to patients transitioning from the progression free health state and adjusted by the proportion of events that are progression to approximate transitions to the progressed disease heath state. This captures the additional investigations and imaging required to confirm progression. According to TA208 and TA857, clinical experts indicated that patients would receive a CT scan at the start of the treatment then again at signs of progression. Those appraisals also expected no incremental difference in cost between the treatment arms. According to clinical experts consulted by MSD, a CT scan would be required to confirm a progression. Thus, the cost of one CT scan (£128.84, see Table 59) is assumed for the progression cost. The total cost of progression-associated scans differs between arms due to the number and timing of progression events.

3.5.5.3 PD-L1 testing

In clinical practice, patients with advanced gastric cancer receive a HER2 test as standard, in line with NG83 for TA208, at the point at which they are deemed incurable (metastatic).(20) Given that the anticipated licence for pembrolizumab plus doublet chemotherapy will be for patients expressing CPS≥1, the administration of PD-L1 testing would also be required to identify eligible patients.

Clinical experts consulted by MSD confirmed that PD-L1 testing has been integrated into NHS clinical practice since the approval of nivolumab (TA857) and pembrolizumab (TA737).(21, 22) Furthermore, HER2 tests and PD-L1 tests are usually administered concurrently, in order to proactively identify HER2 negative patients eligible for nivolumab (TA857) or pembrolizumab (TA737), pending the outcome of the HER2 test. Where possible, a sequential approach to testing is avoided as it could lead to delays in a patient receiving treatment.

To align with clinical practice in the NHS, PD-L1 tests would be administered to all patients in both treatment arms of the model, leading to no incremental difference. Therefore, PD-L1 testing costs are not included in the economic model.

B.3.6 Severity

In line with NICE's new health technology evaluations manual of process and methods, the absolute and proportional QALY shortfall was calculated to assess the severity of the condition.(36) The absolute QALY shortfall is the future health, including quality and length of life, that is lost by people living with a condition over the remaining lifetime of the patients. The absolute QALY shortfall is calculated as the expected total QALYs that people living with a condition would be expected to have with current treatment over their remaining lifetime subtracted from the QALYs that the general population with the same age and sex distribution would be expected to have. The proportional QALY shortfall, is the absolute QALY shortfall divided by the remaining QALYs for the general population.

To calculate the remaining QALYs for the general population (i.e., people without the condition), the QALY shortfall calculator developed by Schneider *et al*. 2021(63) was

reviewed and the sources informing their reference case calculator were included in the economic model:

- UK national life tables collected and sourced from the ONS to calculate the life expectancy(45)
- The Adjusted Limited Dependent Variable Mixture Model by Hernandez Alava, et al. 2022 to derive mean utility scores based on age and sex(52)

The quality-adjusted life expectancy population norms were then derived by combining age- and sex-based mean utility scores with life expectancy estimates. The values for age and sex used in the shortfall estimation were consistent with those informing the patient characteristics in base case economic analysis (Table 67). A discount rate of 3.5% per annum for QALYs was also assumed.

Table 67. Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
CPS≥1		B.3.2
Proportion female	29.6%	
Starting age, years	60.1	
CPS≥10		
Proportion male	27.8%	
Starting age, years	60.7	
Abbreviations: CPS, combined positive score; QALY, quality-adjusted life year.		

For validation, the QALYs without the disease calculated from the economic model were compared with those estimated in the QALY shortfall calculator developed by Schneider *et al.* 2022; the economic model provided a conservative estimate of the QALYs without the disease (12.40 versus 12.65) and the same QALY weight as the QALY shortfall calculator.

To calculate the QALYs expected with current treatment, utilities consistent with those used in the base case were applied (Table 68). The resulting QALY shortfall estimates for the current evaluation are presented in Table 69.

Table 68. Summary of health state benefits and utility values for QALY shortfall analysis

Treatment arm	State	Mean utility	Reference to section in submission	Undiscounted LYs	Discounted QALYs*
CPS≥1					
Doublet chemotherapy	≥360 days to death	[redacted]	B.3.4	[redacted]	[redacted]
	180 to 359 days to death				
	30 to 179 days to death				
	<30 days to death				
	One-off QALYs loss due to AEs	[redacted]		[redacted]	[redacted]
	Total			[redacted]	[redacted]
CPS≥10					
Nivolumab plus doublet chemotherapy	≥360 days to death	[redacted]	B.3.4	[redacted]	[redacted]
	180 to 359 days to death				
	30 to 179 days to death				
	<30 days to death				
	One-off QALYs loss due to AEs	[redacted]		[redacted]	[redacted]
	Total			[redacted]	[redacted]

Abbreviations: AE, adverse event; CPS, combined positive score; LY, life year; QALY, quality-adjusted life year.
*Without QALY weighting

Table 69. Summary of QALY shortfall analysis

Population	Current treatment	Expected total QALYs for general population	Expected total QALYs for patients with the condition receiving current treatment†	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
CPS≥1	Doublet chemotherapy	12.40	[redacted]	[redacted]	[redacted]	1.2*
CPS≥10	Nivolumab plus doublet chemotherapy	12.40	[redacted]	[redacted]	[redacted]	1.0

Abbreviations: AE, adverse event; CPS, combined positive score; QALY, quality-adjusted life year.
*Proportional QALY shortfall falls in the 0.85 to 0.95 category which is associated with a 1.2 QALY weight
†Includes the one-off QALY loss associated with AEs

Under NICE's previous methods for evaluating new medicines and based on the poor prognosis associated with locally advanced unresectable or metastatic GC or GOJ adenocarcinoma, pembrolizumab plus doublet chemotherapy would have met the end-of-life criteria in the assessment versus doublet chemotherapy (treatment is for patients with a short life expectancy [less than 24 months] and expected to extend life by at least 3 months compared to current NHS treatment) and would therefore have qualified for a higher cost-effectiveness willingness-to-pay (WTP) threshold of £50,000/QALY.(29) It should be noted that the NICE appraisal of nivolumab for untreated HER2 negative advanced gastric, GOJ or oesophageal adenocarcinoma (TA857) met NICE's end-of-life criteria, and a higher decision-making threshold was applied.(21)

MSD cannot estimate what the QALY shortfall would have been in TA857 as total QALYs are redacted from committee papers. Based on the NMA results and a visual inspection of the naïve curves from CheckMate 648 and KEYNOTE-859 (digitised from CheckMate 649 by MSD, see Figure 49 and Figure 50), it is likely that the same QALY weighting would apply to both appraisals when current treatment is doublet chemotherapy.

Considering the higher decision-making threshold applied in TA857, the ability of committee to adopt a suitable approach, and the remaining unmet need in patients expressing CPS≥1, a QALY weighting of 1.7 is applied in the base case for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy. The QALY weighting calculated in the economic model and verified in the QALY shortfall calculator developed by Schneider *et al.* 2022 (1.2) is employed in scenario analysis.

Figure 49. Overall survival in patients expressing CPS≥1 receiving standard care: CheckMate 649 vs KEYNOTE-859

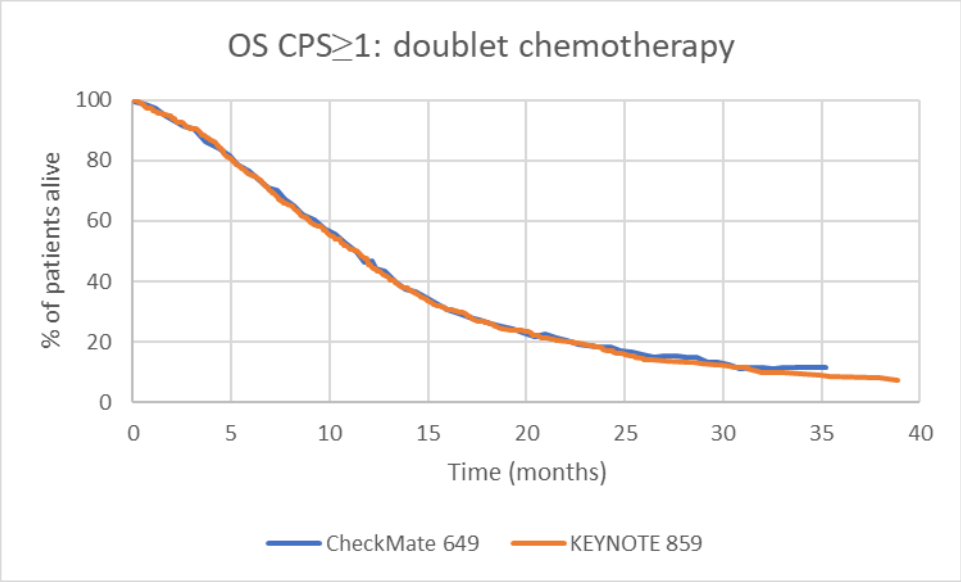
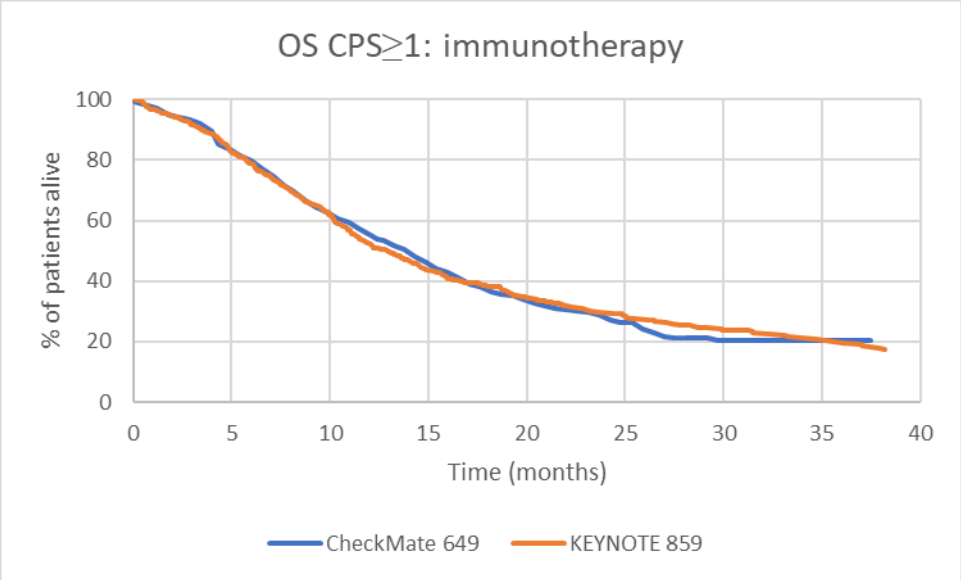


Figure 50. Overall survival in patients expressing CPS≥1 receiving immunotherapy: CheckMate 649 vs KEYNOTE-859



B.3.7 Uncertainty

Uncertainty in the available evidence base has been thoroughly explored where possible through evaluation of the associated parameter uncertainty and testing of the various assumptions made within the economic model. The key areas of uncertainty in the economic model are considered to be the following:

- Data according to CPS level:

The cost-effectiveness results for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy are presented for the full anticipated licensed indication (i.e., patients expressing a CPS≥1). MSD acknowledges that the patient population receiving doublet chemotherapy in NHS practice could be narrower than this (i.e., patients expressing a CPS<5) as patients with a CPS≥5 may be offered nivolumab plus doublet chemotherapy, as per the recommendation in TA857. In the KEYNOTE-859 trial, CPS≥5 was not a prespecified cut-off and subgroup data for the CPS≥5 population of KEYNOTE-859 is not currently available. To help address this uncertainty, CPS 1 to 9 results for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy from the KEYNOTE-859 trial have been presented and discussed (see Section 3.3.1.2).

- Data availability for nivolumab:

  Some modelling inputs for nivolumab were not available in patients expressing CPS≥10. In the absence of data, data from pembrolizumab was used as a proxy or another CPS level was used. Clinical expert opinion was sought on the appropriateness of these assumptions and alternative assumptions to fill these data gaps were explored in scenario analysis.

- Time-to-death utility values:

  There is uncertainty related to whether using a time-to-death approach for estimating utility is preferential to a progression-based approach that has historically been more widely used. The utility value for patients with a time-to-death >360 days is also similar to the age-adjusted utility value expected for the general population. The potential limitations of the data collection schedule in the KEYNOTE-859 trial with regards to the number of PD assessments and studies which found disease progression to not fully capture all predictive factors of patient utility have been discussed. The impact was investigated in scenario analysis by using health state utility values.

- Overall survival:

There is a paucity of longer-term survival data for the intervention or comparators in patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma. As a result, clinical expert opinion was sought to inform plausible survival predictions and all estimated survival extrapolations are included as options in the economic model.

- Treatment stopping rules:

  To align more closely with UK clinical practice, treatment caps of 6 cycles were applied to all chemotherapy regimens, as clinical expert opinion confirmed this is what happens in the NHS. These maximum durations were not imposed in the KEYNOTE-859 trial, but centres participating in the trial could apply caps as per local standard. Nevertheless, there is uncertainty over whether continuing to administer chemotherapy beyond 6 cycles is associated with clinical benefit. The impact was investigated in scenario analysis by removing the treatment caps.

- Subsequent treatments:

  As the KEYNOTE-859 trial is a global trial, patients could receive subsequent treatments that are not offered by the NHS. The progressed disease health state gains were close enough to suggest QALY gains within this health state do not depend on the type of subsequent treatment receive, thus UK clinical practice was used as the base case. The impact was instead investigated in scenario analysis by using the subsequent treatment data in KEYNOTE-859.

- Doublet chemotherapy backbones:

  The model base case reflects the distribution of chemotherapies administered in the KEYNOTE-859 trial for pembrolizumab plus doublet chemotherapy (CAPOX or FP) and CheckMate 649 for nivolumab plus doublet chemotherapy (FOLFOX or CAPOX). Clinical expert opinion indicates the more commonly used regimen in clinical practice to be CAPOX and for the choice of chemotherapy to independent of the IO it is given with. This divergence between the trials and clinical practice is source of uncertainty, however clinical

expert opinion indicates doublet chemotherapies to be clinically equivalent in this population. The administration cost differentials are important for nivolumab as the nivolumab regimen is 240mg Q2W with FOLFOX and 360mg Q3W with CAPOX. The impact was investigated in scenario analysis by using the backbones suggested by the clinical experts and the KEYNOTE-859 backbones for nivolumab.

- Health care resource use estimates:

  For the progressed disease health state, resource use estimates previously reported in TA857 were informed by TA208. These estimates were based on those reported in the NICE clinical guideline for advanced breast cancer (CG81), which was published in 2009. An alternative and more recent source was identified in the SLR, which was also subject to limitations. Clinical experts consulted by MSD disagreed with the estimates in both sources and considered it important to distinguish between a patient who is progressed and on treatment (second line plus) and off treatment. Due to time constraints, a structured elicitation framework could not be undertaken and both sources were explored in the economic analysis; the impact of using the alternative source was found to be minimal.

B.3.8 Managed access proposal

As noted in Section B.3.3, pembrolizumab with doublet chemotherapy showed a statistically significant and clinically meaningful improvement in the trial's primary endpoint of OS versus chemotherapy alone in the ITT, CPS≥1 and CPS≥10 populations at the pre-specified IA1 conducted by an independent Data Monitoring Committee.

Given the maturity of the dataset available from KEYNOTE-859 and IA1 deemed the final analysis for statistical analysis, this intervention is a candidate for baseline NHS funding. However, MSD remains committed to patient access as a priority, and are willing to discuss options for managed access should it prove necessary.

B.3.9 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

For the full list of variables used in the base case analysis, see Appendix O.

Assumptions

For a list of key assumptions included in the base case analysis, see Table 70.

Table 70. Summary of assumptions applied in the economic model

Category	Assumption made for base case analysis	Justification
Model structure	Partitioned survival model.	Established modelling precedent in the disease area. Uses trial primary (OS) secondary (PFS) endpoints.
Time horizon	30 years (lifetime).	Sufficient to capture all relevant and important differences in the future costs or outcomes among the treatments.
Perspective	NHS and PSS.	NICE reference case.
Discount rates	3.5% for costs and QALYs.	NICE reference case.
Doublet chemotherapy backbones	Pembrolizumab plus doublet chemotherapy and doublet chemotherapy informed by KEYNOTE-859. Nivolumab plus doublet chemotherapy informed by CheckMate 649. According to CPS level (KEYNOTE-859 CPS≥1 and ≥10, CheckMate 649 CPS≥5).	To align with the trial data.
OS: pembrolizumab plus doublet chemotherapy	Informed by KEYNOTE-859 and according to CPS level. CPS≥1: Independent spline 2 knot hazards. CPS≥10: Independent spline 2 knot odds.	Statistical goodness-of-fit statistics, visual inspection and clinical plausibility.
OS: doublet chemotherapy	Informed by KEYNOTE-859 and according to CPS level. CPS≥1: Independent spline 2 knot hazards	Statistical goodness-of-fit statistics, visual inspection and clinical plausibility.
OS: nivolumab plus doublet chemotherapy	CPS≥10: HR of [redacted] calculated from the NMA applied to pembrolizumab plus doublet chemotherapy	An NMA is needed to obtain estimates of the relative efficacy. PH assumption between IOs reasonable.
PFS: pembrolizumab	Informed by KEYNOTE-859 and according to CPS level.	Statistical goodness-of-fit statistics, visual inspection and clinical plausibility.

plus doublet chemotherapy	CPS≥1: Independent spline 1 knot hazards CPS≥10: Independent spline 1 knot hazards	
PFS: doublet chemotherapy	Informed by KEYNOTE-859 and according to CPS level. CPS≥1: Independent spline 1 knot hazards.	Statistical goodness-of-fit statistics, visual inspection and clinical plausibility.
PFS: nivolumab plus doublet chemotherapy	CPS≥10: HR of [redacted] assumed and applied to pembrolizumab plus doublet chemotherapy.	An NMA is needed to obtain estimates of the relative efficacy. PH assumption between IOs reasonable. OS relative efficacy is a reasonable proxy for PFS efficacy.
ToT: pembrolizumab plus doublet chemotherapy	KM ToT data from the KEYNOTE-859 trial for all drug components separately. Data according to CPS level.	KM data is mature.
ToT: doublet chemotherapy	KM ToT data from the KEYNOTE-859 trial for all drug components separately. Data according to CPS level.	KM data is mature.
ToT: nivolumab plus doublet chemotherapy	Assumed HR of 1 versus pembrolizumab plus doublet chemotherapy. FOLFOX ToT is made up of oxaliplatin from CAPOX and 5-FU from FP.	KM data is mature. ToT is not an included endpoint in the NMA.
Treatment stopping rules: immunotherapy	No additional rule applied in the economic model. ToT informed by KEYNOTE-859 which allowed a maximum of 35 treatment cycles (approximately 2 years).	To align with the KEYNOTE-859 trial and NHS clinical practice.
Treatment stopping rules: chemotherapy	6 treatment cycles assumed.	To align with the local standards applied by some centres participating in the KEYNOTE-859 trial and NHS clinical practice.
Treatment waning	No.	No evidence to indicate a treatment waning, curves fit independently.
Pembrolizumab administration	Q3W, as per the KEYNOTE-859 trial.	To align with the trial.
Nivolumab administration	Q2W with FOLFOX and Q3W with CAPOX, as per the CheckMate 649 trial.	To align with the trial.
Drug wastage costs	Included (no vial sharing).	Conservative assumption.
Relative dose intensity	Included and informed by the ITT population of KEYNOTE-859.	To estimate the true cost to the NHS.

AE type	Treatment-related Grade 3+ AEs occurring in ≥3% of patients receiving either treatment arm. Laboratory type AEs excluded.	To align with previous NICE appraisals.
AE incidence source	ITT population of KEYNOTE-859 for pembrolizumab plus doublet chemotherapy and doublet chemotherapy. ITT population of CheckMate 649 for nivolumab plus doublet chemotherapy.	To align with the trial data.
AE costs	One-off application in the first model cycle. Costs are sourced from the National Schedule of NHS Costs.	NICE preferred source for costs. To align with previous NICE appraisals.
Utilities	Time-to-death approach (treatment arms in KEYNOTE-859 pooled) Utilities according to CPS level.	HRQoL deteriorates as the patient nears death. Data collection in the trial provided more robust data for this approach.
AE disutility	One-off application in the first model cycle. Informed by KEYNOTE-859 and according to CPS level.	To align with the trial data and implementation method in previous NICE appraisals.
Drug acquisition costs	Costs sourced from the BNF for branded products and eMIT for generic products. Dosages according to the KEYNOTE-859 and CheckMate 649 trials.	NICE preferred source for costs. To align with the trial data.
Drug administration costs	Costs sourced from the National Schedule of NHS Costs. Cost codes depend on the complexity of the combination and one cost code covers all treatments within a combination.	NICE preferred source for costs. To align with previous NICE appraisals.
Disease management costs	Costs sourced from the National Schedule of NHS Costs or the Unit Costs of Health and Social Care. Frequencies sourced from TA857/TA208.	NICE preferred source for costs. To align with previous NICE appraisals.
Subsequent treatment costs	Subsequent treatments assumed to be used after progression and based on those administered in NHS practice	To align with NHS clinical practice.
Progression costs	CT scans at progression were noted in TA857 and TA208. Cost sourced from the National Schedule of NHS Costs.	NICE preferred source for costs.
End-of-life costs	One-off cost application to those entering the death health state Cost sourced from the Unit Costs of Health and Social Care.	NICE preferred source for costs. To align with previous NICE appraisals.
Abbreviations: AE, adverse event; CPS, combined positive score; CT, computed tomography; HR, hazard ratio; HRQoL, health-related quality of life; IO, immunotherapy; ITT, intention-to-treat; KM, Kaplan Meier; NHS, National Health Service; NMA, network		

meta-analysis; OS, overall survival; PFS, progression free survival; PSS, Personal and Social Services; Q2W, every 2 weeks; Q3W, every 3 weeks; RDI, relative dose intensity; ToT, time on treatment; TSD, technical support document

B.3.10 Base-case results

The deterministic results of the base case analysis are presented in Table 71. For disaggregated base case results, see Appendix J.

As discussed in Section B.3.5, a commercial access agreement is currently in place for pembrolizumab. Results including this discount are provided for the comparison with doublet chemotherapy. Given that the CAA discount associated with nivolumab is unknown, results for this comparison are based on list prices. Table 73 presents results using the pembrolizumab CAA discount and assumed nivolumab CAA discounts in 10% increments.

Also, as discussed in Section B.3.6, there is justifiable rationale for why the comparison versus doublet chemotherapy should qualify for a QALY weighting of 1.7. With this weight, pembrolizumab plus doublet chemotherapy would be considered cost-effective compared to doublet chemotherapy as the ICER is [redacted] (Table 71).

The incremental net health benefit (NHB) and incremental net monetary benefit (NMB) resulting from the base case analysis were also generated in the economic model (Table 72). A positive NHB means that overall population health is increased because of the new technology and indicates that the intervention is cost-effective compared with the alternative at the given WTP threshold. A negative NHB mean that the health benefits associated with the new technology are not large enough to prevent overall health loss because of healthcare not being funded elsewhere in the system. The NMB represents the value of an intervention in monetary terms. A positive NMB means the cost to derive the benefit is less than the maximum amount that the decision-maker would be willing to pay for this benefit and indicates that the intervention is cost-effective compared with the alternative at the given WTP threshold. Table 72 shows a [redacted] NHB and NMB for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy in the CPS≥1 population using a WTP threshold of £30,000/QALY.

Table 71. Base case results (ICER)

Treatment	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER (£/QALY)
CPS≥1 population (pembrolizumab CAA price)							
Chemo	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembro + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.09 (0.64)	[redacted]
CPS≥10 population (pembrolizumab list price)							
Nivo + chemo	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembro + chemo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06	[redacted]
Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; WTP, willingness-to-pay QALYs in brackets are not weighted for the severity modifier							

Table 72. Base case results (NMB and NHB)

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	NMB		NHB	
					£20,000/ QALY	£30,000/ QALY	£20,000/ QALY	£30,000/ QALY
CPS≥1 population (pembrolizumab CAA price)								
Chemo	[redacted]	[redacted]	-	-	-	-	-	-
Pembro + chemo	[redacted]	[redacted]	[redacted]	1.09 (0.64)	[redacted]	[redacted]	[redacted]	[redacted]
CPS≥10 population (pembrolizumab list price)								
Nivo + chemo	[redacted]	[redacted]	-	-	-	-	-	-
Pembro + chemo	[redacted]	[redacted]	[redacted]	0.06	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; WTP, willingness-to-pay QALYs in brackets are not weighted for the severity modifier								

Table 73. Base case results (versus nivolumab plus doublet chemotherapy using the CAA price for pembrolizumab and various CAA prices for nivolumab)

Nivolumab CAA	ICER (£/QALY)	NMB (£30,000/QALY)	NHB (£30,000/QALY)
0% (pembrolizumab list price)	[redacted]	[redacted]	[redacted]
0% (pembrolizumab CAA price used hereafter)	[redacted]	[redacted]	[redacted]
10%	[redacted]	[redacted]	[redacted]
20%	[redacted]	[redacted]	[redacted]
30%	[redacted]	[redacted]	[redacted]
40%	[redacted]	[redacted]	[redacted]
45%	[redacted]	[redacted]	[redacted]
50%	[redacted]	[redacted]	[redacted]
60%	[redacted]	[redacted]	[redacted]
70%	[redacted]	[redacted]	[redacted]
80%	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMB, net monetary benefit; CAA, commercial access agreement discount; QALY, quality adjusted life year

[redacted]

B.3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the economic model, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples (deemed sufficient to produce results which converge around a mean value). The mean values, distributions around the means and sources used to estimate the parameters have been presented in Appendix N. Generally, baseline patient characteristics were varied using a normal distribution, HRs from the NMA using a log normal distribution, costs using a normal or gamma distribution, frequencies (disease management resource use and AE incidence) using a gamma distribution, and utility values, RDI and subsequent treatment proportions using a beta distribution. Survival curves were varied using a multivariate normal distribution.

PSA results for the base case analysis are summarised in Table 74. These results show that the mean PSA ICERs are highly congruent to the deterministic base case ICERs presented in Table 71. The mean PSA ICERs appear robust to additional PSA draws, as illustrated by the convergence plot in Figure 51 and Figure 54. The corresponding cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) are presented in Figure 52 and Figure 53 for the CPS≥1 population and Figure 55 and Figure 56 for the CPS≥10 population, respectively.

Table 74. PSA results

Treatment	Total costs	Total QALYs	Inc. costs	Inc. QALYs	ICER (£/QALY)	NMB	NHB
CPS≥1 (pembrolizumab CAA price)							
Chemo	[redacted]	[redacted]	-	-	-	-	-
Pembro + chemo	[redacted]	[redacted]	[redacted]	1.05	[redacted]	[redacted]	[redacted]
CPS≥10 (pembrolizumab list price)							
Nivo + chemo	[redacted]	[redacted]	-	-	-	-	-
Pembro + chemo	[redacted]	[redacted]	[redacted]	0.06	[redacted]	[redacted]	[redacted]

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; WTP, willingness-to-pay
Note: NMB and NHB calculated using a WTP threshold of £30,000/QALY

Figure 51. ICER convergence plot: CPS≥1 population

Figure 52. Cost-effectiveness plane: CPS≥1 population

Figure 53. CEAC: CPS≥1 population

Figure 54. ICER convergence plot: CPS≥10 population

Figure 55. Cost-effectiveness plane: CPS≥10 population

Figure 56. CEAC: CPS≥10 population

3.11.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted by varying key model parameters between the upper and lower values of the expected value used in the deterministic base case. The upper and lower values were informed by the 95% CI. A standard error of 20% was assumed if measures of uncertainty were not reported. Baseline age was also varied using a standard error of 20% as the range observed in the trial was considered too narrow to assess the variation that can occur NHS practice (see Section B.3.2.1).

The key model parameters varied in OWSA include: baseline patient characteristics, NMA results, AE incidence, utility values, AE disutility values, chemotherapy acquisition

costs, RDI, disease management frequency, AE treatment costs, administration costs, disease management costs, the progression cost, the end-of-life cost and subsequent treatment proportions.

The NHB is used as the summary statistic for the OWSA as the magnitude of a dominated ICER (the intervention is more expensive and less effective than the comparator) or dominant ICER (the intervention is less expensive and more effective than the comparator) is difficult to interpret. The WTP threshold applied to the NHB is £30,000/QALY.

Results in the CPS≥1 population were most sensitive to subsequent treatment parameters (Figure 57 and Table 75). Results in the CPS≥10 population were most sensitive to relative efficacy (HRs) for nivolumab versus pembrolizumab and the RDI for nivolumab (Figure 58).

Figure 57. Results of OWSA: CPS≥1 population

Figure 58. Results of OWSA: CPS≥10 population

Table 75. Results of OWSA: CPS≥1 population

Base case NHB		
Parameter (lower bound, upper bound)	**NHB at lower value of parameter**	**NHB at upper value of parameter**
Doublet chemotherapy % who receive subsequent treatment (0.56, 0.84)		
Pembrolizumab + chemotherapy % who receive subsequent treatment (0.56, 0.84)		
Pembrolizumab + chemotherapy subsequent treatment market share: FOLFIRI (0.53, 0.79)		
Doublet chemotherapy subsequent treatment market share: FOLFIRI (0.49, 0.73)		

Doublet chemotherapy subsequent treatment market share: Pembrolizumab (0.04, 0.06)	[redacted]	[redacted]
Age (years) (48.08, 72.12)	[redacted]	[redacted]
IV administration cost (229.60, 344.40)	[redacted]	[redacted]
CPS ≥ 1: Doublet chemotherapy : Pooled TTD utility: 30-179 days (0.71, 0.73)	[redacted]	[redacted]
Base-case Resource use cost: Oncologist consultation (during chemotherapy) (291.06, 436.60)	[redacted]	[redacted]
Base-case Resource use cost: Oncologist conultation (after chemotherapy) (177.18, 265.78)	[redacted]	[redacted]
Base-case Frequency PF: Therapist (0.27, 0.40)	[redacted]	[redacted]
Base-case Frequency PF: Oncologist consultation (during chemotherapy) (0.13, 0.20)	[redacted]	[redacted]
Doublet chemotherapy subsequent treatment market share: Paclitaxel (0.34, 0.50)	[redacted]	[redacted]
CPS ≥ 1: Pembrolizumab + chemotherapy : Pooled TTD utility: 360 + days (0.83, 0.84)	[redacted]	[redacted]
Pembrolizumab + chemotherapy subsequent treatment market share: Paclitaxel (0.34, 0.50)	[redacted]	[redacted]
CPS ≥ 1: Pembrolizumab + chemotherapy : Pooled TTD utility: < 30 days (0.42, 0.52)	[redacted]	[redacted]
CPS ≥ 1: Doublet chemotherapy : Pooled TTD utility: < 30 days (0.42, 0.52)	[redacted]	[redacted]
CPS ≥ 1: Doublet chemotherapy : Pooled TTD utility: 360 + days (0.83, 0.84)	[redacted]	[redacted]
RDI: Pembrolizumab Q3W (0.95, 0.96)	[redacted]	[redacted]
AE disutility: CPS >=1 during Grade 3+ AE: Pooled (0.63, 1.00)	[redacted]	[redacted]

Table 76. Results of OWSA: CPS≥10 population

Base case NHB	[redacted]	
Parameter (lower bound, upper bound)	**NHB at lower value of parameter**	**NHB at upper value of parameter**
OS hazard ratio: Nivolumab + doublet chemotherapy vs Pembrolizumab + chemotherapy (0.79, 1.31)	[redacted]	[redacted]
ToT hazard ratio: Nivolumab + doublet chemotherapy vs Pembrolizumab + chemotherapy (0.80, 1.20)	[redacted]	[redacted]
RDI: Nivolumab Q2W (0.76, 1.00)	[redacted]	[redacted]
RDI: Nivolumab Q3W (0.76, 1.00)	[redacted]	[redacted]
Pembrolizumab + chemotherapy % who receive subsequent treatment (0.56, 0.84)	[redacted]	[redacted]
Nivolumab + doublet chemotherapy % who receive subsequent treatment (0.56, 0.84)	[redacted]	[redacted]
Pembrolizumab + chemotherapy subsequent treatment market share: FOLFIRI (0.53, 0.79)	[redacted]	[redacted]
Nivolumab + doublet chemotherapy subsequent treatment market share: FOLFIRI (0.53, 0.79)	[redacted]	[redacted]
PFS hazard ratio: Nivolumab + doublet chemotherapy vs Pembrolizumab + chemotherapy (0.82, 1.22)	[redacted]	[redacted]

CPS ≥ 10: Pembrolizumab + chemotherapy : Pooled TTD utility: 360 + days (0.83, 0.85)	[redacted]	[redacted]
RDI: Pembrolizumab Q3W (0.95, 0.96)	[redacted]	[redacted]
Age (years) (48.56, 72.84)	[redacted]	[redacted]
CPS ≥ 10: Nivolumab + doublet chemotherapy : Pooled TTD utility: 360 + days (0.83, 0.85)	[redacted]	[redacted]
IV administration cost (229.60, 344.40)	[redacted]	[redacted]
Pembrolizumab + chemotherapy subsequent treatment market share: Paclitaxel (0.34, 0.50)	[redacted]	[redacted]
Nivolumab + doublet chemotherapy subsequent treatment market share: Paclitaxel (0.34, 0.50)	[redacted]	[redacted]
CPS ≥ 10: Pembrolizumab + chemotherapy : Pooled TTD utility: 180-360 days (0.80, 0.83)	[redacted]	[redacted]
CPS ≥ 10: Nivolumab + doublet chemotherapy : Pooled TTD utility: < 30 days (0.38, 0.55)	[redacted]	[redacted]
CPS ≥ 10: Nivolumab + doublet chemotherapy : Pooled TTD utility: 30-179 days (0.71, 0.75)	[redacted]	[redacted]
CPS ≥ 10: Nivolumab + doublet chemotherapy : Pooled TTD utility: 180-360 days (0.80, 0.83)	[redacted]	[redacted]

3.11.3 Scenario analysis

A range of scenarios have been performed which vary key assumptions in the economic model. Table 77 lists these scenarios with their justification.

Table 77. List of scenarios

Base case	Scenario	Justification
Model set up		
Chemotherapy backbones based on trial data	Chemotherapy backbones based on clinical expert opinion	The scenario will reflect the cost of chemotherapy backbones used in NHS practice.
Chemotherapy backbones based on trial data	Nivolumab chemotherapy backbones informed by the pembrolizumab arm in KEYNOTE-859	Clinical experts did not expect the chemotherapy backbone to depend on the IO it is given in combination with.
Without half-cycle correction	With half-cycle correction	Half-cycle corrections are recommended for long cycle lengths to account for events occurring at any point during a cycle. The scenario will assess the impact of this recommendation on a short cycle length.
30-year time horizon	10-year time horizon	A shorter time horizon may be long enough to reflect all important differences in costs or outcomes between the treatments being compared.
30-year time horizon	20-year time horizon	A shorter time horizon may be long enough to reflect all important differences in costs or outcomes between the treatments being compared.
3.5% discount rate	1.5% discount rate	The NICE manual recommends alternative analyses using rates of 1.5% for both costs and health effects.
HRQoL		
Pooled time-to-death utility values	Pooled health state utility values	Health state utility values were also collected in the trial.
AE disutility values from KEYNOTE-859	AE disutility values from TA857	Alternative approach to estimate disutility values.
Pooled time-to-death utility values	Treatment specific time-to-death utility values	Alternative approach to account for different toxicity and administration profiles
Without general population utility adjustment	With general population utility adjustment	The impact of aging may not be inherently captured in the utility values.
Resource use and costs		

Pembrolizumab 200mg Q3W dosing schedule as per the trial	Pembrolizumab 400mg Q6W dosing schedule	Q6W schedule is more commonly used in NHS practice to reduce the burden for patients and clinic capacity.
No treatment cap for IO	2-year treatment cap for IO	The duration of treatment in the trial may overestimate the cost of treatment to the NHS. A 2-year stopping rule may apply in NHS practice.
18-week (6 treatment cycles) stopping rule for doublet chemotherapy	No treatment cap	Treatment caps in the trial depended on local standard. The scenario reflects the cost of chemotherapy used in the trial.
Include RDI	Exclude RDI (RDI=100%)	The RDI in the trial may not be reflective of NHS practice.
Include wastage costs	Exclude wastage costs	Some centres may promote vial sharing and the base case may overestimate the acquisition cost of treatment.
PD health state costs informed by TA857/TA208/CG81	PD health state costs informed by Gómez-Ulloa *et al.* 2020	The scenario provides a more contemporary representation of clinical practice in patients with GC receiving second line treatment.
Subsequent treatment distributions based on clinical expert opinion	Subsequent treatment distributions based on KEYNOTE-859 trial data	The scenario reflects the cost and benefits of subsequent treatment received in the trial.
With one-off progression cost	Without one-off progression cost	A one-off progression cost has been excluded in previous appraisals.
KM ToT curves	Parametric ToT curves	The scenario will reduce the stepped nature of KM data.
Clinical effectiveness (survival)		
Nivolumab plus doublet chemotherapy AE data informed by CheckMate 649	Nivolumab plus doublet chemotherapy AE data informed by KEYNOTE-859	AE profile may not depend on the type of IO
HRs for nivolumab plus doublet chemotherapy vs pembrolizumab plus doublet chemotherapy based on NMA	HRs for nivolumab plus doublet chemotherapy vs pembrolizumab plus doublet chemotherapy equal to 1	[redacted]
No treatment waning effect	Gradual treatment waning effect 7 years from the start of IO treatment, where the cycle-specific hazard for the IO gradually becomes equal to that of doublet chemotherapy over the subsequent 2 years	A conservative assumption is explored in scenario analysis.
Clinical effectiveness (survival) CPS≥1		

OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot hazards	Spline 2 knot odds	Alternative extrapolation with good statistical and visual fit.
OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot hazards	Spline 2 knot normal	Alternative extrapolation with good statistical and visual fit.
OS: Doublet chemotherapy: spline 2 knot hazards	Log-logistic	Best fitting parametric model.
OS: Doublet chemotherapy: spline 2 knot hazards	Spline 2 knot odds	Alternative extrapolation with good statistical and visual fit.
PFS: Pembrolizumab plus doublet chemotherapy: spline 1 knot hazards	Spline 2 knot hazards	Alternative extrapolation with good statistical and visual fit.
PFS: Doublet chemotherapy: spline 1 knot hazards	Spline 2 knot hazards	Alternative extrapolation with good statistical and visual fit.
Clinical effectiveness (survival) CPS≥10		
OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot odds	Log-logistic	Best fitting parametric model.
OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot odds	Spline 1 knot odds	Alternative extrapolation with good statistical and visual fit.
PFS: Pembrolizumab plus doublet chemotherapy: spline 1 knot hazards	Spline 2 knot odds	Alternative extrapolation with good statistical and visual fit.
Severity modifier		
Pembrolizumab plus doublet chemotherapy vs doublet chemotherapy: 1.7	1.2	The scenario analysis reflects the severity modifier calculated by the economic model.
Pembrolizumab plus doublet chemotherapy vs nivolumab plus doublet chemotherapy: 1.0	1.2	An unmet need still exists with current treatments; first-line treatment of an advanced cancer should be considered a severe disease setting.
Abbreviations: AE, adverse event; CPS, combined positive score; Crl, credible interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IO, immunotherapy; KM, Kaplan Meier; NHS, National Health Service; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PFS, progression free survival; Q6W, every 6 weeks; RDI, relative dose intensity; ToT, time on treatment; TSD, technical support document		

Results of deterministic scenario analyses are provided in Table 78 and Table 79. In the CPS≥1 population were most sensitive to assuming a severity modifier of 1.2, a treatment waning effect and alternative OS extrapolations (Table 78). Results in the CPS≥10 population were most sensitive to assuming a HR of 1 between pembrolizumab

and nivolumab for survival outcomes, a shorter time horizon and alternative OS extrapolations (Table 79).

The economic model also has the option to run scenarios probabilistically. For the CPS≥1 population, these are presented using 100 iterations; a pragmatic number given the time required to run the scenarios probabilistically. These results are provided in Table 80. Most probabilistic results are associated with a larger % change from the base case. The scenario using treatment-specific time-to-death utility values was associated with the greatest change (probabilistic ICER [redacted]). Based on the convergence plot for the probabilistic base case (Figure 51), more iterations should be explored.

Table 78. Results of scenario analysis: CPS≥1 population (deterministic)

Scenario	ICER (pembrolizumab CAA price)	% change from base case
Base case	[redacted]	[redacted]
Chemotherapy backbones: NHS practice	[redacted]	[redacted]
Half-cycle correction: Yes	[redacted]	[redacted]
Time horizon: 10-year	[redacted]	[redacted]
Time horizon: 20-year	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]
Utility source: Pooled health state utility values	[redacted]	[redacted]
Utility: General population utility adjustment	[redacted]	[redacted]
Utility: Literature-based AE disutility	[redacted]	[redacted]
Utility: Treatment-specific time to death	[redacted]	[redacted]
Pembrolizumab: 100% Q6W	[redacted]	[redacted]
Treatment administration: 2 yr chemo cap	[redacted]	[redacted]
Pembrolizumab & Nivolumab: 2 yr cap	[redacted]	[redacted]
RDI = 100%	[redacted]	[redacted]
Include wastage costs	[redacted]	[redacted]
Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
Subsequent treatment distribution: KEYNOTE 859	[redacted]	[redacted]
One-off progression cost: No	[redacted]	[redacted]
Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
Treatment waning effect: Yes	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot odds spline model	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot normal spline model	[redacted]	[redacted]
OS Doublet chemotherapy: Log-logistic	[redacted]	[redacted]
OS Doublet chemotherapy: 2-knot odds model	[redacted]	[redacted]
PFS Pembrolizumab + chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]

PFS Doublet chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
Severity modifier of x1.2	[redacted]	[redacted]
Abbreviations: AE, adverse event; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OS, overall survival; CAA, commercial access agreement; PFS, progression free survival; Q6W, every 6 weeks; RDI, relative dose intensity Note: results include a severity modifier of 1.7		

Table 79. Results of scenario analysis: CPS≥10 population (deterministic)

Scenario	ICER (list prices)	% change from base case
CPS10: Base case	[redacted]	[redacted]
CPS10: Chemotherapy backbone: NHS	[redacted]	[redacted]
CPS10: Nivolumab chemotherapy backbones: KEYNOTE-859	[redacted]	[redacted]
CPS10: Half-cycle correction: Yes	[redacted]	[redacted]
CPS10: Time horizon: 10-year	[redacted]	[redacted]
CPS10: Time horizon: 20-year	[redacted]	[redacted]
CPS10: Discount rate: 1.5%	[redacted]	[redacted]
CPS10: Utility source: Pooled health state utility values	[redacted]	[redacted]
CPS10: Utility: General population utility adjustment	[redacted]	[redacted]
CPS10: Utility: Literature-based AE disutility	[redacted]	[redacted]
CPS10: Utility: Treatment-specific time to death	[redacted]	[redacted]
CPS10: Pembrolizumab: 100% Q6W	[redacted]	[redacted]
CPS10: Treatment administration: 2 yr chemo cap	[redacted]	[redacted]
CPS10: Pembrolizumab & Nivolumab: 2 yr cap	[redacted]	[redacted]
CPS10: RDI = 100%	[redacted]	[redacted]
CPS10: Exclude wastage costs	[redacted]	[redacted]
CPS10: Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
CPS10: Subsequent treatment distribution: KEYNOTE 859	[redacted]	[redacted]
CPS10: One-off progression cost: No	[redacted]	[redacted]
CPS10: Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
CPS10: AEs for nivolumab = pembrolizumab	[redacted]	[redacted]
CPS10: Nivolumab vs pembrolizumab HR = 1	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-odds model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-hazard model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: log-logistic model	[redacted]	[redacted]
Abbreviations: AE, adverse event; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OS, overall survival; PFS, progression free survival; Q6W, every 6 weeks; RDI, relative dose intensity		

Table 80. Results of scenario analysis: CPS≥1 population (probabilistic: 100 iterations)

Scenario	ICER (pembrolizumab CAA price)	% change from base case
Base case	[redacted]	[redacted]
Chemotherapy backbones: NHS practice	[redacted]	[redacted]
Half-cycle correction: Yes	[redacted]	[redacted]
Time horizon: 10-year	[redacted]	[redacted]
Time horizon: 20-year	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]
Utility source: Pooled health state utility values	[redacted]	[redacted]
Utility: General population utility adjustment	[redacted]	[redacted]
Utility: Literature-based AE disutility	[redacted]	[redacted]
Utility: Treatment-specific time to death	[redacted]	[redacted]
Pembrolizumab: 100% Q6W	[redacted]	[redacted]
Treatment administration: 2 yr chemo cap	[redacted]	[redacted]
Pembrolizumab & Nivolumab: 2 yr cap	[redacted]	[redacted]
RDI = 100%	[redacted]	[redacted]
Include wastage costs	[redacted]	[redacted]
Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
Subsequent treatment distribution: KEYNOTE 859	[redacted]	[redacted]
One-off progression cost: No	[redacted]	[redacted]
Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
Treatment waning effect: Yes	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot odds spline model	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot normal spline model	[redacted]	[redacted]
OS Doublet chemotherapy: Log-logistic	[redacted]	[redacted]
OS Doublet chemotherapy: 2-knot odds model	[redacted]	[redacted]
PFS Pembrolizumab + chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
PFS Doublet chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
Severity modifier of x1.2	[redacted]	[redacted]

Abbreviations: AE, adverse event; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OS, overall survival; CAA, commercial access agreement; PFS, progression free survival; Q6W, every 6 weeks; RDI, relative dose intensity
Note: results include a severity modifier of 1.7

B.3.12 Subgroup analysis

The base case patient population included in the economic analysis is patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma, expressing a

CPS≥1, in line with the anticipated licenced population in the UK. As detailed in Section B.3.2.2, the comparators in the NICE final scope vary depending on CPS level.(37) Thus, cost-effectiveness results are also estimated for patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma, expressing a CPS≥10. No further subgroups were considered.

B.3.13 Benefits not captured in the QALY calculation

Pembrolizumab 200mg was given Q3W in the KEYNOTE-859 trial. 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.

B.3.14 Validation

Clinical expert opinion

As referenced throughout this dossier, clinical input was sought from three expert clinicians who are experienced in the management of HER2 negative advanced gastric or GOJ cancer patients in England. This helped to ensure that the inputs and assumptions used in the base case analysis were relevant to UK clinical practice to validate the clinical plausibility of the outcomes predicted by the model. The input was sought in individual consultation meetings of a two-hour duration. Topics covered in the discussions included:

- Current management of untreated HER2 negative advanced gastric or GOJ adenocarcinoma
- The types of chemotherapy regimens offered and how long they are given for
- The types of subsequent treatments offered and the proportion of patients who receive them
- Use of HER2 and PD-L1 testing
- The generalisabiltiy of the KEYNOTE-859 population to UK practice

- The generalisability of health care resource use reported in the literature to UK practice

- Discussion of the KEYNOTE-859 efficacy and safety results

- Survival estimates for patients currently treated with doublet chemotherapy and nivolmab plus doublet chemotherapy, and how this compares to the survival estimates in KEYNOTE-859

Model quality checks

Health economists working on the project routinely checked the internal validity and technical accuracy of the model through all stages of model development. The internal validity and technical accuracy of the model were also checked by an independent health economist not involved in the model programming using an extensive quality checklist. The full checklist includes basic validity checks of costs, utilities, clinical inputs, model settings, sensitivity analysis, additional sheet-by-sheet checks, editorial checks, strategic checks, and data sources checks.

Comparison with other trial data

As discussed previously, there is a paucity of trials conducted in the HER2 negative advanced GC therapy area, and only one relevant trial was identified (CheckMate 649). This limited the potential for cross-trial comparison of results.

B.3.15 Interpretation and conclusions of economic evidence

An economic SLR identified no previous economic evaluations of pembrolizumab in combination with doublet chemotherapy for patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma. Therefore, a de novo economic model, consistent with the NICE reference case, was developed to support this appraisal.

The economic model was based on a partitioned survival analysis structure, which has been accepted by NICE in previous advanced gastric, GOJ and oesophageal cancer submissions. This structure enables the primary (OS) and secondary endpoints (PFS) of the KEYNOTE-859 trial to be utilised.

The KEYNOTE-859 trial was the primary source of evidence for the efficacy and safety of pembrolizumab plus doublet chemotherapy versus doublet chemotherapy treatment. An NMA was required to compare pembrolizumab plus doublet chemotherapy with nivolumab plus doublet chemotherapy. This NMA utilised data from the CheckMate 649 trial, which was the pivotal trial in the TA857 submission. An NMA was feasible for OS in patients expressing a CPS≥10 and infeasible in the population eligible to receive nivolumab (CPS≥5). As such, the OS HR was used as a proxy for the PFS HR, and cost-effectiveness results were provided for a population expressing CPS≥10.

Based on a comparison of clinical effectiveness evidence identified in the EMA EPAR assessment report of nivolumab, the OS HR in patients expressing CPS 1 to 9 in KEYNOTE-859 was statistically significant and better than the OS HRs from CheckMate 649 at CPS levels of 1 to 4 and 5 to 9 (point estimates of 0.83 versus 0.97 and 0.92, respectively). Therefore, MSD would expect pembrolizumab plus doublet chemotherapy to be an effective option versus nivolumab plus doublet chemotherapy in patients expressing CPS≥5.

The model applied a number of other assumptions, such as: clinical equivalence between doublet chemotherapies, that current treatment caps on chemotherapy regimens will persist with the addition of pembrolizumab to the regimen, and that subsequent treatments offered in the NHS do not depend on previous IO treatment. Discussions with clinical experts who treat patients in the NHS with this cancer supported the above assumptions. Alternative assumptions were also explored in scenario analysis.

Results of the economic evaluation, evaluated deterministically and probabilistically, demonstrate the addition of pembrolizumab to doublet chemotherapy to be a cost-effective treatment in the anticipated licensed population in the UK, and that this conclusion is robust and consistent, as shown by a range of sensitivity and scenario analyses. Compared to doublet chemotherapy, patients receiving pembrolizumab plus doublet chemotherapy benefit from significantly improved survival outcomes, as well as longer time spent in health states associated with an improved quality of life. Improved health outcomes are associated with greater costs for patients treated with

pembrolizumab, largely as a function of higher drug acquisition costs in addition to an increase in disease management costs due to patients surviving longer.

The CAA discount associated with nivolumab is unknown; therefore, pembrolizumab plus doublet chemotherapy may be considered cost-effective compared to nivolumab plus doublet chemotherapy in the CPS≥10 population after commercial access agreements are taken into consideration. A key strength of pembrolizumab is that the label permits pembrolizumab 400mg to be given Q6W. Therefore, 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.

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 and broadening the available treatment options for clinicians when treating CPS positive GC and GOJ adenocarcinoma patients.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

September 2023

File name	Version	Contains confidential information	Date
MSD submission (ID4030) SIP [CON]	V2	No	09 February 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Pembrolizumab (KEYTRUDA®) in combination with chemotherapy

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The patient population being appraised by NICE is adult patients that have certain types of gastric cancer that is at an advanced stage. Advanced gastric cancer means that a cancer that began in the stomach has spread into the tissues around the stomach or nearby lymph nodes (locally advanced) or other parts of the body (metastatic). The aim of treatment is to control the cancer and relieve its symptoms, as well as try to improve the patient's quality of life (QoL).(1) The exact wording of the patient population being appraised by NICE is as follows: Adult patients that have untreated, locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) negative gastric or gastro-oesophageal junction adenocarcinoma whose tumours express programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥1.(2)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response: The marketing authorisation is expected to be granted in November 2023.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The table below shows you MSD's involvement with the patient groups that are listed as stakeholders for this appraisal.

Stakeholder	Financial transaction in 2022	Have met with MSD	Relationship
Cancer 52	£10,000	Yes	MSD is a corporate supporter of Cancer52. Our support runs from December 2022-December 2023.
Guts UK	No	Yes	Guts UK provided a quote for inclusion in a press release in Q1 2022. We met the CEO of Guts UK in March 2023 to discuss 2023 priorities. Guts UK provide a quote for inclusion in a press release in Q3 2023.
Macmillan Cancer Support	No	Yes	MSD met with Macmillan in Q1, Q2 and Q3 2023 to discuss 2023 shared priorities and health inequalities.
Oesophageal Patients Association	No	No	MSD have a meeting scheduled with OPA in September 2023 to discuss both organisations' priorities in GI.
Tenovus Cancer Care	Yes	Yes	MSD are a corporate member of Wales Cancer Industry Forum' which Tenovus are a leading partner. MSD provided sponsorship for, and attended, a policy roundtable hosted by Tenovus in April 2023. The total sponsorship in 2023 came to £6,300.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Although often reported as a single entity, gastric cancers can generally be classified into two categories: cardia gastric cancer arising in the area of the stomach adjoining the oesophageal-gastric junction, and non-cardia gastric cancer arising from more distal regions of the stomach. This appraisal covers both parts of the stomach, and we are referring to it as gastric (non-cardia gastric cancer) and gastroesophageal junction (cardia gastric cancer). In England, there approximately 5,000 new cases of gastric cancer each year, and most of these are of the type know as

adenocarcinoma.(3-5) Adenocarcinomas are cancers that develop in gland cells; these cells make mucus and stomach fluids.

Incidence of gastric cancer in the UK is strongly related to age, occurring most commonly in older people. Dietary factors increase risk; foods preserved by salting, low fruit intake, alcohol consumption and active tobacco smoking are established risk factors. Other factors, such as smoking and a high body mass index also increase the risk of developing gastric cancer.(6, 7)

Approximately 12% of GC are locally advanced (stage 3) and ~ 45% of GC are metastatic (stage 4).(3).

HER2* is overexpressed in about 30% of intestinal type gastric cancers, 15% of mixed type tumours, and about 5% of diffuse type. According to tumour location, about 30% of tumours at cardia/gastro–oesophageal junction and 15% of gastric cancers show HER2 positivity. A PD-L1** with CPS*** expression of ≥1 is expressed in about 85% of gastric cancers. The expression of PD-L1 is observed in many malignant tumours and is associated with poor survival in patients with gastric cancer.(8, 9)

Each year, approximately 600 patients in England with untreated HER2 negative unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, expressing a CPS≥1 are expected to be eligible for treatment with pembrolizumab with chemotherapy.

Locally advanced unresectable or metastatic gastric cancer, regardless of HER2 status and CPS expression, is associated with a significant patient burden. Common signs and symptoms include difficulty in swallowing, persistent indigestion/heartburn, feeling full after eating small amounts, loss of appetite and unexpected weight loss and feeling or being sick, tiredness due to anaemia (10). For more information on how pembrolizumab plus chemotherapy impacts QoL, see Section 3f.

* *HER2 is a protein on the surface of their cells, which encourages the cells to grow. Cells taken during a biopsy or surgery to remove the cancer are tested for HER2 status.*
** *Programmed death-ligand 1 (PD-L1) is a protein which naturally occurs on cells, plays an important role in maintaining balanced immune response. PD-L1 binds to its PD-1 receptor on immune T cells, which lessens the ability of immune T cells to attack. This ensures that normal cells are protected from excessive damage.*
*** *Combined positive score (CPS) - to calculate a CPS, the pathologist must first score the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages), then divide that total by the number of viable tumour cells and multiply by 100.*

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Currently there is no national screening programme for gastric cancer in the UK. Some people start by seeing their GP if they have symptoms that could be due to cancer. After examination the GP may make a referral to a specialist. Some people are diagnosed with cancer after they become unwell and go to accident and emergency (A&E). The most common method for diagnosing gastric cancer is via a specific type of endoscopy, called gastroscopy. Many patients with gastric cancers are diagnosed when their disease is at an advanced stage, owing to the vagueness of, or even lack of, symptoms, as well as limited understanding of the symptoms and their relevance to possible underlying cancer.(11)

Given the anticipated licence will be for patients expressing CPS≥1, the administration of PD-L1 testing is required to identify eligible patients. Patients with advanced gastric cancer receive a HER2 test as standard to identify patients eligible for trastuzumab (in line with TA208)(12), at the point at which they are deemed incurable. Clinical expert opinion indicates that in current NHS practice, HER2 tests and PD-L1 tests are administered at the same time, in order to proactively identify HER2-negative patients eligible for nivolumab (in line with TA857)(13), pending the outcome of the HER2 test. Therefore, no additional diagnostic tests are required for pembrolizumab with chemotherapy.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Advanced cancer cannot be cured. But the aim of treatment is to control the cancer and relieve its symptoms, as well as try to improve patient's QoL.

In England and Wales, patients with HER2-negative untreated locally advanced metastatic adenocarcinoma of the stomach or gastro-oesophageal junction generally receive first-line treatment with platinum/fluoropyrimidine doublet regimens containing cisplatin or oxaliplatin and 5-FU or capecitabine. It is recognised worldwide as standard first-line chemotherapy regimens for participants with untreated advanced metastatic disease. The most used doublet regimens are capecitabine plus cisplatin (XP), 5-FU plus cisplatin (FP), capecitabine plus oxaliplatin (CAPOX), and 5-FU plus oxaliplatin. There are only a few head-to-head comparisons between these regimens, and these trials have demonstrated similar efficacy between these doublet chemotherapy regimens in advanced gastric cancer (14), (8). As such, choices between these regimens are made based on patients' general medical condition and comorbidities which may be affected by the different toxicity profiles of the regimens.
Patients whose cancer express CPS $\geq$5 are treated with nivolumab in combination with fluoropyrimidine based chemotherapy (TA 857) (13).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients with advanced cancers are faced with many challenges, including symptoms of tumour and its spread to other organs, the difficulties with taking chemotherapy, and the mental and emotional impacts associated with the diagnosis of a fatal illness.

Section 2a outlines the general symptoms of advanced cancers. Further symptoms are experienced based on the site of the cancer and where it has spread. For example, the general symptoms of advanced gastric cancer include fatigue and suppressed appetite, however further symptoms may be felt based on if cancer has spread to the liver, lungs, or bones. If the cancer spreads to the liver, it can cause stomach pain and sickness. Spreading to the lungs can cause a long-lasting cough and breathlessness. Spreading to the bones can cause constipation and irritability. Cancer Research UK details the main symptoms associated with each cancer site and where it spreads (15).

By targeting the rapidly dividing cancer cells, chemotherapy aims to ease some of these symptoms. However further issues can be caused by the side effects of chemotherapy. Each person experiences side effects from chemotherapy differently, and different chemotherapy drugs cause different side effects (16). Many people feel fine for the first few hours following chemotherapy. Usually, some reaction occurs about four to six hours later. However, some people do not react until 12 or even 24 to 48 hours after treatment. Some people experience many of the side effects described, while others experience almost none. Some of the most common side effects are summarised below(17):

- Infection and fever – due to chemotherapy reducing a patient's white blood cell count (the cells that help fight infection), chemotherapy patients are more susceptible to infection. This can result in a fever.
- Flu-like symptoms - Around the third day following a chemotherapy treatment, some people may experience flu-like symptoms such as muscle aches and pains.
- Nausea (though not all chemotherapy drugs cause nausea).
- Fatigue, which can range from mild (usually cured by additional rest) to severe which may routinely impact a patient's ability to carry out everyday tasks such as cooking or bathing (18).
- Hair loss - begins about two to three weeks after starting chemotherapy. Some people will lose relatively little hair, while others may lose the hair on their head, eyelashes and eyebrows, as well as other body hair. Many people feel that hair loss is one of the most difficult aspects of chemotherapy treatment.

Beyond the impacts of the disease and treatment, advanced cancer patients must also deal with several significant changes to their way of life. Below we summarise a study into all the known research done into understanding these life transitions (19).

During change, people have to let go of familiar ways of living and redefine who they are. Other studies describe how patients and significant others experience transitions during the course of advanced cancer. For instance, patients say it feels like navigating through 'troubled water and landmines'. And, understanding that suffering from advanced cancer takes time, at first denial can be felt by patients. Also, significant others feel transitions when caring for their loved one. For instance, when their loved one is taken to hospital, they experience both guilt and relief, because care and judgement is often handed over to hospital staff. Significant others also experience transitioning into feelings of helplessness and loneliness during the course of advanced cancer.

When reaching the point where cancer is advanced, patients use metaphors such as "getting a death sentence" and "losing their fight against cancer" to describe their situation.

Patients have multiple reactions when being given a diagnosis of advanced cancer, they need to connect with fellow travellers as they undergo a constant process of adaptation. Patients also experience the major change of being in a state of both living and dying. In this state, patients experience death moving closer, they try to make the best of what is left in life and they struggle with living in a sick body. As for significant others, they experience being in a constant process of both having and loosing. They struggle with entering and leaving caregiving, they have thoughts related to death and, throughout the course of the advanced cancer of their loved one, they need hope.

Living with advanced cancer involves a process of constant adaptation due to the changes caused by cancer. This experience is described as "opening one door after the other". Patients said they had feelings of uncertainty, unpredictability, powerlessness, living under constant pressure and changes. This results in patients living in at times indescribable and uncontrollable emotional chaos.

Patients experience changes within their body caused by cancer and cancer treatment. Their body becomes a threat; patients experience being prisoners in their own bodies; their body could not be trusted anymore; it becomes difficult to recognise their own body; the decay and deterioration of their body, for some patients, resulted in experiencing being afraid of themselves and being dependent on others.

Significant others take part in the dying process of their loved one during the course of advanced cancer. Death becomes impending and anticipated, but they strive to focus on living with a living person instead of a dying one. How significant others approach death varies, for instance by: thinking death is far off in the future; experiencing death moving closer when you talk about it; denying death - described with the metaphor: "Like the ostrich with my head in the sand". However, significant others prepare themselves for the death of their loved one by: facing that they are going to be left behind; talking about the facts of death; learning to face the fact that their loved one is going to die and having concerns of how to manage life afterwards.

During the course of advanced cancer, significant others also have experiences of hope. They describe the phenomena of hope as: a gradual, individual process, always changing and shifting; a struggle to maintain. Significant others hope for many things during their loved ones illness: improvement; a miracle; a cure and survival; prolonging of their loved ones life; illness phase to be over and finding balance; experiencing comfort; retaining everyday life - something potentially meaningful to look forward to. The presence of hope varies: significant others experience both living in hope, hopelessness and with low levels of hope during the course of illness - however, choosing hope allowed them to have some control of ups and downs and therefore, searching for new hope was a deliberate process; hope helped them to make sense of their completely changed situation; but hope could also be experienced as unrealistic.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

An important role of the immune system is the ability to differentiate between healthy and unhealthy cells. The level of activity of immune cells, such as T cells, is crucial to maintaining a balanced immune response.
Under normal conditions, a protein called programmed death-ligand 1 (PD-L1) which naturally occurs on cells, plays an important role in maintaining this balanced immune response. PD-L1 binds to its PD-1 receptor on immune T cells, which lessens the ability of immune T cells to attack. This ensures that normal cells are protected from excessive damage. However, PD-L1 is produced in larger amounts on cancerous cells than normal cells. As a result, when binding to PD-1 on immune T cells, this interaction tricks the immune system thereby protecting the tumour from being attacked by the body's immune system.

PD-1 inhibitors, such as pembrolizumab, act to block the checkpoint interaction between PD-1 and PD-L1 and by doing so, boost the immune response which helps the person's own immune cells to attack the cancer cells.(20)

The summary of product characteristics (SmPC) and the patient information leaflet (PIL) for pembrolizumab can be found by following this link:
MHRA Products | Substance

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Pembrolizumab is intended to be used with the health care professional's choice of doublet chemotherapy. Section 3a describes pembrolizumab and Section 2c describes doublet chemotherapy.

The combined effect of pembrolizumab with chemotherapy presents an opportunity to improve survival and duration of clinical benefit.

Safety data from two phase two trials (NCT02954536 (21) and NCT02901301(22)) and one phase 3 trial (NCT03615326) (9) have demonstrated an acceptable safety profile for pembrolizumab plus chemotherapy. For further information on safety and side effects, see Section 3g.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Pembrolizumab comes in a 25mg/mL concentrate solution for infusion. One 4mL vial of concentrate contains 100mg of pembrolizumab. Trastuzumab for gastric cancer comes in a 150mg or 420mg powder for concentrate for solution for infusion vials. One vial contains 150mg or 420mg of trastuzumab.

The recommended dose of pembrolizumab is 200mg administered by intravenous injection through an infusion into your vein (intravenous) over 30 minutes. Treatment will usually take place at an infusion clinic once every 3 weeks. Pembrolizumab can also be administered as a 400mg dose once every 6 weeks (17, 20).

In line with its licence, pembrolizumab may be given for up to 35 cycles (approximately two years) as long as it is working (i.e. as long as the cancer does not progress) and side effects are tolerable. Trastuzumab may be continued for longer than 35 cycles if it remains effective.

Pembrolizumab will be given with chemotherapy, usually two types of chemotherapy are given at the same time. Each chemotherapy is made up for each individual patient, depending on their height, weight, and blood results.

The doublet chemotherapy CAPOX (capecitabine + oxaliplatin). However, if patients experience swallowing difficulties, capecitabine would be substituted with fluorouracil (FOLFOX or FP). Also, if patients are at risk of neuropathy, oxaliplatin would be substituted with cisplatin (FP or XP), but this does not occur often. Clinical experts also noted that the choice of doublet chemotherapy would not depend on CPS level or the IO it was given in combination with.

Of these different chemotherapies, only capecitabine is given in a tablet.(23) Cisplatin and oxaliplatin are given as an infusion into a vein (intravenous) (24, 25). 5FU is usually given over 5 days as a continuous infusion through a small portable pump which can be taken home.(26) People with gastric cancer usually have a maximum of 6 cycles of chemotherapy (approximately 18 weeks); most people may continue to receive pembrolizumab without chemotherapy.

Scans are conducted regularly to keep track of response to treatment. Patients need to be monitored while on treatment for symptoms or side effects, and blood tests may be conducted to check for side effects.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

A search on clinicaltrials.gov for recruited, enrolling by invitation, active but not recruiting, or completed studies on pembrolizumab returns 830 (search conducted 12th September 2023). Of these, 37 are in gastric adenocarcinoma and listed below. Further details of these studies can be found by searching for the study identifiers (NCT number or study name) on clinicaltrials.gov.

NCT Number	Study Title	Study Status	Phases

NCT02589496	Study of Pembrolizumab in Subjects With Advanced Gastric or Gastroesophageal Junction Adenocarcinoma Who Progressed After First-Line Therapy With Platinum and Fluoropyrimidine: Integration of Molecular Subtypes Through Integrative Genomic Analysis	Completed	Phase2	
NCT02370498	A Study of Pembrolizumab (MK-3475) Versus Paclitaxel for Participants With Advanced Gastric/Gastroesophageal Junction Adenocarcinoma That Progressed After Therapy With Platinum and Fluoropyrimidine (MK-3475-061/KEYNOTE-061)	Completed	Phase3	
NCT04164979	Ph II Study of Cabozantinib With Pembrolizumab in Metastatic Gastric and Gastroesophageal Adenocarcinoma	Active not recruiting	Phase2	
NCT02494583	Study of Pembrolizumab (MK-3475) as First-Line Monotherapy and Combination Therapy for Treatment of Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-062/KEYNOTE-062)	Completed	Phase3	
NCT04089904	Phase II Trial of Neoadjuvant Pembrolizumab for Patients With Early Stage Gastroesophageal Adenocarcinoma	Completed	Phase2	
NCT03488667	Perioperative mFOLFOX Plus Pembrolizumab in Gastroesophageal Junction (GEJ) and Stomach Adenocarcinoma	Active not recruiting	Phase2	
NCT02335411	A Study of Pembrolizumab (MK-3475) in Participants With Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-059/KEYNOTE-059)	Completed	Phase2	
NCT03675737	Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (MK-3475-859/KEYNOTE-859)	Active not recruiting	Phase3	
NCT04798781	Safety and Efficacy of Telatinib in Combination With Keytruda in Subjects With Advanced Stomach and Gastroesophageal Junction Cancers or Hepatocellular Carcinoma	Active not recruiting	Phase2	
NCT05268510	Chemotherapy and Pembrolizumab, Followed by Pembrolizumab and Olaparib as Firstline Therapy in Her-2 Negative Gastric/GEJ Adenocarcinoma	Active not recruiting	Phase2	
NCT03395847	Pembrolizumab in Treating Patients With Metastatic or Unresectable Gastroesophageal Adenocarcinoma	Completed	Early_phase1	

NCT03196232	Epacadostat and Pembrolizumab in Treating Patients With Metastatic or Unresectable Gastroesophageal Junction or Gastric Cancer	Completed	Phase2	
NCT03615326	Pembrolizumab/Placebo Plus Trastuzumab Plus Chemotherapy in Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (MK-3475-811/KEYNOTE-811)	Active not recruiting	Phase3	
NCT02918162	Perioperative Chemo and Pembrolizumab in Gastric Cancer	Completed	Phase2	
NCT04682431	A Phase 1a/1b FIH Study of PY159 and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors	Active not recruiting	Phase1	
NCT03221426	Study of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants With Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (MK-3475-585/KEYNOTE-585)	Active not recruiting	Phase3	
NCT04882241	Study of Pembrolizumab (MK-3475) Plus Chemotherapy Versus Placebo Plus Chemotherapy in Participants With Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (MK-3475-585/KEYNOTE-585)-China Extension	Active not recruiting	Phase3	
NCT02443324	A Study of Ramucirumab Plus Pembrolizumab in Participants With Gastric or GEJ Adenocarcinoma, NSCLC, Transitional Cell Carcinoma of the Urothelium, or Biliary Tract Cancer	Completed	Phase1	
NCT02013154	A Study of DKN-01 in Combination With Paclitaxel or Pembrolizumab	Completed	Phase1	
NCT03921021	Phase 2 Study of Telomelysin (OBP-301) in Combination With Pembrolizumab in Esophagogastric Adenocarcinoma	Completed	Phase2	
NCT05104567	A Study of SAR444245 Combined With Other Anticancer Therapies for the Treatment of Participants With Gastrointestinal Cancer (Master Protocol) (Pegathor Gastrointestinal 203)	Active not recruiting	Phase2	
NCT03918499	IRX-2, Cyclophosphamide, and Pembrolizumab in Treating Participants With Recurrent or Metastatic Gastric or Gastroesophageal Junction Cancer	Completed	Phase1|phase2	
NCT02599324	Study to Evaluate Ibrutinib Combination Therapy in Patients With Selected Gastrointestinal and Genitourinary Tumours	Completed	Phase1|phase2	
NCT02830594	Pembrolizumab and Palliative Radiation Therapy in Treating Patients With Metastatic	Active not recruiting	Phase2	

	Oesophagus, Stomach, or Gastroesophageal Junction Cancer		
NCT02178722	Study to Explore the Safety, Tolerability and Efficacy of MK-3475 in Combination With INCB024360 in Participants With Selected Cancers	Completed	Phase1|phase2
NCT02730546	Pembrolizumab, Combination Chemotherapy, and Radiation Therapy Before Surgery in Treating Adult Patients With Locally Advanced Gastroesophageal Junction or Gastric Cardia Cancer That Can Be Removed by Surgery	Active not recruiting	Phase1|phase2
NCT03849469	A Study of XmAbÂ®22841 Monotherapy & in Combination w/ Pembrolizumab in Subjects w/ Selected Advanced Solid Tumours	Completed	Phase1
NCT05207722	CYNK-101 in Combination With Trastuzumab and Pembrolizumab in Patients With Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction (G/GEJ) Adenocarcinoma	Active not recruiting	Phase1|phase2
NCT04032704	A Study of Ladiratuzumab Vedotin in Advanced Solid Tumours	Active not recruiting	Phase2
NCT02903914	Arginase Inhibitor INCB001158 as a Single Agent and in Combination With Immune Checkpoint Therapy in Patients With Advanced/Metastatic Solid Tumours	Completed	Phase1|phase2
NCT03861793	A Dose Escalation and Cohort Expansion Study of Subcutaneously-Administered Cytokine ALKS 4230 (Nemvaleukin Alfa) as a Single Agent and in Combination With Anti-PD-1 Antibody (Pembrolizumab) in Subjects With Select Advanced or Metastatic Solid Tumours (ARTISTRY-2)	Active not recruiting	Phase1|phase2
NCT03329950	A Study of CDX-1140 (CD40) as Monotherapy or in Combination in Patients With Advanced Malignancies	Completed	Phase1
NCT04485013	TTX-080 HLA-G Antagonist in Subjects With Advanced Cancers	Active not recruiting	Phase1
NCT04336098	Study of SRF617 in Patients With Advanced Solid Tumours	Completed	Phase1
NCT03841110	FT500 as Monotherapy and in Combination With Immune Checkpoint Inhibitors in Subjects With Advanced Solid Tumours	Completed	Phase1
NCT04116320	Focused Ultrasound Ablation and PD-1 Antibody Blockade in Advanced Solid Tumours	Active not recruiting	Phase1
NCT03228667	QUILT-3.055: A Study of Combination Immunotherapies in Patients Who Have Previously Received Treatment With Immune Checkpoint Inhibitors	Active not recruiting	Phase2

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The KEYNOTE-859 trial provides the data to support this appraisal. KEYNOTE-859 is a phase 3, randomised, placebo-controlled, multi-site, double-blind study in participants diagnosed with previously untreated, locally advanced unresectable or metastatic HER2 negative gastric or gastro-oesophageal junction adenocarcinoma. Approximately 1579 participants from 33 countries (including 42 participants from the UK) were randomised in a 1:1 ratio to receive pembrolizumab or placebo each in combination with chemotherapy. This appraisal focuses on the results of the PD-L1 CPS≥1 subgroup (1235 participants representing 78.2% of the global cohort).

To work out how well pembrolizumab plus chemotherapy works, the following key outcomes were measured:

1. **Progression-free survival –** typically measured in months or weeks, progression-free survival, or PFS, measures how long a person lives from the start of the trial without the disease worsening. PFS is considered an indication of disease control and stabilisation. Taking the median PFS in a trial can be a useful measure of how long a patient may expect to live without the disease worsening after starting to take the medicine in the trial.
2. **Overall survival –** typically measured in months or weeks, overall survival, or OS, measures how long a person lives from the start of the trial until death. Taking the median OS in a trial can be a useful measure of how long a patient may expect to live after starting to take the medicine in the trial.

The hazard ratio (HR) is a summary statistic for PFS and OS which compares the probability of events in one treatment arm (pembrolizumab with trastuzumab plus chemotherapy), with the probability of events in another treatment arm (trastuzumab plus chemotherapy). It is used to see if patients receiving one treatment experience the outcome faster (or slower) than another treatment. A HR of 1 indicates that there is no difference between the treatments. Here, a HR of less than 1 indicates that pembrolizumab with chemotherapy decreases the chance of the outcome and a HR exceeding 1 indicates that the pembrolizumab plus chemotherapy increases the chance of the outcome.

The results are as follows in the CPS≥1population:

- OS
    - The OS HR was 0.74 (95% CI: 0.65, 0.84), in favour of pembrolizumab plus chemotherapy
    - This represents a 26% reduction in the risk of death when treated with pembrolizumab plus chemotherapy compared to chemotherapy alone
    - The median OS was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (13.0 months vs 11.4 months, respectively).
- PFS
    - The PFS hazard ratio (HR) was 0.72 (95% confidence interval [CI]: 0.63, 0.82; p<0.0001), in favour of pembrolizumab plus chemotherapy
    - This represents a 28% reduction in the risk of disease progression when treated with pembrolizumab plus chemotherapy compared to chemotherapy alone

- Median PFS was longer in the pembrolizumab plus chemotherapy group (6.9 months compared with the chemotherapy group (5.6 months), in favour of pembrolizumab plus chemotherapy

Comparison versus nivolumab with chemotherapy

- At the time of company submission, an NMA for OS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1 or CPS ≥10. The results show that in participants with PD-L1 CPS ≥1 and CPS ≥10, efficacy of pembrolizumab in combination with chemotherapy is similar to nivolumab in combination with chemotherapy. The difference between treatments was not statistically meaningful.
- An NMA for PFS versus nivolumab in combination with chemotherapy was feasible only in participants with PD-L1 CPS ≥1. The results show that pembrolizumab in combination with chemotherapy performed similarly to nivolumab in combination with chemotherapy. The difference between treatments was not statistically meaningful.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The KEYNOTE-859 trial used three types of questionnaires to measure the QoL of patients: EORTC QLQ-C30, EORTC QLQ-STO-22 that looks specifically at the quality of life of cancer patients, and the EQ-5D, that looks at the general health status of a patient, and EQ-5D-5L.

The EQ-5D is of most relevance to a NICE appraisal and consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system has five questions on mobility, self-care, pain, usual activities, and psychological status with three possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem). Results from these questions can then be combined and scaled to produce a single score with a maximum score of 1. Scores can vary from 0, which represents death, to 1 which represents the best possible health state. The EORTC uses different questions, however it also produces a score that is meant to represent a patient's quality of life. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. From this we can gather three scores (from the EQ-5D questionnaire, the EQ-5D VAS and the EORTC questionnaires) that can assess how a patient feels throughout their treatment.

Results

Across all three methods, on average the patients reported a small improvement in quality of life after 18 weeks of treatment. However, the scores were different depending on whether the patients achieved a response on pembrolizumab (i.e. their tumours shrank by a significant amount). Patients who had a significant tumour shrinkage (a response) reported the largest improvement. Patients whose tumours neither grew nor shrank (stable disease) reported a smaller improvement. Patients whose tumours grew (progressive disease) reported a worsening score on the EQ-5D and EORTC questionnaires, and the smallest improvement on the EQ-5D VAD. Full details are available in the submission documents.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Pembrolizumab has been used in hospitals in England since 2015 (27). Section 1b describes the different cancers that pembrolizumab is licensed to treat. The safety and side effects data from all the trials that have led to these licences are included in the pembrolizumab Summary of Product Characteristics (SmPC)(17). A summary of relevant safety information from the pembrolizumab SmPC has been provided below, giving doctors and other hospital staff clear guidance on what to do if a patient experiences an immune-related side effect.

The safety of pembrolizumab as monotherapy has been evaluated in 7,631 patients across tumour types. In this patient population, the median observation time was 8.5 months (range: 1 day to 39 months) and the most frequent adverse reactions with pembrolizumab were fatigue (31%), diarrhoea (22%), and nausea (20%). The majority of adverse reactions reported for monotherapy were of mild or moderate severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions. The incidences of immune-related adverse reactions were and 24.2% all Grades and 6.4% for Grades 3-5 in the metastatic setting.

Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. Most immune-related adverse reactions occurring during treatment with pembrolizumab were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of pembrolizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

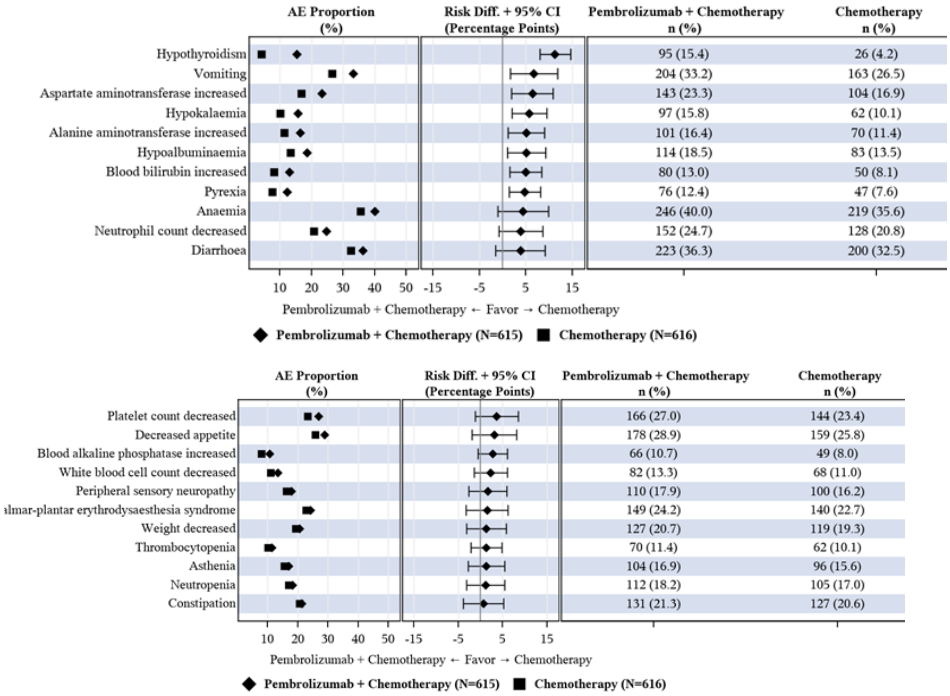
Pembrolizumab may be restarted within 12 weeks after last dose of pembrolizumab if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones

The grading system for adverse reactions, or side effects, referred to above is explained in section 4a.

The side effects that were reported in the KEYNOTE-859 clinical trial are consistent with the common side effects listed in the pembrolizumab SmPC. Provided below are figures of the most common side effects (occurring in more than 10% of patients) from patients relevant to this appraisal in KEYNOTE-859. Please note that the below figures include any adverse effects (side effects) experienced whilst patients were on

the clinical trial, including but not limited to the side effects caused by pembrolizumab. “n” refers to the number of patients in the trial and “%” refers to the proportion.



KEYNOTE – 859 trial data shows that patients in pembrolizumab arm had more adverse events than in the comparator arm, however the immune related adverse events are minor.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

The key benefits to patients, caregivers and communities may include:

- Based on the KEYNOTE-859 data an overall survival HR of 0.74 translates into a statistically significant and clinically meaningful 26% reduction in the risk of death for patients taking pembrolizumab + chemotherapy versus chemotherapy alone.
- The risk of disease progression is also reduced by 28% (based on a HR of 0.72) when treated with pembrolizumab + chemotherapy versus chemotherapy alone, which again is both statistically significant and clinically meaningful.
- Some patients’ tumours may shrink: As described in sections 3e and 3f, the study found more than a third of patients in each of the tumour sites evaluated found their tumours shrinking. The results from the patient reported outcomes suggests this may result in improved quality of life.
- The average patient may have fewer serious side effects on pembrolizumab vs standard of care. The side effects that could be expected while taking pembrolizumab are well known and clinicians have experience in treating them.

- The infusion time of pembrolizumab is short compared to some of the common currently used chemotherapies (i.e. fluorouracil), and pembrolizumab can be given every 6 weeks.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:
The key disadvantages to patients, caregivers and communities may include:

- Patients are at an increased risk of developing immune related side effects, some of which may last beyond the patient stopping pembrolizumab. Please note there is clear guidance provided in the SmPC that instructs healthcare providers on how to manage these side effects.

Pembrolizumab, like any other medicine, does not work the same in every patient. Not all patients' tumours shrink and it may not result in an extended life expectancy.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness relates to how much new health (or quality-adjusted life years, QALYs) the new medicine produces compared to its additional cost (vs. current care), for a typical/average patient and whether the new health is worth the extra cost required to pay for it.

The cost-effectiveness of pembrolizumab plus doublet chemotherapy in this indication (versus doublet chemotherapy [in the CPS ≥1 population] or nivolumab plus doublet chemotherapy [in the

CPS ≥10 population]) is evaluated for the typical/average patient via modelling that uses short-term trial data to predict efficacy and costs over a lifetime horizon. The challenges of modelling average lifetime outcomes (overall survival, progression and quality of life) from trial data arise from the short-term nature of trials (KEYNOTE-859 has around 3 years of patient survival data).

The cost-effectiveness model is often used in oncology and produces lifetime outcomes by tracking a typical/average patient cohort as they move through 3 health states - progression free, progressed and death – and averaging everything at the end to produce results for the typical/average patient receiving pembrolizumab plus doublet chemotherapy (or the comparator) in this indication.

How long patients stay in each health state depends on the data from the key clinical trials evaluating pembrolizumab plus doublet chemotherapy versus doublet chemotherapy (KEYNOTE-859), and nivolumab plus doublet chemotherapy versus doublet chemotherapy (CheckMate-649). These trials report Kaplan Meier curves for overall and progression-free survival (curves constructed by plotting survivor events against time). For the period beyond the trial, data extrapolation methods are used ("parametric survival models") and there is always uncertainty about which extrapolated curve fits the trial data the best and which curve estimates more plausible outcomes in the long term. There will also be debates about whether additional adjustments should be made to survival extrapolations that make the risks of progression or death closer to the comparator treatments after patients stop taking pembrolizumab or nivolumab (what is called "treatment effect waning") and if the duration of treatment should reflect NHS practice or the trial.

A characteristic of this appraisal is that the most relevant comparator depends on a patient's CPS level. Based on current guidance, doublet chemotherapy can be offered to the full anticipated licensed indication (i.e., patients expressing a CPS≥1), but nivolumab plus doublet chemotherapy can only be offered to patient's expressing a CPS≥5.

Furthermore, the key clinical trials evaluating these treatments pre-specified different CPS levels. Because pembrolizumab and nivolumab modify PD-1/PD-L1 pathways, the level of PD-L1 expression (measured as CPS) plays an important role in the effectiveness of treatments in both KEYNOTE-859 and CheckMate 649. In KEYNOTE-859, CPS levels of CPS≥1 and CPS≥10s were prespecified. In CheckMate-649, CPS levels of CPS≥5 and CPS≥10 were prespecified. Therefore, a comparison between pembrolizumab and nivolumab in the CPS≥5 population is not currently possible and a comparison between pembrolizumab and nivolumab in CPS≥10 is presented.

Quality of life tends to be better for cancer patients who are further from the date of their death, compared to later time periods, and for those in the progression-free survival state (i.e., who have not progressed) compared with the progressed state. Given that pembrolizumab plus doublet chemotherapy works by both helping to prevent patients from progressing and keeping progressed patients alive for longer than if they were receiving chemotherapies, the typical pembrolizumab plus doublet chemotherapy patient will tend to have a better quality of life than a patient receiving doublet chemotherapy (and similar quality of life to a patient receiving nivolumab plus doublet chemotherapy). How the model applies quality-of-life "weights" to time spent in the progression-free and progressed states depends on the method chosen: one method applies fixed weights to each health state and the other focusses more on the time to death which may be more relevant to patients who receive an immunotherapy like pembrolizumab. Different side-effect profiles of treatments can also impact overall quality of life, but this is not a big driver of results compared with the time spent in health states and time spent alive.

Results of the economic analysis show that pembrolizumab plus doublet chemotherapy is cost-effective compared with doublet chemotherapy in the CPS ≥1 population and could also offer a cost-effective alternative option to nivolumab plus doublet chemotherapy in the CPS ≥10 population. A significant amount of scenario analyses that use different methods are presented. Some make the results look better and some worse.

Under NICE's previous methods for evaluating new medicines, pembrolizumab plus doublet chemotherapy would have met the end-of-life criteria (treatment is for patients with a short life expectancy [less than 24 months] and should extend life by at least 3 months compared to current NHS treatment) and would therefore have qualified for a higher willingness-to-pay threshold of £50,000/QALY, which means the NHS is willing to spend more for health gained with this treatment. NICE's new health technology evaluation manual replaces the end-of-life criteria with a new, broader severity modifier. The severity modifier determines a weight which can be assigned to the QALYs accrued by the treatments. The severity modifier depends on the current standard of care. For patients with a CPS≥1 the current standard of care is doublet chemotherapy and for patient with a CPS≥5 the current standard of care is nivolumab doublet chemotherapy.

Given that survival and quality of life outcomes for patients on doublet chemotherapy are severe compared with the general population of a similar age, a severity modifier of 1.2 or 1.7 is likely to apply for this condition, which means NICE can consider a higher threshold for pembrolizumab plus doublet chemotherapy to be cost effective. Nivolumab plus doublet chemotherapy is more effective than doublet chemotherapy, which means a severity modifier of 1.0, and the standard threshold for cost-effectiveness is likely to apply when the comparator is nivolumab plus doublet chemotherapy.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

NICE's TA857 recommends nivolumab in combination with chemotherapy, as an option for the treatment of people with HER2-negative advanced metastatic gastric cancer or GOJ adenocarcinoma whose tumours express CPS≥5. Patients whose tumours express CPS<5 are treated with doublet chemotherapy regimens. This appraisal will address the ongoing unmet need and offer the first immunotherapy treatment option for patients with advanced metastatic HER2 negative gastric cancer and gastro-oesophageal junction adenocarcinoma in a broader patient group, thereby broadening the available treatment options for clinicians to use for these patients. Addressing a profound unmet need is positive news for patients which may not be reflected in the QALYs estimated by the economic analysis.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here
No equality issues are anticipated.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

CTCAE grading

In oncology clinical trials, the severity of adverse events are usually graded according to US National Cancer Institute's AE Severity Grading Scale - Common Terminology Criteria for Adverse Events (CTCAE) (28). CTCAE can also be used to grade the AE for non-oncology studies, but generally not appropriate for studies using healthy volunteers.

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g. bathing, dressing or feeding).
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:
Abdominal pain – Pain in your belly or tummy area.
Alanine aminotransferase increased - In general, high levels of alanine aminotransferase (ALT) may be a sign of liver damage.
Anaemia - A low red-blood count. Your blood does not have enough of the cells that carry oxygen (haemoglobin) to your body. Also called "tired blood" or "low iron".
Antigen - a toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies.
Arthralgia - Pain in your joints.
Aspartate aminotransferase increased - In general, high levels of aspartate aminotransferase (AST) may be also be a sign of liver damage.
Asthenia - Asthenia, also known as weakness, is the feeling of body fatigue or tiredness.
Constipation - Constipation is generally described as having fewer than three bowel movements a week.
Decreased appetite - A decreased appetite occurs when you have a reduced desire to eat.
Diarrhoea - Loose, watery stools three or more times a day.
Dyspnoea - When you have trouble breathing.
Extrapolation - the action of estimating or concluding something by assuming that existing trends will continue or a current method will remain applicable
Fatigue - tired, weak feeling of the whole body, feeling tired all over.
Hypothyroidism - When your thyroid makes too much thyroid hormone.
Nausea - When you have an upset stomach or feel like throwing up.
Overexpression - excessive expression of a gene (as that caused by increasing the frequency of transcription)
Prognosis - the likely course of a medical condition
Pruritus - Pruritus is a medical term that means itching. It refers to a feeling or sensation on your skin that you want to scratch.
Pyrexia - A body temperature that is higher than normal. Also called fever.
Rash - An area of skin that is itchy or swollen.
Urinary tract infection - A common infection anywhere in the body's waste and excess water "drainage" system (urinary tract). This includes kidneys, ureter, bladder, and urethra. Also called a UTI.
Vomiting - To throw up

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:
1. Cancer Research UK. What is advanced stomach cancer? 2022 [Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/advanced-cancer/about-advanced-cancer.
2. National Institute for Health and Care Excellence. Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer [ID3742]: In development [GID-TA10615] 2023 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10615.
3. Park MH WM, Maynard N, Crosby T, Thomas B, Trudgill N, Geisler J, Napper R. Cromwell D. . National Oesophago-Gastric Cancer Audit. 2022 Annual Report. 2023 [Available from: https://www.nogca.org.uk/reports/2022-annual-report/.

4. Office for National Statistics. Cancer registration statistics, England: 2017 edition of this dataset Final 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland.
5. National Cancer Registration and Analysis Service. CancerData: Detailed Statistics from the 'Get Data Out' programme 2019 [Available from: https://www.cancerdata.nhs.uk/getdataout/oes.
6. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49.
7. Cancer Research UK. Risks and causes of stomach cancer 2022 [Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/causes-risks.
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12. National Institute for Health and Care Excellence. Trastuzumab for the treatment of HER2-positive metastatic gastric cancer: Technology appraisal guidance [TA208] 2010 [Available from: https://www.nice.org.uk/guidance/ta208.
13. National Institute for Health and Care Excellence. Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma: Technology appraisal guidance [TA857] 2023 [Available from: https://www.nice.org.uk/guidance/ta857.
14. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358(1):36-46.
15. Cancer Research UK. Your Cancer Type. Available from: https://www.cancerresearchuk.org/about-cancer/type . [Access Date: 11 January 2023].
16. Cancer Research UK. Symptoms of advanced bowel cancer. Available from: https://www.cancerresearchuk.org/about-cancer/bowel-cancer/advanced/symptoms-advanced-cancer . [Access Date: 11 January 2023].
17. Medicines and Healthcare products Regulatory Agency. KEYTRUDA® Summary of Product Characteristics [Available from: https://products.mhra.gov.uk/search/?search=keytruda&page=1&doc=Spc&rerouteType=0.
18. Cancer Research UK. What is cancer fatigue? Available from: https://www.cancerresearchuk.org/about-cancer/coping/physically/fatigue/what-is-cancer-fatigue . [Access Date: 11 January 2023].
19. Madsen R, Birkelund R, Uhrenfeldt L. Patients experience major changes in life and significant others struggle with caregiving during the course of incurable cancer: a systematic review and meta-synthesis. European Journal for Person Centered Healthcare. 2018;6.
20. European Medicines Agency. European public assessment report (EPAR): Keytruda, pembrolizumab [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda.
21. ClinicalTrials.gov. Phase II Trial of Pembrolizumab With Trastuzumab and Chemotherapy in Advanced HER2 Positive Esophagogastric (EG) Cancer [Available from: https://clinicaltrials.gov/ct2/show/results/NCT02954536.
22. ClinicalTrials.gov. Pembrolizumab, Trastuzumab, HER2 Positive Gastric Cancer [Available from: https://clinicaltrials.gov/ct2/show/study/NCT02901301.

23. Macmillan Cancer Support. Cancer information and support: Capecitabine 2021 [Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/capecitabine.
24. Macmillan Cancer Support. Cancer information and support: Oxaliplatin 2021 [Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/oxaliplatin.
25. Macmillan Cancer Support. Cancer information and support: Cisplatin 2022 [Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/cisplatin.
26. Macmillan Cancer Support. Cancer information and support: Fluorouracil (5-FU) 2022 [Available from: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/fluorouracil-5fu.
27. National Institute for H, Care E. Pembrolizumab for advanced melanoma not previously treated with ipilimumab [TA366]. Available from: https://www.nice.org.uk/guidance/ta366. [Access Date: 11 January 2023]. 2015.
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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 clarification questions

October 2023

File name	Version	Contains confidential information	Date
ID4030 MSD response to clarification questions	V2	No	19/01/2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Literature searches

A 1. Priority question: A number of major synonyms for gastro-oesophageal cancer appear to have been omitted from the literature searches, for example gastroesophageal junction/ (EMTREE), 'gastro-oesophageal', 'gastro-esophageal', 'oesophagogastric', 'GOJ' and 'GEJ' in the clinical effectiveness searches (Appendix D) and 'gastro-oesophageal', 'gastro-esophageal', 'oesophagogastric', 'esophagogastric' and 'GEJ' in the cost-effectiveness/HRQoL searches (Appendices G/H).

The Evidence Assessment Group (EAG) is concerned that the population facet may therefore have been overly restrictive, and adversely affected the recall of results. Please re-run the searches with these additional terms to assess whether any relevant records have been missed by the original strategies.

MSD response:

The clinical searches were re-run with the additional suggested search terms as below:

- gastroesophageal junction/
- ((gastro-esophageal or gastro-oesophageal or oesophagogastric) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).mp.
- ((gastro-esophageal or gastro-oesophageal or oesophagogastric) adj3 adenocarcinoma*).mp.
- GOJ.mp.
- GEJ.mp.

Ultimately, 177 additional citations were identified with the expanded population search terms across the databases, namely, EMBASE, MEDLINE and Cochrane CENTRAL. Out of these 177, 8 citations were identified as potentially relevant to include: 5 for the KEYNOTE-62 trial which was ultimately excluded from the SLR for being a failed trial (primary end point not met); 2 for the KEYNOTE-590 trial which was ultimately excluded from the feasibility assessment since pembrolizumab for gastro-oesophageal junction carcinoma was not included in the NICE final scope and 1 for the KEYNOTE-859 trial for which data included in the SLR and NMA was available from a clinical study report which is considered to be the most comprehensive reporting of results.

For the cost-effectiveness/HRQoL searches, synonyms for all the terms in the search strategy utilised the /syn command to ensure comprehensive coverage of possible synonyms indexed with Embase (keywords with /syn command used to cover all possible synonyms of the search terms: ('stomach cancer'/syn OR 'gastroesophageal junction'/syn).

Search string for reference: (('gastric' OR 'stomach' OR 'gastroesophageal junction' OR 'gej') NEAR/4 (cancer* OR carcin* OR adenocarcin* OR tumour* OR tumor* OR neoplasm* OR malign*)) OR 'gastric cancer' OR 'stomach cancer'/syn OR 'gastroesophageal junction'/syn OR 'gastro-esophageal junction' OR 'gastro-oesophageal junction'.

The cost-effectiveness search was re-run using the suggested additional keywords on the Embase database using the embase.com interface for Embase and MEDLINE,

from inception to 10 October. Following this, 300 additional records were identified, and none were considered relevant for inclusion.

In conclusion, running the searches with the expanded population terms did not identify any additional relevant citations.

A 2. On page 52 of Appendix D of the company submission (CS), it states that *"No additional citations were identified from searches of the grey literature (i.e., clinicaltrials.gov and conference proceedings) or relevant treatment guidelines (i.e., NCCN and ESMO)"*. Please provide full details of the searches conducted on these resources, including names, dates and search terms used.

MSD response:

The following grey literature sources were searched for the purposes of this SLR:

American Society of Clinical Oncology (ASCO) **2020-2022** abstracts searched via Northern Lights using structured search strings (Refer to Table 1). Please note abstracts from the ASCO Annual meeting **2023** were not available at the time of running these searches.

Table 1: Northern Lights search strategy for ASCO 2020-2022

No.	Criteria	Search Algorithm	Results
1	Population	exp stomach cancer/	14819
2	Population	((stomach or gastric) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	11347
3	Population	((stomach or gastric) adj3 adenocarcinoma*).ti,ab.	1311
4	Population	((gastroesophageal or esophagogastric) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	758
5	Population	((gastroesophageal or esophagogastric) adj3 adenocarcinoma*).ti,ab.	572
6	Population	(advance$ or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or spread$ or migration$ or progress$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or secondary or incurable or "not curable").mp.	537287
7	Population	(1 or 2 or 3 or 4 or 5) and 6	6746
8	Conference	American Society of Clinical Oncology.cf.	72133
9	Limits	7 and 8	1026
10	Limits	limit 9 to yr = 2020	92
11	Limits	limit 9 to yr = 2021	101
12	Limits	limit 9 to yr = 2022	84

No.	Criteria	Search Algorithm	Results
13	Limits	limit 9 to yr = 2023	0
14	Limits	10 or 11 or 12 or 13	277

- ASCO Gastrointestinal Cancers Symposium **2020-2021** abstracts searched from Journal of Clinical Oncology. Search term used: Esophageal and Gastric cancer.

- ASCO Gastrointestinal Cancers Symposium **2022-2023** abstracts searched using conference abstract PDF booklet. Search term used: Esophageal and Gastric cancer.

- European Society for Medical Oncology (ESMO) **2020-2022** abstracts searched via Northern Lights using structured search strings (Refer to Table 2). Please note abstracts from the ESMO Congress **2023** were not available at the time of running these searches.

Table 2: Northern Lights search strategy for ESMO 2020-2022

No.	Criteria	Search Algorithm	Results
1	Population	exp stomach cancer/	14819
2	Population	((stomach or gastric) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	11347
3	Population	((stomach or gastric) adj3 adenocarcinoma*).ti,ab.	1311
4	Population	((gastroesophageal or esophagogastric) adj3 (cancer* or carcinoma* or tumo?r* or neoplasm*)).ti,ab.	758
5	Population	((gastroesophageal or esophagogastric) adj3 adenocarcinoma*).ti,ab.	572
6	Population	(advance$ or metasta$ or recurr$ or unresect$ or non-resect$ or disseminated or stage 3 or stage III* or stage 4 or stage IV* or spread$ or migration$ or progress$ or invasive or aggressive or "not operable" or untreatable or "not treatable" or secondary or incurable or "not curable").mp.	537287
7	Population	(1 or 2 or 3 or 4 or 5) and 6	6746
8	Conference	European Society for Medical Oncology.cf.	20811
9	Limits	7 and 8	595
10	Limits	limit 9 to yr = 2020	51
11	Limits	limit 9 to yr = 2021	32
12	Limits	limit 9 to yr = 2022	28
13	Limits	limit 9 to yr = 2023	0
14	Limits	10 or 11 or 12 or 13	111

ESMO World Congress on Gastrointestinal Cancer **2020-2023** searched from Annals of Oncology, Abstract Book. All abstracts from this conference were searched without restriction on search terms.

US National Institutes of Health Clinical Trial Registry (http://www.clinicaltrials.gov) searched using search term “Gastric cancer”.

Grey literature citations included in the evidence base are as follows:

Table 3: List of grey literature citations included in the evidence base

Trial Name/ Author Year	Author	Year	Title
KEYNOTE-859	Clinical study report	2022	MK3475-859: A Phase III, Randomized, Double-blind Trial Comparing Chemotherapy and Pembrolizumab With Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Negative, Previously Untreated, Unresectable or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-859)
CheckMate-649	Clinicaltrials.gov	--	Efficacy Study of Nivolumab Plus Ipilimumab or Nivolumab Plus Chemotherapy Against Chemotherapy in Stomach Cancer or Stomach/Esophagus Junction Cancer
	Elimova et al	2021	Health-related quality of life (hrqol) in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer (gc/gejc) or esophageal adenocarcinoma (eac): Results of nivolumab plus chemotherapy (nivo+chemo) versus chemo from CheckMate-649
	Janjigian et al	2021	Nivolumab (nivo) plus chemotherapy (chemo) or ipilimumab (ipi) vs chemo as first-line (1l) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (gc/gejc/eac): CheckMate-649 study
	Janjigian et al	2023	Nivolumab (NIVO) plus chemotherapy (chemo) vs chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): 3-year follow-up from CheckMate-649.
	Moehler et al	2020	Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1l) treatment for advanced gastric cancer/gastroesophageal junction cancer (gc/gejc)/esophageal adenocarcinoma (eac): First results of the CheckMate-649 study
	Moehler et al	2021	First-line (1l) nivolumab (nivo) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (gc/gejc/eac): Expanded efficacy and safety data from CheckMate-649

Trial Name/ Author Year	Author	Year	Title
	Shen et al	2022	First-line nivolumab (NIVO) plus chemotherapy (chemo) vs chemo in patients with advanced gastric cancer/ gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate-649 Chinese subgroup analysis 2-year follow-up
	Shen et al	2023	First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) vs chemo in patients (pts) with advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate-649 Chinese subgroup analysis with 3-year follow-up.
	Shitara et al	2022	Nivolumab (NIVO) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy, safety, and subgroup analyses from CheckMate-649.
	Wyrwicz et al	2021	Health-related quality of life (hrqol) in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer (gc/gejc) or esophageal adenocarcinoma (eac): Interim results of nivolumab plus chemotherapy (n+c) versus (c) from CheckMate-649

A 3. Please explain why the MEDLINE and Embase searches conducted on 9 May 2023 (Tables 2 and 3, Appendix D) were only searched up until 10 January 2023, and why the Cochrane CENTRAL search (Table 4, Appendix D) searched on 9 May 2023 only covered the period to December 2022. Please update the searches to cover the period not previously searched, if needed.

MSD response:

There was a typo in the table headers, MSD can confirm that the searches were conducted on 9 May 2023 and covered all citations indexed until the following Ovid (database search tool) predetermined cut-offs for databases:

- EMBASE: Embase 1974 to May 8, 2023
- MEDLINE: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions® 1946 to May 8, 2023
- Cochrane CENTRAL: EBM Reviews - Cochrane Central Register of Controlled Trials April 2023

A 4. Please clarify why conference proceedings were excluded from the Embase search (Table 2, Appendix D).

MSD response:

The intent of the database searches was to screen through peer-reviewed journal articles with available full-text publications as they provide the highest quality of literature; while conference abstracts represent a lower level of evidence given that they do not undergo the same peer review process as fully published results and are, at times, restricted by data availability. Hence, search terms for conference proceedings were excluded from the highly sensitive search strings. We do, however, recognize that certain later breaking data for clinical trials may only be presented at scientific conferences. To ensure comprehensive data capture, we supplemented the database searches with hand-searches of the following protocol predefined conferences covering a span of 4 years (2020-2023), where available:

- American Society of Clinical Oncology (ASCO) 2020-2022
- ASCO Gastrointestinal Cancers Symposium 2020-2023
- European Society for Medical Oncology (ESMO) 2020-2022
- ESMO World Congress on Gastrointestinal Cancer 2020-2023

A 5. The search methods in Appendices G and H report a single search strategy for both MEDLINE and Embase searches. Please confirm if this is a simultaneous search of both resources using a single strategy or a single search of the Embase database conducted on the understanding that it now contains all records from MEDLINE.

MSD response:

MEDLINE® and Embase® were both included in the search methodology. A single search on the Embase database using the embase.com interface for Embase and MEDLINE was conducted. This approach was taken because Embase contains

records from MEDLINE and additional unique content, making it a comprehensive source of relevant literature.

To ensure the retrieval of non-indexed citations (citations not yet indexed in Embase), MEDLINE® In-Process through PubMed was searched separately. This was to capture citations that might not have been incorporated into Embase at the time of the search.

We searched “ahead of print” publications not yet indexed in Medline or Embase from Medline-in-process (PubMed).

The same search strategy was utiltised for both embase.com and PubMed and a different syntax relevant to PubMed for searching MEDLINE® In-Process citations was required.

A 6. Please provide the dates on which the Tufts cost-effectiveness analysis (CEA) Registry and National Health Service (NHS) Economic Evaluations Database (EED) searches were conducted (Appendix G).

MSD response:

12th May 2023

A 7. Please provide the search terms used for the searches of conference proceedings and health technology assessment (HTA) websites in Appendix G, and the conference proceedings in Appendix H.

MSD response:

Please find the search terms used for the searches of conference proceedings and health technology assessment (HTA) websites in Appendix G, and the conference proceedings in Appendix H below.

HTA/Conference proceedings	Search terms used
HTA	Gastric/gastro, gastric cancer, Gastroesophageal junction, gej, gastroesophageal
Conference proceedings HRQoL & Economic SLRs	Gastric/ gastro, gej, cancer of the esophagus and stomach, gastrointestinal cancer, gastr, esophageal and gastric cancer, other GI cancer, gastric cancer,

Decision problem

A 8. Priority question: The NICE final scope highlighted the subgroup of patients with programmed cell death ligand 1 (PD-L1) combined positive score (CPS) ≥5. However, the CS only provided data for a subgroup of patients with PD-L1 CPS ≥10 but did not provide data for those patients with PD-L1 CPS ≥5. Therefore, the CS did not address the NICE final scope relating to this subgroup with PD-L1 CPS ≥5. Please comment on this issue and, if possible, provide all relevant data for the aforementioned subgroup.

MSD response:

The final NICE scope for this appraisal suggested that the evidence in subgroups by PD-L1 status would be considered if evidence allowed. Because the CPS 5 data cut was not a pre-specified subgroup in KEYNOTE-859 trial, the results for this subgroup were not initially available and therefore were not provided at the time of the evidence submission. In the decision problem Table 1 of the company submission (page 10) under the comparator section, where the CPS>=5 subgroup was mentioned, MSD explained that it was not feasible to conduct an indirect treatment comparison (ITC) versus nivolumab in CPS>=5 subgroup of patients due to differences between the two trials (KEYNOTE- 859 and CheckMate-649) and the lack of CPS>=5 subgroup efficacy results from the KEYNOTE- 859 trial. The rationale for not providing the efficacy and ITC results was further provided in section 2.9 of the company submission.

KEYNOTE-859 was not designed using the CPS 5 cut point for statistical analyses or study conduct nor were the patients stratified by this cut point. Per protocol, stratification was performed based on PD-L1 CPS <1 vs. CPS ≥1, while PD-L1 CPS ≥1 and PD-L1 CPS ≥10 were prespecified subgroups for the primary and secondary efficacy objectives. The PD-L1 IHC 22C3 analytical validation conducted by Agilent Technologies, which included sensitivity/specificity, precision, and reproducibility, was conducted at the diagnostic cut points of CPS ≥1 and CPS ≥10. In addition, the assay was validated at the PD-L1 testing laboratory to demonstrate accuracy and precision at the CPS ≥1 and CPS ≥10 cut points and the pathologists at the testing laboratory were trained and tested specifically for these diagnostic cut points. No such analytical validation or pathologist training was conducted for the CPS ≥5 cut point. These factors may negatively impact the accuracy of the PD-L1 raw scores at CPS 5.

The data from CPS ≥1, CPS ≥10, and ITT hypothesis-testing populations (provided in the company submission) support a clinical benefit for pembrolizumab in combination with chemotherapy for the first-line treatment of locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma with clinically meaningful improvements in OS, PFS and ORR compared with chemotherapy for the CPS ≥1 and CPS ≥10 populations.

Enrichment of PD-L1 expression is known to result in comparatively greater benefit for immunotherapies across a variety of tumour types. Demographics and baseline characteristics have now been analysed using the CPS ≥5 cut point and results are similar to those for the overall population.

OS and PFS efficacy results, conducted post-hoc, for the patients with HER2 negative locally advanced metastatic GC or GOJ adenocarcinoma whose tumours express PD-L1 CPS ≥5 are presented from the KEYNOTE-859 study, based on the interim analysis 1 (IA1), which had a data cut-off date of 3 October 2022. Given that CPS 5 was not validated nor a prespecified endpoint, efficacy analyses based on the CPS ≥5 cut point should be interpreted with caution as the data could be subject to random variability.

Overall survival results in participants with PD-L1 CPS>=5

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

- The OS HR was [redacted] (95% CI: [redacted], which is [redacted] than the p-value crossing boundary of [redacted] for statistical significance) in favour of pembrolizumab plus chemotherapy, representing a statistically significant [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.

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

Table 4: Analysis of Overall Survival (ITT Population with CPS>=5)

	Pembrolizumab + Chemotherapy (N=379)	Chemotherapy (N=388)
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-valuec	[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 unstratified cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on unstratified log-rank test. Database Cut-off Date: 03OCT2022

Figure 1 Kaplan-Meier Plot of Overall Survival (ITT Population with CPS>=5)

[redacted]

Progression Free Survival in participants with CPS>=5

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] (95% CI: [redacted], which is [redacted] than the *p-value* crossing boundary of [redacted] for statistical significance) in favour of pembrolizumab plus chemotherapy, representing a statistically significant [redacted] reduction 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 higher 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 5: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR assessment per RECIST 1.1 (ITT Population with CPS>=5)

	Pembrolizumab + Chemotherapy (N=379)	Chemotherapy (N=388)
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-valuec	[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 unstratified cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on unstratified log-rank test. Database Cut-off Date: 03OCT2022

Figure 2 Kaplan-Meier Plot of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS>=5)

Objective response rate

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

- The confirmed ORR was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (% [95% CI:] vs % [95% CI:]), reflecting a clinically meaningful and statistically significant difference of % (95% CI: , which is less than the *p-value* crossing boundary of for statistical significance).

Table 6: Analysis of Objective Response (Confirmed) Based on BICR Assessment per RECIST 1.1 (ITT Population with CPS>=5)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + Chemotherapy vs. Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy					
Chemotherapy					

[a] Based on unstratified Miettinen & Nurminen method.
[b] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Responses are based on BICR assessment per RECIST 1.1.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 03OCT2022

If CPS cut points other than >=1 or >=10 are randomly chosen based on raw scores to dissect data when it is neither a stratification factor, nor a prespecified or validated cut point, nor has it been statistically tested with adequate sample size, such analyses

may naturally be prone to arbitrary findings which can be unreliable. In KEYNOTE-859, the clinically meaningful improvements in OS and PFS based on the validated, stratified cut point of CPS ≥1, can fulfil an unmet medical need for a larger segment of patients with gastric or gastro-oesophageal cancer. Therefore, MSD's opinion is that treatment benefit is best observed based on the validated data in the CPS ≥1 population in keeping with the study design and pre-specified endpoints.

During the regulatory review of this indication, the CHMP acknowledged (CHMP assessment outcomes awaiting publication) the methodological limitations of the exploratory analyses around the CPS 5 cut point and considered the results as a whole to be supportive to select the CPS>=1 cut point as the most appropriate one in the proposed indication.

Systematic review

A 9. It is not described how studies were screened and identified. Please describe how screening was conducted at title/abstract stage as well as at full text stage e.g., include details on the number of reviewers involved, whether screening was conducted independently and in duplicate, and how any disagreements between reviewers were resolved.

MSD response

Study selection followed a two-stage screening process based on the review of titles and abstracts (stage I) and then, full-text articles (stage II). All titles/abstracts identified by the literature searches were reviewed against the predefined PICOS selection criteria. Following completion of title/abstract review, all publications identified for inclusion during this first pass were retrieved for further review in full text. Ultimately, full-text articles that met all of the inclusion criteria and none of the exclusion criteria were included in the SLR and underwent data extraction.

During both stages of study selection (i.e. title/abstract and full-text article) each publication was assessed by two, independent investigators. Any disagreements were resolved by discussion between investigators, including a third more senior researcher, if needed. The process of study identification and selection were

summarized in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (1).

A 10. On page 46 of the CS, it states that further details on the complete quality assessment is included in Appendix D1.4. However, there is no D1.4 in the attached appendices. Furthermore, no details are provided on how quality assessment was conducted anywhere in the CS. Please provide details on how quality assessments for included studies/trials were carried out, and include number of reviewers involved, whether quality assessment was conducted independently and in duplicate, and how any disagreements between reviewers were resolved.

MSD response:

Study quality assessment of included trials was conducted using the Cochrane Collaboration's Risk of Bias tool. This instrument was used to evaluate fixed set of domains focusing on aspects of trial design, conduct and outcome reporting (Refer to Table 7). [1] The risk of bias instrument was used to assign summary assessments of within study bias: low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high risk of bias (high risk of bias for one or more key domains). A proposed judgement about the risk of bias arising from each domain was generated by an algorithm tracked in a Microsoft Excel Workbook, based on answers to the signalling questions.(2) The assessment was performed by a single reviewer and validated by a senior researcher.

Table 7: Cochrane risk of bias assessment tool (Version 2)

Domain	Issues addressed
Bias arising from the randomization process	Whether: the allocation sequence was random; the allocation sequence was adequately concealed; baseline differences between intervention groups suggest a problem with the randomization process.
Bias due to deviations from intended interventions	Whether: participants were aware of their assigned intervention during the trial; carers and people delivering the interventions were aware of the participant's assigned intervention during the trial. When the review authors' interest is in the effect of assignment to intervention: (if applicable) deviations from the intended intervention arose because of the experimental context (i.e. do not reflect usual practice); and; if so; whether they were unbalanced between groups and likely to have affected the outcome;

Domain	Issues addressed
	An appropriate analysis was used to estimate the effect of assignment to intervention; and; if not; whether there was potential for a substantial impact on the result. When the review authors' interest is in the effect of adhering to intervention: (if applicable) important non-protocol interventions were balanced across intervention groups; (if applicable) failures in implementing the intervention could have affected the outcome; (if applicable) study participants adhered to the assigned intervention regimen; (if applicable) an appropriate analysis was used to estimate the effect of adhering to the intervention.
Bias due to missing outcome data	Whether: data for this outcome were available for all; or nearly all; participants randomized; (if applicable) there was evidence that the result was not biased by missing outcome data; (if applicable) missingness in the outcome was likely to depend on its true value (e.g. the proportions of missing outcome data; or reasons for missing outcome data; differ between intervention groups).
Bias in measurement of the outcome	Whether: the method of measuring the outcome was inappropriate; measurement or ascertainment of the outcome could have differed between intervention groups; outcome assessors were aware of the intervention received by study participants (if applicable) assessment of the outcome was likely to have been influenced by knowledge of intervention received.
Bias in selection of the reported result	(if applicable) assessment of the outcome was likely to have been influenced by knowledge of intervention received. Whether: the trial was analysed in accordance with a pre-specified plan that was finalized before unblended outcome data were available for analysis; the numerical result being assessed is likely to have been selected; on the basis of the results; from multiple outcome measurements within the outcome domain; the numerical result being assessed is likely to have been selected; on the basis of the results; from multiple analyses of the data.

The completed quality assessment was included in Appendix D1.2 table 17, page 103, also please see it provided below.

Table 8: Cochrane risk of bias assessment results

Type of bias	KEYNOTE-859		CheckMate-649	
	Review authors' judgement	Support for judgement	Review authors' judgement	Support for judgement
Bias arising from the	Low	Treatment allocation/randomization will occur centrally using	Low	Randomisation was done using interactive web

randomization process		an interactive response technology (IRT) system. No apparent imbalances in baseline characteristics between intervention arms		response technology (block sizes of six) No apparent differences in baseline characteristics between intervention groups
Bias due to deviations from intended interventions	Low	Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. No apparent changes from assigned intervention that were inconsistent with the trial protocol ITT analysis	Low	Reported as open label trial Changes in assigned intervention consistent with what could occur outside of trial protocol ITT analysis
Bias due to missing outcome data	Low	Outcome reported for all patients assigned to each intervention arm	Low	Outcomes reported for all patients randomized to intervention arms
Bias in measurement of the outcome	Low	Prespecified survival outcome assessment in statistical analysis plan Observer reported outcome not involving judgement Blinded independent central review for response outcomes	Low	Prespecified statistical analysis plan Observer reported outcome not involving judgement Blinded independent central assessment
Bias in selection of the reported result	Low	Prespecified statistical analysis plan All eligible reported results for the outcome domain correspond to all intended outcome measurements. All eligible reported results for the outcome measurement correspond to all intended analyses.	Low	Prespecified statistical analysis plan All eligible reported results for the outcome domain correspond to all intended outcome measurements. All eligible reported results for the outcome measurement correspond to all intended analyses.
Overall bias	Low	All subcategories had low risk of bias	Low	All subcategories had low risk of bias

Clinical effectiveness evidence

A 11. Priority question: Page 48 of the CS states that the data cut for the interim analysis of the KEYNOTE-859 trial was 3 October 2022. If available, please provide more mature data from the KEYNOTE-859 trial for all outcomes reported in the CS, including safety outcomes.

MSD response:

More mature data from the KEYNOTE-859 trial is not available and not planned. Final analysis will be completed for the manuscript only; therefore, the full analysis is not planned.

A 12. Page 9 of the CS states *"For patients with CPS≥5, the proposed new technology would offer an additional immuno-oncology treatment option thereby broadening the available treatment options for clinicians to use for these patients"*. However, there were no relevant data for this subgroup of CPS≥5 from the CS. Please clarify the rationale for this statement and provide supporting evidence, see also question A8 above.

MSD response:

The marketing authorisation for the proposed indication includes patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 CPS ≥1 which also covers patients with CPS>=5 who already have an IO treatment option (NICE TA 857). If pembrolizumab recommended, it would offer an additional IO treatment for patients with CPS>=5. In patients with CPS>=1 and CPS<5 pembrolizumab with chemotherapy would be a new IO which would address current unmet need in those patients.

A 13. Please provide further information on the methods and results of testing proportional hazards assumptions for the overall survival (OS) and progression-free survival (PFS) outcomes of the KEYNOTE-859 trial.

MSD response

Where RCTs identified in the SLR formed a connected network and were deemed to be sufficiently similar for each population and outcome of interest, their results were synthesized using NMAs. The NMA of reported hazard ratios (HRs) in terms of OS and PFS assuming proportional hazards between treatments was performed using random and fixed-effects models with a contrast-based normal likelihood for the log HR of each trial in the network. Normal non-informative prior distributions were used for all parameters. Relative treatment effects were expressed as HRs with 95% credible intervals, reflecting a 95% probability that the estimate is within the specified range. Additionally, time-varying HR analysis was conducted. This involved a

multidimensional treatment effect as an alternative to the synthesis of the constant HRs. The hazard functions of the interventions in a trial were modeled using fractional polynomials, and the difference in the parameters were considered the multidimensional treatment effect. These were synthesized (and indirectly compared) across studies to produce relative effects between treatments.

Fixed and random-effects models

Both fixed and random-effects models were considered. In general, the assumptions of random-effects models are preferred as they are expected to be more plausible than fixed effect models. For the random-effects models, one parameter for the between-study heterogeneity was used, assuming that the between-study heterogeneity was the same for each intervention relative to the overall reference treatment of choice. If there was insufficient evidence to estimate between-study heterogeneity, fixed-effects models were used.

Time-to-event outcomes using constant hazard ratios

The proportional hazard assumption regarding time-to-event outcomes for each individual trial was assessed using the Grambsch and Therneau test (3) The NMA of reported HRs in terms of OS and PFS (assuming proportional hazards between treatments) was performed using a regression model with a contrast-based normal likelihood for the log HR (and corresponding standard error) of each trial (or comparison) in the network according to Dias et al (4) . Normal non-informative prior distributions for the parameters were estimated with a mean of 0 and a variance of 10,000.

Time-to-event outcomes using Kaplan-Meier curves

Traditional NMA for survival outcomes are based on HR estimates and rely on the proportional hazards assumption, which is implausible if the hazard functions of competing interventions cross. The hazard function describes the instantaneous event (e.g. death or progression) rate at any point in time. Ouwens et al and Jansen et al have presented methods for NMA of survival data using a multidimensional treatment effect as an alternative to the synthesis of the constant HRs (5), (6). The hazard functions of the interventions in a trial are modeled using known parametric survival

functions or fractional polynomials, and the difference in the parameters are considered the multidimensional treatment effect, which are synthesized (and indirectly compared) across studies. With this approach, the treatment effects are represented by multiple parameters rather than a single parameter. The model introduced by Jansen will be used for the NMA of OS and PFS (5), (7).

For OS and PFS, the following competing survival distributions were considered using the multivariate NMA framework: Weibull, Gompertz, and second order fractional polynomials including p1=0 or 1 and p2= -1, 0.5, 0, 0.5, or 1. In essence, these second order fractional polynomial models are extensions of the Weibull and Gompertz model and allow arc- and bathtub shaped hazard functions, which emulate parametric distributions such as log normal and log logistic. For the relative treatment effects in the 2nd order fractional polynomial framework, we assessed models which assume: 1) treatment only has an impact on two of the three parameters describing the hazard function over time (i.e. one scale and one shape parameter), and 2) treatment has an impact on all three parameters describing the hazard function over time (i.e. one scale and two shape parameters).

For each treatment arm of each study in the NMA, the reported KM curves were digitized (DigitizeIt; http://www.digitizeit.de/). The KM curves can be divided into q consecutive intervals over the follow-up period: $[t_1, t_2], (t_2, t_3], \ldots, (t_q, t_{q+1}]$ with $t_1 = 0$. For each time interval m=1,2,3,…,.q, extracted survival proportions were used to calculate the patients at risk at the beginning of that interval and incident number of deaths (7). A binomial likelihood distribution of the incident events for every interval can be described according to:

$$r_{ikm} \sim Bin(p_{ikm}, n_{ikm})$$

where r_{jkt} is the observed number of events in the mth interval ending at time point $t_{m+1}$for treatment k in study j. n_{jkt} is the number of subjects at risk just before the start of that interval, adjusted for the subjects censored in the interval. p_{jkt} is the corresponding underlying event probability. When the time intervals are relatively short, the hazard rate h_{jkt} at time point t for treatment k in study j can be assumed to be constant for any time point within the corresponding mth time interval. The hazard rate corresponding to p_{jkt} for the mth interval can be standardized by the unit of time

used for the analysis (e.g. months) according to $h_{jkt} = -\ln(1 - p_{jkt})/\Delta t_{jkt})$, where Δt_{jkt} is the length of the interval. For the model estimation, we assigned this underlying hazard to time point t_{m+1}.

The prior distributions for model 9 are:

$$\begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 10^4 & 0 \\ 0 & 10^4 \end{pmatrix}\right)$$

$$\begin{pmatrix} d_{0Ak} \\ d_{1Ak} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 10^4 & 0 \\ 0 & 10^4 \end{pmatrix}\right)$$

For model 10 the prior distributions for the study effects are:

$$\begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 10^4 & 0 & 0 \\ 0 & 10^4 & 0 \\ 0 & 0 & 10^4 \end{pmatrix}\right)$$

$$\begin{pmatrix} d_{0Ak} \\ d_{1Ak} \\ d_{2Ak} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 10^4 & 0 & 0 \\ 0 & 10^4 & 0 \\ 0 & 0 & 10^4 \end{pmatrix}\right)$$

Non-informative priors were used for both mean hazards and treatment effects. These are multivariate normal, with mean vectors centered at 0, and covariance matrices with diagonals of 10,000, and off diagonal elements of 0.

Model selection

The deviance information criterion (DIC) was used to compare the goodness-of-fit of competing survival models that do not allow for time-varying hazard ratios (8). DIC provides a measure of model fit that penalizes model complexity according to $DIC = \overline{D} + pD, pD = \overline{D} - \widehat{D}$. $\widehat{D}$ ("Dbar") is the posterior mean residual deviance, pD is the effective number of parameters, and $\widehat{D}$ is the deviance evaluated at the posterior mean of the model parameters. In general, a more complex model will result in a better fit to the data, demonstrating a smaller residual deviance. The model with the better trade-off between fit and parsimony has a lower DIC. A difference in DIC of about 5 points can be considered meaningful. In the case of time-to-event outcomes using KM curves, model selection was based on the best fitting second-order time-varying

fractional polynomial model according to DIC as well as the plausibility of the HRs by comparing corresponding survival functions with the results observed in the underlying RCTs. Specifically, time-varying NMA models were selected based on the following steps:

1. Run full and less complex fractional polynomial models for all combinations of P1 and P2
2. Rank models according to DIC
3. Review curve fits and extrapolation for top four best fitting models according to DIC
4. Compare full models with less complex models based on best choice of P1 and P2; opt for less complex model if similar goodness of fit (most parsimonious model).

Evaluation of consistency between direct and indirect comparisons

The consistency between direct and indirect comparisons was evaluated for networks that include closed loops. A synthesis of only direct evidence was performed using independent-means models where pooled estimates for all the different direct comparisons were obtained simultaneously (9). Additionally, if appropriate based on network structure (e.g. if closed loops were present), relative treatment effects for all the possible comparisons in the network based on indirect evidence only were assessed with 'edge-splitting' (9). This involves repeatedly performing an NMA, where for every analysis the direct evidence for a particular comparison is removed from the dataset. This step was conducted prior to finalizing the network of evidence, so that any inconsistencies in the model could be explored and addressed.

Results of testing proportional hazards assumptions for the overall survival and progression-free survival outcomes

The results of testing proportional hazards assumptions for the overall survival and progression-free survival outcomes of the KEYNOTE-859 trial for participants with PD-L1 CPS≥1 and CPS≥10 are provided below.

Overall survival

KM plotted from KEYNOTE-859 CSR October 2022 data cut-off

Figure 3: KEYNOTE-859, PD-L1 CPS ≥1, OS, KM

Figure 4: KEYNOTE-859, PD-L1 CPS ≥1, OS, Schoenfeld residuals

Figure 5: KEYNOTE-859, PD-L1 CPS ≥1, OS, Log Cumulative hazard

Figure 6: KEYNOTE-859, PD-L1 CPS ≥10, OS, KM

Figure 7: KEYNOTE-859, PD-L1 CPS ≥10, OS, Schoenfeld residuals

Figure 8: KEYNOTE-859, PD-L1 CPS ≥10, OS, Log Cumulative hazard

Progression free survival

Figure 9: KEYNOTE-859, PD-L1 CPS ≥1, PFS, KM

Figure 10: KEYNOTE-859, PD-L1 CPS ≥1, PFS, Schoenfeld residuals

Figure 11: KEYNOTE-859, PD-L1 CPS ≥1, PFS, Log Cumulative hazard

Figure 12: KEYNOTE-859, PD-L1 CPS ≥10, PFS, KM

Figure 13: KEYNOTE-859, PD-L1 CPS ≥10, PFS, Schoenfeld residuals

Figure 14: KEYNOTE-859, PD-L1 CPS ≥10, PFS, Log Cumulative hazard

Results of proportional hazards tests for KEYNOTE 859 CPS>=5 population

Overall survival

Figure 15: KEYNOTE-859, PD-L1 CPS ≥ 5, OS, KM

Figure 16: KEYNOTE-859, PD-L1 CPS ≥ 5, OS, Schoenfeld residuals

Figure 17: KEYNOTE-859, PD-L1 CPS ≥ 5, OS, Log Cumulative hazard

Progression free survival

Figure 18: KEYNOTE-859, PD-L1 CPS ≥ 5, PFS, KM

Figure 19: KEYNOTE-859, PD-L1 CPS ≥ 5, PFS, Schoenfeld residuals

Figure 20: KEYNOTE-859, PD-L1 CPS ≥ 5, PFS, Log Cumulative hazard

A 14. It is noted in the KEYNOTE-859 trial that only 42 participants from 3 United Kingdom (UK) centres were included in this trial. Furthermore, the patient characteristics of the intention-to-treat (ITT) population provided in Table 6 of the CS, confirms that 55.5% of participants were white. Current data from England and Wales indicates that ~82% of population is white. Please justify the generalisability of this trial with regards ethnic representation of the population in England and Wales.

MSD response

KEYNOTE-859 is a global trial that recruited patients with HER2 negative locally advanced metastatic gastric cancer or GOJ across 33 countries. The aim of the trial is to represent patients with HER2 negative locally advanced metastatic gastric or GOJ adenocarcinoma globally.

MSD has conducted a post-hoc analysis of participant baseline characteristics by treatment group for European participants with CPS≥1, presented in Table 9. The analysis shows that [redacted] of European participants in the KEYNOTE-859 trial were White. Also, a post-hoc analysis of the UK participants (Table 10) in the KEYNOTE-859 trial show that [redacted] of participants were White. Therefore, we believe that KEYNOTE-859 trial results are generalisable to England and Wales population.

It should also be noted that CheckMate-649 trial included 68-70% of White participants which is below the proportion of White population in England and Wales, however the NICE appraisal committee concluded that the CheckMate-649 trial was generalisable to NHS practice (10), (11).

Table 9: Participant Baseline Characteristics by Treatment Group European Participants with CPS≥1 (Intention-to-Treat Population) - race

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]		[redacted]		[redacted]	
Race						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

European participants are defined as participants from the geographical location of Europe.
CAPOX: Backbone chemotherapy oxaliplatin + capecitabine; FP: Backbone chemotherapy cisplatin + 5-FU.
Database Cut-off Date: 03OCT2022

Table 10: Participant Baseline Characteristics by Treatment Group UK Participants with CPS≥1 (Intention-to-Treat Population) - race

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]		[redacted]		[redacted]	
Race						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

UK participants are defined as participants from the geographical location of United Kingdom.
CAPOX: Backbone chemotherapy oxaliplatin + capecitabine; FP: Backbone chemotherapy cisplatin + 5-FU.
Database Cutoff Date: 03OCT2022

A 15. According to page 16 of the CS, the condition in the UK *"is most common in people with Black ethnicity, then White ethnicity, and least common in those with Asian ethnicity"*. In England and Wales, black ethnicity sits at around 4% but would therefore likely be over-represented in patients suffering from this condition. Those defined as black or African American in the KEYNOTE-859 trial constitute only 1.3% of included participants in the ITT population (Table 6 of the CS). Please comment on this and provide justification for the generalisability of this to likely characterises of patients in England and Wales.

MSD response:

As described in the response to the question A14, KEYNOTE-859 is a global trial that aims to represent patients with advanced or metastatic gastric cancer or GOJ adenocarcinoma globally.

COVID-19 pandemic has highlighted the lack of representation of Black people in clinical trials in the UK (12). The reasons for the under-representation of the Black population in clinical trials are multifactorial (12). Szczepura (13) classified the challenges in access to health care by ethnic minority populations into four groups: (i) extrinsic, (ii) organisational factors, (iii) intrinsic or (iv) personal factors. Extrinsic

factors include language difficulties in a population whose first language is not English. Screening potential trial patients against an ever-growing list of eligibility criteria is complex and sometimes challenging. Other obstacles to participation include distance to treatment centres and low social-economic status (14). Higher social-economic status has been shown as a statistically significant predictor of involvement in oncology trials (15). Intrinsic factors include a lack of education on the importance of clinical trials and an inherent distrust of institutions due to racial discrimination. Black communities have been subject to historic scandals linked with clinical trials, such as the Tuskegee syphilis study of untreated syphilis in Negro males (16), unethical experiments by James Marion Sims and the cases of multiple medical experimentations in Africa (17). These historical racial abuses under the umbrella of clinical trials have hindered the participation of Black patients (12).

MSD has conducted a post-hoc analysis of participant baseline characteristics by treatment group for the UK participants with CPS≥1. The analysis shows that [redacted] of the UK participants in the KEYNOTE-859 trial were Black (Table 10). Therefore, we believe that KEYNOTE-859 trial results are generalisable to England and Wales population.

Similarly as described above in the response to question A14, it should be noted that CheckMate-649 trial included only around 1% of Black participants which is below the proportion of Black population in England and Wales, however the NICE appraisal committee concluded that the CheckMate-649 trial was generalisable to NHS practice (10), (11).

Indirect treatment comparison (ITC)

A 16. Priority question: Please provide a Table that summarizes patient characteristics at baseline for the subgroup of PD-L1 CPS ≥1 and the subgroup of PD-L1 CPS ≥10 from the two randomised controlled trials (RCTs; KEYNOTE-859 and CheckMate-649). It is important to make sure that the assumption of exchangeability for the purpose of the network meta-analysis is acceptable (as highlighted in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document 2).

MSD response:

The baseline characteristics for patients with CPS ≥1 and ≥10 were not reported in any of the publications associated with CheckMate-649; therefore, a between-studies comparison of baseline characteristics in these populations is not feasible.

Baseline characteristics for the KEYNOTE-859 participants with PD-L1 CPS≥1 are provided in the company submission on page 35, Table 6. Participant baseline characteristics for participants with PD-L1 CPS≥10 are provided below.

Table 11: Participant Baseline Characteristics by Treatment Group Participants with CPS≥10 (Intention-to-Treat Population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	279		272		551	
Sex						
Male	193	(69.2)	205	(75.4)	398	(72.2)
Female	86	(30.8)	67	(24.6)	153	(27.8)
Age (Years)						
< 65	161	(57.7)	159	(58.5)	320	(58.1)
>= 65	118	(42.3)	113	(41.5)	231	(41.9)
Mean	60.6		60.8		60.7	
SD	11.6		11.1		11.3	
SE	0.7		0.7		0.5	
Median	63.0		63.0		63.0	
Range	26 to 84		25 to 82		25 to 84	
Race						
American Indian Or Alaska Native	7	(2.5)	11	(4.0)	18	(3.3)
Asian	98	(35.1)	89	(32.7)	187	(33.9)
Black Or African American	2	(0.7)	5	(1.8)	7	(1.3)
Multiple	16	(5.7)	8	(2.9)	24	(4.4)
American Indian Or Alaska Native White	12	(4.3)	5	(1.8)	17	(3.1)
Black Or African American White	4	(1.4)	3	(1.1)	7	(1.3)
Native Hawaiian Or Other Pacific Islander	1	(0.4)	0	(0.0)	1	(0.2)
White	155	(55.6)	157	(57.7)	312	(56.6)
Missing	0	(0.0)	2	(0.7)	2	(0.4)
Ethnicity						
Hispanic Or Latino	59	(21.1)	51	(18.8)	110	(20.0)
Not Hispanic Or Latino	211	(75.6)	215	(79.0)	426	(77.3)
Not Reported	6	(2.2)	5	(1.8)	11	(2.0)
Unknown	3	(1.1)	1	(0.4)	4	(0.7)
Age Category 2 (Years)						

< 65	161	(57.7)	159	(58.5)	320	(58.1)
>=65 to <75	96	(34.4)	92	(33.8)	188	(34.1)
>=75 to <85	22	(7.9)	21	(7.7)	43	(7.8)
Age Category 3 (Years)						
18-39	16	(5.7)	12	(4.4)	28	(5.1)
40-49	30	(10.8)	35	(12.9)	65	(11.8)
50-59	68	(24.4)	61	(22.4)	129	(23.4)
60-69	99	(35.5)	104	(38.2)	203	(36.8)
70-79	61	(21.9)	54	(19.9)	115	(20.9)
>=80	5	(1.8)	6	(2.2)	11	(2.0)
Geographic Region for Randomization						
Western Europe/Israel/North America/Australia	78	(28.0)	64	(23.5)	142	(25.8)
Asia	96	(34.4)	88	(32.4)	184	(33.4)
Rest of the World	105	(37.6)	120	(44.1)	225	(40.8)
Combination Chemotherapy for Randomization						
CAPOX	242	(86.7)	235	(86.4)	477	(86.6)
FP	37	(13.3)	37	(13.6)	74	(13.4)
PD-L1 Status for Randomization						
Positive	279	(100.0)	271	(99.6)	550	(99.8)
Negative	0	(0.0)	1	(0.4)	1	(0.2)
Baseline PD-L1 Status (CPS Cut Point: 1)						
CPS >=1	279	(100.0)	272	(100.0)	551	(100.0)
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS >=10	279	(100.0)	272	(100.0)	551	(100.0)
MSI Status						
MSI-High	20	(7.2)	16	(5.9)	36	(6.5)
non-MSI-High	227	(81.4)	224	(82.4)	451	(81.9)
	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Unknown	0	(0.0)	1	(0.4)	1	(0.2)
Missing	32	(11.5)	31	(11.4)	63	(11.4)
ECOG Performance Scale						
0	99	(35.5)	103	(37.9)	202	(36.7)
1	180	(64.5)	169	(62.1)	349	(63.3)
Primary Location						
Adenocarcinoma of the gastroesophageal junction	65	(23.3)	73	(26.8)	138	(25.0)
Adenocarcinoma of the stomach	214	(76.7)	199	(73.2)	413	(75.0)
Overall Stage						
IIA	0	(0.0)	1	(0.4)	1	(0.2)
IIB	0	(0.0)	2	(0.7)	2	(0.4)
IIIA	2	(0.7)	3	(1.1)	5	(0.9)
IIIB	8	(2.9)	2	(0.7)	10	(1.8)
IIIC	4	(1.4)	2	(0.7)	6	(1.1)
IV	265	(95.0)	262	(96.3)	527	(95.6)
Disease Status						

Locally advanced	14	(5.0)	11	(4.0)	25	(4.5)
Metastatic	265	(95.0)	261	(96.0)	526	(95.5)
Histological Subtype (Lauren classification)						
Diffuse	102	(36.6)	89	(32.7)	191	(34.7)
Intestinal	111	(39.8)	99	(36.4)	210	(38.1)
Indeterminate	65	(23.3)	84	(30.9)	149	(27.0)
Unknown	1	(0.4)	0	(0.0)	1	(0.2)
Number of Metastasis						
0-2	151	(54.1)	144	(52.9)	295	(53.5)
>=3	128	(45.9)	128	(47.1)	256	(46.5)
Liver Metastases						
Yes	119	(42.7)	110	(40.4)	229	(41.6)
No	160	(57.3)	162	(59.6)	322	(58.4)
Prior Gastrectomy/Esophagectomy						
Yes	48	(17.2)	40	(14.7)	88	(16.0)
No	231	(82.8)	231	(84.9)	462	(83.8)
Missing	0	(0.0)	1	(0.4)	1	(0.2)
Weight (kg)						
Participants with data	279		272		551	
Mean	65.2		68.2		66.7	
SD	14.3		15.7		15.1	
SE	0.9		1.0		0.6	
Median	62.0		66.0		64.5	
Range	38.5 to 131.0		33.0 to 128.8		33.0 to 131.0	
Body Surface Area (m^2)						
Participants with data	266		258		524	
Mean	1.7		1.8		1.7	
SD	0.2		0.2		0.2	
SE	0.0		0.0		0.0	
Median	1.7		1.8		1.7	
Range	1.3 to 2.5		1.2 to 2.5		1.2 to 2.5	
Body Mass Index						
Participants with data	279		271		550	
Mean	23.5		24.0		23.7	
SD	4.4		4.5		4.5	
SE	0.3		0.3		0.2	
Median	22.9		23.1		23.1	
Range	14.2 to 44.8		13.7 to 44.4		13.7 to 44.8	

CAPOX: Backbone chemotherapy oxaliplatin + capecitabine; FP: Backbone chemotherapy cisplatin + 5-FU.
Database cut-off Date: 03OCT2022

A 17. Priority question: Please provide the network meta-analysis (NMA) results for the subgroup of PD-L1 CPS ≥5. Please also provide a table that summarizes patient characteristics at baseline for the subgroup of PD-L1 CPS ≥5 from the two RCTs (KEYNOTE-859 and CheckMate-649), see also question A8 above.

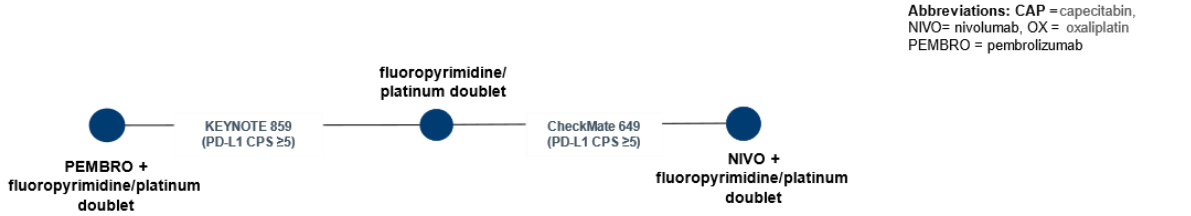
MSD response

As described in the response to question A8 and was explained in the evidence submission section 2.9, page 58, an NMA in participants with PD-L1 CPS ≥5 was not undertaken at the time of the evidence submission because KEYNOTE-859 did not have PD-L1 CPS ≥5 as a prespecified cut point and the results in this subgroup of patients were not available. Also, differences between the KEYNOTE-859 and CheckMate-649 trials (different PD-L1 CPS cuts were pre-specified) impacted the feasibility assessment conclusion. MSD has conducted a post-hoc analysis of KEYNOTE-859 in the PD-L1 CPS>=5 subgroup of patients, which made the NMA between pembrolizumab + chemotherapy and nivolumab + chemotherapy feasible. The feasibility assessment for NMA and NMA results are provided in the following sections.

Feasibility assessment for network meta-analysis

Because pembrolizumab and nivolumab modulate PD-1/PD-L1 pathways, PD-L1 expression was considered to be an important relative treatment effect modifier in both KEYNOTE-859 and CheckMate-649. Therefore, the balance of PD-L1 expression levels in the included populations for each of the trials was considered when constructing the network meta-analysis. Overall survival and progression-free survival in the PD-L1 CPS ≥ 5 population were reported as primary endpoints in the CheckMate-649 trial while reported as a post-hoc subgroup analysis in KEYNOTE-859, hence it was feasible to compare pembrolizumab + chemotherapy to nivolumab + chemotherapy in patients expressing PD-L1 CPS ≥ 5 as depicted in Figure 21.

Figure 21 Illustration of connected network in PD-L1 CPS ≥5 population



For both OS and PFS, NMA was conducted using constant and time-varying HRs. Since results of proportional hazard tests were consistent with the proportional hazards assumption, only constant HR NMA results are presented.

NMA results

Overall survival in PD-L1 CPS ≥5 population

The evidence network informing the NMA of OS consisted of two RCTs. The 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.

Results of the constant HR NMA are presented in Table 12. Treatment with pembrolizumab and chemotherapy performed similarly when compared to nivolumab and chemotherapy (HR, 95% CrI: [redacted]), with no statistically meaningful difference between the treatments.

Table 12: Results of fixed-effects NMA of OS 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

Progression-free survival in PD-L1 CPS ≥5 population

Results of the constant HR NMA are presented in Table 13. Treatment with pembrolizumab and chemotherapy performed similarly when compared to nivolumab and chemotherapy in participants with CPS>=5 (HR, 95% CrI: [redacted]). The difference between treatments was not statistically meaningful.

Table 13: 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

In this population, pembrolizumab + chemotherapy performed similarly to nivolumab + chemotherapy under a constant hazard ratio assumption for both OS and PFS. NMA accounted for changes in hazard ratios over time by incorporating both constant HR and time-varying HR methods; the results were consistent with the proportional hazards assumption.

Overall, the results for PD-L1 CPS ≥ 5 subgroup were generally consistent with those observed in the ITT, PD-L1 CPS ≥ 1, and CPS ≥ 10 population for both OS and PFS, wherever available (reported in the company submission).

It should be noted that the results in this subgroup of patients should be treated with caution as the PD-L1 CPS>=5 data cut was not a pre-specified subgroup in the KEYNOTE- 859 trial. Please see response to question A8.

KEYNOTE-859 and CheckMate-649 patient characteristics in participants with PD-L1 CPS≥5 are provided in tables below.

Table 14: CheckMate-649 baseline characteristics (Age; sex; race/ethnicity; location)

Trial ID	Intervention	Population	Age; median	Male; n (%)	Race/ethnicity			Location		
					Caucasian; n (%)	Black; n (%)	Asian; n (%)	North America; n (%)	Asia; n (%)	Others; n (%)
CheckMate649[c,d]	NIVO + CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 5	63 (54, 69)b	331 (70)	328 (69)	2 (<1)	119 (25)	67 (14)	117 (25)	289 (61)
	CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 5	62 (54, 68)b	349 (72)	327 (68)	7 (1)	117 (24)	70 (15)	111 (23)	301 (62)
Notes: a, Range; b, Interquartile range; c, Baseline characteristics were not available separately for patients pre-assigned to CAPOX, d, Baseline characteristics were not available separately for PD-L1 CPS ≥1 and PD-L1 CPS ≥10 subgroups. Abbreviations: CAP, Capecitabine; CHEMO, Chemotherapy; CIS, Cisplatin; CPS, Combined Positive Score; ITT, Intent to treat; NIVO, Nivolumab; OX, Oxaliplatin; PEMBRO, Pembrolizumab; 5-FU, 5-Fluorouracil										

Table 15: CheckMate-649 baseline characteristics (Performance status; disease stage; histology)

Trial ID	Intervention	Population	ECOG Performance Status, n(%)				Disease stage, n(%)				Histology, n(%)		
			0	1	0-1	2	Recurrent	Unresectable	Locally advanced	Metastatic	Intestinal	Diffuse	Others
CheckMate649b	NIVO + CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 544(18)	194 (41)	279 (59)	473 (100) a	0	3 (1)	--	16 (3)	454 (96)	171 (36)	137 (29)	37 (8) d
	CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 544(18)	203 (42)	278 (58)	482 (100) a	0	1 (<1)	--	20 (4)	461 (96)	176 (37)	141 (29)	60 (6) d
Notes: a, Range; b, Interquartile range; c, Baseline characteristics were not available separately for patients pre-assigned to CAPOX, d, Baseline characteristics were not available separately for PD-L1 CPS ≥1 and PD-L1 CPS ≥10 subgroups. Abbreviations: CAP, Capecitabine; CHEMO, Chemotherapy; CIS, Cisplatin; CPS, Combined Positive Score; ITT, Intent to treat; NIVO, Nivolumab; OX, Oxaliplatin; PEMBRO, Pembrolizumab; 5-FU, 5-Fluorouracil													

Table 16: CheckMate-649 baseline characteristics (tumour site; number of metastatic sites; PD -L1 expression status and MSI status)

Trial ID	Intervention	Population	Primary tumor site, n (%)			Number of metastatic sites, n (%)				Microsatellite stability/mismatch repair status, n (%)	
			Gastric	GEJ	Esophagus	1	>1	≥2	≥3	MSI-H	Non-MSI high
CheckMate 649a,b	NIVO + CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 5	333 (70)	84 (18)	56 (12)	98 (21)	--	361 (76)	--	18 (4)	423 (89)c
	CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 5	334 (69)	86 (18)	62 (13)	105 (22)	--	362 (75)	--	16 (3)	423 (88)c
Notes: a, Range; b, Interquartile range; c, Baseline characteristics were not available separately for patients pre-assigned to CAPOX, d, Baseline characteristics were not available separately for PD-L1 CPS ≥1 and PD-L1 CPS ≥10 subgroups. Abbreviations: CAP, Capecitabine; CHEMO, Chemotherapy; CIS, Cisplatin; CPS, Combined Positive Score; ITT, Intent to treat; NIVO, Nivolumab; OX, Oxaliplatin; PEMBRO, Pembrolizumab; 5-FU, 5-Fluorouracil											

Table 17: KEYNOTE-859 Participant Characteristics (ITT Population with CPS>=5)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]		[redacted]		[redacted]	
Sex						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age Category 1 (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Age Category 2 (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 65 to <75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>= 75 to <85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age Category 3 (Years)						
18-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70-79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian Or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region for Randomization						
Western Europe/Israel/North America/Australia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Combination Chemotherapy for Randomization						
CAPOX	[redacted]					
FP	[redacted]					
PD-L1 Status for Randomization						
CPS >= 1	[redacted]					
CPS < 1	[redacted]					
Baseline PD-L1 Status (CPS Cut Point: 1)						
CPS >= 1	[redacted]					
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS >= 10	[redacted]					
CPS < 10						
Missing						
MSI Status						
MSI-High	[redacted]					
non-MSI-High						
Unknown						
Missing						
ECOG Performance Scale						
0	[redacted]					
1	[redacted]					
Primary Location						
Adenocarcinoma of the gastroesophageal junction	[redacted]					
Adenocarcinoma of the stomach	[redacted]					
Overall Stage						
IIA	[redacted]					
IIB						
IIIA						
IIIB						
IIIC						
IV						
Disease Status						
Locally advanced	[redacted]					
Metastatic	[redacted]					
Histological Subtype (Lauren classification)						
Diffuse	[redacted]					
Intestinal						
Indeterminate						
Unknown						
Number of Metastasis						
0-2	[redacted]					
>=3	[redacted]					
Tumour Burden						
>= Median	[redacted]					
< Median						
Missing						

Liver Metastases						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Gastrectomy/Esophagectomy						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CAPOX: Backbone chemotherapy oxaliplatin + capecitabine. FP: Backbone chemotherapy cisplatin + 5-FU.
Database Cut-off Date: 03OCT2022

Section B: Clarification on cost-effectiveness data

MSD presents revised cost-effectiveness results incorporating the following changes:

- In response to clarification question B15, AE durations have been revised from treatment-specific to pooled.
- In response to clarification question B10b, an error in the economic model was identified. This related to QALY calculations in the doublet chemotherapy arm 180 to 360 days before death (worksheet 'COMP 1', column BO).
- In response to clarification question B17, treatment waning calculations have been corrected (scenario analysis only).

Revised results incorporating these changes are provided below. A revised economic model is also provided.

Table 18. Revised base case results

Treatment	Total costs	Total LYs	Total QALYs	Total Modified QALYs	Incremental costs	Incremental LYs	Incremental QALYs*	ICER (£/QALY)	NMB	NHB
CPS≥1 (pembrolizumab CAA price)										
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.05	[redacted]	[redacted]	[redacted]
CPS≥10 (pembrolizumab list price)										
Nivolumab + doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-		-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06	[redacted]	[redacted]	[redacted]

Abbreviations: CAA, commercial access agreement; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMB, net monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay
Note: NMB and NHB calculated using a WTP threshold of £30,000/QALY
*Modified by 1.7 and 1.0 in the CPS≥1 and CPS≥10 populations, respectively.

Table 19. Revised probabilistic results

Treatment	Total costs	Total LYs	Total Modified QALYs	Incremental costs	Incremental LYs	Incremental QALYs*	ICER (£/QALY)	NMB	NHB
CPS≥1 (pembrolizumab CAA price)									
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.06	[redacted]	[redacted]	[redacted]
CPS≥10 (pembrolizumab list price)									

Nivolumab + doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.06	[redacted]	[redacted]	[redacted]
Abbreviations: CAA, commercial access agreement; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMB, net monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay Note: NMB and NHB calculated using a WTP threshold of £30,000/QALY *Modified by 1.7 and 1.0 in the CPS≥1 and CPS≥10 populations, respectively.									

Figure 22. Revised CEAC: CPS≥1 population

Figure 23. Revised cost-effectiveness plane: CPS≥1 population

Figure 24. Revised convergence plot: CPS≥1 population

Figure 25. Revised CEAC: CPS≥10 population

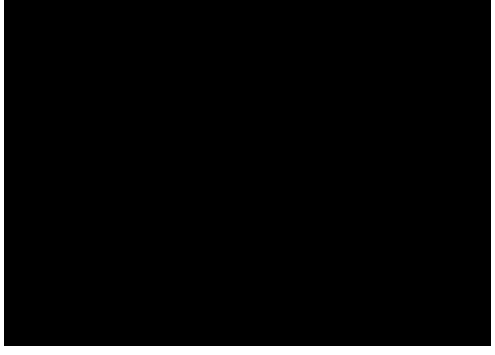


Figure 26. Revised cost-effectiveness plane: CPS≥10 population

Figure 27. Revised convergence plot: CPS≥10 population

Figure 28. Revised OWSA: CPS≥1 population

Figure 29. Revised OWSA: CPS≥10 population

Table 20. Revised results of scenario analysis: CPS≥1 population (deterministic)

Scenario	ICER (CAA price)	% change from base-case
Base-case	[redacted]	[redacted]
Chemotherapy backbones: NHS practice	[redacted]	[redacted]
Half-cycle correction: Yes	[redacted]	[redacted]
Time horizon: 10-year	[redacted]	[redacted]
Time horizon: 20-year	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]
Utility source: Descriptive pooled health state utility values	[redacted]	[redacted]
Utility: General population utility adjustment	[redacted]	[redacted]
Utility: Literature-based AE disutility	[redacted]	[redacted]
Utility: Descriptive treatment-specific time to death	[redacted]	[redacted]
Pembrolizumab: 100% Q6W	[redacted]	[redacted]
Treatment administration: mean # doses	[redacted]	[redacted]
Pembrolizumab & Nivolumab: 2 yr cap	[redacted]	[redacted]
RDI = 100%	[redacted]	[redacted]
Exclude wastage costs	[redacted]	[redacted]
Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
Subsequent treatment distribution: KEYNOTE 859	[redacted]	[redacted]
One-off progression cost: No	[redacted]	[redacted]
Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
Treatment waning effect: Yes	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot odds spline model	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot normal spline model	[redacted]	[redacted]
OS Doublet chemotherapy: Log-logistic	[redacted]	[redacted]
OS Doublet chemotherapy: 2-knot odds model	[redacted]	[redacted]

PFS Pembrolizumab + chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
PFS Doublet chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
Severity modifier of x1.2	[redacted]	[redacted]

Table 21. Revised results of scenario analysis: CPS≥10 population (deterministic)

Scenario	ICER (list prices)	% change from base-case
CPS10: Base case	[redacted]	[redacted]
CPS10: Chemotherapy backbone: NHS	[redacted]	[redacted]
CPS10: Nivolumab chemotherapy backbones: KEYNOTE-859	[redacted]	[redacted]
CPS10: Half-cycle correction: Yes	[redacted]	[redacted]
CPS10: Time horizon: 10-year	[redacted]	[redacted]
CPS10: Time horizon: 20-year	[redacted]	[redacted]
CPS10: Discount rate: 1.5%	[redacted]	[redacted]
CPS10: Utility source: Pooled health state utility values	[redacted]	[redacted]
CPS10: Utility: General population utility adjustment	[redacted]	[redacted]
CPS10: Utility: Literature-based AE disutility	[redacted]	[redacted]
CPS10: Utility: Treatment-specific time to death	[redacted]	[redacted]
CPS10: Pembrolizumab: 100% Q6W	[redacted]	[redacted]
CPS10: Treatment administration: mean # doses	[redacted]	[redacted]
CPS10: Pembrolizumab & Nivolumab: 2 yr cap	[redacted]	[redacted]
CPS10: RDI = 100%	[redacted]	[redacted]
CPS10: Exclude wastage costs	[redacted]	[redacted]
CPS10: Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
CPS10: Subsequent treatment distribution: KEYNOTE 859	[redacted]	[redacted]
CPS10: One-off progression cost: No	[redacted]	[redacted]
CPS10: Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
CPS10: AEs for nivolumab = pembrolizumab	[redacted]	[redacted]
CPS10: Nivolumab vs pembrolizumab HR = 1	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-odds model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-hazard model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: log-logistic model	[redacted]	[redacted]

Economic analysis

B 1. Priority question: At several places in the cost-effectiveness section of document B it is mentioned that clinical experts were consulted by MSD. Please provide details about the number of experts, their expertise, which

questions were asked, and the answers provided by the individual experts, and the conclusion for the cost effectiveness (CE) model e.g., by providing detailed minutes of the meetings.

MSD response:

Meetings were held with three experts; the detailed minutes from these meetings are provided as separate documents. The experts were consultant medical or clinical oncologists working at major cancer centres in England. An expert was engaged from the London region, the Midlands, and the North of England to encourage a breadth of responses and experiences; experts ranged in years of experience from 14-19 years in oncology. All clinical experts engaged with specialised in upper GI cancers, alongside other GI tumours. All have extensive experience of treating gastric/GOJ cancers and are experienced in using chemotherapy regimens and available immunotherapies in eligible patients. Two of the three experts engaged are actively involved in clinical research in upper GI cancers.

In addition to these meetings, MSD's Medical Science Liaisons (MSLs) keep up to date with the latest scientific research affecting how pembrolizumab is being used and feedback information from clinical experts. For example, NICE's recent recommendation for previously treated gastric cancer will affect the subsequent treatment pathway in patients with high microsatellite instability or mismatch repair deficiency (TA914). These discussions between MSLs and clinical experts are not formally documented.

B 2. Priority question: At several places in the cost-effectiveness section of document B a reference is made to HTA HECON reports and the HTA disposition and demographics report. Please provide these.

MSD response:

Relevant extracts from the following reports are provided as separate documents:

- MSD Keytruda (MK-3475) KN859 HTA Baseline and Efficacy report
- MSD Keytruda (MK-3475) KN859 HTA Disposition and Demographics report
- MSD Keytruda (MK-3475) KN859 HTA Drug Utilization report

- MSD Keytruda (MK-3475) KN859 HTA PRO report
- MSD Keytruda (MK-3475) KN859 HTA Safety report

Please note, Table 52 in Document B refers to Tables 68 and 112 of the HTA PRO report, which is incorrect as these Tables refer to US valuations. The correct Tables from the HTA PRO report using UK valuations are Tables 74 and 118.

B 3. Priority question: Section B3.6, Severity: Please provide the base-case analysis results and all companying tables and figures including the probabilistic sensitivity analysis (PSA) results using the 1.2 severity weight.

MSD response:

MSD maintains that the appropriate severity weight is 1.7 when doublet chemotherapy is standard care.

As explained in Section B.3.6 of the CS, the NICE appraisal of nivolumab for untreated HER2 negative advanced gastric, GOJ or oesophageal adenocarcinoma (TA857) met NICE's end-of-life criteria, and a higher decision-making threshold was applied (£50,000 per QALY). This current appraisal also meets all qualifying criteria to be considered as an end-of-life medicine, and the revised base case ICER (without a severity modifier) versus doublet chemotherapy sits comfortably below £50,000 (£37,624) demonstrating that pembrolizumab plus doublet chemotherapy should be considered a cost-effective use of NHS resources.

Moreover, TA857 would qualify for the same severity weight as this appraisal when standard care is doublet chemotherapy as the expected QALYs for patients with the condition receiving standard care would be the same.

In summary, a severity weight of 1.7 would promote consistent decision making in the absence of end-of-life criteria and address the remaining unmet need in patients expressing a CPS≥1.

As requested, results using the 1.2 severity weight are provided below.

Please note, when using the existing macros to run sensitivity analysis with alternative severity modifier, ensure the severity weight in the default value (‘Control for Input Parameters’D31:F31) is amended to the severity modifier of interest.

Table 22. Deterministic results using a 1.2 severity modifier (CPS≥1 population)

Treatment	Total costs	Total LYs	Total QALYs	Total Modified QALYs	Incremental costs	Incremental LYs	Incremental QALYs*	ICER (£/QALY)	NMB	NHB
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.74	[redacted]	[redacted]	[redacted]

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; LY, life year; NHB, net health benefit; NMB, net monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay
Note: NMB and NHB calculated using a WTP threshold of £30,000/QALY
*Modified by 1.2

Table 23. Probabilistic results using a 1.2 severity modifier (CPS≥1 population)

Treatment	Total costs	Total LYs	Total Modified QALYs	Incremental costs	Incremental LYs	Incremental QALYs*	ICER (£/QALY)	NMB	NHB
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.76	[redacted]	[redacted]	[redacted]

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; LY, life year; NHB, net health benefit; NMB, net monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay
Note: NMB and NHB calculated using a WTP threshold of £30,000/QALY
*Modified by 1.2

Figure 30. Cost-effectiveness plane: CPS≥1 population

Figure 31. OWSA: CPS≥1 population

Table 24. Results of scenario analysis: CPS≥1 population (deterministic)

Scenario	ICER	% change from base-case
Base-case	[redacted]	[redacted]
Chemotherapy backbones: NHS practice	[redacted]	[redacted]
Half-cycle correction: Yes	[redacted]	[redacted]
Time horizon: 10-year	[redacted]	[redacted]
Time horizon: 20-year	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]
Utility source: Descriptive pooled health state utility values	[redacted]	[redacted]
Utility: General population utility adjustment	[redacted]	[redacted]
Utility: Literature-based AE disutility	[redacted]	[redacted]
Utility: Descriptive treatment-specific time to death	[redacted]	[redacted]
Pembrolizumab: 100% Q6W	[redacted]	[redacted]
Treatment administration: mean # doses	[redacted]	[redacted]
Pembrolizumab & Nivolumab: 2 yr cap	[redacted]	[redacted]

RDI = 100%	[redacted]	[redacted]
Exclude wastage costs	[redacted]	[redacted]
Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
Subsequent treatment distribution: KEYNOTE 859	[redacted]	[redacted]
One-off progression cost: No	[redacted]	[redacted]
Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
Treatment waning effect: Yes	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot odds spline model	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot normal spline model	[redacted]	[redacted]
OS Doublet chemotherapy: Log-logistic	[redacted]	[redacted]
OS Doublet chemotherapy: 2-knot odds model	[redacted]	[redacted]
PFS Pembrolizumab + chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
PFS Doublet chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
Severity modifier of x1.2	[redacted]	[redacted]

Table 25. Deterministic results using a 1.2 severity modifier (CPS≥10 population)

Treatment	Total costs	Total LYs	Total QALYs	Total Modified QALYs	Incremental costs	Incremental LYs	Incremental QALYs*	ICER (£/QALY)	NMB	NHB
Nivolumab + doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.08	[redacted]	[redacted]	[redacted]

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMB, net monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay
Note: NMB and NHB calculated using a WTP threshold of £30,000/QALY
*Modified by 1.2

Table 26. Probabilistic results using a 1.2 severity modifier (CPS≥10 population)

Treatment	Total costs	Total LYs	Total Modified QALYs	Incremental costs	Incremental LYs	Incremental QALYs*	ICER (£/QALY)	NMB	NHB
Nivolumab + doublet chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-	-	-	-
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.07	[redacted]	[redacted]	[redacted]

Abbreviations: CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMB, net monetary benefit; QALY, quality adjusted life year; WTP, willingness-to-pay
Note: NMB and NHB calculated using a WTP threshold of £30,000/QALY
*Modified by 1.2

Figure 32. Cost-effectiveness plane: CPS≥10 population

Figure 33. OWSA: CPS≥10 population

Table 27. Results of scenario analysis: CPS≥10 population (deterministic)

Scenario	ICER (list prices)	% change from base case
CPS10: Base case	[redacted]	[redacted]
CPS10: Chemotherapy backbone: NHS	[redacted]	[redacted]
CPS10: Nivolumab chemotherapy backbones: KEYNOTE-859	[redacted]	[redacted]
CPS10: Half-cycle correction: Yes	[redacted]	[redacted]
CPS10: Time horizon: 10-year	[redacted]	[redacted]
CPS10: Time horizon: 20-year	[redacted]	[redacted]
CPS10: Discount rate: 1.5%	[redacted]	[redacted]
CPS10: Utility source: Pooled health state utility values	[redacted]	[redacted]
CPS10: Utility: General population utility adjustment	[redacted]	[redacted]
CPS10: Utility: Literature-based AE disutility	[redacted]	[redacted]
CPS10: Utility: Treatment-specific time to death	[redacted]	[redacted]
CPS10: Pembrolizumab: 100% Q6W	[redacted]	[redacted]
CPS10: Treatment administration: mean # doses	[redacted]	[redacted]

CPS10: Pembrolizumab & Nivolumab: 2 yr cap	[redacted]	[redacted]
CPS10: RDI = 100%	[redacted]	[redacted]
CPS10: Exclude wastage costs	[redacted]	[redacted]
CPS10: Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
CPS10: Subsequent treatment distribution: KEYNOTE 859	[redacted]	[redacted]
CPS10: One-off progression cost: No	[redacted]	[redacted]
CPS10: Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
CPS10: AEs for nivolumab = pembrolizumab	[redacted]	[redacted]
CPS10: Nivolumab vs pembrolizumab HR = 1	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-odds model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-hazard model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: log-logistic model	[redacted]	[redacted]
Abbreviations: AE, adverse event; CPS, combined positive score; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; OS, overall survival; PFS, progression free survival; Q6W, every 6 weeks; RDI, relative dose intensity		

B 4. Priority question: Regarding Section B.3.3 (clinical parameters and variables),

a) Please explain what is defined as the optimal statistical fit. Is this defined by the lowest Akaike information criterion (AIC) value, as highlighted in bold within the tables?

b) On page 109 of the CS, it is mentioned that the 1-knot hazard scale provides the best statistical fit for pembrolizumab plus doublet chemotherapy. However, the lowest AIC value indicated corresponds to the 3-knot normal model. Additionally, for doublet chemotherapy, the reasoning is somewhat unclear. Please clarify the criteria used here to determine the best statistical fit.

c) **Please provide hazard curves (such as figures 16 and 17) for all cubic spline extrapolations, both for OS and PFS, for pembrolizumab + doublet chemotherapy and doublet chemotherapy, for separate and joint models.**

MSD response:

a)Optimal statistical fit was determined using the lowest AIC. We also considered BIC values to be important when determining the optimal number of parameters for a model as the BIC penalises models with more parameters. It is important to note that optimal statistical fit was not used in isolation when choosing the best fitting parametric curves. Base case parametric curves in the CS were selected using a number of methods including: statistical goodness-of-fit statistics (AIC and BIC), visual inspection (comparing the survival curves to the observed KM data), and clinical plausibility of the predicted survival. Also, as noted in the response to part b, cues were also selected to minimise the crossing of OS and PFS. For ease of inspection, bold values in the tables show the lowest AIC and BIC values.

b)The intention was not to infer most appropriate choice of spline model is based solely on best statistical fit in isolation. In the pembrolizumab plus doublet chemotherapy arm, the spline 3-knot normal is associated with a lower AIC than the spline 1-knot hazard, but the spline 3-knot normal PFS curve exceeds the base case OS curve between 4-5 years which is clinically implausible. The spline 1-knot curves minimise the crossing of OS and PFS. The pembrolizumab plus doublet chemotherapy base case PFS curve of spline 1-knot hazard displays minimal crossing with the base case OS curve and has the lowest AIC of the 1-knot curves. The choice of PFS curve has minimal influence on the ICER.

c)The requested graphs are provided in a separate document.

B 5. In Section 3.2.1 of the CS (patient population), it is described that the baseline characteristics of the KEYNOTE-859 trial are used in the model (presented in Table 30 CS). The CS mentions that according to clinical experts the trial patients are a few years younger than those in clinical practice.

a) Please provide a value for this assumed age difference in years.

b) Please provide information about the other characteristics of the patients i.e., proportion of female, weight and body surface area (BSA); what are their values in the population of England and Wales?

MSD response:

a)The National Oesophago-Gastric Cancer Audit 2022 reports the median age of patients diagnosed with oesophago-gastric (OG) cancer.(19) The relevant extract from this report is presented in Table 28.

Table 28. Deterministic Patient characteristics by type of OG tumour among patients diagnosed between April 2019 and March 2021 in England and Wales

Patient characteristic	Oes ACA Lower (w SI,SII)	Stomach (w SIII)
Median age, years	72	74
KEY: Oes – oesophageal, ACA – adenocarcinoma, SI, SII, SIII - Siewert classification of the gastro-oesophageal junction (GOJ)		

It is important to note that this report does not provide the median age of patients diagnosed with OG cancer that would be fit and eligible for first-line treatment. MSD considers it reasonable to expect that the total diagnosed population would have a higher median age. For the purpose of this appraisal, the focus should be on the population who are eligible to receive treatment.

As noted in the CS, although the clinical experts consulted by MSD confirmed that (based on the baseline patient characteristics in the KEYNOTE-859 trial) the trial participants were a few years younger than those treated in clinical practice, they did not consider that this would bias our results. We therefore consider the baseline characteristics of patients in KEYNOTE-859 to be broadly representative of patients who would be treated in practice. Also, in KEYNOTE-859, there is no evidence of a difference in treatment effect based on age: OS HR in the subgroup of patients <65 years of age and in the subgroup of patients ≥65 years of age was 0.73 (0.62 to 0.86) and 0.73 (0.59 to 0.89), respectively. Similarly, the TA857 committee concluded that there was no evidence treatment would be less effective in older people and treatment should be based on patient fitness and comorbidities, regardless of age.

The baseline age accepted by committee in TA857, calculated from Cancer Research UK, was 64.15 years, which is approximately 4 years older than participants who

enrolled in the KEYNOTE-859 trial. When 64.15 years of age is employed in the economic model, the revised base case ICER in the CPS≥1 population changes by less than 1% (from [redacted] to [redacted]).

b)The National Oesophago-Gastric Cancer Audit 2022 also reports the proportion of male patients diagnosed with OG cancer. The relevant extract from this report is presented in Table 29.

Table 29. Deterministic Patient characteristics by type of OG tumour among patients diagnosed between April 2019 and March 2021 in England and Wales

Patient characteristic	Oes ACA Lower (w SI,SII)	Stomach (w SIII)
Male, %	81%	66%
KEY: Oes – oesophageal, ACA – adenocarcinoma, SI, SII, SIII - Siewert classification of the gastro-oesophageal junction (GOJ)		

During the clarification stage, to inform our response to this question, MSD requested average BSA and weight data (for patients with metastatic gastric or GOJ adenocarcinoma before initiating first line treatment) from a large cancer centre in London. This cancer centre was able to confirm the following:

- BSA (Du Bois Method): mean, 1.73m^2; median, 1.74m^2; IQR, 1.57 - 1.84m^2
- Bodyweight: mean, 66.7kg; median 64.9kg; IQR, 53.8 - 74.5kg
- Female: 39.4%

The estimates provided by the cancer centre in London align closely with those obtained from the KEYNOTE-859 trial (see Table 30 in the CS). Also, results of OWSA demonstrate that gender, bodyweight and BSA are not key drivers of cost-effectiveness. For these reasons, the generalisability of patients in the KEYNOTE-859 trial to clinical practice should not be considered as an issue.

B 6. According to Section 3.2.2 of the CS (intervention technology and comparators), the pembrolizumab label also permits a 400 mg every 6 weeks dosing (page 85 CS) and this dosing regime is modelled in a scenario analysis. Please provide information about:

a) The adverse event (AE) rates of this alternative dosing schedule,

b) The preference of patients regarding the 200 mg every 3 weeks vs a 400 mg every 6 weeks dosing schedule, and

c) The expected preference of health care providers in England & Wales.

MSD response:

a)The EMA EPAR and SmPC for KEYTRUDA® (pembrolizumab) states the following on alternative dosing schedules, “Based on the modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg every 3 weeks, 2 mg/kg bw every 3 weeks, and 400 mg every 6 weeks.”(20)

The trial used to evaluate Q6W dosing is KEYNOTE-555 Cohort B; an open-label, clinical study in patients with metastatic melanoma. This trial has previously been compared with the EU Reference Safety Dataset (RSD) which represents the established safety profile of pembrolizumab monotherapy using the following dosing regimens:

- KEYNOTE-001: 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W
- KEYNOTE-006: 10 mg/kg Q3W and 10 mg/kg Q2W
- KEYNOTE-252: 200 mg Q3W
- EU RSD: pooled 2 mg/kg Q3W, 10 mg/kg Q3W, 10 mg/kg Q2W, and 200 mg Q3W

Overall, the types, incidence, and severity of AEs and adverse event of special interest (AEOSI) were similar across the 4 studies and the pembrolizumab EU RSD (Figure 34). No new safety concerns were identified. Pembrolizumab 400mg Q6W in KEYNOTE-555 Cohort B had a tolerable and manageable safety profile that was generally consistent with the reported safety data across the other studies and dose levels in participants with melanoma as well as the pembrolizumab EU RSD.

Mehta et al. 2023 retrospectively reviewed pembrolizumab prescribing for patients with melanoma across multiple UK centres to compare the safety of Q6W with Q3W in real-world clinical practice.(21) Toxicity outcomes were found to be broadly similar for Q6W and Q3W: 14.9% and 15.5% ≥ grade 3 Common Terminology Criteria for Adverse Events, respectively.

As per the KEYTRUDA® (pembrolizumab) SmPC, all currently approved adult indications have a recommended dose of pembrolizumab of either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

For these reasons, MSD is satisfied that AE rates for the Q3W dosing schedule can be used to inform a scenario using the Q6W dosing schedule.

Figure 34. Adverse Event Summary (Q6W versus EU RSD)

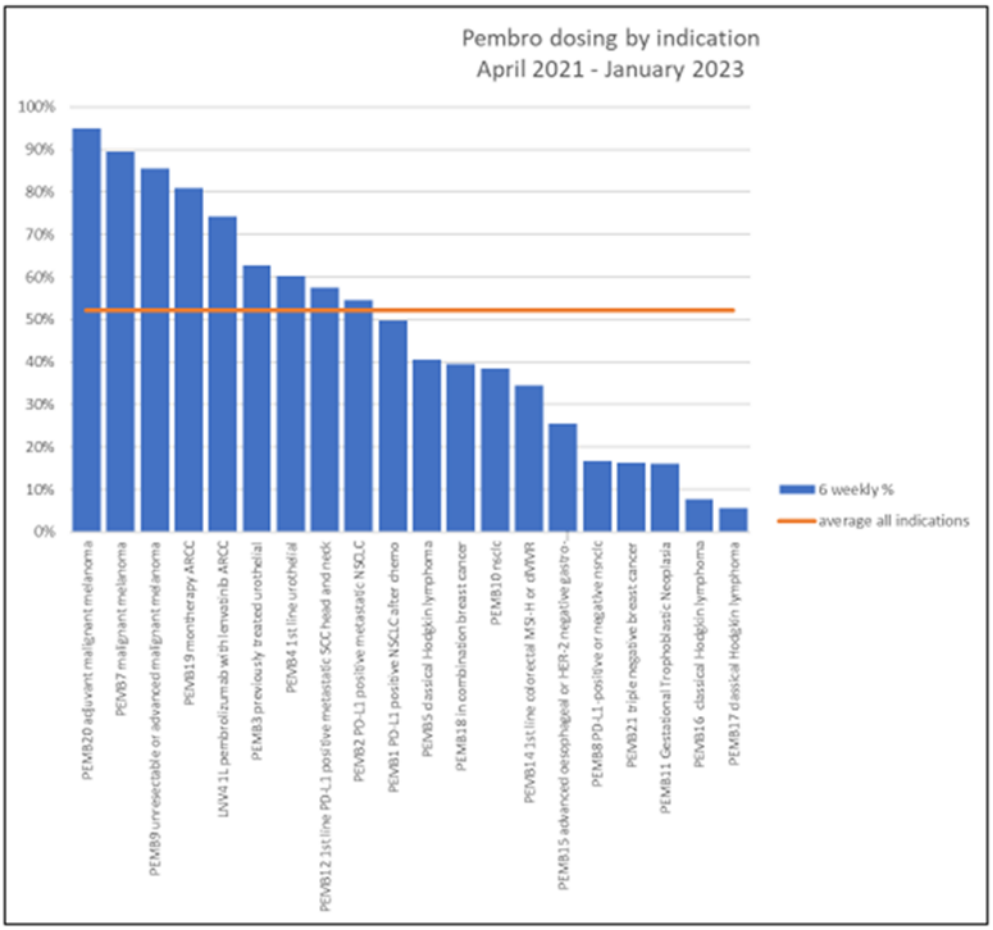
b)MSD expects that the majority of patients would prefer the Q6W dosing schedule due to a reduced number of in-patient visits associated with a Q6W dosing schedule versus a Q3W dosing schedule. No patient preference data is available to quantify the percentage of patients who would prefer this regimen.

c)MSD expects the preference of the healthcare providers within England and Wales will be for Q6W dosing, given the reduction in in-patient visits associated with this regimen.

The criteria listed in Blueteq forms generated by NHS England following recent NICE recommendations for pembrolizumab indications demonstrate that NHS England recommends the use of Q6W pembrolizumab whenever appropriate.(22) It is a requirement for all Providers to use Blueteq for these products/indications as there is no reimbursement without it having been completed. Thus, the proportion of Q6W usage is expected to be higher than Q3W in NHS practice.

Additionally, data from NHS England shows the usage of Q6W by indication (Figure 35). The data covers the period April 21- Jan 23; hence, for some indications there will have been an increase in the proportion of Q6W usage and therefore the slide will not necessarily reflect the higher (more-recent) usage. For some indications where NHS England has not expressed a preference on the Blueteq form (e.g. melanoma, due to the indication being approved prior to the introduction of Q6W dosing regimen and our understanding that NHS England does not routinely go back to earlier forms to update them unless there are pathway considerations), the level of Q6W usage was nevertheless very high.

Figure 35. NHS England data on pembrolizumab Q6W dosing



B 7. Page 113 contains the following sentence: “Based on their experience, the experts provided the proportion of patients they would expect to be progression free on doublet chemotherapy at 2 and 5 years (Table 43). The experts also noted that their estimates at 5 years would apply at 4 years”. Please clarify the meaning of the second sentence.

MSD response:

The experts were asked to provide PFS estimates at years 2 and 5. In their response, one expert expected the proportion of progression free patients at year 5 to be similar to year 4 (99% progressed).

B 8. In Table 46 of the CS, it appears that there is a mistake in the incidence rates of the treatment-specific AE data for the pembrolizumab column, as these are the same as in the doublet chemotherapy only column. Please confirm that this is indeed an error in the report, and that the values used in the model are correct.

MSD response:

The values in the model are correct. Table 46 of the CS is provided below, with corrected incidence rates.

Table 30. Grade 3+ treatment-specific AE data

Adverse event	Pembrolizumab plus doublet chemotherapy (N=785)		Doublet chemotherapy (N=787)		Nivolumab plus doublet chemotherapy (N=782)	
	Number of events	Incidence rate	Number of events	Incidence rate	Number of events	Incidence rate
Anaemia	69	8.8%	59	7.5%	47	6.0%
Neutropenia	82	10.4%	78	9.9%	118	15.1%
Diarrhoea	51	6.5%	40	5.1%	35	4.5%
Vomiting	39	5.0%	34	4.3%	17	2.2%
Fatigue	29	3.7%	34	4.3%	30	3.8%
Nausea	28	3.6%	31	3.9%	20	2.6%
Hypokalaemia	30	3.8%	24	3.0%	0	0.0%
Palmar-plantar erythrodysaesthesia syndrome	25	3.2%	14	1.8%	11	1.4%
Neuropathy peripheral	10	1.3%	25	3.2%	31	4.0%
Source: Table 6 of the HTA HECON Safety report						

B 9. In section 3.3.6 it is remarked that AE incidence rates and types are not dependent on CPS level. Please justify this claim.

MSD response:

Because pembrolizumab modulates PD-1/PD-L1 pathways, CPS expression is an important treatment effect modifier. There is no evidence or clinical rationale to suggest CPS expression modifies AE incidence rates. Also, the incidence rates across the ITT, CPS≥1 and CPS≥10 populations are similar and do not consistently decrease or increase from the ITT population to the CPS≥10 population. The highest incidence rates observed for each AE and treatment arm are highlighted in bold in Table 31 and occur across the three populations.

Table 31. Grade 3+ treatment-specific AE incidence rates according to population

	ITT	CPS≥1	CPS≥10

Adverse event	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy
Anaemia	8.2%	6.5%	8.0%	**7.0%**	**10.0%**	5.9%
Neutropenia	**7.0%**	**7.6%**	6.0%	7.0%	6.8%	7.4%
Diarrhoea	5.9%	4.7%	**6.3%**	**4.9%**	5.7%	4.8%
Vomiting	4.5%	**4.07%**	**4.6%**	3.7%	4.3%	4.06%
Fatigue	3.4%	**4.1%**	3.1%	3.7%	**3.6%**	3.0%
Nausea	3.3%	**3.7%**	3.7%	3.4%	**4.7%**	3.3%
Hypokalaemia	3.3%	2.3%	4.1%	2.1%	**6.8%**	**2.6%**
Palmar-plantar erythrodysaesthesia syndrome	3.1%	**1.8%**	3.6%	1.3%	**5.0%**	1.5%
Neuropathy peripheral	1.3%	**3.2%**	**1.6%**	2.9%	0.7%	3.0%
Source: Tables 6, 14 and 22 of the HTA HECON Safety report						

Health-related quality of life

B 10. Priority question: On page 128 of the CS, the company provides a rationale for not using a repeated measures adjustment and refer to a publication by Hickey 2018. However, it is not clear where in that paper the suggestion is made that no linear mixed model should be used for unbalanced longitudinal data.

a) Please clarify how this can be concluded from the cited paper.

b) Please provide results based on an analysis using a linear mixed model that accounts for the correlations between within-patient measurements.

MSD response:

a)The publication by Hickey has not been cited to rule out the use of a linear mixed model for unbalanced longitudinal data. As per the text in CS page 128, the paper points out that it is not appropriate to adjust for repeated measures in circumstances where the number of measures available per subject may be correlated with the value

of the measure of interest e.g. that a higher number of utility measures is associated with a higher utility value.

In the case of oncology trials, however, a number of correlations are typically present. For instance, compared to trial subjects with multiple measurements, subjects with only a single measurement for a given health state are more likely to have:

- Died shortly after the measurement (e.g. from progression-free state)
- Transitioned to another worse health state (e.g. from time-to-death 30-180 days to time-to-death <30 days)
- Relatively lower utilities within the health state than patients with repeated utility assessments, due to:
    - Being near to the point of transition to a worse health state
    - Having older age, greater comorbidities, worse functional status, etc. which correlates with, or contributes to, the transition.

b)The requested analysis was conducted in R. Specification of the software system and libraries to execute the analysis are provided below.

System	Specification
platform	x86_64-w64-mingw32
arch	x86_64
os	mingw32
crt	ucrt
system	x86_64, mingw32
status	
major	4
minor	2.2
year	2022
month	10
day	31
svn rev	83211
language	R
version.string	R version 4.2.2 (2022-10-31 ucrt)
nickname	Innocent and Trusting

Package	Version
officer	0.4.1
haven	2.5.1
lmerTest	3.1.3
dplyr	1.0.10
ggplot2	3.4.0
bshazard	1.1
lsmeans	2.30.0
flextable	0.6.10
stringr	1.4.1
reshape2	1.4.4

The analysis output for the CPS≥1 population is provided in Figure 36 and

Figure 37, and included in the economic model as an executable option ('Utility'D16). If this option is selected, the revised base case ICER changes by less than 1% (from [redacted] to [redacted]). Thus, the decision to use a descriptive analysis or regression analysis has no meaningful impact on the cost-effectiveness results. Equivalent output for the CPS≥10 population can be found in

Figure 38 and Figure 39. Due to time constraints, the analysis for the CPS≥10 population has not been implemented in the economic model.

Figure 36. Utility regression analysis: CPS≥1 population (covariance matrix)

Figure 37. Utility regression analysis: CPS≥1 population (regression model)

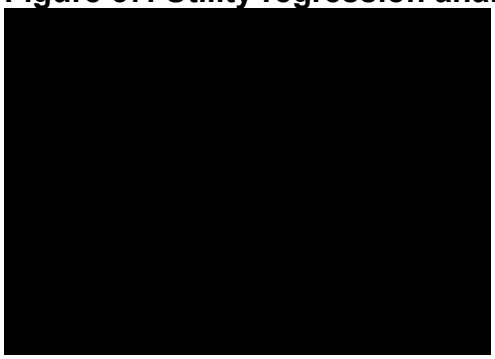


Figure 38. Utility regression analysis: CPS≥10 population (covariance matrix)

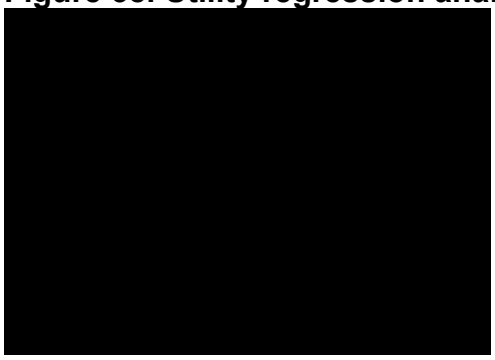


Figure 39. Utility regression analysis: CPS≥10 population (regression model)

B 11. Priority question: Regarding Table 52 of the CS:

a) **Please provide the number of observations (per treatment arm) of EQ-5D-5L questionnaires administered during an AE and not during an AE, the mean utility in each group, and the 95% confidence interval for the disutilities reported.**

b) **Please provide an explanation for the relatively large difference between the disutility values of pembrolizumab plus doublet chemotherapy vs. doublet chemotherapy in the CPS≥1 population, especially given that both treatment arms receive doublet chemotherapy.**

c) **Please elaborate on why the disutility values as used in TA857 are systematically higher than the disutility for the pembrolizumab + doublet chemotherapy arm.**

MSD response:

a)This data can be found in Tables 74 and 118 of the MSD Keytruda (MK-3475) KN859 HTA PRO report (see attached reference in response to CQ B2)

b)Differences between the treatment arms are observed in the overall population, CPS≥1 population and CPS≥10 population, as shown in Table 32.

The disutility value could be lower in the pembrolizumab plus doublet chemotherapy arm than the doublet chemotherapy arm as the disutility encompasses all types of

Grade 3+ AEs and the incidence rate of each type of Grade 3+ AEs is not the same in both treatment arms. For example, peripheral neuropathy has a higher incidence in the doublet chemotherapy arm and may impact mobility and the ability to carry out usual activities more than other types of AEs, thus impacting the patient response and hence disutility.

Table 32. AE disutility data

Population	KEYNOTE-859 Data	Mean utility	Disutility
Overall population	During G3+ AE PEM + CHEMO	[redacted]	[redacted]
	Without G3+ AE PEM + CHEMO	[redacted]	
	During G3+ AE CHEMO	[redacted]	[redacted]
	Without G3+ AE CHEMO	[redacted]	
	During G3+ AE Pooled	[redacted]	[redacted]
	Without G3+ AE Pooled	[redacted]	
CPS≥1	During G3+ AE PEM + CHEMO	[redacted]	[redacted]
	Without G3+ AE PEM + CHEMO	[redacted]	
	During G3+ AE CHEMO	[redacted]	[redacted]
	Without G3+ AE CHEMO	[redacted]	
	During G3+ AE Pooled	[redacted]	[redacted]
	Without G3+ AE Pooled	[redacted]	
CPS≥10	During G3+ AE PEM + CHEMO	[redacted]	[redacted]
	Without G3+ AE PEM + CHEMO	[redacted]	
	During G3+ AE CHEMO	[redacted]	[redacted]
	Without G3+ AE CHEMO	[redacted]	
	During G3+ AE Pooled	[redacted]	[redacted]
	Without G3+ AE Pooled	[redacted]	
Source: Tables 74 and 118 of the HTA HECON PRO report			

The treatment-specific disutility values due to AEs from the KEYNOTE-859 trial reported in Table 52 are included in the economic model but do not inform the base case analysis. Pooled disutility values due to AEs from the KEYNOTE-859 trial are used to inform the base case, which is a conservative approach. MSD acknowledges the CS could be clearer on this point. For clarity, the disutility values due to AEs applied in the base case are provided in Table 33 below. In the economic model, see 'Adverse Events'E159:J169.

When treatment-specific AE disutility values are employed (the values from the KEYNOTE-859 trial in Table 52 of the CS), the ICER in the CPS≥1 population falls from [redacted] to [redacted].

Table 33. AE disutility data applied in the CS base case

Adverse event	Disutility		
	CPS≥1		CPS≥10
	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy	Pembrolizumab plus doublet chemotherapy*
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Palmar-plantar	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Source: Tables 74 and 118 of the HTA HECON PRO report *Nivolumab plus doublet chemotherapy disutility assumed to equal pembrolizumab plus doublet chemotherapy			

c)The disutility values obtained from TA857 came from a number of published studies which used different methods to measure and value health states:

- Swinburn *et al.* 2010(23) - health states in metastatic RCC were developed with clinicians and valued by the public using the TTO method
- Doyle *et al.* 2008(24) - health states in advanced NSCLC were developed by clinicians and valued by the public using the SG method
- Lloyd *et al.* 2006(25) - health states in metastatic breast cancer were developed with clinicians and valued by the public using the SG method
- Nafees *et al*. 2008(26) - health states in metastatic NSCLC were developed with clinicians and valued by the public using the SG method
- Tolley *et al.* 2013(27) - health states in chronic lymphocytic leukaemia were developed with clinicians and valued by the public using the TTO method

In these studies, health states including toxicities/AEs could be described using language which may lead the public valuing the health state to value it less than a patient with the condition experiencing the AE. Also, none of the studies focussed on

a population with advanced gastric/GOJ cancer. However, MSD cannot say with certainty these are the reasons why the disutility values from the KEYNOTE-859 trial are smaller than the aforementioned studies.

As shown in Tables 78 and 79 of the CS, changing the disutility source in the economic model from KEYNOTE-859 to TA857 changes the base case ICER by less than 1% in each population. As such, MSD does not consider the AE disutility value source to be a model driver.

B 12. For the compliance percentages for the EuroQol-5 Dimension 5 levels (EQ-5D-5L) reported in Table 47:

a) Please clarify how “among those who are expected to complete the questionnaire” is defined.

b) Please provide the number of patients that were expected to respond and those that did respond for each time point and for both CPS≥1 and CPS≥10.

MSD response:

a) Trial participants expected to complete the EQ-5D-5L questionnaire are those who are not missing by design such as death, discontinuation, translation not available.

b) This data can be found in Tables 14.2-93 to -94 (pages 880 to 936) of the CSR.

B 13. For page 130 of the CS, please clarify the rationale for the pre-specified time intervals as used across MSD trials i.e., why have these exact 4 intervals been defined, rather than for instance a range of monthly intervals.

MSD response:

In the absence of specific external evidence to justify an alternative set of time-to-death intervals for utility analysis, MSD aim for consistency in specifying the intervals. In previous trials, analysis results have generally revealed there to be a differentiation in health utility values between these different intervals (lower utilities for each successive interval closer to death), suggesting they differentiate from one another in measuring patient health utility. Furthermore, maintaining a consistent approach

avoids potential concerns around ‘cherry picking’ an alternative set of intervals within a given trial, to derive utility values associated with the lowest ICER.

B 14. On page 133 of the CS, the company compares the observed utility score for the progressed health state to the utility values found in the systematic literature review, and notes that the values from the KEYNOTE-859 trial [redacted]. Please provide a rationale for this difference, if possible.

MSD response:

MSD cannot state with certainty a rationale for the difference in progressed disease health state utility values between that elicited from the KEYNOTE-859 participants and those reported in the literature (presented in NICE TA179, which was published in 2009). However, it is important to note that the value reported in the current submission was elicited directly from participants receiving the study treatments using the nominated EQ-5D instrument and mapped to 3L values using the approved algorithm, in accordance with the reference case. In contrast, the TA179 values were reported by patients in a trial of a tyrosine kinase inhibitor (sunitinib) for a different cancer type, gastrointestinal stromal tumours. Furthermore, treatment practices have evolved over time since the reporting of the previous values. The impact of this is uncertain.

B 15. Regarding Table 53 of the CS:

a) Please provide the number of observations/sample size for each AE on which the estimated duration is based, plus the 95% confidence intervals.

b) Please provide some clinical reasoning on why differences in adverse event duration indeed exist between the two different interventions.

c) Please provide the pooled estimates of AE durations and incorporate these as a scenario or base case in the Excel model.

MSD response:

a)This data can be found in Table 6 of the MSD Keytruda (MK-3475) KN859 HTA Safety report (see attached reference in response to CQ B2)

b)MSD cannot provide with certainty a rationale why the AE duration would differ between the treatment arms.

c)The base case has been revised to employ pooled estimates of AE durations. Pooled AE durations are presented alongside treatment-specific durations in Table 34.

Table 34. Pooled estimates of AE durations applied in the revised base case

Adverse event	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy	Pooled
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]
Source: Table 6 of the HTA HECON Safety report			

Costs

B 16. Page 147 states that the overall cost for the resource use estimates for progressed disease lie somewhere in between the two sources, TA857/TA208/CG81 and the Gomez-Ulloa paper. Please clarify how this information is implemented in the model.

MSD response:

Clinical experts consulted by MSD were asked which source (TA857/TA208/CG81 or the Gomez-Ulloa paper) best reflects disease management in clinical practice. Their responses to this question could not be implemented as a scenario in the economic model without making additional assumptions. Structured expert elicitation, to identify a consensus judgment on the model inputs to inform a scenario, was not undertaken as health state costs are not a key driver in the economic model.

As shown in Tables 78 and 79 of the CS, changing the source in the economic model from TA857/TA208/CG81 to the Gomez-Ulloa paper changes the base case ICER by

less than 2% in each population. If the average cost per week estimated from these two sources (£38.23 and £115.33) is applied in the economic model (£76.78) the ICER changes by less than 1% (from [redacted] to [redacted], and from [redacted] to [redacted] in the CPS≥1 and CPS≥10 populations, respectively).

Uncertainty results

B 17. Regarding section 3.11, could you please clarify if the quality-adjusted life years (QALYs) presented in the sensitivity analysis results are weighted for the severity modifier. And if so, please clarify which weights have been used.

MSD response:

For the CPS≥1 population, the comparison with doublet chemotherapy employs a severity modifier of 1.7 in all sensitivity analysis, except for one scenario reported in Tables 78 and 80 of the CS, which employs a severity modifier of 1.2. The total QALYs and incremental QALYs in Table 74 (PSA results) for the CPS≥1 population include a severity modifier of 1.7.

For the CPS≥10 population, the comparison with nivolumab plus doublet chemotherapy employs a severity modifier of 1.0 in all sensitivity analysis. The total QALYs and incremental QALYs in Table 74 (PSA results) for the CPS≥10 population include a severity modifier of 1.0.

QALYs with and without the severity modifier have been made more explicit in the Tables reporting the revised base case (see Table 18 to Table 21).

Results can be generated using alternative QALY weights by amending the user defined QALY weight in 'Model Setup'I79. The severity modifier applied in PSA does not vary as this employs the user defined QALY weight. If the user defined value is removed the severity modifier can be dynamic in PSA.

Excel model

B 18. If the model is set to include treatment waning, on the worksheet OS, column BE, the last value before 0% starts may be negative, with larger negative values

if the duration of waning is smaller. Please check if this is an error and if so, please provide a corrected version of the model.

MSD response:

MSD has identified the described error and corrected it by amending the time measurement from months to weeks. The revised economic model and scenario analysis results in Table 20 include this correction.

Section C: Textual clarification and additional points

C 1. Priority question: Regarding the references cited in the CS and the related appendices,

a) **Please provide all references (as the number of references provided alongside the CS is lower than the number of references cited in the submission documents) and**

b) **Explain the term *"Uncategorized References"* (used in the document B of the CS)**

MSD response:

References have been provided separately.

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NICE 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]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	**David Chuter**
2. Name of organisation	Together OG Support Group
3. Job title or position	Chai
4a. Brief description of the organisation (including who funds it). How many members does it have?	OG cancer support group network, supporting and offering information for all Oesophageal-gastric cancer patients. Membership is currently at 178, a mix of patients, caregivers and family members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No
4c. Do you have any direct or indirect links	No

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	At support group meetings, a mix of both virtual and face to face, also by email when needed.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It is a difficult time for both patient and caregiver, as the option of curative surgery is not there so they are looking for best treatment available. Swallowing and eating can be an issue and often stents are used which are not aways successful and can cause other issues. Some patients will need to be J tube feed as the cancer progresses.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers often have no other choice to the current treatment if there are no studies being carried out at the treatment centre, but as nearly all are able to look online, they are more likely to ask about a trial. So patients and carers are looking for more than the current treatment to have a chance of longer survival and better QoL.
8. Is there an unmet need for patients with this condition?	Yes there is, especially with the younger patients we are seeing being diagnosed at a later stage.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	New technology is being proven all the time with treating cancer and are looking for the treatment that gives them a longer outcome or survivorship. At the moment there is not much choice with treatment, patients and carers will be looking for options and will be asking about new technology.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	With any new treatment, there may be side effects that can reduce the patient's quality of life, as long as the side effects are known by the patient then an informed decision can be made. Patient's treatment choice is a big part of the journey.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This will certainly benefit the younger patients as will be fitter and healthier to be able to cope with the treatment. Older patients will still benefit from this treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.

Other issues

13. Are there any other issues that you would like the committee to consider?	No

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• New technology. • New treatment • Better outcomes. • Will benefit younger patients. • Will give patients hope.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE 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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with **HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma** or caring for a patient with **HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma**. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

NICE National Institute for Health and Care Excellence

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

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

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma

Table 1 About you, HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma, current treatments and equality

1. Your name	Ceri Steele
2. Are you (please tick all that apply)	☐ A patient with HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma? ☐ A patient organisation employee or volunteer? x Other (please specify): Squamous cell oesophageal cancer survivor (don't know if HER2 negative)
3. Name of your nominating organisation	Together Support Group
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) x Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations

Patient expert statement

	submission ☐ I agree with it and **do not wish to** complete this statement x I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	x I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma? **If you are a carer (for someone with HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma) please share your experience of caring for them**	I didn't have HER2 negative gastro-oesophageal junction adenocarcinoma but had squamous cell carcinoma (unknown if HER2 negative) – treatment for adenocarcinoma and squamous cell carcinoma are comparable – I had chemo and radiotherapy followed by surgery – during my treatment, I was lucky enough to have employers who were very understanding and allowed me to have time out – I had to rely a lot on my family to take me to many of my treatment cycles, which involved them rearranging their working lives too – my quality of life, especially towards the end of the radiotherapy, wasn't great due to the demands made of my body
7a. What do you think of the current treatments and care available for HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	a. Treatment is only aimed as being primarily palliative and side effects can affect quality of life to quite a large degree b. I don't know

8. If there are disadvantages for patients of current NHS treatments for HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	If taken in tablet form, this can present difficulties - swallowing is impaired (a common symptom of OC)
9a. If there are advantages of pembrolizumab with chemotherapy over current treatments on the NHS, please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does pembrolizumab with chemotherapy help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Don't know
10. If there are disadvantages of pembrolizumab with chemotherapy over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab with chemotherapy? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Don't know
11. Are there any groups of patients who might benefit more from pembrolizumab with chemotherapy or any who may benefit less? If so, please describe them and explain why?	OC is presenting in increasing numbers of younger people, and due to its symptoms being relatively nebulous until later stages, any improvement in treatment is welcome.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering HER2 negative advanced gastric or gastro-oesophageal junction adenocarcinoma and pembrolizumab with chemotherapy? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	No
13. Are there any other issues that you would like the committee to consider?	The lack of advance in survival rates for oesophageal cancer means it is imperative to find effective treatments with manageable side effects

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Survival rates need to be improved for OC
- Oesophageal cancer is presenting more frequency at a younger age
- Quality of life is also an important factor
- Delivery method should take into account that one of main side effects is loss of swallow
-

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

Produced by Kleijnen Systematic Reviews (KSR) Ltd., in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rider on responsibility for report

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

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Contributions of authors

Huiqin Yang acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Eline Krijkamp and Venetia Qendri acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Xiaoyu Tian and Nigel Armstrong acted as systematic reviewers as well as health economists on this assessment. Robert Wolff critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike information criterion
APaT	All participants as treated
ASCO	American Society of Clinical Oncology
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BID	Twice daily
BNF	British National Formulary
BPI	Brief Pain Inventory
BSA	Body surface area
CAA	Commercial Access Agreement
CADTH	Canadian Agency for Drugs and Technologies
CAP	Capecitabine
CAPOX	Capecitabine and oxaliplatin
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Clinical Guideline
CHEMO	Chemotherapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIS	Cisplatin
COVID-19	Coronavirus disease 2019
CPS	Combined positive score
CR	Complete response
CRD	Centre for Reviews and Dissemination
Crl	Credible interval
CS	Company submission
CSR	Clinical Study Report
CT	Computed tomography
DMC	Data Monitoring Committee
DOR	Duration of response
DP	Disease progression
DSA	Deterministic sensitivity analyses
DSU	Disease Support Unit
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC QLQ-C30	European Organization For Research And Treatment Of Cancer Core Quality of Life questionnaire
EORTC QLQ-STO22	European Organization For Research And Treatment Of Cancer Quality of Life Questionnaire – Gastric Cancer Module
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life-5 dimensions-5 levels
ESHPM	Erasmus School of Health Policy & Management
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-Ga	Functional Assessment of Cancer Therapy – Gastric Cancer
FAD	Final Appraisal Determination
FAS	Full analysis set

FOLFOX	Folinic acid, fluorouracil and oxaliplatin
FP	Cisplatin + fluorouracil
5-FU	5-fluorouracil
GB	Great Britain
GC	Gastric cancer
GEJ	Gastroesophageal junction
GOJ	Gastro-oesophageal junction
H1	Hypothesis 1
H3	Hypothesis 3
HER-2	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
HR	Hazard ratio
HTA	Health Technology Assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
iDBC	Disease Burden Calculator
iMTA	Institute for Medical Technology Assessment
IO	Immune oncology
IPD	Individual Patient Data
IPI	Ipilimumab
IQR	Interquartile range
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LS	Least sum
LY	Life years
LYG	Life years gained
M&N	Stratified Miettinen and Nurminen method
MHRA	Medicines and Healthcare Products Regulatory Agency
MSD	Merck Sharp and Dohme
MSI	Microsatellite instability
MUGA	Multiple-gated acquisition
NHB	Net-health benefits
NHS	National Health Service
NHSCII	National Health Service Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIVO	Nivolumab
NL	Netherlands
NMA	Network meta-analysis
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
OX	Oxaliplatin
PD	Progressed disease
PD-L1	Programmed cell death ligand 1
PEMBRO	Pembrolizumab
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazard
PR	Partial response

PRESS	Peer Review of Electronic Search Strategies
PRO	Patient reported outcomes
PS	Performance Status
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY	Quality-adjusted life year
QoL	Quality of life
OS	Overall survival
Q1	25th percentile
Q3	75th percentile
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
RR	Response rate
SAEs	Serious adverse events
SD	Stable disease
SD	Standard deviation
SE	Standard error
SF-12	Short Form 12 Health Survey Questionnaire
SF-36	Short Form 36 Health Survey Questionnaire
SR	Systematic review
STA	Single Technology Appraisal
TA	Technology Appraisal
ToT	Time on treatment
TRAE	Treatment-related adverse events
Tx	Treatment
UK	United Kingdom
VAS	Visual analogue scale
WTP	Willingness-to-pay
XP	Cisplatin + capecitabine

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the Evidence Assessment Group (EAG) as being potentially important for decision making. If possible, it also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relates to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. A summary is presented in Section 1.6.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main EAG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID4030	Summary of issue	Report Sections
1	It is unclear whether the assumption of exchangeability for the purpose of ITC analysis for the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations is met.	Section 3.2 Section 3.3 Section 3.4
2	The rejection of the proportional hazards assumption for OS in patients with PD-L1 CPS ≥1 and those 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 ITC where constant HRs were presented.	Section 3.4
3	There is uncertainty on long term OS and the treatment effect of pembrolizumab plus chemotherapy versus chemotherapy from the KEYNOTE-859 trial. More mature data from the KEYNOTE-859 trial are not available yet.	Section 3.2 Section 3.3
4	Insufficient evidence regarding the duration of the pembrolizumab treatment effect	Section 4.2.6.2
5	Limiting duration of chemotherapies to 6 cycles likely to influence OS and PFS.	Section 4.2.6.5
6	QALY weight for patients expressing CPS ≥1	Section 4.2.10

CPS = combined positive score; HR = hazard ratio; ITC = indirect treatment comparison; OS = overall survival; PD-L1 = programmed death ligand 1; PFS – progression-free survival; QALY = quality-adjusted life year

1.2 Overview of key model outcomes

A NICE Technology Appraisal (TA) compares how much a new technology improves length (overall survival) and quality of life (QoL) in a quality-adjusted life year (QALY) compared to the available alternatives. An ICER is the ratio of the extra cost for every QALY gained.

Overall, treatment with pembrolizumab plus doublet chemotherapy is modelled to affect QALYs in the combined positive score (CPS) ≥1 population by:

- Delaying disease progression (DP), thus maintaining a good QoL for longer
- Extending life

For patients expressing a CPS ≥10, the impact on QALYs due to pembrolizumab plus chemotherapy treatment is fairly limited as its comparator in this population, which is nivolumab immunotherapy plus chemotherapy, has a similar mode of action.

Overall, treatment with pembrolizumab plus doublet chemotherapy is modelled to affect costs mostly by its higher price per treatment cycle, causing the total costs to increase.

The modelling assumptions that have the greatest effect on the ICER are, for the patients expressing a CPS ≥1:

- The duration that the treatment effect will remain present after discontinuing treatment with pembrolizumab after 35 cycles.
- The severity weight applied to the QALY gain.
- Potentially, but not quantified, the duration of time-on-treatment (ToT) for the various chemotherapies in relation to overall survival (OS) and progression-free survival (PFS).
- The cost and (potentially impact on survival and PFS) of subsequent treatments.

For patients expressing a CPS ≥10 this is:

- The comparative effectiveness between pembrolizumab and nivolumab, which was derived from a network meta-analysis (NMA) in the absence of head-to-head trial data.
- The duration that the treatment effect will remain present after discontinuing treatment with pembrolizumab and nivolumab after 35 cycles, and what the OS and PFS will be once the effect of these treatments has completely waned.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there were no relevant data on the subgroup of patients with programmed cell death ligand 1 (PD-L1) CPS ≥5 in the CS. Therefore, the CS did not address the NICE scope relating to this subgroup (see Table 1.2).

Table 1.2: Key issue 1: Lack of evidence on the subgroup of PD-L1 CPS ≥5 in the CS

Report Sections	**2.3, 3.2, 3.3, and 3.4**
Description of issue and why the EAG has identified it as important	The NICE final scope specified the subgroup of patients with PD-L1 CPS ≥5 for the comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy for the locally advanced metastatic gastric or gastro-oesophageal junction adenocarcinoma patients with PD-L1 CPS ≥5. However, there were no data relating to the subgroup of PD-L1 CPS ≥5 in the CS. Therefore, the CS did not address the NICE scope relating to this subgroup. The CS states that an ITC in patients with PD-L1 CPS ≥5 was not conducted at the time of evidence submission because the KEYNOTE-859 trial did not have PD-L1 CPS ≥5 as a prespecified subgroup. The EAG requested an ITC for the comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy to be carried out for the PD-L1 CPS ≥5 population.
What alternative approach has the EAG suggested?	An ITC analysis for the comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy should be conducted for the PD-L1 CPS ≥5 population.

Report Sections	2.3, 3.2, 3.3, and 3.4
What is the expected effect on the cost effectiveness estimates?	Cost effectiveness analysis should be conducted for the PD-L1 CPS ≥5 population when relevant data are available.
What additional evidence or analyses might help to resolve this key issue?	In responding to EAG's request, the company provided an additional analysis of ITC for the subgroup of patients with PD-L1 CPS ≥5 for the comparison between pembrolizumab plus chemotherapy and nivolumab plus hemotherapy between the two trials (KEYNOTE-859 and CheckMate-649). The company has conducted a post-hoc analysis for the subgroup of patients with PD-L1 CPS ≥5 of the KEYNOTE-859 trial at the clarification stage following EAG's request, which made the ITC analysis feasible for this subgroup. The additional analysis of ITC showed that the results of the analysis for patients with PD-L1 CPS ≥5 were consistent with those results of the analysis for patients with PD-L1 CPS ≥1 and patients with PD-L1 CPS ≥10.
CPS = combined positive score; CS = company submission; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death ligand 1	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

A full summary of the clinical effectiveness evidence review conclusions can be found in Section 3.6 of this report. The EAG identified two major concerns with the evidence presented on the clinical effectiveness: the lack of evidence for assessing the comparability of the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations between the two trials included in the indirect treatment comparison (ITC) analysis (see Table 1.3) and the lack of consistency between the violation of proportional hazard assumptions for OS in the PD-L1 CPS ≥1 and PD-L1 CPS ≥5 populations and the approach used for the base-case analysis of ITC (see Table 1.4).

Table 1.3: Key issue 2: Lack of evidence for the assessment of comparability of the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations between the two trials included in the ITC analysis

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The company did not provide a comparison of baseline characteristics for the two subgroups of patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 from the two trials (KEYNOTE-859 and CheckMate-649) in the CS. It is unclear whether the baseline characteristics of patients with PD-L1 CPS ≥1 and those with PD-L1 CPS ≥10 from the two included trials are similar. The EAG requested data on the comparison of baseline characteristics for the subgroups of patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 between the two trials. In responding to EAG's request, the company stated that because the baseline characteristics for patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 were not reported in any of the publications associated with the CheckMate-649 trial, a comparison of baseline characteristics in these subgroups between the two trials was not feasible. Therefore, it is unclear whether the assumption of exchangeability for the purpose of ITC for the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations is met.

Report Sections	3.3 and 3.4
What alternative approach has the EAG suggested?	The feasibility assessment for the populations in the scope of ITC (PD-L1 CPS ≥1 and CPS ≥10 CPS populations) should be conducted where data are available.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The EAG recommends the comparison of baseline characteristics for the PD-L1 CPS≥1 and PD-L1 CPS ≥10 populations between the two trials included in the ITC, where data are available. The EAG recognises the lack of evidence on the baseline characteristics of the CheckMate-649 trial.
CPS = combined positive score; EAG = Evidence Assessment Group; ITC = indirect treatment comparison; PD-L1 = programmed death ligand 1	

Table 1.4: Key issue 3: Lack of consistency between the violation of proportional hazards assumptions for OS in the PD-L1 CPS≥1 and PD-L1 CPS≥5 populations and the approach used for the base-case analysis of the ITC

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	There was evidence to reject the proportional hazards assumption for OS in patients with PD-L1 CPS ≥1 and those patients with PD-L1 CPS ≥5 in the KEYNOTE-859 trial.The rejection of the proportional hazards assumption for OS in patients with PD-L1 CPS ≥1 and those 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 ITC where constant hazard ratios (HRs) were presented. Given that the proportional hazards assumptions for OS in these two subgroups of the KEYNOTE-859 trial may not be valid, the EAG considers that the time-varying method seems to be the more valid approach for the base-case analysis of ITC. However, constant HRs for OS were used in the base-case analysis of ITC for patients with PD-L1 CPS ≥1 and those patients with PD-L1 CPS ≥5, this may have compromised the validity of the results.
What alternative approach has the EAG suggested?	The company must provide full details of justification on whether the method used in the ITC was supported by underlying proportional hazards assumptions.
What is the expected effect on the cost effectiveness estimates?	The effect on the cost effectiveness estimates is difficult to predict.
What additional evidence or analyses might help to resolve this key issue?	The company should provide full details of the rationale/justification. A time varying method (such as the polynomial fractional method) of conducting the ITC should be employed.
CPS = combined positive score; EAG = Evidence Assessment Group; HR = hazard ratio; ITC = indirect treatment comparison; OS = overall survival; PD-L1 = programmed death ligand 1	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 6, the EAG's summary

and detailed critique in Section 5, and the EAG's amendments to the company's model and results are presented in Section 6. For patients expressing CPS≥1, the main EAG's results throughout this report are produced while accounting for a simple discount of [redacted] for pembrolizumab treatment as included in the original CS. For patients expressing CPS≥10, the EAG's results throughout this report are produced while using the list prices of pembrolizumab and nivolumab treatments. The main EAG's results for both populations are reproduced using confidential patient access schemes for other treatments in the comparator lists (i.e., for nivolumab and treatments included in doublet chemotherapy) and respective results are included in a confidential appendix.

The key issues in the cost effectiveness evidence part of the appraisal are discussed in Tables 1.5 to Table 1.7.

Table 1.5: Key issue 4: Insufficient evidence regarding the duration of the pembrolizumab treatment effect

Report Section	**4.2.6.2**
Description of issue and why the EAG has identified it as important	The EAG does not agree with the company's assumption that patients receiving pembrolizumab treatment will receive a lifetime ongoing benefit following treatment cessation. The EAG thinks that the currently available data do not substantiate this assumption.
What alternative approach has the EAG suggested?	The EAG limited the duration of the treatment effect to 5 years with a gradual treatment waning over the two subsequent years, in which period the hazard in each cycle of pembrolizumab treatment eventually becomes equal to that of the doublet chemotherapy arm.
What is the expected effect on the cost effectiveness estimates?	For patients expressing CPS≥1, incorporating a treatment waning impact for pembrolizumab treatment increased the ICER to [redacted] per QALY gained from the company base-case of [redacted] per QALY gained after clarification phase. For patients expressing CPS≥10, the company's ICER increased from [redacted] (after the clarification phase) to [redacted] per QALY gained. When applying the company's scenario for treatment waning, where waning does not start until 7 years from treatment initiation, the ICERs become [redacted] and [redacted] for CPS≥1 and CPS≥10, respectively.
What additional evidence or analyses might help to resolve this key issue?	This issue might be (partially) resolved if longer-term follow-up data from KEYNOTE-859 and other IO treatments become available.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; IO = immune oncology; OS = overall survival; QALY = quality-adjusted life year	

Table 1.6: Key issue 5: Limiting duration of chemotherapies to 6 cycles likely to influence OS and PFS

Report Section	**4.2.6.5**
Description of issue and why the EAG has identified it as important	In the KEYNOTE-859 trial the treatment with cisplatin or oxaliplatin could be capped at 6 cycles per local standard. From the observed data, it is clear that around 50% of patients were longer on treatment than 18 weeks (6 cycles * 3 weeks). Within the NHS, these treatments are capped at 6 cycles, and thus, for the base-case analysis, the company included a stopping rule so that no patient receives cisplatin or oxaliplatin. However, this is

Report Section	4.2.6.5
	likely to impact the OS and PFS that were used in the model. Thus, in the current base-case, the true LYs and QALYs are likely to be overestimated, in turn also influencing the total costs per treatment arm.
What alternative approach has the EAG suggested?	At this point in time, it seems plausible that an OS and PFS curve should be used that are less favourable that those currently used. However, it is completely unclear how strong the impact of prolonged use of cisplatin and oxaliplatin is on OS and PFS, so any alternative curve would be highly speculative.
What is the expected effect on the cost effectiveness estimates?	Adjusting the OS and PFS in both groups slightly downwards is likely to have some effect on the ICER, but as these chemotherapies are given in both treatment arms, it is difficult to predict what the net-effect will be on the ICER.
What additional evidence or analyses might help to resolve this key issue?	There are two potential approaches that might help to resolve this issue to some extent. First, it might be possible to find a subpopulation in the KEYNOTE-859 data from jurisdictions where chemo was limited to 6-8 cycles and compare the OS and PFS of those patients to the whole group. This could give guidance on how to adjust OS and PFS for UK clinical practice. Alternatively, there might be literature where such time-on-treatment – survival relationship has already been investigated that can be used to make plausible adjustments.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LY = life year; NHS = National Health Service; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; UK = United Kingdom	

Table 1.7: Key issue 6: Quality-adjusted life year weight for patients expressing CPS ≥1

Report Section	4.2.10
Description of issue and why the EAG has identified it as important	The company used a QALY weight of 1.7 for patients expressing CPS ≥1, although they estimated that a QALY weight of 1.2 would be applicable in patients expressing CPS ≥1 based on the most up-to-date NICE guidelines.
What alternative approach has the EAG suggested?	In accordance to the most up-to-date NICE guidelines, the EAG prefers a QALY weight of 1.2 for patients expressing CPS ≥1.
What is the expected effect on the cost effectiveness estimates?	Using a QALY weight of 1.2 for patients expressing CPS ≥1 increased the ICER to [redacted] per QALY gained from the company base-case of [redacted] per QALY gained after clarification phase.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence or analyses are needed to resolve this issue.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year	

1.6 Summary of the EAG's view

Tables 1.8 and 1.9 summarise the ICERs of both the company's and EAG's preferred base-cases, as well as the impact of each EAG preferred assumption applied separately to the company base-case.

For patients expressing CPS ≥1, each of the changes increases the company base-case ICERs for both populations, with the largest impact seen when the EAG preferred QALY weight is used. For patients expressing CPS ≥10, it is noteworthy that results should be interpreted with care, as treatment waning in this population means that over time the small difference between pembrolizumab OS and nivolumab OS wanes, but not that the OS slowly reverts to the OS that would have been observed if that patient had not received one of the IO treatments (i.e., only doublet chemotherapy). If a waning effect for both IO treatments was modelled instead, it would likely again be expected that the ICER would increase, as the incremental costs and QALYs would both become smaller, but still, it would be difficult to appropriately assess the extent of the relative increase. To conclude, it would be difficult to assess the potential impact of a waning effect in both IO therapies without making further assumptions of which the plausibility would still be questionable.

Combining all changes in the model lead to an EAG preferred base-case incremental cost-effectiveness result of [redacted] per QALY gained for patients expressing CPS ≥1, which is higher than the company ICER of [redacted] per QALY gained (after clarification). For patients expressing CPS ≥10, the EAG base-case incremental cost-effectiveness result of [redacted] per QALY gained is higher than the company ICER of [redacted] per QALY gained (after clarification), but as explained in the previous paragraph this difference should be treated with care.

The probabilistic ICERs of [redacted] and [redacted] per QALY gained, for patients with CPS ≥1 and patients with CPS ≥10, respectively, were comparable to the EAG deterministic base-case ICERs. The probabilistic sensitivity analysis (PSA) shows that the probability that pembrolizumab plus doublet chemotherapy is cost-effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], using the EAG preferred base-case assumptions for patients with CPS ≥1. For patients with CPS ≥10, the probability that pembrolizumab plus doublet chemotherapy is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively, when using the EAG base-case assumptions.

Several scenarios were explored, and most of these led to only small changes in the ICER. The most substantial changes occurred when cost due to subsequent treatments were omitted in patients expressing CPS ≥1. This scenario yielded an ICER of [redacted] per QALY gained.

In the group patients expressing CPS ≥10, the results were very sensitive to changes in the hazard ratio (HR) for OS between pembrolizumab plus chemotherapy versus nivolumab plus chemotherapy. Changing the HR from of [redacted] to 1.0 leads to a very small difference in QALYs, which in turn leads to a very large ICER, of [redacted].

Table 1.89: Summary of EAG's preferred assumptions and ICER, patients with CPS ≥1

Technologies	Total costs^	Total QALYs*	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Doublet chemotherapy	[redacted]	[redacted]			
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS base-case following the clarification phase					
Doublet chemotherapy	[redacted]	[redacted]		[redacted]	

Technologies	Total costs^	Total QALYs*	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual impact on EAG base-case: Assume treatment waning					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual impact on EAG base-case: Use EAG preferred QALY weight					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab.
*For patients with CPS ≥1, the company's severity adjusted ICERs were based on a QALY weight equal to 1.7.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Table 1.10: Summary of EAG's preferred assumptions and ICER, patients with CPS ≥10

Technologies	Total costs^	Total QALYs*	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Nivolumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS base-case following the clarification phase					
Nivolumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case (assume treatment waning – the only change implemented in this population)					

Technologies	Total costs^	Total QALYs*	Incremental costs	Incremental QALYs	ICER (£/QALY)
Nivolumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^For patients expressing CPS ≥10 the list price of pembrolizumab has been used.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
Population	People with previously untreated HER2 negative advanced gastric or GOJ adenocarcinoma.	Patients with locally advanced unresectable or metastatic HER2 negative gastric or GOJ adenocarcinoma whose tumours express CPS ≥1.	In line with the anticipated GB MHRA marketing authorisation population wording.	The narrower population considered in the CS is in line with the anticipated marketing authorisation for pembrolizumab.
Intervention	Pembrolizumab with chemotherapy.	As per final scope.	-	The intervention is in line with the NICE scope.
Comparator(s)	Chemotherapy only, which includes: doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin For people with untreated HER2 negative advanced or metastatic gastric or GOJ adenocarcinoma whose tumours express PD-L1 with a CPS of 5 or more: nivolumab with platinum- and fluoropyrimidine-based chemotherapy.	Mainly as per final scope. A comparison between pembrolizumab CPS ≥5 and nivolumab CPS ≥5 was not feasible at the time of writing the submission. In response to clarification, a post-hoc analysis was provided and the results of this analysis should be interpreted with caution.	KEYNOTE-859 trial results provide direct evidence between: pembrolizumab plus CAPOX or FP versus CAPOX or FP. Based on previous appraisals in this setting, ESMO guidelines and clinical opinion received, doublet chemotherapy regimens are considered to be clinically equivalent. Differences exist between the respective trial multiplicity analysis strategies in KEYNOTE-859 and CheckMate-649. In KEYNOTE-859, CPS ≥1 and CPS ≥10 cuts were prespecified and adjusted for type 1 error, however CheckMate-649 trial had a prespecified CPS ≥5 cut for the primary outcome measure. Therefore, the analysis for pembrolizumab in CPS ≥5 is not considered to be statistically	The comparators are generally in line with the NICE scope.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG Comment
			appropriate. Instead, a comparison between pembrolizumab and nivolumab in CPS ≥1 and CPS ≥10 has been undertaken and results are presented in this submission Section B.2.9.	
Outcomes	The outcome measures to be considered include: OS PFS response rate adverse effects of treatment HRQoL	As per final scope.	-	The outcomes reported are in line with the NICE scope.
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: subgroups by PD-L1 status subgroups by tumour location.	As per final scope.	KEYNOTE-859 trial included a small proportion of patients with GOJ, and it was a pre-specified subgroup in the trial, however it was not powered to be tested. Results for this subgroup of patients is included within the subgroup analysis Section B.2.7.	The HE model presents analyses and outcomes separately for patients expressing a CPS ≥1 and those expressing a CPS ≥10. No subgroup analyses were done by tumour location.

Based on Table 1 of CS [document B][1]

CAPOX = capecitabine and oxaliplatin; CPS = combined positive score; CS = company submission; ESMO= European Society for Medical oncology; FP = cisplatin + fluorouracil; GB = Great Britain; GOJ = gastro-oesophageal junction; HE = health economics; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; MHRA = Medicines and Healthcare Products Regulatory Agency; NICE = National Institute for Clinical and Health Excellence; OS= overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival

2.1 Population

The population defined in the National Institute for Health and Care Excellence (NICE) final scope is: people with previously untreated human epidermal growth factor receptor 2 (HER2) negative advanced gastric or gastro-oesophageal junction (GOJ) adenocarcinoma.[2] The population in the company submission (CS) is limited to *"Patients with locally advanced unresectable or metastatic HER-2 negative gastric or gastroesophageal junction adenocarcinoma whose tumours express CPS≥1".*[1]

According to the company the decision problem addressed in the CS is slightly narrower than that specified in the final scope. The broader population specified in the final scope may include patients with locally advanced unresectable or metastatic HER2 negative gastric or GOJ adenocarcinoma whose tumours express combined positive score (CPS) <1.

The population considered in the CS is in line with the anticipated marketing authorisation for the use of pembrolizumab (CS, Table 1, page 10).[1]

A European marketing authorisation application to the use of pembrolizumab for the treatment of patients with previously untreated HER2 negative advanced gastric or GOJ adenocarcinoma was submitted to the European Medicines Agency (EMA) in July 2023.[3, 4] A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was received.[5] The marketing authorisation on the use of pembrolizumab for the treatment of patients with previously untreated HER2 negative advanced gastric or GOJ adenocarcinoma has now been received.[3, 4]

2.2 Intervention

The intervention (pembrolizumab with chemotherapy) is in line with the NICE final scope. Pembrolizumab 200 mg is administered every 3 weeks (Q3W) or pembrolizumab 400 mg every 6 weeks (Q6W), which is delivered via intravenous (IV) infusion (up to a maximum 35 cycles).[1]

Fluoropyrimidine containing chemotherapy:[1]

- Capecitabine: 1000 mg/m^2 administered orally twice daily (BID) on Days 1 to 14 Q3W; or,
- Fluorouracil (5-FU): 800 mg/m^2 IV administered on Days 1–5 Q3W

Platinum containing chemotherapy:

- Oxaliplatin: 130 mg/m^2 IV administered on Day 1 Q3W; or,
- Cisplatin: 80 mg/m^2 IV administered on Day 1 Q3W[1]

2.3 Comparators

The description of the comparators in the NICE final scope[2] is as follows:

"Chemotherapy only, which includes doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin;

For people with untreated HER2 negative advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS of 5 or more:

- *Nivolumab with platinum- and fluoropyrimidine-based chemotherapy."*[2]

The company states that "*KEYNOTE-859 trial results provide direct evidence between pembrolizumab plus CAPOX or FP vs. CAPOX or FP. Based on previous appraisals in this setting, ESMO guidelines and clinical opinion received, doublet chemotherapy regimens are considered to be clinically*

equivalent. An indirect comparison between nivolumab in CPS ≥5 and pembrolizumab in CPS ≥1 is not currently feasible".[1]

The company further states that *"differences exist between the respective trial multiplicity analysis strategies in KEYNOTE-859 and CheckMate-649. In KEYNOTE-859, CPS ≥1 and CPS ≥10 cuts were prespecified and adjusted for type 1 error, however CheckMate-649 trial had a prespecified CPS ≥5 cut for the primary outcome measure. Therefore, the analysis for pembrolizumab in CPS ≥5 is not considered to be statistically appropriate. Instead, a comparison between pembrolizumab and nivolumab in CPS ≥1 and CPS ≥10 has been undertaken and results are presented in this submission section B.2.9."*[1]

The Evidence Assessment Group (EAG) requested additional data on the subgroup analysis of patients with locally advanced unresectable or metastatic HER2 negative gastric or GOJ adenocarcinoma whose tumours express CPS ≥5.[6] Following the EAG's request, the company provided post-hoc analysis relating to this subgroup from the KEYNOTE-859 trial.[7] In addition, the company also provided the results of indirect treatment comparison (ITC) for the subgroup of patients with PD-L1 CPS ≥5 for the comparison between pembrolizumab plus chemotherapy and nivolumab plus hemotherapy following EAG's request (see Section 3.4).[7]

2.4 Outcomes

The NICE final scope[2] lists the following outcome measures:

- overall survival (OS)
- progression-free survival (PFS)
- response rate (RR)
- adverse effects of treatment
- health-related quality of life (HRQoL)

These outcomes were all assessed in the KEYNOTE–859 trial, see Sections 3.2.5 and 3.2.6.

2.5 Other relevant factors

According to the company, no equality issues related to pembrolizumab in combination with fluoropyrimidine chemotherapy for the first-line treatment for patients with previously untreated HER2 negative advanced gastric or GOJ adenocarcinoma were identified (CS, Section B.1.4).[1]

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

The company performed a systematic review (SR) up to May 2022 to identify and summarise the available randomised controlled trial (RCT) evidence relating to the efficacy and safety of pembrolizumab in combination with chemotherapy and relevant comparators in patients with locally advanced unresectable or metastatic HER2 negative gastric cancer (GC) or GOJ adenocarcinoma. The company state in that the intention of the SR was to *"identify relevant studies to inform direct and indirect comparisons between the intervention and comparators of interest included in this submission"*.[8].

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[1] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[9, 10] The CS[1] was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[11] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the SR undertaken to identify RCTs relating to the efficacy and safety of pembrolizumab in combination with chemotherapy and relevant comparators in patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma.[1] The searches were conducted in May 2023.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	1974-8/5/23	9/5/23
CENTRAL	Ovid	To April 2023	9/5/23
Conferences			
ASCO	Northern Light (Ovid)	2020-2022	Not stated
ASCO Gastrointestinal Cancers Symposium	J Clin Oncol Conference PDF	2020-2021 2022-2023	
ESMO	Northern Light (Ovid)	2020-2022	
ESMO World Congress on Gastrointestinal Cancer	Ann Oncol	2020-2023	
Trials registries			
ClinicalTrials.gov	Internet	Not stated	Not stated
ASCO = American Society of Clinical Oncology; CENTRAL = Cochrane Central Register of Controlled Trials; ESMO = European Society for Medical Oncology			

EAG comment:

- Searches were undertaken in May 2023 to identify relevant clinical evidence for the efficacy and safety of pembrolizumab in combination with chemotherapy and relevant comparators in patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma. The

CS, Appendix D and the company's response to the request for clarification provided sufficient details for the EAG to appraise the literature searches.[1, 7]

- Bibliographic databases, conferences and trials registers were searched. Reference checking was conducted.
- The company conducted a single search of Embase.com on the understanding that it now contains all MEDLINE content. The response to the request for clarification states that PubMed was searched to ensure retrieval of non-indexed citations, although this search strategy was not provided.[7] Whilst the EAG accepts this approach as adequate, it considers it preferable to conduct a separate MEDLINE search in order to fully utilise the power of database-specific study design filters developed to make the most of an individual databases subject headings.
- The database searches for the clinical effectiveness SR contained a population facet for locally advanced unresectable or metastatic HER2 negative GC/GOJ adenocarcinoma, and an intervention facet for pembrolizumab in combination with chemotherapy and relevant comparators. In the Embase and MEDLINE searches, this was then combined with a study design filter for RCTs. The recognised SIGN study design filter was used.
- Searches were well structured, transparent and reproducible. Following a query by the EAG,[6] searches were re-run by the company to include additional search terms in the population facet. No further included studies were identified by these searches.[7]
- Database searches were not limited by date; however, they were limited to English language studies only. Limiting the results to only studies published in English may have introduced language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"[12] and that "research related to language bias supports the inclusion of non-English studies in systematic reviews".[13, 14]
- Separate adverse events (AE) searches were not performed. Guidance by the Centre for Reviews and Dissemination (CRD)[15] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed.

3.1.2 Inclusion criteria

As stated above, a SR was conducted to identify and summarise the relevant evidence. Study eligibility criteria as described in Appendix D, page 3, are presented in Table 3.2.

It was noted by the EAG that the CS did not provide detail on the screening process used to identify relevant evidence. It is important that an SR is conducted and reported with all necessary efforts to reduce risk of bias and human error. An essential component of this principle is that screening is optimal if conducted in duplicate and independently by two reviewers, with any disagreements then resolved either by consensus or by intervention of a third reviewer. The EAG addressed this concern and raised this for clarification. In their response[7] the company stated that *"Study selection followed a two-stage screening process based on the review of titles and abstracts (stage I) and then, full-text articles (stage II). All titles/abstracts identified by the literature searches were reviewed against the predefined PICOS selection criteria. Following completion of title/abstract review, all publications identified for inclusion during this first pass were retrieved for further review in full text. Ultimately, full-text articles that met all of the inclusion criteria and none of the exclusion criteria were included in the SR and underwent data extraction.' In the same response the company also clarified that 'During both stages of study selection (i.e. title/abstract and full-text article) each publication was assessed by two, independent investigators. Any disagreements were resolved by discussion between investigators, including a third more senior researcher, if needed".*

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Inclusion criteria	Exclusion criteria
Population	Adult (≥18 years old) patients with previously untreated, HER2- locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma who received no prior systemic therapy for treatment of locally advanced or metastatic disease. The following subgroups are of interest: • Locally advanced or metastatic HER2- gastric/GEJ adenocarcinoma irrespective of PD-L1 expression status • Locally advanced or metastatic HER2- gastric/GEJ adenocarcinoma whose tumors express PD-L1 with a CPS of 1 or more • Locally advanced or metastatic HER2- gastric/GEJ adenocarcinoma whose tumors express PD-L1 with a CPS of 10 or more • Locally advanced or metastatic HER2- gastric/GEJ adenocarcinoma whose tumors express PD-L1 with a CPS of 5 or more	Studies that recruited patients who had previous therapy for locally advanced, unresectable, or metastatic gastric/GEJ adenocarcinoma, had squamous cell gastric cancer had exclusively ECOG of 2 or higher
Interventions	For locally advanced or metastatic HER2- gastric/GEJ adenocarcinoma irrespective of PD-L1 expression status: • Doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin • Fluorouracil + oxaliplatin: (FOLFOX) • Capecitabine + oxaliplatin (CAPOX) • Cisplatin + fluorouracil (FP) • Cisplatin + capecitabine (XP) For locally advanced or metastatic HER2- gastric/GEJ adenocarcinoma whose tumors express PD-L1 with a CPS of 5 or more: • Nivolumab with platinum and fluoropyrimidine based chemotherapy	• Interventions not evaluated in advanced unresectable or metastatic gastric/GEJ adenocarcinoma. • Any other interventions not listed

	Inclusion criteria	Exclusion criteria
Comparators	• Any intervention listed above • Placebo • BSC	No comparator of interest reported
Outcomes	Efficacy outcomes*: • OS • PFS • DOR • ORR • CR • PR • PD • SD Safety outcomes: • Any AE, overall or grade ≥3 • TRAE, overall or Grade ≥3 • SAEs • Immune-related AEs • Discontinuations, due to AEs or TRAEs • Death, due to any or TRAEs Generic patient-reported outcome measures: • EORTC QLQ-C30 • EQ-5D • FACT-G • SF-36 • SF-12 • BPI Disease-specific PRO measures: • EORTC QLQ-STO22 • FACT-Ga	No comparator of interest reported
Study design	RCTs**	• Non-randomised and single-arm trials • Observational studies (prospective or retrospective cohort, case-control) • Case reports, editorials, comments/commentary, guidelines, news, or narrative reviews • Animal studies, in vitro/ex vivo studies, gene expression/protein expression studies, pharmacokinetic/ pharmacodynamics studies
Language restrictions	English language only	Non- English language studies

	Inclusion criteria	Exclusion criteria
Time	No restrictions	N/A

Based on Table 1 of Appendix D of the CS[8].
AE = adverse events; BPI = Brief Pain Inventory; BSC = best supportive care; CAPOX = Oxaliplatin and capecitabine; CPS = combined positive score; CS = company submission; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; CR = complete response; EORTC QLQ-C30 = European Organization For Research And Treatment Of Cancer Core Quality of Life questionnaire; EORTC QLQ-STO22 = EORTC Quality of Life Questionnaire – Gastric Cancer Module; EQ-5D = European Quality of Life Five Dimension; FACT-G = Functional Assessment of Cancer Therapy – General; FACT-Ga = Functional Assessment of Cancer Therapy – Gastric Cancer; FOLFOX = folinic acid, fluorouracil and oxaliplatin; GEJ = gastro-oesophageal junction; FP = cisplatin + fluorouracil; HER2 = human epidermal growth factor receptor 2; N/A = not applicable; OS = overall survival; PD = progressive disease; PD-L1 = programmed death ligand 1; PFS= progression-free survival; ORR = objective response rate; PR = partial response; PRO = patient reported outcomes; RCT = randomised controlled trial; SAEs = serious adverse events; SF-36 = Short Form 36 Health Survey Questionnaire; SF-12 = Short Form 12 Health Survey Questionnaire; SD = standard deviation; TRAE = treatment-related adverse events; XP = cisplatin + capecitabine
Notes: *Only efficacy outcomes will be used for study selection; although, all outcomes listed will be extracted; **In order to be eligible for inclusion in the SR, a study needed to have at least two arms evaluating an intervention of interest A final check will be performed to identify any studies that evaluate a non-relevant common intervention in order perform indirect treatment comparisons.

3.1.3 Critique of data extraction

Best practice would be to have two independent reviewers extract data in duplicate, with any disagreements resolved by consensus or by the intervention of a third reviewer[16]. This optimises the likelihood of accurate and relevant data being extracted and reduces opportunity for bias and human error. The company do not provide any information in the CS[1] or the associated appendices[8] to indicate how this task was conducted. This is of concern to the EAG considering the fundamental importance of conducting a robust SR and identifying the relevant evidence. While we do not suggest that data extraction may be impacted by bias or error, the lack of reporting around this area means that an elevated risk must be assumed. The EAG emphasises the importance of robust methodologies and clear and descriptive reporting.

3.1.4 Quality assessment

The company confirmed in the CS that *"Quality Assessment of KEYNOTE-859 was conducted using the Cochrane risk of bias tool. Based on this analysis, the study was determined to be at 'low risk' across all six key domains. The complete quality assessment is included in Appendix D1.4".*[1]

The appendix document does not contain a Section D1.4 and on reviewing the mentioned appendix document it was apparent that this was an error and should have referred to Section D1.2. Section D1.1 briefly states "*that Study quality was assessed using the Cochrane Risk of Bias instrument for included RCTs and the Newcastle Ottawa Scale for single-arm trials*."[8]

Section D1.4 contains results of the quality appraisal of KEYNOTE-859 alongside that of the CheckMate-649 study[8]. However, it is not clear how this appraisal was conducted. Like screening, and data extraction, quality appraisal of included studies should be conducted and reported so as to provide confidence that risk of bias and human error is minimised. As stated in Sections 3.1.2 and 3.1.3 of this report, it is optimal to conduct such tasks in duplicate, independently, and where disagreements exist, to resolve by consensus or by intervention of a third reviewer. It is important not only that these principles are adhered to, but also that they are reported with clarity. Again, the EAG was concerned by the lack of information and requested details from the company. In their response to the request for

clarification[7] the company state that the Cochrane Collaboration's risk of bias tool was used and that '*A proposed judgement about the risk of bias arising from each domain was generated by an algorithm tracked in a Microsoft Excel Workbook, based on answers to the signalling questions. The assessment was performed by a single reviewer and validated by a senior researcher'.*

3.1.5 Evidence synthesis

The CS states that pairwise meta-analysis was not undertaken because data from a direct comparison between pembrolizumab with chemotherapy versus chemotherapy was only available from the KEYNOTE-859 RCT. However, data from another RCT (CheckMate-649) comparing nivolumab with chemotherapy versus chemotherapy were combined with the data of KEYNOTE-859 in an ITC analysis. Further details are provided in Section 3.3 of this report.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

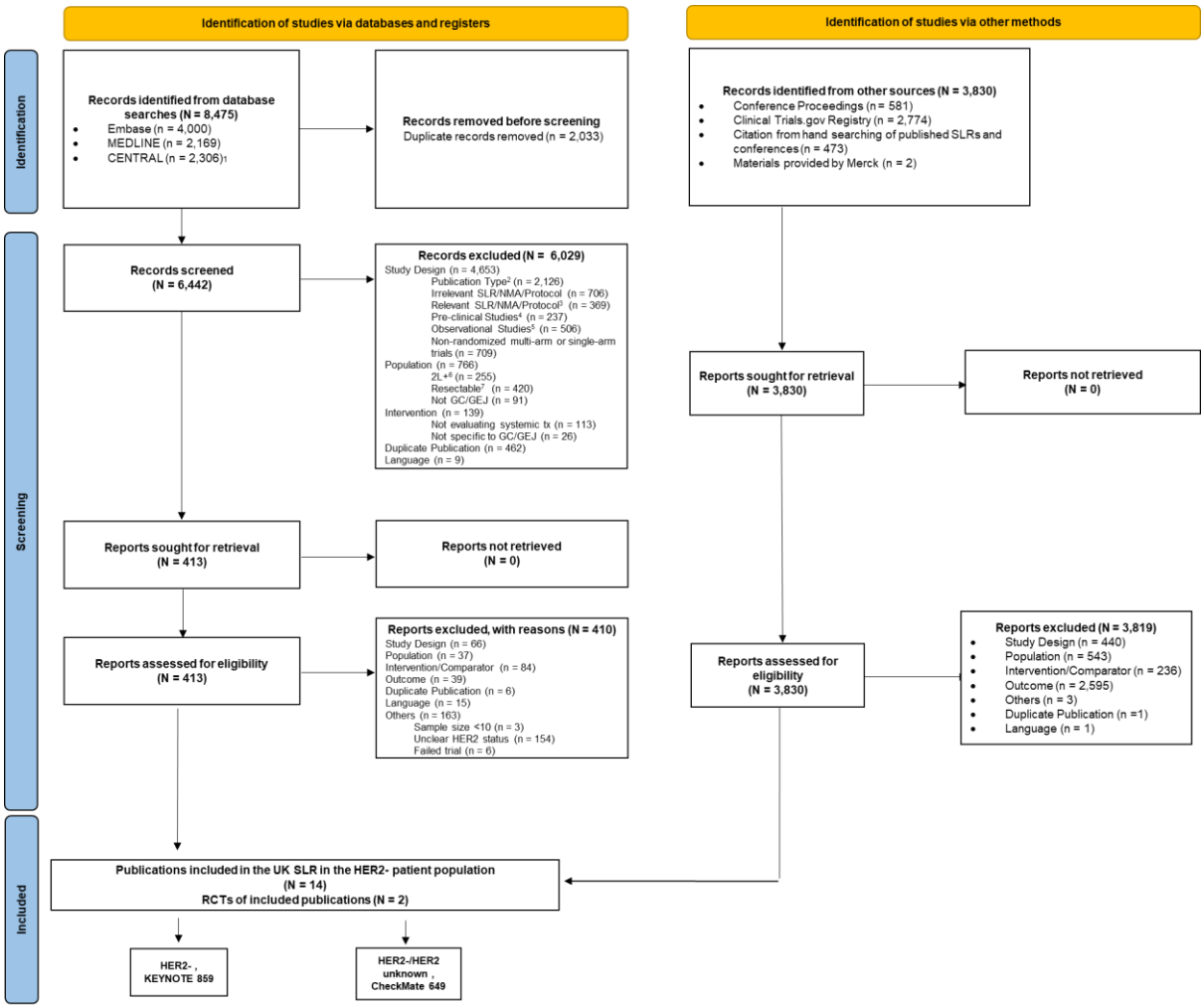
This Section of the report provides an overview of details of the sources of evidence in the CS[1] for the clinical effectiveness of pembrolizumab.

Section B.2.2 of the CS[1] details two RCTs which were identified by the SR: one trial reporting evidence for the relevant comparators: CheckMate-649, and one reporting evidence for pembrolizumab in combination with chemotherapy: KEYNOTE-859.

3.2.1 Study retrieval

The SR was conducted to identify clinical studies relevant to this submission and to identify RCTs relating to the efficacy and safety of pembrolizumab in combination with chemotherapy and relevant comparators, see Figure 3.1.

Figure 0.1: Flow Diagram to identify studies



Based on Figure 1 of Appendix D of the CS[8]
CS = company submission; GC = gastric cancer; GEJ = gastroesophageal junction; NMA = network meta-analysis; RCT = randomised controlled trial; Tx = treatment
Notes: 1) CCTR database searches identified 2,302 hits, upon matching with prior iteration of the SR, four additional citations were identified and added to the evidence base which were excluded as duplicate publications; 2) conference abstract, letters, narrative review, comment, editorial, etc.; 3) relevant SR/NMA/study protocols were excluded and flagged for bibliographic review of relevant SRs; 4) animal studies, in-vitro/ex vivo studies, studies on molecular mechanisms, gene expression or protein expression, studies on pharmacokinetics and/or pharmacodynamics; 5) prospective and retrospective cohort studies, cross-sectional studies, case reports/series, case-control studies, cost-effectiveness analysis, decision models, budget impact analysis, etc.; 6) ≥ second-line GC/GEJ population only; and 6) 100% resectable/local/early stage GC/GEJ

Briefly, database searches of Embase, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) identified 8,475 records, while 3,830 were identified through other methods. After removing 2,033 duplicates, 6,442 records were screened at title and abstract stage and 6,049 were subsequently excluded. Four hundred and thirteen records initially identified through database searching were retrieved for full text screening, while 3,80 records identified through other methods were retrieved.

After full text screening, 413 records were excluded from those identified through database searching, while 3,819 were excluded from those identified via other methods. Fourteen records were identified which satisfied all eligibility criteria and were included in the SR. Of these, two RCTs were identified.

Namely the KEYNOTE-859 trial of HER2- patients, and the CheckMate-649 trial of HER2/HER2 unknown status. The CS describes all records identified and excluded at the full text screening stage in Table 5 and 6 of Appendix D[8]. Methods of study identification and record screening employed by the company are described in Section 3.1 of this report.

3.2.2 Summary of details for the KEYNOTE-859 trial

The KEYNOTE-859 trial is a Phase III randomised, double-blind, multi-centre, placebo-controlled clinical trial investigating the use of pembrolizumab plus either cisplatin plus 5-fluorouracil or capecitabine and oxaliplatin (CAPOX) as a first-line treatment versus placebo plus cisplatin plus 5-fluorouracil or CAPOX in HER2 negative participants with advanced gastric or GOJ adenocarcinoma, see Table 3.3 for summary of trial.

The KEYNOTE-859 trial was conducted globally with 33 countries collectively hosting 215 research centres. These included Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Czech Republic, Denmark, France, Germany, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, New Zealand, Peru, Poland, Russia, South Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, and United States. The EAG noted that 42 participants from three United Kingdom (UK) centres participated in the KEYNOTE-859 trial and sought clarification on this point from the company as to its generalisability to the clinical population in England and Wales.

3.2.2.1 Baseline characteristics

The CS describes the baseline characteristic of the trial population as being '*generally reflective for this population with previously untreated, HER2 negative, advanced gastric or GOJ adenocarcinoma based on clinical expert feedback and were generally well balanced between the 2 intervention groups'.*[1]

Table 3.3 summarises the baseline demographic and disease characteristics of the intention-to-treat (ITT) population with CPS ≥1 that is described in Table 5 of the CS. The majority of patients in the study as a whole were in the age range <65 (60%), male (70.4%), white (55%), from study centres in Asia or Western Europe/Israel/North America/Australia (59.4%), had adenocarcinoma of the stomach (78.7%), had an Eastern Cooperative Oncology Group (ECOG) performance of Grade 1 (63.5%), had tumour programmed cell death ligand 1 (PD-L1) status of CPS ≥1 (78.2%), and were on a CAPOX regimen (86.3%). 96.4% of patients were stage IV and 95.9% had confirmed metastasis, with 0-2 metastatic sites in 54.6% of patients.

Baseline characteristics between the two groups in the ITT population with CPS ≥1 were generally balanced and well matched (see Table 3.4). The EAG noted that there were differences beyond 5% with regards to the primary locations of the tumours with adenocarcinoma of the GOJ being present in 19.9% of the pembrolizumab plus chemotherapy group as opposed to 26.6% of the chemotherapy only group. Adenocarcinoma of the stomach was also increased beyond 5% in the pembrolizumab plus chemotherapy group, with 79.9% as opposed to 73.5% in the chemotherapy only group.

Table 0.3: Baseline characteristics (ITT population with CPS ≥1)

	Pembrolizumab + Chemotherapy	**Chemotherapy**		**Total**
	n (%)	**n**	**(%)**	**n (%)**
Participants in population	618	617		1,235

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n (%)		n	(%)	n (%)	
Sex						
Male	422	(68.3)	448	(72.6)	870	(70.4)
Female	196	(31.7)	169	(27.4)	365	(29.6)
Age Category 1 (Years)						
< 65	377	(61.0)	364	(59.0)	741	(60.0)
≥ 65	241	(39.0)	253	(41.0)	494	(40.0)
Mean	59.8		60.5		60.1	
SD	11.8		11.6		11.7	
Median	62.0		63.0		62.0	
Range	24 to 86		25 to 85		24 to 86	
Age Category 2 (Years)						
< 65	377	(61.0)	364	(59.0)	741	(60.0)
≥ 65 to <75	195	(31.6)	203	(32.9)	398	(32.2)
≥ 75 to <85	44	(7.1)	49	(7.9)	93	(7.5)
≥ 85	2	(0.3)	1	(0.2)	3	(0.2)
Age Category 3 (Years)						
18-39	42	(6.8)	34	(5.5)	76	(6.2)
40-49	70	(11.3)	75	(12.2)	145	(11.7)
50-59	150	(24.3)	141	(22.9)	291	(23.6)
60-69	236	(38.2)	230	(37.3)	466	(37.7)
70-79	110	(17.8)	121	(19.6)	231	(18.7)
≥80	10	(1.6)	16	(2.6)	26	(2.1)
Race						
American Indian Or Alaska Native	24	(3.9)	29	(4.7)	53	(4.3)
Asian	206	(33.3)	203	(32.9)	409	(33.1)
Black Or African American	7	(1.1)	9	(1.5)	16	(1.3)
Multiple	32	(5.2)	25	(4.1)	57	(4.6)
Native Hawaiian Or Other Pacific Islander	1	(0.2)	1	(0.2)	2	(0.2)
White	342	(55.3)	343	(55.6)	685	(55.5)
Missing	6	(1.0)	7	(1.1)	13	(1.1)
Ethnicity						
Hispanic Or Latino	135	(21.8)	124	(20.1)	259	(21.0)
Not Hispanic Or Latino	461	(74.6)	480	(77.8)	941	(76.2)
Not Reported	12	(1.9)	11	(1.8)	23	(1.9)
Unknown	7	(1.1)	2	(0.3)	9	(0.7)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n (%)		n	(%)	n (%)	
Missing	3	(0.5)	0	(0.0)	3	(0.2)
Geographic Region for Randomisation						
Western Europe/Israel/North America/Australia	166	(26.9)	166	(26.9)	332	(26.9)
Asia	201	(32.5)	200	(32.4)	401	(32.5)
Rest of the World	251	(40.6)	251	(40.7)	502	(40.6)
Combination Chemotherapy for Randomisation						
CAPOX	528	(85.4)	528	(85.6)	1,056	(85.5)
FP	90	(14.6)	89	(14.4)	179	(14.5)
PD-L1 Status for Randomisation						
CPS ≥ 1	618	(100.0)	616	(99.8)	1,234	(99.9)
CPS < 1	0	(0.0)	1	(0.2)	1	(0.1)
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS ≥ 10	279	(45.1)	272	(44.1)	551	(44.6)
CPS < 10	337	(54.5)	345	(55.9)	682	(55.2)
Missing	2	(0.3)	0	(0.0)	2	(0.2)
MSI Status						
MSI-High	34	(5.5)	29	(4.7)	63	(5.1)
non-MSI-High	454	(73.5)	471	(76.3)	925	(74.9)
Missing	130	(21.0)	117	(19.0)	247	(20.0)
ECOG Performance Scale						
0	223	(36.1)	228	(37.0)	451	(36.5)
1	395	(63.9)	389	(63.0)	784	(63.5)
Primary Location						
Adenocarcinoma of the gastroesophageal junction	123	(19.9)	164	(26.6)	287	(23.2)
Adenocarcinoma of the stomach	494	(79.9)	453	(73.4)	947	(76.7)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Overall Stage						
IIA	0	(0.0)	1	(0.2)	1	(0.1)
IIB	0	(0.0)	2	(0.3)	2	(0.2)
IIIA	2	(0.3)	7	(1.1)	9	(0.7)
IIIB	10	(1.6)	7	(1.1)	17	(1.4)
IIIC	9	(1.5)	5	(0.8)	14	(1.1)
IV	596	(96.4)	595	(96.4)	1,191	(96.4)
Missing	1	(0.2)	0	(0.0)	1	(0.1)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n (%)		n	(%)	n (%)	
Disease Status						
Locally advanced	26	(4.2)	24	(3.9)	50	(4.0)
Metastatic	591	(95.6)	593	(96.1)	1,184	(95.9)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Histological Subtype (Lauren classification)						
Diffuse	236	(38.2)	220	(35.7)	456	(36.9)
Intestinal	239	(38.7)	215	(34.8)	454	(36.8)
Indeterminate	141	(22.8)	182	(29.5)	323	(26.2)
Unknown	1	(0.2)	0	(0.0)	1	(0.1)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Number of Metastasis						
0-2	345	(55.8)	329	(53.3)	674	(54.6)
≥3	272	(44.0)	288	(46.7)	560	(45.3)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Tumour Burden						
≥ Median	308	(49.8)	285	(46.2)	593	(48.0)
< Median	277	(44.8)	299	(48.5)	576	(46.6)
Missing	33	(5.3)	33	(5.3)	66	(5.3)
Liver Metastases						
Yes	258	(41.7)	253	(41.0)	511	(41.4)
No	359	(58.1)	364	(59.0)	723	(58.5)
Missing	1	(0.2)	0	(0.0)	1	(0.1)
Prior Gastrectomy/Esophagectomy						
Yes	109	(17.6)	105	(17.0)	214	(17.3)
No	506	(81.9)	508	(82.3)	1,014	(82.1)
Missing	3	(0.5)	4	(0.6)	7	(0.6)

Based on Table 6 of the CS[1]
CAPOX = capecitabine and oxaliplatin; CPS = combined positive score; CS = company submission; ECOG = Eastern Cooperative Oncology Group; FP = Backbone chemotherapy cisplatin + 5-FU; MSI = microsatellite instability; PD-L1 = programmed death ligand 1; SD = standard deviation

The EAG noted that the participant characteristics did not seem to represent what would be expected in clinical practice in England and Wales. Of particular attention was the ethnic and geographical distribution of the included participants. The EAG questioned the generalisability of this population based on the minimal involvement of UK based patients (42 participants from three UK centres participated in the KEYNOTE-859 trial), and the under representation of black patients, given that in England and Wales, black patients represent those more likely to be affected.

The EAG raised these points with the company. With regards to the generalisability of the study population, the company in their response to the request for clarification[7] state that *"KEYNOTE-859 is a global trial that recruited patients with HER2 negative locally advanced metastatic gastric cancer or*

GOJ across 33 countries. The aim of the trial is to represent patients with HER2 negative locally advanced metastatic gastric or GOJ adenocarcinoma globally". The company response continues and states that they "conducted a post-hoc analysis of participant baseline characteristics by treatment group for European participants with CPS≥1. The analysis shows that [redacted] *of European participants in the KEYNOTE-859 trial were White.'* [7] Finally the company point to *'a post-hoc analysis of the UK participants in the KEYNOTE-859 trial show that* [redacted] *of participants were White. Therefore, we believe that KEYNOTE-859 trial results are generalisable to England and Wales population".*[7]

With regards to the point of black patient representation in the trial, the response from the company[7] again stated that *"KEYNOTE-859 is a global trial that aims to represent patients with advanced or metastatic gastric cancer or GOJ adenocarcinoma globally.' Additionally, 'COVID-19 pandemic has highlighted the lack of representation of Black people in clinical trials in the UK. The reasons for the under-representation of the Black population in clinical trials are multifactorial. Szczepura classified the challenges in access to health care by ethnic minority populations into four groups: (i) extrinsic, (ii) organisational factors, (iii) intrinsic or (iv) personal factors. Extrinsic factors include language difficulties in a population whose first language is not English. Screening potential trial patients against an ever-growing list of eligibility criteria is complex and sometimes challenging. Other obstacles to participation include distance to treatment centres and low social-economic status. Higher social-economic status has been shown as a statistically significant predictor of involvement in oncology trials. Intrinsic factors include a lack of education on the importance of clinical trials and an inherent distrust of institutions due to racial discrimination. Black communities have been subject to historic scandals linked with clinical trials, such as the Tuskegee syphilis study of untreated syphilis in Negro male, unethical experiments by James Marion Sims and the cases of multiple medical experimentations in Africa. These historical racial abuses under the umbrella of clinical trials have hindered the participation of Black patients".*

The EAG notes the complexity and political and historical aspect of this response however, this is does not specifically relate to the trial in question, or the actual representativeness of the population characteristics and as such we cannot see the relevance as a justification. The company does clarify that they have conducted a *"post-hoc analysis of participant baseline characteristics by treatment group for the UK participants with CPS≥1. The analysis shows that 5.9% of the UK participants in the KEYNOTE-859 trial were Black. Therefore, we believe that KEYNOTE-859 trial results are generalisable to England and Wales population."*[7]

The company in their response, also provided the baseline data of the post-hoc analysis of participant baseline characteristics by treatment group for European participants with CPS ≥1 in the ITT population (Table 3.4), and for UK based participants (Table 3.5).

Table 0.4: Participant baseline characteristics by treatment group European participants with CPS ≥1 (ITT population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]		[redacted]		[redacted]	
Race						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 9 of the response to the request for clarification[7] CAPOX = capecitabine and oxaliplatin; FP = Backbone chemotherapy cisplatin + 5-FU. European participants are defined as participants from the geographical location of Europe.						

Table 0.5: Participant baseline characteristics by treatment group UK participants with CPS ≥1 (ITT population)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	21		13		34	
Race						
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 10 of the response to the request for clarification[7] CAPOX = Backbone chemotherapy oxaliplatin + capecitabine; FP = Backbone chemotherapy cisplatin + 5-FU UK participants are defined as participants from the geographical location of United Kingdom						

On reviewing the post-hoc data supplied by the company, it is apparent that the majority of participants in both the European ([redacted]) and the UK ([redacted]) subsets are defined as being white. The EAG notes that in the UK population only 34 participants are detailed, and no information is included to describe this missing data. It is also of note that in the UK subpopulation, 15.4% of those in the chemotherapy only group are black, while no black patients are detailed in the pembrolizumab plus chemotherapy group. The EAG acknowledged that this represents a difference only a difference of two participants, however if the data is to be generalisable to the relevant National Health Service (NHS) population, then this could be of note, given that no black participants in the UK actually received pembrolizumab. The company in their request to clarification[7] also emphasised that *"CheckMate-649 trial included only around 1% of Black participants which is below the proportion of Black population in England and Wales, however the NICE appraisal committee concluded that the CheckMate-649 trial was generalisable to NHS practice".*

Given that the company provided an indirect comparison and utilised a network meta-analysis (NMA), the EAG requested additional baseline details to sufficiently describe and compare the populations to ensure that exchangeability for the purpose of the NMA is acceptable. We asked that patient characteristics at baseline for the subgroup of PD-L1 CPS ≥10 from the two RCTs (KEYNOTE-859 and CheckMate-649) could be provided. In their response the company clarified that *"baseline characteristics for patients with CPS…≥10 were not reported in any of the publications associated with CheckMate-649; therefore, a between-studies comparison of baseline characteristics in these populations is not feasible".*[7] The company did provide baseline characteristics for the KEYNOTE-859 participants with PD-L1 CPS ≥10 and are detailed below in Table 3.6.

Table 0.6: Participant baseline characteristics by treatment group participants with CPS ≥10 (ITT population)

	Pembrolizumab + chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	279		272		551	
Sex						
Male	193	(69.2)	205	(75.4)	398	(72.2)
Female	86	(30.8)	67	(24.6)	153	(27.8)
Age (Years)						
< 65	161	(57.7)	159	(58.5)	320	(58.1)
≥ 65	118	(42.3)	113	(41.5)	231	(41.9)
Mean	60.6		60.8		60.7	
SD	11.6		11.1		11.3	
SE	0.7		0.7		0.5	
Median	63.0		63.0		63.0	
Range	26 to 84		25 to 82		25 to 84	
Race						
American Indian Or Alaska Native	7	(2.5)	11	(4.0)	18	(3.3)
Asian	98	(35.1)	89	(32.7)	187	(33.9)
Black Or African American	2	(0.7)	5	(1.8)	7	(1.3)
Multiple	16	(5.7)	8	(2.9)	24	(4.4)
American Indian Or Alaska Native White	12	(4.3)	5	(1.8)	17	(3.1)
Black Or African American White	4	(1.4)	3	(1.1)	7	(1.3)
Native Hawaiian Or Other Pacific Islander	1	(0.4)	0	(0.0)	1	(0.2)
White	155	(55.6)	157	(57.7)	312	(56.6)
Missing	0	(0.0)	2	(0.7)	2	(0.4)
Ethnicity						
Hispanic Or Latino	59	(21.1)	51	(18.8)	110	(20.0)
Not Hispanic Or Latino	211	(75.6)	215	(79.0)	426	(77.3)
Not Reported	6	(2.2)	5	(1.8)	11	(2.0)
Unknown	3	(1.1)	1	(0.4)	4	(0.7)
Age Category 2 (Years)						
<65	161	(57.7)	159	(58.5)	320	(58.1)
≥65 to <75	96	(34.4)	92	(33.8)	188	(34.1)
≥75 to <85	22	(7.9)	21	(7.7)	43	(7.8)
Age Category 3 (Years)						
18-39	16	(5.7)	12	(4.4)	28	(5.1)

	Pembrolizumab + chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
40-49	30	(10.8)	35	(12.9)	65	(11.8)
50-59	68	(24.4)	61	(22.4)	129	(23.4)
60-69	99	(35.5)	104	(38.2)	203	(36.8)
70-79	61	(21.9)	54	(19.9)	115	(20.9)
≥80	5	(1.8)	6	(2.2)	11	(2.0)
Geographic Region for Randomization						
Western Europe/Israel/North America/Australia	78	(28.0)	64	(23.5)	142	(25.8)
Asia	96	(34.4)	88	(32.4)	184	(33.4)
Rest of the World	105	(37.6)	120	(44.1)	225	(40.8)
Combination Chemotherapy for Randomization						
CAPOX	242	(86.7)	235	(86.4)	477	(86.6)
FP	37	(13.3)	37	(13.6)	74	(13.4)
PD-L1 Status for Randomization						
Positive	279	(100.0)	271	(99.6)	550	(99.8)
Negative	0	(0.0)	1	(0.4)	1	(0.2)
Baseline PD-L1 Status						
CPS ≥1	279	(100.0)	272	(100.0)	551	(100.0)
CPS ≥10	279	(100.0)	272	(100.0)	551	(100.0)
MSI Status						
MSI-High	20	(7.2)	16	(5.9)	36	(6.5)
non-MSI-High	227	(81.4)	224	(82.4)	451	(81.9)
ECOG Performance Scale						
0	99	(35.5)	103	(37.9)	202	(36.7)
1	180	(64.5)	169	(62.1)	349	(63.3)
Primary Location						
Adenocarcinoma of the gastroesophageal junction	65	(23.3)	73	(26.8)	138	(25.0)
Adenocarcinoma of the stomach	214	(76.7)	199	(73.2)	413	(75.0)
Overall Stage						
IIA	0	(0.0)	1	(0.4)	1	(0.2)
IIB	0	(0.0)	2	(0.7)	2	(0.4)
IIIA	2	(0.7)	3	(1.1)	5	(0.9)
IIIB	8	(2.9)	2	(0.7)	10	(1.8)
IIIC	4	(1.4)	2	(0.7)	6	(1.1)
IV	265	(95.0)	262	(96.3)	527	(95.6)

	Pembrolizumab + chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Disease Status						
Locally advanced	14	(5.0)	11	(4.0)	25	(4.5)
Metastatic	265	(95.0)	261	(96.0)	526	(95.5)
Histological Subtype (Lauren classification)						
Diffuse	102	(36.6)	89	(32.7)	191	(34.7)
Intestinal	111	(39.8)	99	(36.4)	210	(38.1)
Indeterminate	65	(23.3)	84	(30.9)	149	(27.0)
Unknown	1	(0.4)	0	(0.0)	1	(0.2)
Number of Metastasis						
0-2	151	(54.1)	144	(52.9)	295	(53.5)
≥3	128	(45.9)	128	(47.1)	256	(46.5)
Liver Metastases						
Yes	119	(42.7)	110	(40.4)	229	(41.6)
No	160	(57.3)	162	(59.6)	322	(58.4)
Prior Gastrectomy/Esophagectomy						
Yes	48	(17.2)	40	(14.7)	88	(16.0)
No	231	(82.8)	231	(84.9)	462	(83.8)
Missing	0	(0.0)	1	(0.4)	1	(0.2)
Weight (kg)						
Participants with data	279		272		551	
Mean	65.2		68.2		66.7	
SD	14.3		15.7		15.1	
SE	0.9		1.0		0.6	
Median	62.0		66.0		64.5	
Range	38.5 to 131.0		33.0 to 128.8		33.0 to 131.0	
Body Surface Area (m^2)						
Participants with data	266		258		524	
Mean	1.7		1.8		1.7	
SD	0.2		0.2		0.2	
SE	0.0		0.0		0.0	
Median	1.7		1.8		1.7	
Range	1.3 to 2.5		1.2 to 2.5		1.2 to 2.5	
Body Mass Index						
Participants with data	279		271		550	
Mean	23.5		24.0		23.7	
SD	4.4		4.5		4.5	
SE	0.3		0.3		0.2	

	Pembrolizumab + chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Median	22.9		23.1		23.1	
Range	14.2 to 44.8		13.7 to 44.4		13.7 to 44.8	

Based on Table 11 of the response to the request for clarification[7]
CAPOX = Backbone chemotherapy oxaliplatin + capecitabine; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; FP = Backbone chemotherapy cisplatin + 5-FU; MSI = microsatellite instability; SE = standard error; SD = standard deviation

Given that the NICE final scope highlighted the subgroup of patients with programmed PD-L1 CPS ≥5 and the CS only provided data for a subgroup of patients with PD-L1 CPS ≥10 but did not provide data for those patients with PD-L1 CPS ≥5 we also requested that this baseline data from the two RCTs (KEYNOTE-859 and CheckMate-649) be provided. The company in their response to the request for clarification provided the following data, detailed below in Tables 3.7 to 3.10.

Table 0.7: CheckMate-649 baseline characteristics (Age; sex; race/ethnicity; location)

Trial ID	Intervention	Population	Age; median	Male; n (%)	Race/ethnicity			Location		
					Caucasian; n (%)	Black; n (%)	Asian; n (%)	North America; n (%)	Asia; n (%)	Others; n (%)
CheckMate-649[c,d]	NIVO + CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 5	63 (54, 69)b	331 (70)	328 (69)	2 (<1)	119 (25)	67 (14)	117 (25)	289 (61)
	CHEMO (CAP + OX, or 5-FU + OX)	PD-L1 CPS ≥ 5	62 (54, 68)b	349 (72)	327 (68)	7 (1)	117 (24)	70 (15)	111 (23)	301 (62)

Based on Table 14 of the response to the request for clarification[7]
CAP = Capecitabine; CHEMO = Chemotherapy; CIS = Cisplatin; CPS = Combined Positive Score; ITT = Intent to treat; NIVO = Nivolumab; OX = Oxaliplatin; PEMBRO = Pembrolizumab; 5-FU = 5-Fluorouracil
Notes: a, Range; b, Interquartile range; c, Baseline characteristics were not available separately for patients pre-assigned to CAPOX, d, Baseline characteristics were not available separately for PD-L1 CPS ≥1 and PD-L1 CPS ≥10 subgroups

Table 0.8: CheckMate-649 baseline characteristics (performance status; disease stage; histology)

Trial ID	Intervention	Population	ECOG Performance Status, n(%)				Disease stage, n(%)				Histology, n(%)		
			0	1	0-1	2	Recurrent	Unresectable	Locally advanced	Metastatic	Intestinal	Diffuse	Others
CheckMate-649b	NIVO + CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 5	194 (41)	279 (59)	473 (100) a	0	3 (1)	--	16 (3)	454 (96)	171 (36)	137 (29)	37 (8) d
	CHEMO (CAP + OX, or 5-FU + OX)	PD-L1 CPS ≥ 5	203 (42)	278 (58)	482 (100) a	0	1 (<1)	--	20 (4)	461 (96)	176 (37)	141 (29)	60 (6) d

Based on Table 15 of the response to the request for clarification[7]
CAP = Capecitabine; CHEMO = Chemotherapy; CIS = Cisplatin; CPS = Combined Positive Score; ITT = Intent to treat; NIVO = Nivolumab; OX = Oxaliplatin; PEMBRO = Pembrolizumab; 5-FU = 5-Fluorouracil
Notes: a, Range; b, Interquartile range; c, Baseline characteristics were not available separately for patients pre-assigned to CAPOX, d, Baseline characteristics were not available separately for PD-L1 CPS ≥1 and PD-L1 CPS ≥10 subgroups.

Table 0.9: CheckMate-649 baseline characteristics (tumour site; number of metastatic sites; PD -L1 expression status and MSI status)

Trial ID	Intervention	Population	Primary tumour site, n (%)			Number of metastatic sites, n (%)				Microsatellite stability/mismatch repair status, n (%)	
			Gastric	GEJ	Oesophagus	1	>1	≥2	≥3	MSI-H	Non-MSI high
CheckMate-649[a,b]	NIVO + CHEMO (CAP + OX, or, 5-FU + OX)	PD-L1 CPS ≥ 5	333 (70)	84 (18)	56 (12)	98 (21)	--	361 (76)	--	18 (4)	423 (89)c
	CHEMO (CAP + OX, or 5-FU + OX)	PD-L1 CPS ≥ 5	334 (69)	86 (18)	62 (13)	105 (22)	--	362 (75)	--	16 (3)	423 (88)c

Based on Table 16 of the response to the request for clarification[7]
CAP = Capecitabine; CHEMO = Chemotherapy; CIS = Cisplatin; CPS = Combined Positive Score; ITT = Intent to treat; MSI = microsatellite instability; NIVO = Nivolumab; OX = Oxaliplatin; PEMBRO = Pembrolizumab; 5-FU = 5-Fluorouracil
Notes: a, Range; b, Interquartile range; c, Baseline characteristics were not available separately for patients pre-assigned to CAPOX, d, Baseline characteristics were not available separately for PD-L1 CPS ≥1 and PD-L1 CPS ≥10 subgroups.

Table 0.10: KEYNOTE-859 participant characteristics (ITT population with CPS ≥5)

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]		[redacted]		[redacted]	
Sex						
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age Category 1 (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Age Category 2 (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 to <75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 75 to <85	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age Category 3 (Years)						
18-39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40-49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50-59	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60-69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70-79	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian Or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Geographic Region for Randomization						
Western Europe/Israel/North	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
America/Australia						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combination Chemotherapy for Randomization						
CAPOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status for Randomization						
CPS ≥ 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS < 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PD-L1 Status (CPS Cut Point: 1)						
CPS ≥ 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline PD-L1 Status (CPS Cut Point: 10)						
CPS ≥ 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS < 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MSI Status						
MSI-High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
non-MSI-High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Scale						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary Location						
Adenocarcinoma of the gastroesophageal junction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma of the stomach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall Stage						
IIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab + Chemotherapy		Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Disease Status						
Locally advanced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histological Subtype (Lauren classification)						
Diffuse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intestinal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Indeterminate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Metastasis						
0-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tumour Burden						
≥ Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
< Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver Metastases						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior Gastrectomy/Esophagectomy						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 16 of the response to the request for clarification[7]
CAPOX = oxaliplatin and capecitabine; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; FP = cisplatin + fluorouracil; MSI = microsatellite instability; PD-L1 = programmed death ligand 1; SD = standard deviation

Table 3.10 above details the ITT population with CPS ≥5. Generally, the two arms are comparable although the pembrolizumab plus chemotherapy arm has less males (>5%) than the chemotherapy only arm with 67.5 versus 74% respectively. Location of primary tumour was markedly difference between arms, with adenocarcinoma of the GOJ more frequent in the chemotherapy only group (27.8%), than in the chemotherapy and pembrolizumab group (19.5%). This was consistent with the ITT population with CPS ≥1 where adenocarcinoma of the GOJ being present in 19.9% of the pembrolizumab plus chemotherapy group as opposed to 26.6% of the chemotherapy only group. Adenocarcinoma of the stomach was more frequent in the pembrolizumab plus chemotherapy group with 80.5% of patients as opposed to 72.2% of patients in the chemotherapy only group. Again, this distribution was consistent with the ITT population with CPS ≥1 population.

EAG comment: The baseline characteristics of the pembrolizumab plus chemotherapy arm and the chemotherapy arm of the KEYNOTE-859 trial for subgroups based on different PD-L1 expression status are generally comparable.

3.2.3 Statistical analysis for the KEYNOTE-859 trial

The CS details three defined analysis populations:[1]

1. The ITT population which consisted of all 1,579 randomised participants, whether treatment was administered, which served as the population for primary efficacy analysis of overall survival (OS), PFS, objective response rate (ORR), and duration of response (DOR). The ITT populations with PD-L1 positive tumours defined by CPS ≥1 and CPS ≥10 consisted of 1235 and 551 participants, respectively.
2. Safety analyses were based on all participants as treated (APaT) population, which included all 1,572 randomised participants who received at least one dose of study intervention according to the study intervention they received.
3. Patient reported outcome (PRO) analyses for the European Organization For Research And Treatment Of Cancer Core Quality of Life questionnaire (EORTC-QLQ-C30), European Organization For Research And Treatment Of Cancer Quality of Life Questionnaire – Gastric Cancer Module (EORTC-QLQ-STO22), and European Quality of Life-5 dimensions-5 levels (EQ-5D-5L) questionnaires were based on the PRO full analysis set (FAS) population, which included all 1,543 (EORTC-QLQ-C30 and EQ-5D-5L) and 1,528 (EORTC-QLQ-STO22) randomised participants who had at least one PRO assessment available for the specific endpoint and have received at least one dose of study intervention.

The primary, secondary and exploratory outcomes of the KEYNOTE-859 trial are listed in Table 3.11. The company provided details of statistical methods in Section B 2.4 of the CS.[1]

The company provided an overview of the plan for hypothesis testing in Section B 2.4 of the CS.[1] The primary outcomes (OS in all randomised patients, and in those with PD-L1 CPS ≥1 and those with PD-L1 CPS ≥10) were tested. Secondary outcomes (PFS and ORR, both in all randomised patients, and in those with PD-L1 CPS ≥1 and those with PD-L1 CPS ≥10) were also tested.

Study sample size calculations (described on page 41 of the CS) were based on the primary outcomes and assumed that the prevalence of patients with PD-L1 ≥1 was approximately 78% and the prevalence of patients with PD-L1 ≥10 was approximately 35%. The sample size estimation for the comparison between pembrolizumab-chemotherapy and chemotherapy was as follows:[1]

- *"There will be ~ 463 OS events in CPS ≥10 participants at the OS final analysis (expected ~54 months). With 463 OS events, the study has ~ 87% power for detecting an AHR of 0.73 in CPS ≥10 participants (H1) at an initially assigned 0.017 (1-sided) significance level.*

- *There will be ~ 1057 OS events in CPS ≥1 participants at the OS final analysis. With 1057 OS events, the study has ~ 90% power for detecting an AHR=0.81 in CPS ≥1 participants at the final analysis with an (1-sided) significance level of 0.017 (alpha=0.017 can be passed from H1 to H2 if H1 is rejected).*

- *It is estimated that there will be ~ 1358 OS events in all participants at the OS final analysis. With 1358 OS events, the study has ~ 84% power for detecting an AHR=0.83 in all participants at the final analysis with an initially assigned 0.008 (1- sided) significance level"*

Details of the timing of interim analysis and final analysis was provided in Section B.2.4 on page 40 of the CS).[1] This included the following statements:[1]

"Interim Analysis:

- *Timing: scheduled to be performed after ~ 403 OS events have occurred in CPS ≥10 participants AND ~ 12 months after last participant randomised. If there were fewer than 1187 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number was reached, whichever occurred first.*
- *Primary purpose: the final efficacy analysis for ORR and PFS endpoints and the interim analysis for OS in CPS ≥10, in CPS ≥1 and in all participants.*

Final analysis:

- *Timing: scheduled to be performed after ~ 463 OS events have occurred in CPS ≥10 participants and ~ 23 months after last participant randomised. If there were fewer than 1358 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number was reached, whichever occured first.*
- *Primary purpose: the final efficacy analysis for OS in CPS ≥10, in CPS ≥1, in all participants."*

A summary of statistical methods is described in Sections B.2.4 of the CS[1] and is presented in Table 3.11 below.

Table 0.11: Statistical methods used in the KEYNOTE-859 RCT

Overview of statistical methods	
Study Design Overview	Phase 3, randomised, double-blind clinical study of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as first-line treatment in participants with HER2 negative, previously untreated, unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-859)
Treatment Assignment	Participants were randomised in a 1:1 ratio to the experimental group and the control group.
Analysis Populations	Efficacy: ITT Safety: APaT PRO: FAS
Primary Endpoint	OS
Key Secondary Endpoints	PFS per RECIST 1.1 assessed by BICR OR per RECIST 1.1 assessed by BICR
Statistical Methods for Key Efficacy Analyses	The hypotheses on PFS and OS were evaluated by comparing the experimental group to the control group using a stratified Log-rank test. The HR was estimated using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the K-M method. The stratified M&N method with sample size weights was used for analysis of ORR[17].
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs were provided for between-treatment differences in the percentage of participants with events, these analyses were performed using the M&N method[17].

Overview of statistical methods	
Interim Analyses	One interim analysis was planned in this study. Results were reviewed by an external DMC. **Interim analysis:** Timing: scheduled to be performed after ~ 403 OS events have occurred in CPS ≥10 participants AND ~ 12 months after last participant randomised. If there were fewer than 1,187 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number was reached, whichever occurred first. Primary purpose: the final efficacy analysis for ORR and PFS endpoints and the interim analysis for OS in CPS ≥10, in CPS ≥1 and in all participants. **Final analysis:** Timing: scheduled to be performed after ~ 463 OS events have occurred in CPS ≥10 participants and ~ 23 months after last participant randomised. If there were fewer than 1,358 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number was reached, whichever occurred first. Primary purpose: the final efficacy analysis for OS in CPS ≥10, in CPS ≥1, in all participants.
Multiplicity	The overall type I error over the primary and secondary hypotheses was strongly controlled at 2.5% (1-sided) An initial alpha of 1.7% were assigned to OS in CPS ≥10 participants (H1) and 0.8% to OS in all participants (H3). By using the graphical approach of Mauer and Bretz, if one hypothesis is rejected, the alpha will be shifted to other hypotheses[18].
Sample Size and Power	The overall sample size of the study (i.e., all participants) was ~ 1,579. The sample size for CPS ≥10 was projected to be ~551 based on a prevalence rate of ~ 35% of the CPS ≥10 participants among all participants. The sample size of CPS ≥1 participants was projected to be ~ 1,235 based on a prevalence rate of ~ 78% of the CPS ≥1 participants among all participants. The number of all participants randomised drive the completion of enrolment. There will be ~ 463 OS events in CPS ≥10 participants at the OS final analysis (expected ~ 54 months). With 463 OS events, the study has ~ 87% power for detecting an AHR of 0.73 in CPS ≥10 participants (H1) at an initially assigned 0.017 (1-sided) significance level. There will be ~ 1,057 OS events in CPS ≥1 participants at the OS final analysis. With 1,057 OS events, the study has ~ 90% power for detecting an AHR = 0.81 in CPS ≥1 participants at the final analysis with an (1-sided) significance level of 0.017 (alpha = 0.017 can be passed from H1 to H2 if H1 is rejected). It is estimated that there will be ~ 1,358 OS events in all participants at the OS final analysis. With 1,358 OS events, the study has ~ 84% power for detecting an AHR = 0.83 in all participants at the final analysis with an initially assigned 0.008 (1- sided) significance level.
Data management, patient withdrawals	Subjects may withdraw from the trial at any time for any reason. If a subject withdrew from the trial, he/she no longer received treatment or was followed at scheduled protocol visits. A subject was withdrawn from the trial if: the subject or subject's legally acceptable representative withdrew consent from the trial.

Overview of statistical methods	
	The subject was lost to follow-up. Subjects who withdrew from treatment prior to completion of the trial were encouraged to continue to be followed for all remaining study visits. When a subject withdrew from participation in the trial, all applicable activities scheduled for the end of treatment visit were performed at the time of discontinuation.
Based on Table 8 of the CS[1] AHR = adjusted hazard ratio; APaT = all participants as treated ; BICR = Blinded Independent Central Review; CIs = confidence intervals; CPS = combined positive score; CS = company submission; DMC = Data Monitoring Committee; FAS = full analysis set; HER2 = human epidermal growth factor receptor 2; H1 = Hypothesis 1; H3 = Hypothesis 3; HR = hazard ratio; ITT = intention-to-treat; K-M = Kaplan-Meier; M&N = stratified Miettinen and Nurminen method; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; ORR = objective response rate; OS = overall survival ; RECIST = Response Evaluation Criteria in Solid Tumours	

The company states that the non-parametric Kaplan-Meier (K-M) method was used to estimate the PFS and OS rates over time in each treatment group.[1] The hypotheses of treatment differences in PFS and OS were assessed by the stratified log-rank test. The company further states that a stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate the magnitude of the treatment difference (hazard ratio [HR]) between the treatment groups. The stratification factors used for the randomisation were applied to both the stratified log-rank test and the stratified Cox model.[1] The analysis strategy for key efficacy endpoints is presented in Table 3.12.

Table 0.12: Analysis strategy employed in the KEYNOTE-859 trial

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	Censored at the last known alive date
Key Secondary Endpoints			
PFS per RECIST 1.1 by BICR	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT (CPS ≥10, CPS ≥1, and all participants)	Primary censoring rule Sensitivity analysis 1 Sensitivity analysis 2 (More details are provided in Table 3.13, Censoring Rules for Primary and Sensitivity Analyses of PFS)
ORR per RECIST 1.1 by BICR	Test and Estimation: Stratified M&N method with sample size weight	ITT (CPS ≥10, CPS ≥1, and all participants)	Participants without assessments are considered no responders and conservatively included in the denominator

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Based on Table 9 of the CS[1] BICR = blinded independent central review; CPS = combined positive score; CS = company submission; ITT = intention-to-treat; M&N = Miettinen and Nurminen; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours			

The company further made the following statements:[1]

- *"since PD was assessed periodically, PD could occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD was documented. For the primary analysis, for the subjects who have PD, the true date of PD was approximated by the date of the first assessment at which PD was objectively documented per RECIST 1.1 by investigator. Death was always considered as a confirmed PD event. Subjects who did not experience a PFS event were censored at the last disease assessment.*

- *To evaluate the robustness of the PFS endpoint per RECIST 1.1 by investigator, two sensitivity analyses with different sets of censoring rules were performed for comparison of PFS per RECIST 1.1 by investigator. The first sensitivity analysis followed the intention-to-treat principle. That is, PDs/deaths were counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considered discontinuation of treatment due to reasons other than complete response or initiation of new anti-cancer treatment, whichever occurred later, to be a PD event for subjects without documented PD or death. If a subject met multiple criteria for censoring, the censoring criterion that occurred earliest was applied."*

Subjects in the placebo plus chemotherapy arm were expected to discontinue treatment earlier compared with subjects in the pembrolizumab plus chemotherapy arm and may have switched to another anti PD-1 treatment following the verification of PD by the central imaging vendor.[1] The censoring rules for primary and sensitivity analyses of PFS are described in Sections B.2.4 of the CS[1] and presented in Table 3.13 below.

Table 3.13: Censoring rules for primary and sensitivity analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study intervention or completed study intervention
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

Based on Table 10 of the CS[1]
CS = company submission; PD = progressive disease; PFS = progression-free survival

The CS states that the proportional hazards assumption on PFS was examined using both graphical and analytical methods if warranted.[1]

The company further states that one interim analysis was permitted to be performed in this study on the basis of projection of enrolment.[1] The purpose of each analysis is summarised in Table 3.14 below.

Table 3.14: Summary of interim and final analyses strategy for efficacy

Analyses	Timing	Estimated Months After First Participant Randomised	Primary Purpose of Analysis
Interim Analysis	~ 403 OS events have occurred in CPS ≥10 participants AND ~ 12 months after the last participant has been randomised. If there are fewer than ~1187 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number is reached, whichever occurs first. This is the final analysis of PFS and ORR.	~ 43 months	Efficacy analysis for ORR, PFS, and OS in CPS ≥10, in CPS ≥1, and in all participants.
Final Analysis	~ 463 OS events have occurred in CPS ≥10 participants AND ~ 23 months after the last participant has been randomised. If there are fewer than ~1358 OS events in all participants at the time, then the analysis may be delayed for up to 2 months or when the targeted OS event number is reached, whichever occurs first.	~ 54 months	Efficacy analysis for OS in CPS ≥10, in CPS ≥1, in all participants.

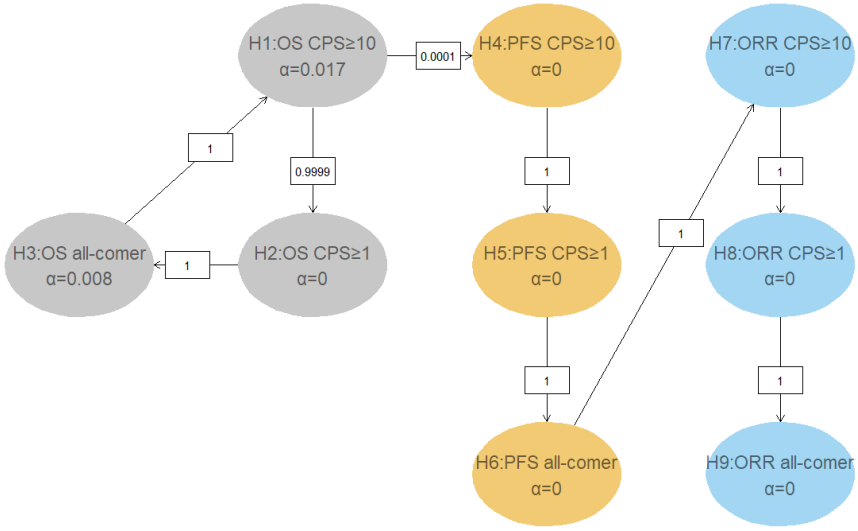
Based on Table 11 of the CS[1]
CPS = combined positive score; CS = company submission; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

3.2.3.1 Multiplicity strategy for PFS, OS and ORR

The CS details that KEYNOTE-859 utilised the graphical method of Maurer and Bretz to provide strong multiplicity control for multiple hypotheses as well as interim analysis. In this method, study hypotheses might be tested repeatedly, and when a particular null hypothesis is rejected, the α allocated to that

hypothesis can be reallocated to other hypothesis tests.[1] Figure 3.2 derived from the CS provides an overview of the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for re-allocation from each hypothesis to the others are detailed in the boxes on the lines connecting hypotheses. The boundaries provided in this section are calculated based on the estimated number of events at each analysis, and the actual boundaries were determined from the actual number of events observed at the time of the analyses, using the spending functions specified.[1] The Maurer and Bretz multiplicity strategy approach used for hypothesis testing in KEYNOTE-859 is presented in Figure 3.2.

Figure 3.2: Maurer and Bretz multiplicity strategy approach used for hypothesis testing in KEYNOTE-859



Based on Figure 4 of the CS[1]
CPS = combined positive score; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Subgroup analyses were pre-specified in the KEYNOTE-859 study protocol to determine whether the treatment effect was consistent across subgroups. The estimate of the between-group treatment effect for the primary endpoints were estimated within each category of the following classification variables:[1]

- Geographic region (Global Cohort only)
  - Europe/Israel/North America/Australia
  - Asia
  - Rest of the World (including South America)
- Disease status (ECOG 0 versus ECOG 1)
- Chemotherapy regimen (FP or CAPOX)

EAG comment: The statistical methods appear to be satisfactory.

3.2.4 Risk of bias assessment of the KEYNOTE-859 trial

The CS (B.2.5) confirms that *"Quality Assessment of KEYNOTE-859 was conducted using the Cochrane risk of bias tool. Based on this analysis, the study was determined to be at 'low risk' across all six key domains"*. The quality assessment of the KEYNOTE- 859 trial is presented in Table 3.15.

Table 0.15: Results of the risk of bias assessment for the KEYNOTE-859 trial

Type of bias	KEYNOTE-859		EAG assessment	
	Review authors' judgement	Support for judgement	Review authors' judgement	Support for judgement
Bias arising from the randomisation process	Low	Treatment allocation/randomisation will occur centrally using an IRT system. No apparent imbalances in baseline characteristics between intervention arms.	Low/unclear	Generally, in agreement with company assessment. Baseline characteristics generally balanced but it's noted that differences exist beyond 5% in the ITT Population with CPS ≥1 with regards to the primary locations of the tumours with Adenocarcinoma of the gastroesophageal junction being present in 19.9% of the pembrolizumab plus chemotherapy group as opposed to 26.6% of the chemotherapy only group. Adenocarcinoma of the stomach was also increased beyond 5% in the pembrolizumab plus chemotherapy group, with 79.9% as opposed to 73.5% in the chemotherapy only group.
Bias due to deviations from intended interventions	Low	Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. No apparent changes from assigned intervention that were inconsistent with the trial protocol ITT analysis	Low	In agreement with company assessment.
Bias due to missing outcome data	Low	Outcome reported for all patients assigned to each intervention arm	Low	In agreement with company assessment.
Bias in measurement of the outcome	Low	Prespecified survival outcome assessment in statistical analysis plan Observer reported outcome not involving judgement	Low	In agreement with company assessment.

Type of bias	KEYNOTE-859		EAG assessment	
	Review authors' judgement	Support for judgement	Review authors' judgement	Support for judgement
		Blinded independent central review for response outcomes		
Bias in selection of the reported result	Low	Prespecified statistical analysis plan All eligible reported results for the outcome domain correspond to all intended outcome measurements. All eligible reported results for the outcome measurement correspond to all intended analyses.	Low	In agreement with company assessment.
Overall bias	Low	All subcategories had low risk of bias	Low	Generally low risk but some baseline differences may have relevance.

Based on Table 17 of the CS appendices[8].
CPS = combined positive score; CS = company submission; IRT = interactive response technology; ITT = intention-to-treat
CheckMate-649 results not included.

EAG comment: The EAG rated the KEYNOTE-859 trial as being at low risk of bias.

3.2.4 External validity of the KEYNOTE-859 trial

KEYNOTE-859 is a global study conducted in 215 centres across 33 countries, including three sites in the UK. Of the patients participating in the study, 42 were enrolled at sites in the UK.

As discussed in Section 3.2.2.5, the EAG expressed some concerns regarding the generalisability of the trial participants to the UK population and sought clarification from the company. These concerns are described in Section 3.2.2.5. Briefly, we noted that the participants did not seem to represent a demographic profile that we would expect to see in England and Wales. Of note was the minimal involvement of participants from England and Wales and an under representation of black participants.

The company response included additional baseline data for UK and European participants with CPS ≥1 and it provided a rationale for the under inclusion of black participants.[7] Firstly, the company stated that *"The aim of the trial is to represent patients with HER2 negative locally advanced metastatic gastric or GOJ adenocarcinoma globally.[7]"* While the EAG accepts this argument, ideally there should be sufficient representation within the trial participants to ensure that the trial can be relevant to the target population in the UK.

Secondly, the company provided tabulated data demonstrating that [redacted] of European participants in the KEYNOTE-859 trial were white while a post-hoc analysis of the UK participants in the KEYNOTE-859 trial demonstrated that [redacted] of participants were white. The company opined that for this reason they believe that KEYNOTE-859 trial results are generalisable to England and Wales population. It should be noted that current data from England and Wales indicates that approximately 82% of population is white.[19] The company also reinforced this belief by stating that the CheckMate-649 trial

included 68-70% of white participants which is below the proportion of white population in England and Wales, but that the NICE appraisal committee concluded that the CheckMate-649 trial was generalisable to NHS practice.

The UK based participant baseline data provided by the company in their response to the request for clarification[7] provides baseline data for 34 participants with CPS ≥1 from the ITT population.

The company state in the CS that the baseline characteristics that were included in KEYNOTE-859, were as expected for patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma. They emphasise that '*Most patients were male, <65 years old, and had an ECOG performance status of 1. The majority of participants had adenocarcinoma of the stomach (78.7%), had tumour PD-L1 status of CPS ≥1 (78.2%), and were on a CAPOX regimen (86.3%). The treatment arms were generally well balanced by all baseline characteristics*.'

Baseline characteristics of patients enrolled in KEYNOTE-859 were as expected for patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma. Most patients were male, <65 years old, and had an ECOG performance status of 1. The majority of participants had adenocarcinoma of the stomach (78.7%), had tumour PD-L1 status of CPS ≥1 (78.2%), and were on a CAPOX regimen (86.3%). The treatment arms were generally well balanced by all baseline characteristics.

On reviewing the post-hoc data supplied by the company, it is apparent that the majority of participants in both the European ([redacted]) and the UK ([redacted]) subsets are defined as being white. The EAG notes that in the UK population only 34 participants are detailed, and no information is included to describe this missing data. It also of note that in the UK subpopulation, 15.4% of those in the chemotherapy only group are black, while no black patients are detailed in the pembrolizumab plus chemotherapy group. The EAG acknowledged that this represents a difference only a difference of two participants, however if the data are to be generalisable to the relevant NHS population, then this could be of note, given that no black participants in the UK actually received pembrolizumab. The company in their response to clarification also emphasised that '*CheckMate-649 trial included only around 1% of Black participants which is below the proportion of Black population in England and Wales, however the NICE appraisal committee concluded that the CheckMate-649 trial was generalisable to NHS practice'*.[7]

3.2.5 Efficacy results of the KEYNOTE-859 trial

Results were presented from the KEYNOTE-859 study on the basis of the interim analysis 1 (IA 1), which had a data cut-off date of 3 October 2022.[1] Efficacy analyses were conducted by using the ITT population. The median duration of follow-up in patients with PD-L1 CPS ≥1 was 11.9 months (ranging from 0.1 month to 45.9 months).

The focus of the company submission was the PD-L1 positive subgroup of patients (defined as CPS ≥1) in line with the population covered by the marketing authorisation.[1] The PD-L1 status was a pre-specified subgroup that was employed as a stratification factor.

3.2.5.1 Overall survival

3.2.5.1.1 Overall survival in patients with PD-L1 CPS ≥1

As of the data cut-off date (3 October 2022) for patients with PD-L1 CPS ≥1, the median duration of follow up was 13.0 months (0.2 to 45.9 months) in the pembrolizumab plus chemotherapy group and 11.5 months (0.1 to 45.5 months) in the chemotherapy group.[1]

Pembrolizumab plus chemotherapy was associated with a statistically significant improvement in OS when compared with chemotherapy alone: HR 0.74 (95% confidence interval (CI): 0.65, 0.84; p<0.0001). The median OS was 13.0 months (95% CI: 11.6, 14.2) and 11.4 months (95% CI: 10.5, 12.0) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.[1]

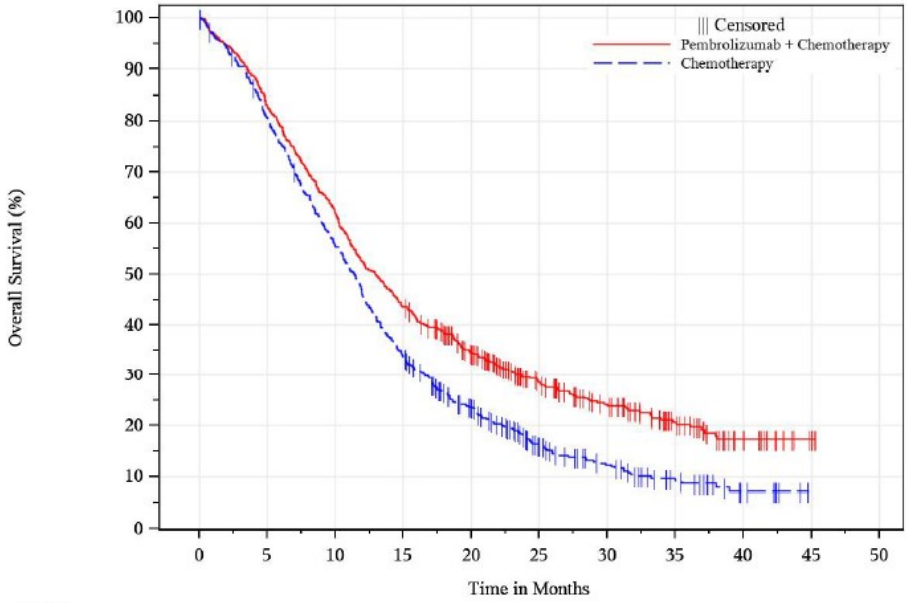
The results of the analysis of OS in patients with PD-L1 CPS ≥1 are presented in Table 3.16. The corresponding K-M survival plots are presented in Figure 3.3.

Table 0.16: Analysis of OS in patients with PD-L1 CPS ≥1

	Pembrolizumab + chemotherapy (N=618)	**Chemotherapy (N=617)**
Number of Events (%)	464 (75.1)	526 (85.3)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)
[Q1, Q3]	[6.9, 28.7]	[6.2, 18.6]
Person-months	9644.5	8008.1
Event Rate / 100 Person-months	4.8	6.6
versus chemotherapy		
Hazard ratio (95% CI)[b]	0.74 (0.65, 0.84)	
p-value[c]	<0.0001	
OS Rate at month 6 (%) (95% CI)	79.0 (75.5, 82.0)	75.7 (72.1, 78.9)
OS Rate at month 12 (%) (95% CI)	52.4 (48.4, 56.3)	45.7 (41.7, 49.6)
OS Rate at month 18 (%) (95% CI)	38.4 (34.6, 42.3)	26.6 (23.2, 30.2)
OS Rate at month 24 (%) (95% CI)	29.6 (25.9, 33.3)	17.7 (14.7, 21.0)
OS Rate at month 30 (%) (95% CI)	23.9 (20.3, 27.6)	12.3 (9.6, 15.4)

Based on Table 12 of the CS[1]
CI = confidence intervals; CS = company submission; Q1 = 25th percentile; Q3 = 75th percentile; OS = overall survival; PD-L1 = programmed death ligand 1
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.

Figure 3.3: Kaplan-Meier plot of OS in patients with PD-L1 CPS ≥1



Based on Figure 5 of the CS[1]
CPS = combined positive score; PD-L1 = programmed cell death ligand 1

3.2.5.2 Progression-free survival

3.2.5.2.1 Progression free survival in patients with PD-L1 CPS ≥1

Pembrolizumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy alone based on Blinded Independent Central Review (BICR) assessment per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) in patients with PD-L1 CPS ≥1: HR 0.72 (95% CI: 0.63, 0.82; p<0.0001).[1] The median PFS was 6.9 months (95% CI: 6.0, 7.2) and 5.6 months (95% CI: 5.4, 5.7) for the pembrolizumab plus chemotherapy and chemotherapy groups, respectively.[1]

The results of the analysis of PFS in patients with PD-L1 CPS ≥1 are presented in Table 3.17. The corresponding K-M survival plots are presented in Figure 3.4.

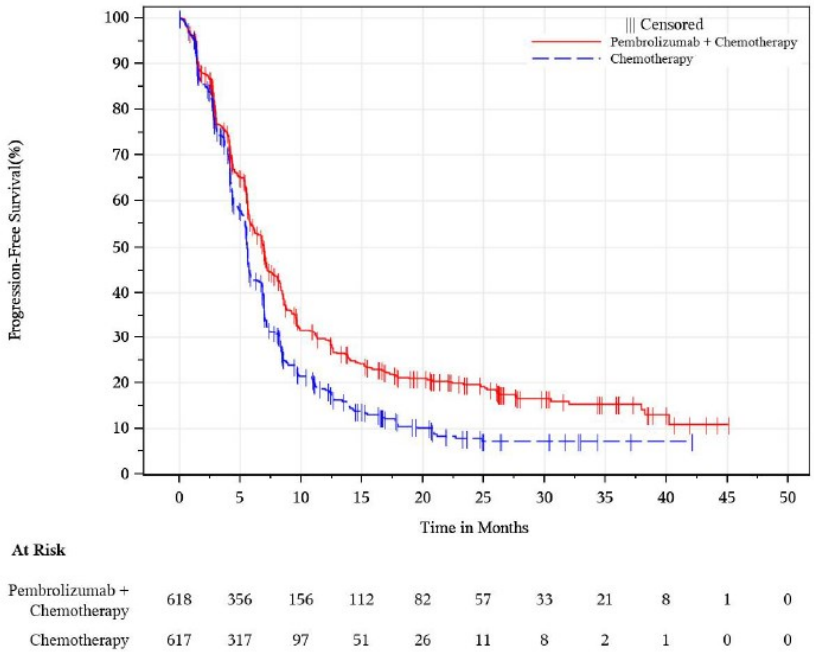
Table 0.17: Analysis of PFS based on BICR assessment (per RECIST 1.1) in patients with PD-L1 CPS ≥1

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Number of events (%)	443 (71.7)	483 (78.3)
Death	91 (14.7)	92 (14.9)
Documented progression	352 (57.0)	391 (63.4)
Kaplan-Meier estimates (months)[a]		
Median (95% CI)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)
[Q1, Q3]	[3.9, 14.0]	[3.2, 8.6]

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Person-months	5538.1	3987.5
Event Rate / 100 Person-months	8.0	12.1
versus chemotherapy		
Hazard ratio (95% CI)[b]	0.72 (0.63, 0.82)	
p-value[c]	<0.0001	
PFS rate at month 6 (%) (95% CI)	54.4 (50.1, 58.4)	43.4 (39.3, 47.5)
PFS rate at month 12 (%) (95% CI)	29.4 (25.5, 33.3)	18.4 (15.1, 21.9)
PFS rate at month 18 (%) (95% CI)	21.2 (17.7, 24.9)	10.4 (7.7, 13.6)
PFS rate at month 24 (%) (95% CI)	19.5 (16.1, 23.2)	7.9 (5.3, 11.0)
PFS rate at month 30 (%) (95% CI)	16.6 (13.2, 20.3)	7.3 (4.7, 10.5)

Based on Table 13 of the CS[1]
CI = confidence intervals; CS = company submission; Q1 = 25th percentile; Q3 = 75th percentile; PD-L1 = programmed death ligand 1; PFS = progression free survival; RECIST=Response Evaluation Criteria in Solid Tumours
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.

Figure 0.4: Kaplan-Meier plot of PFS based on BICR assessment (per RECIST 1.1) in patients with PD-L1 CPS ≥1



Based on Figure 5 of the CS[1]
BICR = Blinded Independent Central Review; CPS = combined positive score; CS = company Submission; PD-L1= programmed cell death ligand 1; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1

3.2.5.3 Objective response rate

3.2.5.3.1 Objective response rate in patients with PD-L1 CPS ≥1

Pembrolizumab plus chemotherapy was associated with a statistically significant improvement in ORR when compared with chemotherapy alone based on BICR assessment per RECIST 1.1 in patients with PD-L1 CPS ≥1.[1]

The BICR assessed ORR was 52.1% (95% CI: 48.1, 56.1) for the pembrolizumab plus chemotherapy group and 42.6% (95% CI: 38.7, 46.6) for the chemotherapy group, reflecting a statistically significant difference of 9.5% (95% CI: 3.9, 15.0; p=0.00041).[1]

The complete response (CR) and partial response (PR) rates were higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group in patients with PD-L1 CPS ≥1 (9.9% versus 5.8% for CR; 42.2% versus 36.8% for PR).[1]

Tables 3.18 and 3.19 provide an overview of the data on ORR.

Table 0.18: Analysis of objective response based on BICR assessment (per RECIST 1.1) in patients with PD-L1 CPS ≥1

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + Chemotherapy versus Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	618	322	52.1 (48.1, 56.1)	9.5 (3.9, 15.0)	0.00041
Chemotherapy	617	263	42.6 (38.7, 46.6)		

Based on Table 14 of the CS[1]
CI = confidence intervals; CPS = Combined positive score; CS = company submission; PD-L1 = programmed death ligand 1; RECIST=Response Evaluation Criteria in Solid Tumours
a Based on Miettinen & Nurminen method 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.
b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Responses are based on BICR assessment per RECIST 1.1.
Database cut-off date: 3 October 2022

Table 0.19: Summary of best objective response based on BICR assessment (per RECIST 1.1) in patients with PD-L1 CPS ≥1

	Pembrolizumab + Chemotherapy			Chemotherapy		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Participants in Population	618			617		
Complete Response (CR)	61	9.9	(7.6, 12.5)	36	5.8	(4.1, 8.0)
Partial Response (PR)	261	42.2	(38.3, 46.2)	227	36.8	(33.0, 40.7)
Overall Response (CR+PR)	322	52.1	(48.1, 56.1)	263	42.6	(38.7, 46.6)
Stable Disease (SD)	194	31.4	(27.7, 35.2)	243	39.4	(35.5, 43.4)
Disease Control (CR+PR+SD)	516	83.5	(80.3, 86.3)	506	82.0	(78.7, 85.0)
Progressive Disease (PD)	54	8.7	(6.6, 11.2)	64	10.4	(8.1, 13.1)
Not Evaluable (NE)	5	0.8	(0.3, 1.9)	12	1.9	(1.0, 3.4)

	Pembrolizumab + Chemotherapy			Chemotherapy		
	n	(%)	(95% CI)	n	(%)	(95% CI)
No Assessment	43	7.0	(5.1, 9.3)	35	5.7	(4.0, 7.8)

Based on Table 15 of the CS[1]
BICR = Blinded independent central review; CI = confidence intervals; CPS= Combined positive score; CR = complete response; CS = company submission; NE = no assessment; PD = progressive disease; PD-L1 = programmed death ligand 1; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease
Responses are based on BICR assessment per RECIST 1.1.
Stable disease includes both SD and non-CR/non-PD and NED.
NED: No lesions were identified at baseline assessment and there remained no lesions at post baseline assessment(s). NE: post-baseline assessment(s) available however not being evaluable.
No Assessment: no post-baseline assessment available for response evaluation.
Database cut-off date: 3 October 2022

3.2.5.3.2 Duration of response in patients with PD-L1 CPS ≥1

Pembrolizumab plus chemotherapy was associated with a longer DOR when compared with chemotherapy alone based on BICR assessment per RECIST 1.1 in patients with PD-L1 CPS ≥1, see Table 3.20. The median BICR-assessed DOR was longer in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (8.3 months versus 5.6 months).[1]

The percentage of responders with extended DOR was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group at ≥6 months (60.2% versus 47.2%) and ≥24 months (30.0% versus 11.1%).[1]

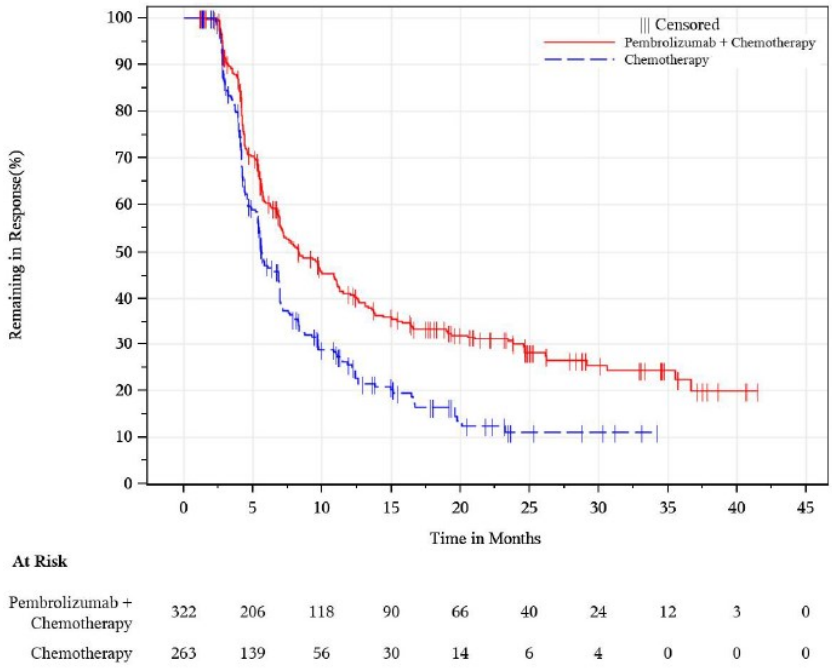
The corresponding K-M survival plots are presented in Figure 3.5.

Table 0.20: Summary of time to response and DOR based on BICR assessment (per RECIST 1.1) in patients with PD-L1 CPS ≥1

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Number of participants with response [a]	322	263
Time to Response (months)		
Mean (SD)	2.1 (1.6)	2.0 (1.3)
Median (Range)	1.5 (1.0-15.2)	1.5 (1.1-13.6)
Response Duration [b] (months)		
Median (Range)	8.3 (1.2+ - 41.5+)	5.6 (1.3+ - 34.2+)
Number (%b) of Participants with Extended Response Duration:		
≥6 months	170 (60.2)	106 (47.2)
≥12 months	106 (41.2)	44 (25.6)
≥18 months	76 (33.6)	20 (16.3)
≥24 months	49 (30.0)	6 (11.1)
≥30 months	24 (25.5)	4 (11.1)

	Pembrolizumab + Chemotherapy (N=618)	Chemotherapy (N=617)
Based on Table 16 of the CS[1] BICR = Blinded Independent Central Review; CPS = combined positive score; CS = company submission; PD-L1 = programmed death ligand 1; RECIST = Response Evaluation Criteria in Solid Tumours; SD = standard deviation a Includes participants with complete response or partial response b From product-limit (Kaplan-Meier) method for censored data "+" indicates there is no progressive disease by the time of last disease assessment Database cut-off date: 3 October 2022		

Figure 0.5: Kaplan-Meier plot of DOR based on BICR assessment (per RECIST 1.1) in patients with PD-L1 CPS ≥1



Based on Figure 7 of the CS[1]
BICR = Blinded Independent Central Review; CPS = combined positive score; PD-L1= programmed cell death ligand 1; RECIST 1.1= Response Evaluation Criteria in Solid Tumours Version 1.1

3.2.5.3.3. Results of the post-hoc analysis for patients with PD-L1 CPS ≥5

The company did not provide any results for patients with PD-L1 CPS ≥5 of the KEYNOTE-859 trial in the CS. The EAG requested relevant results for this subgroup of the KEYNOTE-859 trial. In responding to EAG's request, the company provided the results of a post-hoc analysis for patients with PD-L1 CPS ≥5 from the KEYNOTE-859 trial.

Overall survival in patients with PD-L1 CPS ≥5

As of the data cut-off date of 3 October 2022, pembrolizumab plus chemotherapy was associated with a statistically significant improvement in OS when compared with chemotherapy alone in patients with PD-L1 CPS ≥5: HR [redacted] (95% CI: [redacted]).[7] The median OS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]) for the pembrolizumab plus chemotherapy group and the chemotherapy group, respectively.[7]

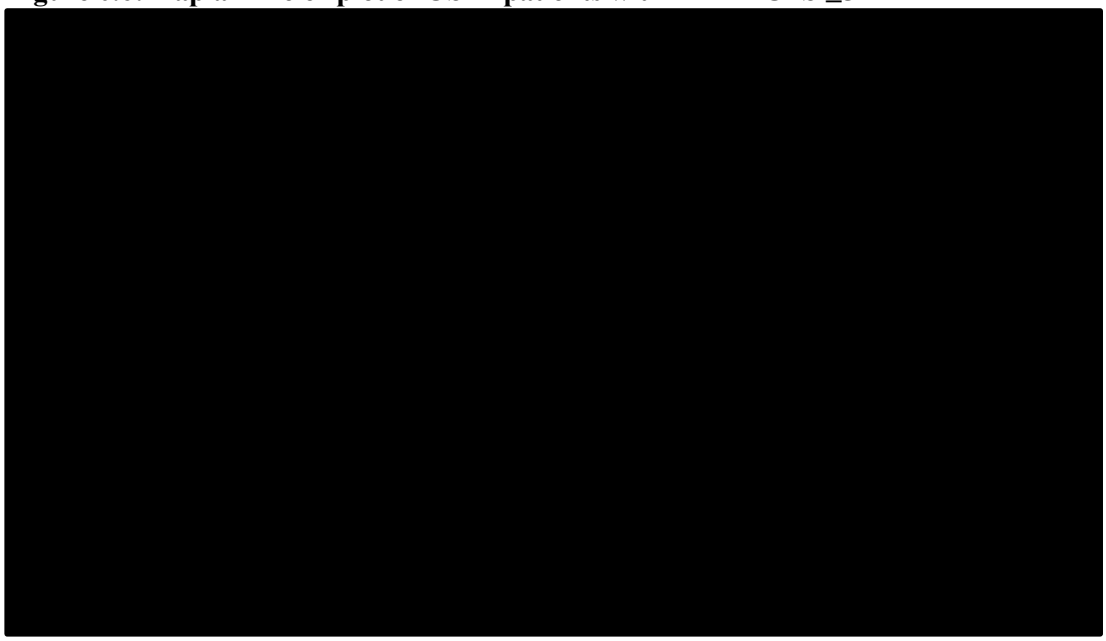
The results of the analysis of OS in patients with PD-L1 CPS ≥5 are presented in Table 3.21. The corresponding K-M survival plots are presented in Figure 3.6.

Table 0.21: Analysis of OS in patients with PD-L1 CPS ≥5

	Pembrolizumab + Chemotherapy (N=379)	Chemotherapy (N=388)
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]
versus 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]

Based on Table 4 of the company response to clarification[7]
CI = confidence intervals; CPS = combined positive score; Q1 = 25th percentile; Q3 = 75th percentile; PD-L1 = programmed death ligand 1; OS = overall survival; RECIST=Response Evaluation Criteria in Solid Tumours
a From product-limit (Kaplan-Meier) method for censored data.
b based on unstratified cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on unstratified log-rank test.
Database cut-off date: 3 October 2022

Figure 0.6: Kaplan-Meier plot of OS in patients with PD-L1 CPS ≥5



Based on Figure 1 of the company response to clarification[7]
CPS = combined positive score; PD-L1= programmed cell death ligand 1

Progression free survival in patients with PD-L1 CPS ≥5

As of the data cut-off date of 3 October 2022, pembrolizumab plus chemotherapy was associated with a statistically significant improvement in PFS compared with chemotherapy alone based on BICR assessment per RECIST 1.1 in patients with PD-L1 CPS ≥5: HR [redacted] (95% CI: [redacted]).[7] The median PFS was [redacted] months (95% CI: [redacted]) and [redacted] months (95% CI: [redacted]) for the pembrolizumab plus chemotherapy group and chemotherapy group, respectively.[7]

The results of the analysis of PFS in patients with PD-L1 CPS ≥5 are presented in Table 3.22. The corresponding K-M survival plots are presented in Figure 3.7.

Table 0.22: Analysis of PFS based on BICR assessment per RECIST 1.1 in patients with PD-L1 CPS ≥5

	Pembrolizumab + Chemotherapy (N=379)	**Chemotherapy (N=388)**
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]
versus Chemotherapy		
Hazard ratio (95% CI)[b]	[redacted]	

	Pembrolizumab + Chemotherapy (N=379)	Chemotherapy (N=388)
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]

Based on Table 5 of the company response to clarification [7]
BICR = Blinded independent central review; CI = confidence intervals; CPS = combined positive score; Q1 = 25th percentile; Q3 = 75th percentile; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours
a From product-limit (Kaplan-Meier) method for censored data.
b based on unstratified cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on unstratified log-rank test.
Database cut-off date: 3 October 2022

Figure 0.7: Kaplan-Meier plot of PFS based on BICR assessment per RECIST 1.1 in patients with PD-L1 CPS ≥5

[redacted]

Based on Figure 2 of the company response to clarification[7]
BICR = Blinded Independent Central Review; CPS = combined positive score; PD-L1 = programmed cell death ligand 1; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1

Objective response rate in patients with PD-L1 CPS ≥5

As of the data cut-off date of 3 October 2022, pembrolizumab plus chemotherapy was associated with a statistically significant improvement in ORR when compared with chemotherapy alone based on BICR assessment per RECIST 1.1 in patients with PD-L1 CPS ≥5.[7]

The BICR assessed ORR was [redacted]% (95% CI: [redacted]) for the pembrolizumab plus chemotherapy group and [redacted]% (95% CI: [redacted]) for the chemotherapy group, reflecting a statistically significant difference of [redacted]% (95% CI: [redacted]).[7]

Table 3.23 provides an overview of the data on ORR in patients with PD-L1 CPS ≥5.

Table 0.23: Analysis of objective response based on BICR assessment (per RECIST 1.1) in patients with PD-L1 CPS ≥5

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + Chemotherapy versus Chemotherapy	
				Estimate (95% CI)[a]	p-Value[b]
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]		

Based on Table 6 of the company response to clarification[7]
BICR = Blinded independent central review; CI = confidence intervals; CPS = combined positive score; PD-L1 = programmed death ligand 1; PFS = progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours
a Based on unstratified Miettinen & Nurminen method.
b One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Responses are based on BICR assessment per RECIST 1.1.
Database cut-off date: 3 October 2022

EAG comment: Given that the survival data and other efficacy outcomes from the CS are not relatively mature, in the clarification letter, the EAG requested more mature data from the KEYNOTE-859 trial for all outcomes reported. In responding to EAG's request, the company stated that more mature data from the KEYNOTE-859 trial is not available as the full analysis is not planned at this stage.

3.2.5.4 Health-related quality of life

Changes in HRQoL was assessed in patients with PD-L1 CPS ≥1 by using the EQ-5D-5L visual analogue scale (VAS). Following the criteria for compliance and completion rates prespecified in the statistical analysis plan, week 18 was selected as the time point for analysing changes from baseline for the EQ-5D-5L.[1]

The EQ-5D-5L measures self-rated health state using five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) at five levels (no problems, slight problems, moderate problems, severe problems and extreme problem).

The mean (standard deviation [SD]) baseline score among patients with PD-L1 CPS ≥1 was 75.21 (17.86) in the pembrolizumab with chemotherapy arm and 74.87 (18.55) for the chemotherapy arm. The baseline EQ-5D-5L VAS scores were similar in both intervention and control groups.[1]

At week 18, the least sum (LS) mean change (95% CI) in EQ-5D-5L VAS was -0.91 (95% CI -2.50, 0.68) for the pembrolizumab with chemotherapy arm and -1.21 (-2.79, 0.38) for the chemotherapy arm (p=0.7772). The difference in LS mean change (95% CI) in EQ-5D-5L VAS between the intervention and control group was 0.30 (95% CI -1.78, 2.38; p=0.7772).[1]

Table 3.24 presents the data of change from baseline in EQ-5D-5L VAS for patients with PD-L1 CPS ≥1.

Table 3.24: Analysis of change from baseline in EQ-5D-5L VAS to week 18 in patients with PD-L1 CPS ≥1

Treatment	Baseline		Week 18		Change from Baseline to Week 18	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)a
Pembrolizumab + Chemotherapy	587	75.21 (17.86)	387	75.83 (16.30)	603	-0.91 (-2.50, 0.68)
Chemotherapy	591	74.87 (18.55)	391	75.44 (17.30)	604	-1.21 (-2.79, 0.38)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
Pembrolizumab + Chemotherapy versus Chemotherapy	0.30 (-1.78, 2.38)	0.7772

Based on Table 17 of the CS[1]
[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and stratification factors (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.
For baseline and Week 18, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.
Two-sided p-value is based on t test.
Database cut-off Date: 3 October 2022
CI = confidence intervals; CPS = combined positive score; CS = company submission; EQ-5D = European Quality of Life-5 dimensions-5 levels; LS = least sum; PD-L1 = programmed death ligand 1; PRO = patient reported outcomes; SD = standard deviation; VAS = visual analogue scale

EAG comment on HRQoL data:

- Based on the data provided by the CS, baseline scores appeared similar between treatment arms in patients with PD-L1 ≥1 as measured by EQ-5D-5L VAS.
- Based on the data provided by the CS, at week 18, the difference of LS mean change in EQ-5D-5L VAS was not statistically significant between the pembrolizumab with chemotherapy arm and the chemotherapy arm.
- Only short-term data at 18 weeks assessed by EQ-5D-5L VAS were provided. There was a lack of long-term follow-up data relating to HRQoL outcomes. In the clarification letter, the EAG requested more mature data from the KEYNOTE-859 trial for all outcomes reported (including HRQoL data). In responding to EAG's request, the company stated that more mature data from the KEYNOTE-859 trial is not available as the full analysis is not planned at this stage.

3.2.5.5 Subgroup analyses in the KEYNOTE-859 trial

Subgroup analyses were reported for the OS and PFS outcomes for the following subgroups:

- Age
- Gender
- Race (Asian/non-Asian)
- Geographic region for randomisation
- Eastern Cooperative Oncology Group Performance Scale (ECOG PS)

- Chemotherapy regimen (cisplatin plus fluorouracil or CAPOX)
- PD-L1 status
- Microsatellite instability (MSI) status
- Primary location of cancer
- Disease status
- Histological subtype
- Number of organs with metastases
- Prior gastrectomy/oesophagectomy

3.2.5.5.1 Subgroup analysis of overall survival in patients with PD-L1 CPS ≥1

The company stated that based on the 3 October 2022 data-cut, an improvement of OS among patients receiving pembrolizumab plus chemotherapy compared with these patients receiving chemotherapy only was consistent across the majority of subgroup analyses in the PD-L1 CPS ≥1 population.[1] The results of subgroup analysis for OS for patients with PD-L1 CPS ≥1 are presented in Table 3.25 below.

Table 0.25: Subgroup analysis of OS in patients with PD-L1 CPS ≥1

	Pembrolizumab + Chemotherapy (N=618)			Chemotherapy (N=617)			Pembrolizumab + Chemotherapy versus Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Overall	618	464	(75.1)	617	526	(85.3)	0.74 (0.652, 0.838)
Age (years)							
<65	377	293	(77.7)	364	319	(87.6)	0.73 (0.621, 0.855)
≥65	241	171	(71.0)	253	207	(81.8)	0.73 (0.595, 0.892)
Sex							
Female	196	154	(78.6)	169	155	(91.7)	0.69 (0.551, 0.865)
Male	422	310	(73.5)	448	371	(82.8)	0.74 (0.638, 0.864)
Race							
Asian	206	145	(70.4)	203	161	(79.3)	0.7 (0.56, 0.878)
Non-Asian	406	315	(77.6)	407	358	(88.0)	0.77 (0.657, 0.891)
Geographic region for randomisation							
Western Europe/Israel/North America/Australia	166	129	(77.7)	166	143	(86.1)	0.76 (0.595, 0.961)
Asia	201	141	(70.1)	200	158	(79.0)	0.7 (0.556, 0.877)
Rest of World	251	194	(77.3)	251	225	(89.6)	0.76 (0.624, 0.918)
Combination chemotherapy for randomisation							
CAPOX	528	386	(73.1)	528	446	(84.5)	0.72 (0.626, 0.824)
FP	90	78	(86.7)	89	80	(89.9)	0.82 (0.601, 1.125)
Baseline PD-L1 status (CPS cut point: 10)							
CPS ≥10	279	188	(67.4)	272	226	(83.1)	0.64 (0.523, 0.772)
CPS <10	337	274	(81.3)	345	300	(87.0)	0.83 (0.705, 0.979)
MSI status							
MSI-H	34	12	(35.3)	29	22	(75.9)	0.28 (0.137, 0.581)

	Pembrolizumab + Chemotherapy (N=618)			Chemotherapy (N=617)			Pembrolizumab + Chemotherapy versus Chemotherapy
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[a]
Non MSI-H	454	358	(78.9)	471	408	(86.6)	0.79 (0.687, 0.914)
ECOG performance scale							
0	223	151	(67.7)	228	190	(83.3)	0.66 (0.535, 0.823)
1	395	313	(79.2)	389	336	(86.4)	0.77 (0.657, 0.894)
Primary location							
Stomach	494	369	(74.7)	453	385	(85.0)	0.73 (0.634, 0.844)
GEJ	123	94	(76.4)	164	141	(86.0)	0.71 (0.547, 0.927)
Disease status							
Metastatic	591	443	(75.0)	593	508	(85.7)	0.73 (0.643, 0.831)
Histological subtype							
Diffuse	236	190	(80.5)	220	201	(91.4)	0.73 (0.601, 0.897)
Intestinal	239	173	(72.4)	215	172	(80.0)	0.78 (0.635, 0.969)
Indeterminate	141	99	(70.2)	182	153	(84.1)	0.64 (0.494, 0.822)
Tumour burden							
≥ Median	308	236	(76.6)	285	251	(88.1)	0.71 (0.598, 0.855)
< Median	277	201	(72.6)	299	250	(83.6)	0.69 (0.577, 0.838)
Number of metastases							
<=2	345	248	(71.9)	329	272	(82.7)	0.75 (0.632, 0.893)
≥3	272	215	(79.0)	288	254	(88.2)	0.71 (0.592, 0.854)
Liver metastases							
Yes	258	198	(76.7)	253	219	(86.6)	0.77 (0.631, 0.929)
No	359	265	(73.8)	364	307	(84.3)	0.71 (0.6, 0.835)
Prior gastrectomy/oesophagectomy							
Yes	109	64	(58.7)	105	81	(77.1)	0.59 (0.422, 0.816)
No	506	398	(78.7)	508	441	(86.8)	0.77 (0.674, 0.885)

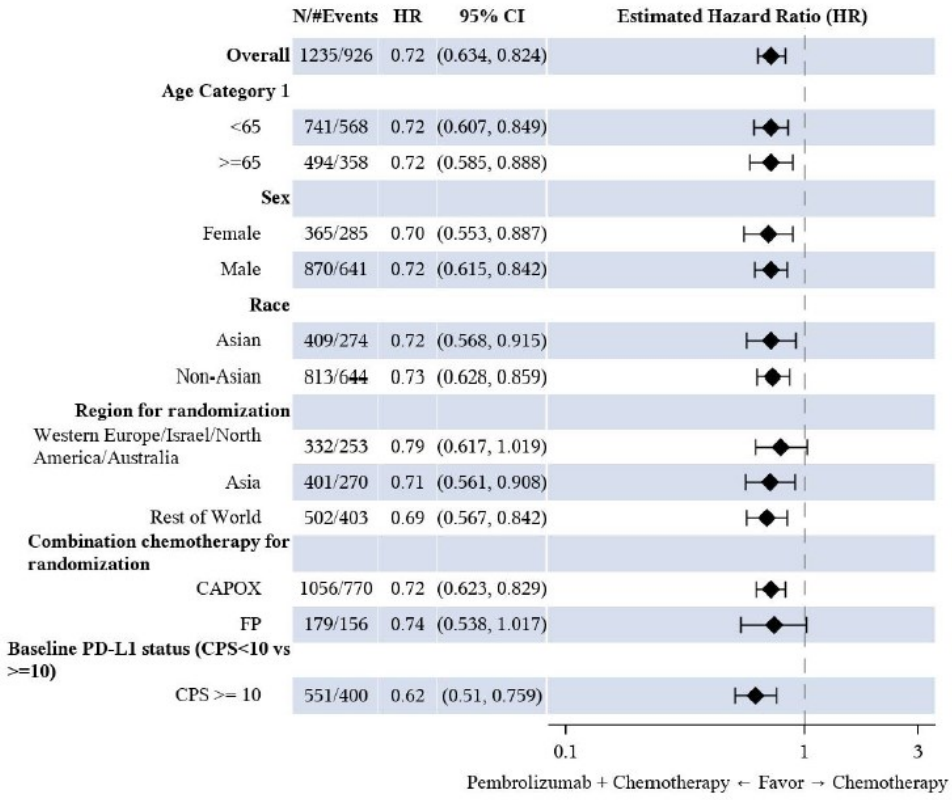
Based on Table 33 of the CS appendices[8]
CAPOX = oxaliplatin and capecitabine; CI = confidence interval; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; FP = cisplatin + fluorouracil; GEJ = gastro-oesophageal junction; MSI = microsatellite instability; PD-L1 = programmed death ligand 1; SD = standard deviation
[a] For overall population, analysis is based on Cox regression model 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.
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.
For subgroups, analysis is based on unstratified Cox regression model with treatment as a covariate.
If any level of a subgroup variable has fewer than approximately 5% of the ITT population, subgroup analysis is not performed in that level of the subgroup variable.
Database cut-off date: 3 October 2022

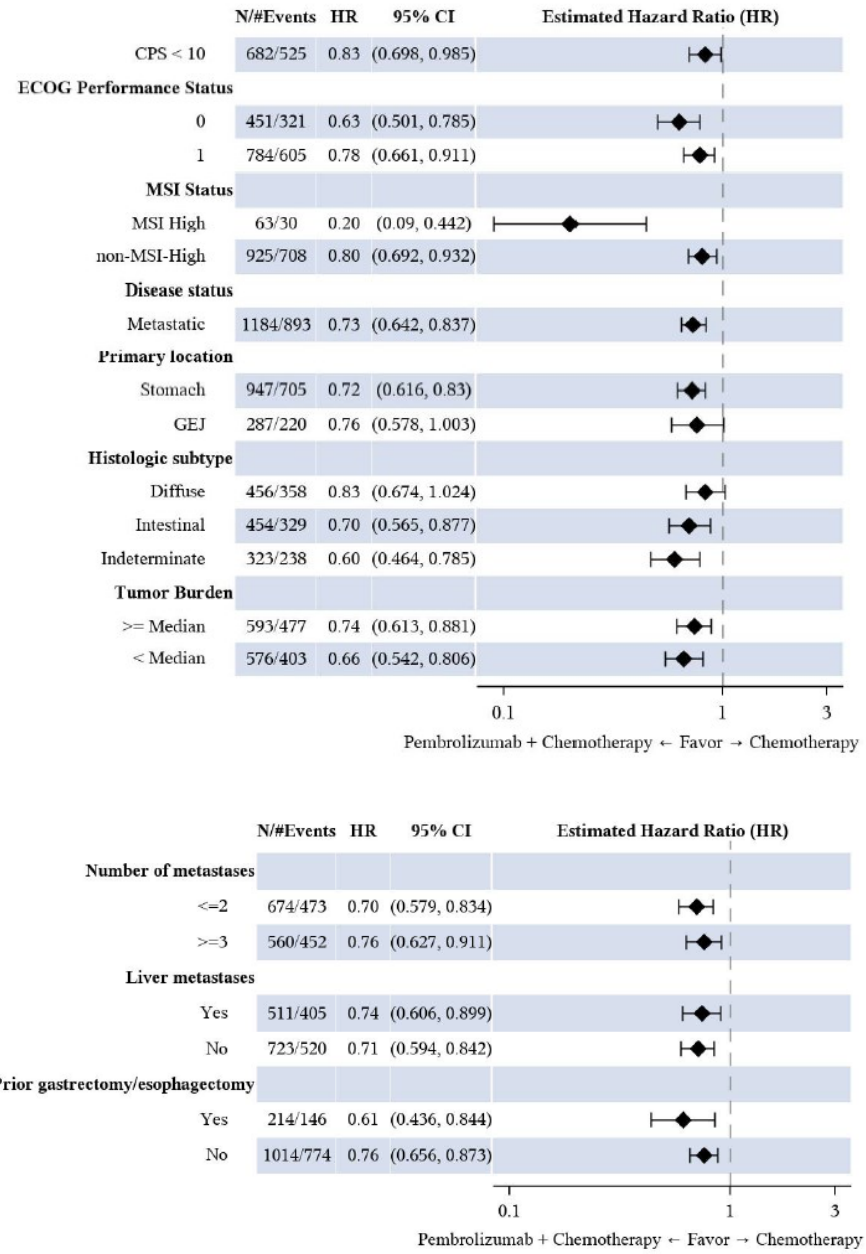
3.2.5.5.2 Subgroup analysis of progression free survival in patients with PD-L1 CPS ≥1

The company stated that based on the 3 October 2022 data-cut, an improvement of PFS for patients receiving pembrolizumab plus chemotherapy compared with these patients receiving chemotherapy was

consistent across the majority of subgroup analyses in the PD-L1 CPS ≥1 population.[1] The results of subgroup analyses for PFS in patients with PD-L1 CPS ≥1 are presented in Figure 3.8.

Figure 0.8: Forest plot of HRs of PFS by subgroups in patients with PD-L1 CPS ≥1





Based on Figure 12 of the CS appendices[8]
BICR = Blinded Independent Central Review; CAPOX = oxaliplatin and capecitabine; CPS = combined positive score; FP = cisplatin + fluorouracil; GEJ = gastro-oesophageal junction; HR = hazard ratio; MSI = microsatellite instability; PD-L1= programmed cell death ligand 1; PFS = progression-free survival

EAG comment: The results of subgroup analyses for OS and PFS were generally consistent across the majority of subgroup analyses in the PD-L1 CPS ≥1 population. There was a lack of overlap between the CIs of HRs for certain subgroups, namely, the subgroup analysis for the comparison of MSI-H versus non MSI-H. The lack of overlap between the CIs of HRs suggests that the efficacy of the intervention varied substantially between subgroups. The HR of OS for the MSI-H subgroup was 0.28 (95% CI 0.137, 0.581) while the HR of OS for the non MSI-H subgroup was 0.79 (0.687, 0.914). Similar effect was observed in the PFS outcome of these two subgroups. The HR of PFS for the MSI-H subgroup was 0.20 (95% CI 0.09, 0.042) while the HR of PFS for the non MSI-H subgroup was 0.80

(95% CI 0.692, 0.932). The subgroup analyses provided by the company contained the results at the 3 October 2022 data-cut. Further longer follow-up data were not available.

3.2.6 Adverse events of KEYNOTE-859 trial

3.2.6.1 Overall adverse events

The primary safety analyses of IA 1 were based on data from APaT population of 1,572 participants (ITT population) of whom 1,231 participants were with CPS ≥1 as of the cut-off date of 3 October 2022.

An overall summary of (AE) data is presented in Table 3.26. In the study, participants in the pembrolizumab plus chemotherapy group had longer exposure to the study drug (9.1 months) compared to the chemotherapy group (7 months). Additionally, the pembrolizumab plus chemotherapy group had a higher mean exposure and received more treatment cycles on average compared to the chemotherapy-only group.[1]

A greater percentage of participants in the pembrolizumab plus chemotherapy group (26.7%) continued treatment for 12 months or longer, while in the chemotherapy group, this percentage was lower at 15.1%.[1] Furthermore, in the pembrolizumab plus chemotherapy group, more participants had a duration of exposure of ≥3, ≥6, ≥12 months compared with participants in the chemotherapy group, as summarised in Table 3.27 below.

The details for estimated median and mean time on treatment participants are summarised in Table 3.28.

Table 0.26: Summary of drug exposure participants with CPS ≥1 (APaT population)

	Pembrolizumab + Chemotherapy (N=615)	Chemotherapy (N=616)	Total (N=1231)
Study Days on Therapy (months)			
n	615	616	1231
Mean (SD)	9.1 (7.8)	7.0 (5.7)	8.0 (6.9)
Median	6.5	5.6	5.8
Range	0.0 to 33.7	0.0 to 29.7	0.0 to 33.7
Number of Cycles			
n	615	616	1231
Mean (SD)	12.6 (10.5)	9.8 (7.6)	11.2 (9.3)
Median	9.0	8.0	8.0
Range	1.0 to 35.0	1.0 to 35.0	1.0 to 35.0

Based on Table 24 of the CS[1]
APaT = all participants as treated; CPS = combined positive score; CS = company submission; SD = standard deviation
Database cut-off date: 3 October 2022

Table 0.27: Exposure by duration participants with CPS ≥1 (APaT population)

Duration of Exposure	Pembrolizumab + Chemotherapy (N=615)			Chemotherapy (N=616)		
	n	(%)	Person-months	n	(%)	Person-months
> 0 m	615	(100.0)	5,613.5	616	(100.0)	4,283.0
≥ 1 m	563	(91.5)	5,591.8	569	(92.4)	4,262.4

Duration of Exposure	Pembrolizumab + Chemotherapy (N=615)			Chemotherapy (N=616)		
	n	(%)	Person-months	n	(%)	Person-months
≥ 3 m	477	(77.6)	5,421.5	459	(74.5)	4,042.8
≥ 6 m	322	(52.4)	4,706.5	280	(45.5)	3,220.4
≥ 12 m	164	(26.7)	3,369.3	93	(15.1)	1,672.7
≥ 18 m	109	(17.7)	2,554.4	40	(6.5)	896.4

Based on Table 25 of the CS[1]
APaT = all participants as treated; CPS = combined positive score; CS = company submission; m = months
Each participant is counted once on each applicable duration category row.
Duration of exposure is the time from the first dose date to the last dose date.
Database cut-off date: 3 October 2022

Table 0.28: Estimated median and mean time on treatment participants with CPS ≥1 (APaT population)

Treatment	N	Number of Events (%)	Estimated Median (95% CI) Time in months	Estimated Mean (SE) Time in months	95% CI of Estimated Mean Time in months
Pembrolizumab + Chemotherapy	615	581 (94.5)	6.47 (5.75, 6.93)	9.4 (0.3)	(8.7, 10.0)
Chemotherapy	616	599 (97.2)	5.55 (5.32, 5.95)	7.1 (0.2)	(6.6, 7.5)

Based on Table 26 of the CS[1]
APaT = all participants as treated; CI = confidence intervals; CPS = combined positive score; SE = standard error
Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method
Time on Treatment is defined as the time from the date of initial dose until the date of last dose
Number of Events is defined as number of participants who had discontinued or completed primary study treatment at the database cut-off date
Database cut-off date: 3 October 2022

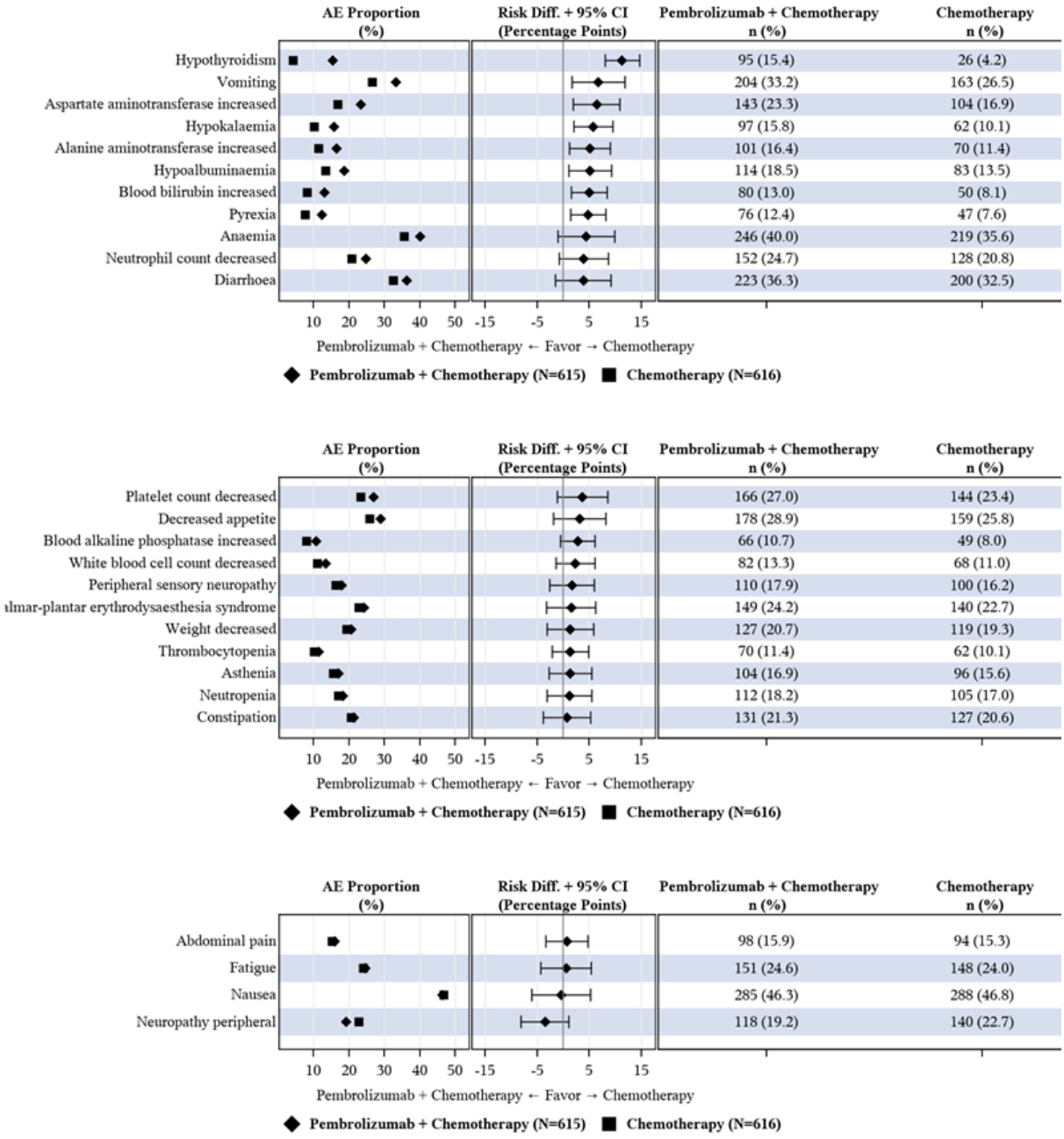
3.2.6.2 Most frequently reported adverse events

The company reported that "*The observed AEs in the pembrolizumab plus chemotherapy group were generally consistent with the known safety profiles of either chemotherapy regimen alone or pembrolizumab monotherapy. No new safety concerns were identifie*d".[1]

The company also concluded that *"The incidences of AEs were generally similar in the pembrolizumab plus chemotherapy group and the chemotherapy group for most AE categories. Notably, generally similar proportions of participants in both intervention groups experienced drug-related AEs*".[1]

The details for between-treatment comparisons in AEs with an incidence of at least 10% are summarised in Figure 3.9.

Figure 0.9: Between-treatment comparisons in AEs selected AEs (≥ 10% incidence) and sorted by risk difference participants with CPS ≥1 (APaT population)



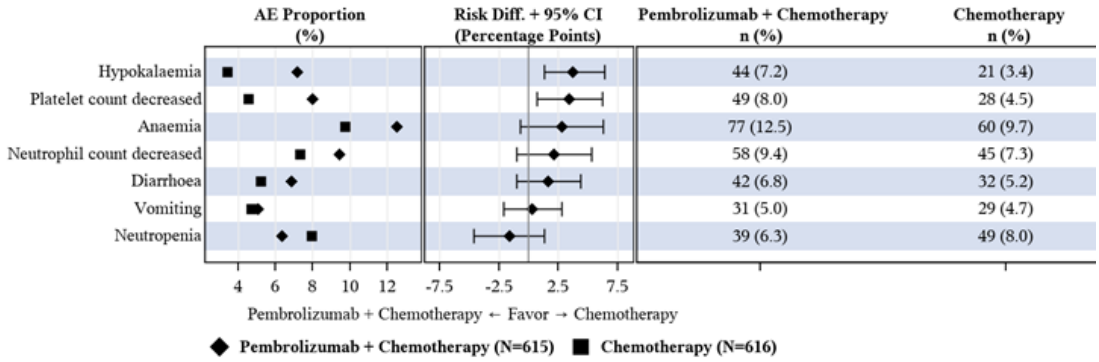
Based on Figure 18 of the CS appendices[8]
APaT = all participants as treated; CI = confidence intervals; CPS= combined positive score; CS = company submission

3.2.6.3 Grade 3 to 5 AEs

The company concluded that "*Generally similar proportions of participants in both intervention groups experienced Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs.*"[1]

The details for between-treatment comparisons in Grade 3-5 AEs with an incidence of at least 10% are summarised as below, in Figure 3.10.

Figure 0.10: Between-treatment comparisons in Grade 3-5 AEs selected AEs (≥ 5% incidence) and sorted by risk difference participants with CPS ≥1 (APaT population)



Based on unlabelled figure (after Figure 18) in the CS appendices[8]
APaT = all participants as treated; CPS = combined positive score; CS = company submission

3.2.6.4 Deaths due to AEs

The company outlined that *"8 participants (1.3%) died due to drug-related AEs in the pembrolizumab plus chemotherapy group and 16 participants (2.3%) died due to drug-related AEs in the chemotherapy group. Based on medical review, the AEs and resulting fatal outcomes were likely related to underlying disease or other comorbidities. No new safety concerns were identified for pembrolizumab".*[1]

Table 3.29 shows the participants with drug-related AEs resulting in death.

Table 0.29: Participants with drug-related AEs resulting in death by decreasing incidence (Incidence >0% in one or more treatment groups) participants with CPS ≥1 (APaT population)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Participants in population	615		616	
with one or more adverse events	8	(1.3)	16	(2.6)
with no adverse events	607	(98.7)	600	(97.4)
Death	1	(0.2)	0	(0.0)
Diarrhea	1	(0.2)	1	(0.2)
Peripheral embolism	1	(0.2)	0	(0.0)
Pneumonitis	1	(0.2)	1	(0.2)
Pulmonary hemorrhage	1	(0.2)	0	(0.0)
Sepsis	1	(0.2)	1	(0.2)
Septic shock	1	(0.2)	3	(0.5)
Thrombotic thrombocytopenic purpura	1	(0.2)	0	(0.0)
Acute myocardial infarction	0	(0.0)	2	(0.3)
Cerebral hemorrhage	0	(0.0)	1	(0.2)
Cerebrovascular accident	0	(0.0)	1	(0.2)
Gastric perforation	0	(0.0)	1	(0.2)
Hepatic function abnormal	0	(0.0)	1	(0.2)
Neurotoxicity	0	(0.0)	1	(0.2)
Pulmonary embolism	0	(0.0)	1	(0.2)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Sudden death	0	(0.0)	1	(0.2)
Urosepsis	0	(0.0)	1	(0.2)

Based on Table 45 of Appendix F of the CS[8]
APaT = all participants as treated; CPS = combined positive score; CS = company submission
Every participant is counted a single time for each applicable row and column.
Serious adverse events up to 90 days of last dose are included.
Database cut-off date: 3 October 2022

3.2.6.5 Other serious adverse events

The company reported the following: *"Generally similar proportions of participants in both intervention groups experienced SAEs, and drug-related SAEs"*.[1] Participants with drug-related serious adverse events (SAEs) are presented in Table 3.30.

Table 0.30: Participants with drug-related SAEs up to 90 days of last dose by decreasing incidence (incidence >0% in one or more treatment groups) participants with CPS ≥1 (APaT population)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Participants in population	615		616	
with one or more adverse events	156	(25.4)	116	(18.8)
with no adverse events	459	(74.6)	500	(81.2)
Drug-related serious adverse events				
Diarrhoea	28	(4.6)	18	(2.9)
Colitis	13	(2.1)	4	(0.6)
Vomiting	10	(1.6)	13	(2.1)
Nausea	9	(1.5)	5	(0.8)
Platelet count decreased	6	(1.0)	5	(0.8)
Pneumonia	6	(1.0)	2	(0.3)
Pneumonitis	6	(1.0)	2	(0.3)
Decreased appetite	5	(0.8)	6	(1.0)
Hypokalaemia	5	(0.8)	3	(0.5)
Acute kidney injury	4	(0.7)	4	(0.6)
Adrenal insufficiency	4	(0.7)	0	(0.0)
Asthenia	4	(0.7)	2	(0.3)
Anaemia	3	(0.5)	6	(1.0)
Dehydration	3	(0.5)	2	(0.3)
Enteritis	3	(0.5)	2	(0.3)
Fatigue	3	(0.5)	2	(0.3)
Infusion related reaction	3	(0.5)	0	(0.0)
Mucosal inflammation	3	(0.5)	5	(0.8)
Pulmonary embolism	3	(0.5)	3	(0.5)
Pyrexia	3	(0.5)	3	(0.5)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Thrombocytopenia	3	(0.5)	0	(0.0)
Alanine aminotransferase increased	2	(0.3)	0	(0.0)
Anaphylactic reaction	2	(0.3)	0	(0.0)
Blood creatinine increased	2	(0.3)	0	(0.0)
Drug hypersensitivity	2	(0.3)	0	(0.0)
Febrile neutropenia	2	(0.3)	4	(0.6)
Hyponatraemia	2	(0.3)	1	(0.2)
Immune-mediated enterocolitis	2	(0.3)	0	(0.0)
Intestinal obstruction	2	(0.3)	0	(0.0)
Neutrophil count decreased	2	(0.3)	2	(0.3)
Oesophagitis	2	(0.3)	1	(0.2)
Pancreatitis	2	(0.3)	0	(0.0)
Sepsis	2	(0.3)	3	(0.5)
Tubulointerstitial nephritis	2	(0.3)	0	(0.0)
Type 1 diabetes mellitus	2	(0.3)	0	(0.0)
Abdominal pain	1	(0.2)	0	(0.0)
Arthritis	1	(0.2)	0	(0.0)
Aspartate aminotransferase increased	1	(0.2)	0	(0.0)
Atrial fibrillation	1	(0.2)	1	(0.2)
Autoimmune hepatitis	1	(0.2)	0	(0.0)
Blood bilirubin increased	1	(0.2)	0	(0.0)
Bradycardia	1	(0.2)	0	(0.0)
Chest pain	1	(0.2)	0	(0.0)
Death	1	(0.2)	0	(0.0)
Deep vein thrombosis	1	(0.2)	0	(0.0)
Diabetes mellitus	1	(0.2)	0	(0.0)
Dizziness	1	(0.2)	1	(0.2)
Electrolyte imbalance	1	(0.2)	0	(0.0)
Enterocolitis	1	(0.2)	0	(0.0)
Epiglottitis	1	(0.2)	0	(0.0)
Face oedema	1	(0.2)	0	(0.0)
Gastric haemorrhage	1	(0.2)	1	(0.2)
Gastritis	1	(0.2)	0	(0.0)
Gastroenteritis	1	(0.2)	1	(0.2)
Gastrointestinal disorder	1	(0.2)	0	(0.0)
Gastrointestinal haemorrhage	1	(0.2)	1	(0.2)
General physical health deterioration	1	(0.2)	0	(0.0)
Haemoptysis	1	(0.2)	0	(0.0)
Hepatitis	1	(0.2)	0	(0.0)
Hepatotoxicity	1	(0.2)	0	(0.0)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Hypertransaminasaemia	1	(0.2)	0	(0.0)
Hypocalcaemia	1	(0.2)	0	(0.0)
Hypoglycaemia	1	(0.2)	0	(0.0)
Immune-mediated hepatitis	1	(0.2)	1	(0.2)
Immune-mediated nephritis	1	(0.2)	0	(0.0)
Infection	1	(0.2)	0	(0.0)
Injection site discolouration	1	(0.2)	0	(0.0)
Interstitial lung disease	1	(0.2)	1	(0.2)
Intestinal pseudo-obstruction	1	(0.2)	1	(0.2)
Laryngospasm	1	(0.2)	0	(0.0)
Myasthenia gravis	1	(0.2)	0	(0.0)
Myelosuppression	1	(0.2)	0	(0.0)
Myositis	1	(0.2)	0	(0.0)
Nephritis	1	(0.2)	0	(0.0)
Neuralgia	1	(0.2)	0	(0.0)
Neutropenia	1	(0.2)	0	(0.0)
Optic neuritis	1	(0.2)	0	(0.0)
Oral pain	1	(0.2)	0	(0.0)
Oropharyngeal oedema	1	(0.2)	0	(0.0)
Peripheral embolism	1	(0.2)	0	(0.0)
Peripheral nerve injury	1	(0.2)	0	(0.0)
Peripheral sensory neuropathy	1	(0.2)	0	(0.0)
Pneumonia cytomegaloviral	1	(0.2)	0	(0.0)
Post procedural diarrhoea	1	(0.2)	0	(0.0)
Pulmonary haemorrhage	1	(0.2)	0	(0.0)
Renal failure	1	(0.2)	1	(0.2)
Septic shock	1	(0.2)	3	(0.5)
Skin infection	1	(0.2)	0	(0.0)
Small intestinal obstruction	1	(0.2)	0	(0.0)
Small intestinal perforation	1	(0.2)	0	(0.0)
Stomatitis	1	(0.2)	0	(0.0)
Thrombotic thrombocytopenic purpura	1	(0.2)	0	(0.0)
Tinea manuum	1	(0.2)	0	(0.0)
Tinea pedis	1	(0.2)	0	(0.0)
Transfusion reaction	1	(0.2)	0	(0.0)
Vertigo	1	(0.2)	0	(0.0)
White blood cell count decreased	1	(0.2)	2	(0.3)
Abdominal pain upper	0	(0.0)	1	(0.2)
Acute coronary syndrome	0	(0.0)	1	(0.2)
Acute myocardial infarction	0	(0.0)	3	(0.5)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Angina unstable	0	(0.0)	1	(0.2)
Cardiac failure chronic	0	(0.0)	1	(0.2)
Cardiomyopathy	0	(0.0)	1	(0.2)
Cellulitis	0	(0.0)	1	(0.2)
Cerebral haemorrhage	0	(0.0)	1	(0.2)
Cerebrovascular accident	0	(0.0)	2	(0.3)
Cholangitis	0	(0.0)	1	(0.2)
Cholecystitis acute	0	(0.0)	1	(0.2)
Dysarthria	0	(0.0)	1	(0.2)
Gastric disorder	0	(0.0)	2	(0.3)
Gastric perforation	0	(0.0)	1	(0.2)
Hepatic function abnormal	0	(0.0)	1	(0.2)
Hepatic infection	0	(0.0)	1	(0.2)
Hypersensitivity	0	(0.0)	1	(0.2)
Hypotension	0	(0.0)	2	(0.3)
Immune thrombocytopenia	0	(0.0)	1	(0.2)
Immune-mediated lung disease	0	(0.0)	1	(0.2)
Immune-mediated myocarditis	0	(0.0)	1	(0.2)
Lipase increased	0	(0.0)	1	(0.2)
Liver injury	0	(0.0)	1	(0.2)
Lower gastrointestinal haemorrhage	0	(0.0)	1	(0.2)
Malaise	0	(0.0)	1	(0.2)
Malnutrition	0	(0.0)	1	(0.2)
Muscular weakness	0	(0.0)	1	(0.2)
Neurotoxicity	0	(0.0)	1	(0.2)
Neutropenic colitis	0	(0.0)	1	(0.2)
Obstruction gastric	0	(0.0)	1	(0.2)
Pancreatitis acute	0	(0.0)	1	(0.2)
Pneumonia fungal	0	(0.0)	1	(0.2)
Rash	0	(0.0)	1	(0.2)
Sinus bradycardia	0	(0.0)	1	(0.2)
Sudden death	0	(0.0)	1	(0.2)
Terminal ileitis	0	(0.0)	1	(0.2)
Upper gastrointestinal haemorrhage	0	(0.0)	1	(0.2)
Urinary tract infection	0	(0.0)	1	(0.2)
Urosepsis	0	(0.0)	1	(0.2)
Ventricular dysfunction	0	(0.0)	1	(0.2)
Weight decreased	0	(0.0)	1	(0.2)

Based on Table 46 of Appendix F of the CS[8]
APaT = all participants as treated; CPS = combined positive score; CS = company submission
Every participant is counted a single time for each applicable row and column. Serious adverse events up to 90 days of last dose are included. Database cut-off date: 3 October 2022

3.2.6.6. Discontinuation of study treatment due to adverse events

The company reported that "*The incidences of AEs resulting in treatment discontinuations were generally similar in the pembrolizumab plus chemotherapy group and the chemotherapy group*". [1]

Table 3.31 shows participants who discontinued treatment with pembrolizumab due to drug-related AEs.

Table 0.31: Participants with drug-related AEs resulting in treatment discontinuation of pembrolizumab/placebo by decreasing incidence (incidence >0% in one or more treatment groups) participants with CPS ≥1 (APaT population)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Participants in population	615		616	
with one or more adverse events	57	(9.3)	35	(5.7)
with no adverse events	558	(90.7)	581	(94.3)
Drug-related adverse events resulting in treatment discontinuation				
Diarrhoea	8	(1.3)	2	(0.3)
Colitis	5	(0.8)	1	(0.2)
Pneumonitis	5	(0.8)	2	(0.3)
Acute kidney injury	3	(0.5)	0	(0.0)
Alanine aminotransferase increased	2	(0.3)	2	(0.3)
Decreased appetite	2	(0.3)	0	(0.0)
Platelet count decreased	2	(0.3)	1	(0.2)
Rash maculo-papular	2	(0.3)	0	(0.0)
Tubulointerstitial nephritis	2	(0.3)	0	(0.0)
Abdominal distension	1	(0.2)	0	(0.0)
Abdominal pain	1	(0.2)	0	(0.0)
Anaemia	1	(0.2)	0	(0.0)
Anaphylactic reaction	1	(0.2)	0	(0.0)
Arrhythmia	1	(0.2)	0	(0.0)
Arthritis	1	(0.2)	0	(0.0)
Aspartate aminotransferase increased	1	(0.2)	2	(0.3)
Back pain	1	(0.2)	0	(0.0)
Chest pain	1	(0.2)	0	(0.0)
Confusional state	1	(0.2)	0	(0.0)
Constipation	1	(0.2)	0	(0.0)
Cutaneous vasculitis	1	(0.2)	0	(0.0)
Dehydration	1	(0.2)	0	(0.0)
Gastric dilatation	1	(0.2)	0	(0.0)
Hepatic cytolysis	1	(0.2)	0	(0.0)
Hypertransaminasaemia	1	(0.2)	0	(0.0)
Immune-mediated enterocolitis	1	(0.2)	0	(0.0)
Immune-mediated hepatitis	1	(0.2)	1	(0.2)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Immune-mediated nephritis	1	(0.2)	0	(0.0)
Infusion related reaction	1	(0.2)	0	(0.0)
Insomnia	1	(0.2)	0	(0.0)
Intestinal obstruction	1	(0.2)	0	(0.0)
Mucosal inflammation	1	(0.2)	0	(0.0)
Myasthenia gravis	1	(0.2)	0	(0.0)
Nausea	1	(0.2)	1	(0.2)
Nephritis	1	(0.2)	0	(0.0)
Optic neuritis	1	(0.2)	0	(0.0)
Pancreatitis	1	(0.2)	0	(0.0)
Peripheral nerve injury	1	(0.2)	0	(0.0)
Peripheral sensory neuropathy	1	(0.2)	0	(0.0)
Pneumonia	1	(0.2)	0	(0.0)
Rash	1	(0.2)	0	(0.0)
Renal failure	1	(0.2)	1	(0.2)
Sepsis	1	(0.2)	2	(0.3)
Septic shock	1	(0.2)	3	(0.5)
Small intestinal obstruction	1	(0.2)	0	(0.0)
Thrombocytopenia	1	(0.2)	0	(0.0)
Thrombotic thrombocytopenic purpura	1	(0.2)	0	(0.0)
Vomiting	1	(0.2)	0	(0.0)
Weight decreased	1	(0.2)	0	(0.0)
White blood cell count decreased	1	(0.2)	0	(0.0)
Acute myocardial infarction	0	(0.0)	2	(0.3)
Angina unstable	0	(0.0)	1	(0.2)
Blood bilirubin increased	0	(0.0)	1	(0.2)
Cerebral haemorrhage	0	(0.0)	1	(0.2)
Cerebrovascular accident	0	(0.0)	2	(0.3)
Gastric perforation	0	(0.0)	1	(0.2)
Hepatic function abnormal	0	(0.0)	1	(0.2)
Immune thrombocytopenia	0	(0.0)	1	(0.2)
Immune-mediated myocarditis	0	(0.0)	1	(0.2)
Liver injury	0	(0.0)	1	(0.2)
Malaise	0	(0.0)	1	(0.2)
Neurotoxicity	0	(0.0)	1	(0.2)
Pulmonary embolism	0	(0.0)	1	(0.2)
Skin exfoliation	0	(0.0)	1	(0.2)
Sudden death	0	(0.0)	1	(0.2)
Urosepsis	0	(0.0)	1	(0.2)
Vascular device infection	0	(0.0)	1	(0.2)
Based on Table 47 of Appendix F of the CS[8]				

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
APaT = all participants as treated; CPS = combined positive score; CS = company submission Every participant is counted a single time for each applicable row and column. Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included. Database cut-off date: 3 October 2022				

3.2.6.7 Treatment interruption due to AEs

The company stated that: "*The incidences of AEs resulting in treatment interruptions were generally similar in the pembrolizumab plus chemotherapy group and the chemotherapy group*." [1]

Table 3.32 shows all participants whose drug therapy was interrupted due to drug-related AEs.

Table 0.32: Participants with drug-related AEs resulting in treatment interruption of all drugs by decreasing incidence (incidence > 0% in one or more treatment groups) participants with CPS ≥1 (APaT population)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Participants in population	615		616	
with one or more adverse events	233	(37.9)	180	(29.2)
with no adverse events	382	(62.1)	436	(70.8)
Neutrophil count decreased	56	(9.1)	44	(7.1)
Platelet count decreased	40	(6.5)	26	(4.2)
Neutropenia	39	(6.3)	43	(7.0)
Diarrhea	17	(2.8)	19	(3.1)
Thrombocytopenia	15	(2.4)	14	(2.3)
Anemia	12	(2.0)	20	(3.2)
Alanine aminotransferase increased	11	(1.8)	4	(0.6)
Aspartate aminotransferase increased	11	(1.8)	1	(0.2)
White blood cell count decreased	10	(1.6)	9	(1.5)
Asthenia	9	(1.5)	2	(0.3)
Nausea	9	(1.5)	5	(0.8)
Blood bilirubin increased	6	(1.0)	4	(0.6)
Colitis	6	(1.0)	2	(0.3)
Hypokalemia	6	(1.0)	2	(0.3)
Pneumonia	6	(1.0)	0	(0.0)
Fatigue	5	(0.8)	6	(1.0)
Decreased appetite	4	(0.7)	2	(0.3)
Palmar-plantar erythrodysesthesia syndrome	4	(0.7)	1	(0.2)
Vomiting	4	(0.7)	5	(0.8)
Hypothyroidism	3	(0.5)	0	(0.0)
Rash maculo-papular	3	(0.5)	0	(0.0)
Adrenal insufficiency	2	(0.3)	0	(0.0)
Autoimmune hepatitis	2	(0.3)	0	(0.0)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Blood creatinine increased	2	(0.3)	1	(0.2)
Dizziness	2	(0.3)	1	(0.2)
Enteritis	2	(0.3)	1	(0.2)
Febrile neutropenia	2	(0.3)	0	(0.0)
Gastritis	2	(0.3)	0	(0.0)
Hemoglobin decreased	2	(0.3)	0	(0.0)
Hyperthyroidism	2	(0.3)	0	(0.0)
Hypocalcemia	2	(0.3)	0	(0.0)
Hypomagnesaemia	2	(0.3)	0	(0.0)
Leukopenia	2	(0.3)	3	(0.5)
Malaise	2	(0.3)	2	(0.3)
Mucosal inflammation	2	(0.3)	3	(0.5)
Neurotoxicity	2	(0.3)	0	(0.0)
Pruritus	2	(0.3)	0	(0.0)
Pulmonary embolism	2	(0.3)	0	(0.0)
Rash	2	(0.3)	1	(0.2)
Stomatitis	2	(0.3)	0	(0.0)
Abdominal pain	1	(0.2)	3	(0.5)
Arthritis	1	(0.2)	0	(0.0)
Blood phosphorus decreased	1	(0.2)	0	(0.0)
Blood potassium decreased	1	(0.2)	0	(0.0)
Dehydration	1	(0.2)	0	(0.0)
Dry mouth	1	(0.2)	0	(0.0)
Epiglottitis	1	(0.2)	0	(0.0)
Face oedema	1	(0.2)	0	(0.0)
Fibrin degradation products increased	1	(0.2)	0	(0.0)
Gamma-glutamyl transferase increased	1	(0.2)	0	(0.0)
Gastroenteritis	1	(0.2)	0	(0.0)
Headache	1	(0.2)	0	(0.0)
Hepatic function abnormal	1	(0.2)	0	(0.0)
Hepatitis	1	(0.2)	0	(0.0)
Hiccups	1	(0.2)	0	(0.0)
Hyperbilirubinaemia	1	(0.2)	0	(0.0)
Hyperkalaemia	1	(0.2)	1	(0.2)
Hypoalbuminaemia	1	(0.2)	0	(0.0)
Hypochloraemia	1	(0.2)	0	(0.0)
Hyponatremia	1	(0.2)	0	(0.0)
Hypophosphatemia	1	(0.2)	0	(0.0)
Hypotension	1	(0.2)	0	(0.0)
Injection site pain	1	(0.2)	0	(0.0)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
Intestinal obstruction	1	(0.2)	0	(0.0)
Lymphopenia	1	(0.2)	0	(0.0)
Myositis	1	(0.2)	0	(0.0)
Neuropathy peripheral	1	(0.2)	2	(0.3)
Oedema	1	(0.2)	0	(0.0)
Oesophagitis	1	(0.2)	0	(0.0)
Oropharyngeal oedema	1	(0.2)	0	(0.0)
Peripheral sensory neuropathy	1	(0.2)	0	(0.0)
Pyrexia	1	(0.2)	3	(0.5)
Renal impairment	1	(0.2)	0	(0.0)
Sinus tachycardia	1	(0.2)	0	(0.0)
Skin infection	1	(0.2)	0	(0.0)
Small intestinal perforation	1	(0.2)	0	(0.0)
Thyroiditis	1	(0.2)	0	(0.0)
Transaminases increased	1	(0.2)	0	(0.0)
Type 2 diabetes mellitus	1	(0.2)	0	(0.0)
Urinary tract infection	1	(0.2)	0	(0.0)
Vasculitis	1	(0.2)	0	(0.0)
Weight decreased	1	(0.2)	2	(0.3)
Acute coronary syndrome	0	(0.0)	1	(0.2)
Acute kidney injury	0	(0.0)	1	(0.2)
Blood alkaline phosphatase increased	0	(0.0)	2	(0.3)
Cellulitis	0	(0.0)	1	(0.2)
Dry skin	0	(0.0)	1	(0.2)
Epistaxis	0	(0.0)	1	(0.2)
Gastric haemorrhage	0	(0.0)	1	(0.2)
Gastrointestinal haemorrhage	0	(0.0)	1	(0.2)
Granulocytopenia	0	(0.0)	1	(0.2)
Hepatic infection	0	(0.0)	1	(0.2)
Neutropenic colitis	0	(0.0)	1	(0.2)
Obstruction gastric	0	(0.0)	1	(0.2)
Supraventricular extrasystoles	0	(0.0)	1	(0.2)

Based on Table 48 of Appendix F of the CS[8]
APaT = all participants as treated; CPS = combined positive score; CS = company submission
Every participant is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database cut-off date: 3 October 2022

3.2.6.8 Adverse events of special interest

The company described that "*As expected, a higher proportion of participants experienced AEOSIs in the pembrolizumab plus chemotherapy group than in the chemotherapy group*."[1]

The company mentioned that "*Observed AEOSIs in the study were generally reversible and manageable with standard therapeutic and supportive care strategies. Most AEOSIs were nonserious and Grade 2 or 3 in severity*."[1]

"*A total of two participants died due to an AEOSI of pneumonitis, including 1 participant in the pembrolizumab plus chemotherapy group and 1 participant in the chemotherapy group*." [1]

"*The most frequently reported AEOSIs in the pembrolizumab plus chemotherapy group were infusion reactions, hypothyroidism, hyperthyroidism, colitis and pneumonitis, while the most frequently reported AEOSI in the chemotherapy group was infusion reactions*."[1]

The company suspected that "*The infusion reactions observed in both groups may be likely attributed to chemotherapy and trastuzumab.*"[1]

The company summarised that "*The severity, outcome, and manageability of the AEOSI events in the pembrolizumab plus chemotherapy group were generally consistent with those previously reported for pembrolizumab monotherapy or for the chemotherapy*".[1]

Table 3.33 summarised adverse event of special interest (AEOSI) participants.

Table 0.33: Adverse event summary (AEOS) participants with CPS ≥1 (APaT population)

	Pembrolizumab + Chemotherapy		**Chemotherapy**	
	n	**(%)**	**n**	**(%)**
Participants in population	615		616	
with one or more adverse events	193	(31.4)	81	(13.1)
with no adverse event	422	(68.6)	535	(86.9)
with drug-related[a] adverse events	179	(29.1)	74	(12.0)
with toxicity grade 3-5 adverse events	60	(9.8)	16	(2.6)
with toxicity grade 3-5 drug-related adverse events	56	(9.1)	15	(2.4)
with serious adverse events	50	(8.1)	12	(1.9)
with serious drug-related adverse events	45	(7.3)	11	(1.8)
with dose modification[b] due to an adverse event	85	(13.8)	35	(5.7)
who died	1	(0.2)	1	(0.2)
who died due to a drug-related adverse event	1	(0.2)	1	(0.2)
discontinued due to an adverse event	34	(5.5)	9	(1.5)
discontinued MK-3475/PLACEBO	25	(4.1)	5	(0.8)
discontinued any chemotherapy	24	(3.9)	7	(1.1)
discontinued all drugs	7	(1.1)	1	(0.2)
discontinued due to a drug-related adverse event	33	(5.4)	9	(1.5)
discontinued MK-3475/PLACEBO	24	(3.9)	5	(0.8)
discontinued any chemotherapy	23	(3.7)	7	(1.1)
discontinued all drugs	7	(1.1)	1	(0.2)
discontinued due to a serious adverse event	24	(3.9)	5	(0.8)
discontinued MK-3475/PLACEBO	21	(3.4)	5	(0.8)
discontinued any chemotherapy	17	(2.8)	3	(0.5)
discontinued all drugs	6	(1.0)	1	(0.2)

	Pembrolizumab + Chemotherapy		Chemotherapy	
	n	(%)	n	(%)
discontinued due to a serious drug-related adverse event	23	(3.7)	5	(0.8)
discontinued MK-3475/PLACEBO	20	(3.3)	5	(0.8)
discontinued any chemotherapy	16	(2.6)	3	(0.5)
discontinued all drugs	6	(1.0)	1	(0.2)

Based on Table 49 of Appendix F of the CS[8]
AEOSI = adverse event of special interest; APaT = all participants as treated; CPS = combined positive score; CS = company submission
a Determined by the investigator to be related to the drug.
b Defined as an action taken of dose reduced, drug interrupted, or drug withdrawn.
Grades are based on NCI CTCAE version 4.03.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
Database cut-off date: 3 October 2022

EAG comment: Given that the data of AEs from the CS are not relatively mature, in the clarification letter, the EAG requested more mature data (including AEs) from the KEYNOTE-859 trial. In responding to EAG's request, the company stated that more mature data from the KEYNOTE-859 trial is not available as the full analysis is not planned at this stage.

3.2.7 Ongoing studies

As confirmed in Section B.2.11 of the CS, KEYNOTE-859 trial remains ongoing to further follow-up, with an estimated study completion date of September 2024.[1]

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Two RCTs (KEYNOTE-859 and CheckMate-649) were identified via SR and the subgroup data from these two RCTs were used in the ITC analysis.[1] KEYNOTE-859 trial is a double-blind RCT while CheckMate-649 trial is an open-label RCT. Table 3.34 presents study characteristics of included trials. The eligibility criteria of patients for both trials are presented in Table 3.35.

Table 0.34: Study characteristics of included trials

Trial ID	NCT Code	Interventions	Phase	Type	N (randomised)	Masking	Allocation	Location	Multi-center	Primary Completion	Cross-over
KEYNOTE-859	NCT03675737	Arm 1: PEMBROLIZUMAB + CHEMO (5-FU + CIS, or, CAP+OX) Arm 2: CHEMO (5-FU + CIS, or, CAP + OX)	III	CSR	Arm 1: 790 Arm 2: 789	Double-blind	Randomised	Multi-national	Yes	September 28, 2024	No
CheckMate-649	NCT02872116	Arm 1: NIVO + CHEMO (CAP + OX, or, 5-FU + OX) Arm 2: CHEMO (CAP + OX, or, 5-FU + OX) Arm 3*: NIVO + IPI	III	Full-text	Arm 1: 789 Arm 2: 792 Arm 3: 409	Open-label	Randomised	Multi-national	Yes	May 2020	--

Based on Table 6 of the CS appendices[8]
CAP = capecitabine; CHEMO = chemotherapy; CIS = cisplatin; CSR = Clinical Study Report; 5-FU = fluorouracil; IPI = ipilimumab; PEMBRO = pembrolizumab; NIVO = nivolumab; OX = oxaliplatin
Notes: *Arm 3 is closed to enrollment as of 05-June-2018 and is not featured in subsequent tables

Table 0.35: Eligibility criteria of included trials

Trial ID	Age (years)	Race/ ethnicity	Performance score	Disease stage	Tumor site	Histology	PD-L1 expression status	HER2 mutation status	Locally advanced unresectable / metastatic (Y/N)
KEYNOTE-859	≥18 years	--	ECOG 0-1	--	Gastric or GEJ	Adenocarcinoma	--	HER2-	Y (100%)
CheckMate-649	>18 years	--	ECOG 0-1	--	Gastric or GEJ	Adenocarcinoma	<1% or > 1%, or indeterminate Positive,	HER2- & Unknown	Y (100%)

Trial ID	Age (years)	Race/ ethnicity	Performance score	Disease stage	Tumor site	Histology	PD-L1 expression status	HER2 mutation status	Locally advanced unresectable / metastatic (Y/N)
							Negative, or Indeterminant		

Based on Table 7 of the CS appendices[8]
CS = company submission; ECOG = Eastern Cooperative Oncology Group; GEJ = gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed death ligand 1

An overview of relevant subgroups from the two trials is presented in Table 3.36.

Table 0.36: Summary of relevant data from two included studies

Trial	Population	Outcome, assessment
KEYNOTE-859	PD-L1 CPS ≥1	OS
	PD-L1 CPS ≥1	PFS
	PD-L1 CPS ≥10	OS
CheckMate-649	PD-L1 CPS ≥1	OS
	PD-L1 CPS ≥1	PFS
	PD-L1 CPS ≥10	OS

Based on Table 18 of the CS[1]
CPS = combined positive score; PD-L1 = programmed death ligand 1; PFS = progression free survival; OS = overall survival

In the KEYNOTE-859 study, pembrolizumab in combination with CAPOX or cisplatin plus fluorouracil was directly compared to placebo plus CAPOX or cisplatin plus fluorouracil in patients with metastatic or locally advanced unresectable HER2-negative GC or GOJ adenocarcinoma.[1]

The KEYNOTE-859 study reported data on participants with PD-L1 CPS ≥1 and PD-L1 CPS≥ 10. Data for the ITC analysis in the CS came from the PD-L1 CPS ≥1 subgroup and PD-L1 CPS ≥10 from the two trials (KEYNOTE-859 and CheckMate-649). The company stated that data for the subgroup of PD-L1 CPS ≥5 from the KEYNOTE-859 trial were not available at the time of CS.[1]

The company performed feasibility assessment for the purpose of ITC. In terms of chemotherapy regimens, for each population, the company assessed the feasibility of conducting an ITC comparing the relative efficacy of pembrolizumab with chemotherapy versus the comparators of interest. Table 3.37 presents specific indirect comparisons of interest as per NICE final scope.

Table 0.37: Indirect comparisons of interest as per NICE final scope

Population	Comparator
Untreated HER2-negative advanced or metastatic gastric or GOJ adenocarcinoma with PD-L1 CPS ≥1	Fluorouracil + oxaliplatin: (FOLFOX) Capecitabine + oxaliplatin (CAPOX) Cisplatin + fluorouracil (FP) Cisplatin + capecitabine (XP)
Untreated HER2-negative advanced or metastatic gastric or GOJ adenocarcinoma with PD-L1 CPS ≥5	Nivolumab with platinum- and fluoropyrimidine-based chemotherapy

Based on Table 19 of the CS[1]
CAPOX = oxaliplatin and capecitabine; CPS = combined positive score; CS = company submission; FOLFOX = folinic acid, fluorouracil and oxaliplatin; FP = cisplatin + fluorouracil; HER2 = human epidermal growth factor receptor 2; NICE = National Institute of Health and Care Excellence; PD-L1 = programmed death ligand 1; XP = cisplatin + capecitabine

Table 3.38 presents a summary of feasibility assessment of conducting an ITC of pembrolizumab versus relevant treatments in untreated HER 2-negative advanced or metastatic GC or GOJ adenocarcinoma.

Table 0.38: Feasibility assessment of indirect comparison of pembrolizumab with chemotherapy to each comparator relevant to untreated HER2-negative advanced or metastatic GC or GOJ adenocarcinoma with PD-L1 CPS ≥1 and PD-L1 CPS ≥10

Population	Treatment	Comparison feasible for OS?	Comparison feasible for PFS?	Rationale
PD-L1 CPS ≥ 1	Nivolumab with platinum and fluoropyrimidine-based chemotherapy	Yes	Yes	Indirect path via combined platinum doublets
PD-L1 CPS ≥ 10	Nivolumab with platinum- and fluoropyrimidine-based chemotherapy	Yes	No	Indirect path via combined platinum doublets. For CheckMate-649, only a hazard ratio for OS is reported in this population.

Based on Table 20 of the CS[1]
CPS = combined positive score; CS = company submission; HER2 = human epidermal growth factor receptor 2; OS = overall survival; PD-L1 = programmed death ligand 1

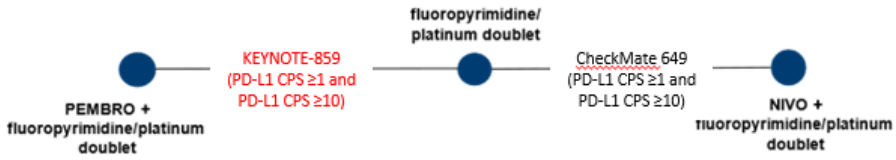
The company states that *"for both OS and PFS, NMA was conducted using constant and time-varying HRs. Since results of proportional hazard tests were consistent with the proportional hazards assumption, only constant HR NMA results are presented"*.[1]

The company further made the following statements:[1]

"A comparison of pembrolizumab plus chemotherapy versus CAPOX and FP can be directly informed from the KEYNOTE-859 study. Comparisons to other specific conventional care chemotherapy regimens used in the UK (XP/FOLFOX) were not feasible as no common comparators were available to form a connected network of RCTs between these treatments and pembrolizumab plus chemotherapy. Based on the widely accepted assumption of clinical equivalence between doublet chemotherapies (as verified by clinical experts consulted), the comparative efficacy of pembrolizumab plus chemotherapy versus XP/FOLFOX is expected to be similar to results seen in KEYNOTE-859."

The network diagram of the NMA in patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 is illustrated in Figure 3.11. As only two trials were included in the analysis, the term of ITC would be a better description of the analysis.

Figure 0.11: Illustration of connected network in patients with PD-L1 CPS ≥1 and CPS ≥10



Based on Figure 15 of the company response to clarification[7]
CPS = combined positive score; NIVO = nivolumab; PD-L1= programmed cell death ligand 1; PEMBRO = pembrolizumab

It should be noted that the NICE scope specified that a comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy is of interest for the locally advanced metastatic GC

or GOJ adenocarcinoma patients with PD-L1 CPS ≥5. However, the CS states that an NMA in participants with PD-L1 CPS ≥5 was not conducted at the time of evidence submission because the KEYNOTE-859 trial did not have PD-L1 CPS ≥5 as a prespecified cut point. Following the EAG's request, the company provided an additional analysis of ITC for the subgroup of participants with PD-L1 CPS ≥5 as the company has now conducted a post-hoc analysis for the PD-L1 CPS ≥5 subgroup of the KEYNOTE-859 trial, which made the ITC analysis feasible for this subgroup.

In responding to the EAG' request, the company provided baseline characteristics data for the subgroup of patients with PD-L1 CPS ≥5 for each trial. However, there was no formal assessment of a comparison of baseline characteristics data between the two studies for the subgroup of PD-L1 CPS ≥5 in their response. The EAG notes that there was heterogeneity of relevant patient baseline characteristics between the two trials for this subgroup. For example, for ECOG PS of the nivolumab plus chemotherapy arm of the CheckMate-649 trial, the proportion of patients with ECOG 0 was 41% while the proportion of patients with ECOG 1 was 59%. However, for ECOG PS of the pembrolizumab plus chemotherapy arm of the KEYNOTE-859 trial, the proportion of patients with ECOG 0 was 35.9% while the proportion of patients with ECOG 1 was 64.1%. Furthermore, the proportion of patients with non-MSI high was 89% for the nivolumab plus chemotherapy arm of the CheckMate-649 trial while the proportion of patients with non-MSI high was 81% for the pembrolizumab plus chemotherapy arm of the KEYNOTE-859 trial. Therefore, there was limited evidence to support the comparability of baseline characteristics for the subgroup of patients with PD-L1 CPS ≥5 between the intervention arms from the two trials.

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 Results of ITC analysis

The company performed the ITC analysis of OS with the goal of including pembrolizumab with chemotherapy, as assessed in the KEYNOTE-859 trial.

The ITC considered the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations, in line with the population reported in the KEYNOTE-859. Therefore, only patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 from the two trials (KEYNOTE-859 and CheckMate-649) were included in the ITC.[1]

The company stated that all ITC analyses for OS and PFS were conducted by using a fixed-effects model because there was insufficient evidence available estimate the between-study heterogeneity required to run random-effects models.[1]

3.4.1.1 Patients with untreated HER2-negative advanced or metastatic gastric or GOJ adenocarcinoma with PD-L1 CPS ≥1

3.4.1.1.1 Overall survival

There was no statistically significant difference on the OS between patients receiving pembrolizumab plus chemotherapy and those patients receiving nivolumab plus chemotherapy (HR [redacted], 95% credible interval (CrI: [redacted]) among patients with PD-L1 CPS ≥1.[1] The results of the constant HR NMA for OS in patients with PD-L1 CPS ≥1 are presented in Table 3.39.

Table 0.39: Results of fixed-effects NMA of OS based on constant HRs in patients with PD-L1 CPS ≥1

Chemotherapy	1.35 (1.20, 1.52)	[redacted]
[redacted]	**Nivolumab + Chemotherapy**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + Chemotherapy**

Based on Table 21 of the CS[1]
CPS = Combined positive score; CrI = credible interval; CS = company submission; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; PD-L1 = programmed death ligand 1
Note: Each cell represents the comparison (HR 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

3.4.1.1.2 Progression-free survival

There was no statistically significant difference in PFS between patients receiving pembrolizumab plus chemotherapy and those patients receiving nivolumab plus chemotherapy (HR [redacted], 95% Crl: [redacted]) among patients with PD-L1 CPS ≥1.[1] The results of the constant HR NMA for PFS in patients with PD-L1 CPS ≥1 are presented in Table 3.40.

Table 0.40: Results of fixed-effects NMA of PFS based on constant HRs in patients with PD-L1 CPS ≥1

Chemotherapy	1.35 (1.18, 1.54)	[redacted]
[redacted]	**Nivolumab + Chemotherapy**	[redacted]
[redacted]	[redacted]	**Pembrolizumab + Chemotherapy**

Based on Table 22 of the CS[1]
CPS = combined positive score; Crl = credible interval; CS = company submission; HR = hazard ratio; NMA = network meta-analysis; PFS = progression-free survival; PD-L1 = programmed death ligand 1
Note: Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 3.36; Deviance: 1.37

3.4.1.2 Patients with untreated HER2-negative advanced or metastatic gastric or GOJ adenocarcinoma with PD-L1 CPS ≥10

3.4.1.2.1 Overall survival

There was no statistically significant difference in OS between patients receiving pembrolizumab with chemotherapy and those patients receiving nivolumab with chemotherapy (HR [redacted], 95% CrI: [redacted]) among patients with PD-L1 CPS ≥10.[1] The results of the constant HR NMA in patients in patients with PD-L1 CPS ≥10 are presented in Table 3.41.

Table 3.41: Results of fixed-effects NMA of OS based on constant HRs in patients with PD-L1 CPS ≥10

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

Based on Table 23 of the CS[1]
CPS = combined positive score; CrI = credible interval; CS = company submission; HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; PD-L1 = programmed death ligand 1
Note: Each cell represents the comparison (HR and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically significant at the 0.05 significance level. DIC: 3.38; Deviance: 1.38

The company stated that the results of PFS for the PD-L1 CPS ≥10 population are not available because the results of this subgroup of patients were not reported in the CheckMate-649 trial.

3.4.1.3 Patients with untreated HER2-negative advanced or metastatic gastric or GOJ adenocarcinoma with PD-L1 CPS ≥5

3.4.1.3.1 Overall survival

There was [redacted] in OS between patients receiving pembrolizumab plus chemotherapy and those patients receiving nivolumab plus chemotherapy (HR [redacted], 95% CrI: [redacted]) among patients with PD-L1 CPS ≥5.[7] The results of the constant HR NMA for OS in patients with PD-L1 CPS ≥5 are presented in Table**Error! Reference source not found.** 3.42.

Table 0.42: Results of fixed-effects NMA of OS based on constant HRs in patients with PD-L1 CPS ≥5

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

Based on Table 12 of the company response to clarification[7]
CPS = combined positive score; CrI = credible interval HR = hazard ratio; NMA = network meta-analysis; OS = overall survival; PD-L1 = programmed death ligand 1
Note: Each cell represents the comparison (HR 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

3.4.1.3.2 Progression free survival

There was [redacted] in PFS between patients receiving pembrolizumab plus chemotherapy and those patients receiving nivolumab plus chemotherapy (HR [redacted], 95% CrI: [redacted]) among patients with PD-L1 CPS ≥5.[7] The results of the constant HR NMA for PFS in patients with PD-L1 CPS ≥5 are presented in Table 3.43.

Table 0.43: Results of fixed-effects NMA of PFS based on constant HRs in patients with PD-L1 CPS ≥5

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

Based on Table 13 of the company response to clarification[7]
CPS = combined positive score; CrI = credible interval; HR = hazard ratio; NMA = network meta-analysis; PFS = progression free survival; PD-L1 = programmed death ligand 1
Note: Each cell represents the comparison (HR 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

3.4.2 Uncertainties in the indirect treatment comparisons

The company discussed the uncertainties associated with the results of ITCs. The company made the following statement:[1]

"The SLR identified two RCTs evaluating the efficacy or safety of interventions of interest for the UK setting in patients with HER2- locally advanced unresectable or metastatic gastric/GEJ adenocarcinoma. Each trial allowed for administration of a mix of fluoropyrimidine and platinum doublet agents, either alone or in combination with pembrolizumab (KEYNOTE-859) or nivolumab (CheckMate-649) The two RCTs were sufficiently similar in study design, sample size, and ECOG performance status (PS) of 0-1. By treating the conventional chemotherapy arms of each study as equivalent, it was deemed feasible to compare pembrolizumab + chemotherapy versus nivolumab + chemotherapy in a network meta-analysis."

Although the company stated that the two RCTs (KEYNOTE-859 and CheckMate-649) were sufficiently similar in study design, sample size, and ECOG PS of 0-1, there are no data for the comparison of baseline characteristics in patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 between the two trials (KEYNOTE-859 and CheckMate-649) in the CS. The EAG requested detailed information on the comparison of baseline characteristics for the subgroup of PD-L1 CPS ≥1 and PD-L1 CPS ≥10 from the two trials.

In responding to EAG's request, the company stated that there were no data on baseline characteristics of CheckMate-649 for PD-L1 CPS ≥1 and CPS ≥10 CPS populations from any of the publications relating to CheckMate-649 trial. Due to the lack of data, it was not feasible to conduct the between-study comparison of baseline characteristics for these two subgroups in the two trials used in the ITC analysis. Therefore, it is unclear whether the assumption of exchangeability for the purpose of ITC for the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations is met.

The company further stated[1] that *"KEYNOTE-859, evaluated CAPOX or FP either with or without pembrolizumab and CheckMate-649 evaluated CAPOX or FOLFOX either with or without nivolumab. Due to the differences in pooled chemotherapy arms between the two RCTs, the trials did not form a connected network via a single common comparator. Based on clinical opinion and ESMO guidelines, the specific fluoropyrimidine and platinum doublets were considered equivalent, and the fluoropyrimidine and platinum arms from both trials were pooled into a single node to form a connected evidence network."*

The company also stated that in the KEYNOTE-859 trial, CPS ≥1 and CPS ≥10 cuts were prespecified and adjusted for type 1 error.[1] However, CheckMate-649 trial had a prespecified CPS ≥5 cut for the primary outcome measure. Therefore, an ITC in patients with PD-L1 CPS ≥5 was not performed at the time of the evidence[1] submission because the KEYNOTE-859 trial did not have PD-L1 CPS ≥5 as a prespecified cut point.

For the subgroup of PD-L1 CPS ≥1, pembrolizumab with chemotherapy performed [redacted] nivolumab with chemotherapy under a constant HR assumption for both OS and PFS.[1]

Likewise, for the subgroup of PD-L1 CPS ≥5, pembrolizumab with chemotherapy performed [redacted] nivolumab with chemotherapy under a constant HR assumption for both OS and PFS.[7]

For the subgroup of PD-L1 CPS ≥10, pembrolizumab plus chemotherapy performed [redacted] nivolumab plus chemotherapy under a constant HR assumption for OS. However, PFS data in this subgroup of the CheckMate-649 trial were not reported.[1]

The company acknowledged that the NMA was limited by the available data as only one study informing each comparison.[1] Therefore, random-effects NMA was not feasible and the fixed-effects NMA were used the basis of an assumption of minimal between-study heterogeneity.[1]

The company concluded[1] that "*In all, results of the NMA suggested that treatment with pembrolizumab + chemotherapy performed similarly in OS and PFS when compared to nivolumab + chemotherapy in locally advanced or metastatic HER-2 negative GC or GOJ adenocarcinoma, irrespective of PD-L1 status*."

EAG comment:

- Given that the NICE final scope specified the subgroup of patients with PD-L1 CPS ≥5 for the comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy, the EAG requested relevant data for this subgroup of patients with PD-L1 CPS ≥5 from the KEYNOTE-859 trial. The EAG also requested an ITC for the subgroup of PD-L1 CPS ≥5 to be carried out. In responding to EAG's request, the company provided a post-hoc analysis for the subgroup of patients with PD-L1 CPS ≥5 from the KEYNOTE-859 trial. In addition, the company also provided the results of ITC for the subgroup of patients with PD-L1 CPS ≥5 for the comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy between the two trials following EAG's request. The results of ITC for the subgroup of PD-L1 CPS ≥5 were consistent with those results of ITC for patients with PD-L1 CPS ≥1 and patients with PD-L1 CPS ≥10.
- The company did not provide a comparison of baseline characteristics for the two subgroups of PD-L1 CPS ≥1 and PD-L1 CPS ≥10 from the two trials (KEYNOTE-859 and CheckMate-649) in the CS. It is unclear whether the baseline characteristics of patients with PD-L1 CPS ≥1 and those with PD-L1 CPS ≥10 between the two included trials are similar. The EAG requested detailed information on the comparison of baseline characteristics for the subgroups of PD-L1 CPS ≥1 and PD-L1 CPS ≥10 between the two trials.
- In responding to EAG's request, the company stated that because the baseline characteristics for patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 were not reported in any of the publications associated with the CheckMate-649 trial, a comparison of baseline characteristics in these subgroups between the two studies was not feasible. Therefore, it is unclear whether the assumption of exchangeability for the purpose of ITC for the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations is met. In addition, there was limited evidence to support the comparability of baseline characteristics for the subgroup of patients with PD-L1 CPS ≥5 between the intervention arms from the two trials.
- The EAG further notes that following the assessment of heterogeneity and uncertainty, the differences in the features of the trials (including different blinding methods: double blind for KEYNOTE-859 versus open label for CheckMate-649) introduced limitations in the results of ITC.
- The EAG requested the methods and results for testing proportional hazard assumptions for the trial data of KEYNOTE-859. The company provided further relevant results for testing proportional hazard assumptions.
    - The proportional hazard assumption may not be valid for the OS outcome in patients with PD-L1 CPS ≥1 given that the p value of testing of scaled Schoenfeld residuals was 0.0248, which was also supported by visual assessment of K-M curves and log cumulative hazard plots.
    - Likewise, the proportional hazard assumption may not be valid for the OS outcome in patients with PD-L1 CPS ≥5 given that the p value of testing of scaled Schoenfeld residuals was 0.0102, which was also supported by visual assessment of K-M curves and log cumulative hazard plots.
    - The proportional hazards assumption was met for the OS outcome in those patients with PD-L1 CPS ≥10.
    - The proportional hazards assumptions were met for all PFS outcomes in patients with PD-L1 CPS ≥1, those patients with PD-L1 CPS ≥10 and those patients with PD-L1 CPS ≥5.

- The rejection of the proportional hazards assumption for OS in patients with PD-L1 CPS ≥1 and those 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 ITC where constant HRs were presented. Given that the proportional hazards assumptions for OS in these two subgroups of the KEYNOTE-859 trial may not be valid, the EAG considers that the time-varying method (such as the polynomial fractional method or the method by Cope et al. 2020[20]) seems to be the more valid approach. However, as constant HRs for OS were used in the base-case analysis of the ITC for patients with PD-L1 CPS ≥1 and those patients with PD-L1 CPS ≥5, this may have compromised the validity of the results.
- In terms of the PFS outcomes in the ITC, the underlying assumptions of proportional hazards for this outcome in all subgroups based on PD-L1 status of the KEYNOTE-859 trial was consistent with the approach used by the company for the base-case analysis of ITC.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS and response to the request for clarification provided sufficient details for the EAG to appraise the literature searches conducted to identify studies on the treatment of pembrolizumab in combination with chemotherapy in patients with untreated HER 2-negative advanced or metastatic GC or GOJ adenocarcinoma. The CS[1] and response to the request for clarification[7] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for the efficacy and safety of pembrolizumab in combination with chemotherapy and relevant comparators in patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma. Searches were conducted in May 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted, although separate AEs searches may have identified additional AEs that were long-term, rare or unanticipated.

The study selection criteria for participants, interventions, comparators and outcomes in the systematic review of clinical effectiveness generally encompassed those specified by the NICE final scope.[2] Study selection was restricted to English language studies only and this may have meant that relevant evidence was missed. In addition, the restriction to RCTs only may have resulted in some relevant AE data that were overlooked.

The data extraction process was satisfactory and in line with recommended good practice in systematic reviews.[16]

The process for the assessment of risk of bias in the included studies was satisfactory. The process of assessing risk of bias and the number of reviewers involved were described. The use of the Cochrane risk of bias tool for included trials was appropriate.

The number of studies retrieved, screened and included was clear from the CS. Two unique RCTs were identified as being relevant to the SR: one RCT (KEYNOTE-859) provided the main source of evidence and another RCT (CheckMate-649) provided comparative data for an ITC.

KEYNOTE-859 was an international, phase III, double-blinded RCT that assessed the efficacy and safety of pembrolizumab in combination with chemotherapy in patients with untreated HER2-negative advanced or metastatic GC or GOJ adenocarcinoma. The CS focused on patients with PD-L1 CPS ≥1

and patients with PD-L1 CPS ≥10. The EAG rated the KEYNOTE-859 trial as being at low risk of bias as this KEYNOTE-859 trial was well conducted.

Baseline variables in the KEYNOTE-859 trial were generally comparable between the two treatment arms. At the data cut of 3 October 2022, OS was more favourable for pembrolizumab in combination with chemotherapy compared with chemotherapy for patients with PD-L1 CPS ≥1, those patients with PD-L1 CPS ≥5 and those patients with PD-L1 CPS ≥10.

At the data cut of 3 October 2022, BICR-assessed PFS was more favourable for pembrolizumab in combination with chemotherapy compared with chemotherapy among patients with PD-L1 CPS ≥1, those patients with PD-L1 CPS ≥5 and those patients with PD-L1 CPS ≥10.

Changes in HRQoL were assessed using the EQ-5D-5L VAS. Baseline scores were comparable between treatment groups. At week 18, the difference of LS mean change in EQ-5D-5L VAS was not statistically significant between the pembrolizumab with chemotherapy arm and the chemotherapy arm in patients with PD-L1 CPS ≥1. However, there was a lack of long-term follow-up data relating to HRQoL outcomes.

There were generally similar proportions of participants who experienced drug-related SAEs between the pembrolizumab with chemotherapy arm and the chemotherapy arm in patients with PD-L1 CPS ≥1 of the KEYNOTE-859 trial.

Subgroup analysis was presented for OS and PFS. The results of subgroup analyses for OS and PFS were generally consistent across the majority of subgroup analyses in the PD-L1 CPS ≥1 population.

The ITC analysis was based on a NMA consisting of only two RCTs (KEYNOTE-859 and CheckMate-649); the latter trial providing data of the intervention of nivolumab with chemotherapy versus chemotherapy alone. Regarding PD-L1 expression, KEYNOTE-859 provided data of patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 as a pre-specified cut off, therefore, these two populations were used in the NMA for both studies in the CS.

Given that the NICE final scope specified the subgroup of patients with PD-L1 CPS ≥5 for the comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy, the EAG requested relevant data for the subgroup of patients with PD-L1 CPS ≥5 from the KEYNOTE-859 trial. The EAG also requested an ITC for the subgroup of patients with PD-L1 CPS ≥5 to be carried out. In responding to the EAG's request, the company provided a post-hoc analysis for the subgroup of patients with PD-L1 CPS ≥5 from the KEYNOTE-859 trial. In addition, the company has also provided the results of ITC for the subgroup of patients with PD-L1 CPS ≥5 for the comparison between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy between the two trials (KEYNOTE-859 and CheckMate-649) following the EAG's request. The results of ITC for the subgroup of patients with PD-L1 CPS ≥5 were consistent with those results of ITC for patients with PD-L1 CPS ≥1 and those with PD-L1 CPS ≥10.

For ITC feasibility assessment, the company did not provide a comparison of baseline characteristics of the two subgroups of patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 between the two trials (KEYNOTE-859 and CheckMate-649) in the CS. In responding to EAG's request, the company stated that because the baseline characteristics for patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥10 were not reported in any of the publications associated with the CheckMate-649 trial, a comparison of baseline characteristics in these subgroups between the two trials was not feasible. Therefore, it is unclear whether the assumption of exchangeability for the purpose of ITC for the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations is met. In addition, there was limited evidence to support the comparability of

baseline characteristics for the subgroup of patients with PD-L1 CPS ≥5 between the intervention arms from the two trials.

Fixed-effects models were used in the ITC analysis. It should be noted that the rejection of the proportional hazards assumption for OS in patients with PD-L1 CPS ≥1 and those 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 ITC where constant HRs were presented. Given that the proportional hazards assumption for OS in these two subgroups of the KEYNOTE-859 trial may not be valid, the EAG considers that the time-varying method (such as the polynomial fractional method or the method by Cope et al. 2020[20]) seems to be the more valid approach. However, as constant HRs for OS were used in the base-case analysis of the ITC in patients with PD-L1 CPS ≥1 and those patients with PD-L1 CPS ≥5, this may have compromised the validity of the results.

In terms of the PFS outcomes in the ITC, the underlying assumptions of proportional hazards for this outcome in all subgroups based on PD-L1 status in the KEYNOTE-859 trial was consistent with the approach used by the company for the base-case analysis of ITC.

The results of the ITC showed that there was no statistically significant difference in OS between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy in patients with PD-L1 CPS ≥1, PD-L1 CPS ≥5 and PD-L1 CPS ≥10. In terms of PFS, the results of the ITC demonstrated that there was no statistically significant difference in this outcome between pembrolizumab plus chemotherapy and nivolumab plus chemotherapy in patients with PD-L1 CPS ≥1 and PD-L1 CPS ≥5. An ITC was not conducted for PFS for patients with PD-L1 CPS ≥10 due to a lack of data for this subgroup from the CheckMate-649 trial.

Given that it is unclear whether the assumption of exchangeability for the purpose of the ITC for the PD-L1 CPS ≥1 and PD-L1 CPS ≥10 populations is met, there were uncertainties in the validity of ITC results.

4. COST EFFECTIVENESS

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of cost effectiveness analysis (CEA) studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement, and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness and resource identification presented in the CS.[1] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[9,10] The CS[1] was checked against the STA specification for company/sponsor submission of evidence.[11] The EAG has presented only the major limitations of each search strategy in the report.

Appendix G of the CS provides details of a SLR conducted on the economic burden of patients with untreated locally advanced unresectable gastric or GOJ. The review includes the identification of studies reporting economic evaluations and studies reporting healthcare resource use and cost data in patients with untreated locally advanced unresectable gastric or GOJ adenocarcinoma.[1] Searches were undertaken in April 2023.

A summary of the sources searched is provided in Table 4.1.

Table 0.1: Data sources searched for economic evaluations/cost resource identification (as reported in the CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Embase.com	DB inception-16/5/23	16/4/23
MEDLINE In-Process	PubMed	DB inception-16/5/23	16/4/23
Additional resources			
NHS EED	Internet	Not stated	12/5/23
Tufts CEA Registry	Internet	Not stated	12/5/23
Conferences			
• ASCO • ASCO-SITC • ASCO-GI • ASTRO • ESMO • ESMO-ASIA • ESMO-GI • ESMO-IO • APGCC • AACR • JSMO • SITC • ECC	Internet	2018-2023	Not stated

Resource	Host/Source	Date Ranges	Date searched
• ISPOR - Europe and International • AMCP • NEXUS			
HTA websites			
• NICE • SMC • IQWiG • HAS • CADTH • PBAC • International Network of Agencies for Health Technology Assessment • International Society for the promotion of health technology assessment (htai.org) • European Network for Health Technology Assessment (EUnetHTA)	Internet	Not stated	Not stated
ASCO GU = American Society of Clinical Oncology Genitourinary Cancers Symposium; AMCP = Academy of Managed Care Pharmacy Annual Meeting; AACR = American Association for Cancer Research; APGCC = Asia-Pacific Gastroesophageal Cancer Congress; ASCO-GI = American Society of Clinical Oncology-Gastrointestinal; ASTRO = American Society for Radiation Oncology; CADTH = Canadian Agency for Drugs and Technologies in Health; ECC = European Cancer Congress; ESMO = European Society for Medical Oncology; ESMO-GI = European Society for Medical Oncology-Gastrointestinal; ESMO-IO = European Society for Medical Oncology- Immuno-Oncology Congress; HAS = Haute Autorité de Santé; IQWiG = Institute for Quality and Efficiency in Health Care; JSMO = Japanese Society of Medical Oncology; SITC= Society for Immunotherapy of Cancer; ISPOR = International Society for Pharmacoeconomics and Outcomes Research (Europe and International); AMCP = Annual Meeting of Academy of Managed Care Pharmacy; NCCN: National Comprehensive Cancer Network; SMC = Scottish Medicines Consortium, NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee			

Appendix H of the CS provides details of a SLR conducted to understand the impact on HRQoL, including outcomes, limitations in daily life, emotional implications, stress, impact on partners, and caregivers using generic and disease-specific QoL instruments among previously untreated patients with locally advanced unresectable gastric or GOJ adenocarcinoma.[1] Searches were undertaken in April 2023.

A summary of the sources searched is provided in Table 4.2.

Table 0.2: Data sources searched for HRQoL studies (as reported in the CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Embase.com	DB inception-16/5/23	16/4/23
MEDLINE In-Process	PubMed	DB inception-16/5/23	16/4/23
CENTRAL CDSR	Cochrane Library		
Conferences			
• ASCO • ASCO-SITC	Internet	2018-2023	Not stated

Resource	Host/Source	Date Ranges	Date searched
• ASCO-GI • ASTRO • ESMO • ESMO-ASIA • ESMO-GI • ESMO-IO • APGCC • AACR • JSMO • SITC • ECC • ISPOR - Europe and International • AMCP • NEXUS			
AMCP = Annual Meeting of Academy of Managed Care Pharmacy; ASCO = American Society of Clinical Oncology; ASCO-SITC = American Society of Clinical Oncology-Society for Immunotherapy of Cancer (ASCO-SITC); ASCO-GI = American Society of Clinical Oncology-Gastrointestinal; ASTRO = American Society for Radiation Oncology; ESMO = European Society for Medical Oncology; ESMO-ASIA = European Society for Medical Oncology ESMO-ASIA; ESMO-GI = European Society for Medical Oncology-Gastrointestinal; ESMO-IO = European Society for Medical Oncology-Immuno-Oncology Congress; APGCC = Asia-Pacific Gastroesophageal Cancer Congress; AACR = American Association for Cancer Research; JSMO = Japanese Society of Medical Oncology; SITC = Society for Immunotherapy of Cancer; ECC = European Cancer Congress; ISPOR = International Society for Pharmacoeconomics and Outcomes Research - Europe and International; AMCP = Annual Meeting of Academy of Managed Care Pharmacy; CENTRAL: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews			

EAG comment:

- Searches were undertaken in April 2023 to identify relevant evidence on the cost effectiveness, economic burden and HRQoL of patients with untreated locally advanced unresectable gastric or GOJ adenocarcinoma. The CS, Appendix G, Appendix H and the company's response to clarification provided sufficient details for the EAG to appraise the literature searches.[1, 7]
- In addition to bibliographic database searches, a good range of Health Technology Assessment (HTA) organisation websites and conference proceedings were searched. Reference checking was conducted.
- Database searches were not limited by date or by language of publication.
- The database searches for the cost effectiveness/healthcare resource use SLR contained a population facet for gastric/GOJ adenocarcinoma. In the Embase and PubMed searches, this was then combined with a filter containing terms for economic evaluations and costs. The filter was not referenced, although the CS states that "A number of published filters were considered when selecting the search terms" (see Appendix G, page 168). It contained an extensive combination of subject heading terms and free text terms, and the EAG considered it appropriate.
- The database searches for the HRQoL SLR contained a population facet for gastric/GOJ adenocarcinoma. In the Embase, PubMed and Cochrane Library searches, this was then combined with a filter containing terms for HRQoL. The filter was not referenced; however, it contained an extensive combination of subject heading terms and free text terms, and the EAG considered it appropriate.

- Searches were well structured, transparent and reproducible. Following a query by the EAG,[6] searches were re-run by the company to include additional search terms in the population facet. No further included studies were identified by these searches.[7]
- The EAG noted that the company's economic searches reported a joint search of MEDLINE and Embase via Embase.com on the understanding that it now contains all MEDLINE content.[7] Whilst the EAG accepts this approach as adequate, it considers it preferable to conduct a separate MEDLINE search in order to fully utilise the power of database-specific study design filters developed to make the most of an individual databases subject headings.

4.1.2 Inclusion/exclusion criteria

The in- and exclusion criteria used by the company are presented in Appendices G and H of the CS, Tables 53 and 70.[8] The EAG considers the inclusion and exclusion criteria suitable to capture all relevant evidence.

4.1.3 Findings of the cost-effectiveness review

The PRISMA flow diagram for the economic SLR can be found in Figure 18 of Appendix G, and for the HRQoL in Figure 19 of Appendix H.[8]

A total of 20 cost effectiveness studies were included, assessing various treatments in various countries. However, cost effectiveness studies evaluating pembrolizumab with doublet chemotherapy compared with doublet chemotherapy alone in the specified population were not identified. Three previous NICE appraisals in similar populations were identified by the review that could potentially inform the model structure, functionality, assumptions, and data sources. Of these, Technology Appraisal (TA) 857 (appraising nivolumab in untreated HER2 negative advanced gastric, GOJ or oesophageal cancer expressing a CPS ≥5) was considered to be the most relevant of those identified as it aligns with the current submission's population regarding HER2 status and largely regarding tumour location. Table 29 of the CS summarises the populations covered by the three appraisals while Table 30 of the CS summarises their cost effectiveness results.[1]

The economic SLR also yielded 17 studies on health care resource use, of which two were European. One study was by Curescu et al. and concerned a Romanian population.[21] The company did not mention this study in their discussion of health care resource use in the CS, possibly because of the population and because the publication was a conference abstract. The other European study was by Guest et al. and involves UK patients.[22] The health care resource use was extracted for patients in the palliative phase of their disease, defined by the start of strong opioids. The duration of this phase was on average approximately 6 months, and an average cost of £3,494 in that period (2000/2001 prices). The company did not mention why this study was not used to inform health care resource use in the model.

For the HRQoL SLR, see Section 4.2.8.

4.1.4 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, utility and resource use and costs studies, but no specific conclusion was formulated. The CS[1] and response to clarification[7] provided sufficient details for the EAG to appraise the literature searches conducted to identify economic, HRQoL and cost data on patients with locally advanced unresectable or metastatic HER2 negative GC or GOJ adenocarcinoma. Searches were conducted in April 2023. Searches were transparent and reproducible, and comprehensive strategies were used. Databases, conference proceedings and trials registers were searched. Overall, the EAG has no major concerns about the literature searches conducted. In general, suitable inclusion criteria were used. Regarding the health care resource use SLR,

it was unclear why the included European papers were not used for the CEA. Overall, the EAG is satisfied that no relevant studies have been omitted.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 0.3: NICE reference case checklist

Element of HTA	Reference case	EAGs comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	As per the reference case.
Perspective on costs	NHS and PSS	As per the reference case.
Type of economic evaluation	Cost utility analysis with fully incremental analysis	As per the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	As per the reference case.
Synthesis of evidence on health effects	Based on systematic review	Population CPS ≥1 based on single RCT; Population CPS ≥5 based on NMA using data from a CPS ≥10 population
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	As per the reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	As per the reference case.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	As per the reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	As per the reference case.

Element of HTA	Reference case	EAGs comment on CS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	As per the reference case.

CS = company submission; EQ-5D = EuroQoL-5 Dimensions; EQ-5D-3L = EuroQoL-5 Dimensions, 3 levels; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

Table 33 of the CS compares the key features of the economic analysis with the previous appraisal TA857.[23]

4.2.2 Model structure

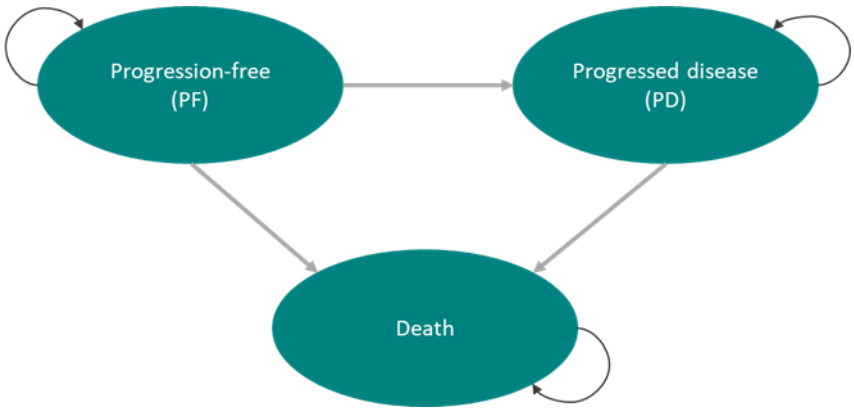
A new cost effectiveness model was built in Microsoft Excel to evaluate the cost effectiveness of treatment with pembrolizumab plus doublet chemotherapy compared to alternatives, considering health outcomes (LY and QALYs) and costs from the NHS and Personal Social Services (PSS) perspective.

4.2.2.1 Health states

The model adopts a partition survival analysis framework with three health states: progression-free (PF), progressed disease (PD), and death, where patients can only occupy one state at the time. This model was chosen by the company over a Markov model to directly use the OS and PFS curves from the KEYNOTE-859 trial as the resulting Markov trace of the model, without the need to estimate transition probabilities. This approach of using a partition survival model have been previously accepted by NICE for oncology submissions (previous TA in the field of advanced gastric, GOJ and oesophageal cancer: TA208[24], TA73[25], TA857[23], TA707[26], TA865[27]).

Figure 4.1 shows the model structure.

Figure 0.1: Model structure



Based on Figure 9 of the CS[1]
CS = company submission; PD = progressed disease; PF = progression-free

4.2.2.2 Transitions and treatments in each health state

In the model, all patients start in the PF state and receive either pembrolizumab plus doublet chemotherapy or a comparator. The proportion of patients in PF is determined by the PFS curve. In the next cycle, patients can stay PF and continue their initial treatment, remain PF but stop the treatment, progress and thus progress to the PD state (possibly receiving further treatment), or die. The proportion

on first-line treatment is represented by the time on treatment (ToT) curve. Costs for subsequent treatments are included in the model as a one-off cost upon progression.

The proportion of patients in the PD state is calculated as the difference between the PFS and OS curves. Progressed patients cannot return to the PF state and may either stay in PD or die, with death being an absorbing state.

Patient-level data from the KEYNOTE-859 were used to estimate parametric curves for PFS, OS, and ToT for pembrolizumab plus doublet chemotherapy and doublet chemotherapy [Section B.3.3 CS]. Hazard ratios for the comparator nivolumab plus doublet chemotherapy resulted from a NMA (Section B.3.3 CS). The OS and PFS were modelled independently. To avoid negative state occupancy in the PD health state, a cap was applied to prevent PFS from exceeding OS.

4.2.2.3 Cycle length

The model adopts a 1-week cycle length to match drug administration timings and to capture a realistic minimum time during which progressions and treatment can change in UK clinical practice. No half-cycle correction was applied due to the short duration, ensuring robust benefit and cost estimated.

4.2.3 Population

The base-case patient population included in the economic analysis is patients with untreated HER2 negative advanced gastric or GOJ adenocarcinoma, expressing a CPS ≥1. This is more narrow than the population defined in the NICE scope,[2] which was not restricted to CPS ≥1, but this population aligns with the anticipated licensed population in the UK. The patient population included in the economic analysis (i.e., CPS ≥1) is a pre-defined subgroup investigated in the KEYNOTE-859 trial.

The NICE scope stated that subgroups by PD-L1 status and by tumour location should be considered if the evidence allows. The CS includes a subgroup analysis by PD-L1 status, by presenting cost effectiveness results both for the CPS ≥1 and the CPS ≥10 population. The latter population was also pre-specified in the KEYNOTE-859 trial. It should be noted that the comparators vary between CPS level. No subgroup analysis was presented for tumour location for several reasons as outlined by the company.

Firstly, based on current NICE recommendations (TA857[23], TA208[24] , TA737[25]), treatments do not depend on tumour location. Secondly, clinical experts consulted by Merck Sharp and Dohme (MSD) explained how the definition of GOJ is subjective and varies between clinics and clinical trials. Thirdly, the patients in KEYNOTE-859 with gastric adenocarcinoma (CPS ≥1) had similar results to patients with GOJ adenocarcinoma (CPS ≥1) (See Table 33 and Figure 13 in Appendix E).[8])

The key baseline patient characteristics in the economic model for both the CPS ≥1 and the CPS ≥10 population were derived from the KEYNOTE-859 study and are listed in Table 4.4 below.

In the CS it was explained that clinical experts had reviewed the baseline patient characteristics in the KEYNOTE-859 trial and noted that these patients were a few years younger than those treated in clinical practice, but that this would not invalidate the results presented in the current appraisal. In the clarification letter, the company was asked to quantify the difference in age between the trials and those treated in clinical practice and to provide a similar comparison for the other characteristics included in the health economics model.[7] In response, the company provided estimates from a large cancer centre in London, specific to patients with metastatic gastric or GOJ adenocarcinoma before initiating first-line treatment, and from the 2022 National Oesophago-Gastric Cancer Audit report, separate for patients with oesophageal adenocarcinoma and with GC (Siewert I+II and Siewert III, respectively).[7]

Regarding the estimates from the latter source, the company noted that the audit report does not provide the age of patients diagnosed with OG cancer that would be fit and eligible for first-line treatment, and that they considered it reasonable to expect that the total diagnosed population would have a higher median age than the population who are eligible to receive treatment. Finally, the company noted that the cost effectiveness outcomes are insensitive to changes in the patient characteristics.

Table 0.4: Comparison key baseline patient characteristics KEYNOTE-859 and England and Wales

Baseline patient characteristic (mean)	KEYNOTE-859*		Large cancer centre London†	National Oesophago-Gastric Cancer Audit 2022 England & Wales	
	CPS≥1	CPS≥10		OAC + GOJ AC	GC
Age, years	60.1	60.7	-	72 (median)	74 (median)
Proportion of females	29.6%	27.8%	39.4%	19%	34%
Weight, kg	66.3	66.7	66.7 (IQR 53.8 – 74.5)	-	-
BSA, m^2	1.7	1.7	1.7 (IQR 1.57 – 1.84)	-	-

Based on Table 30 of the CS[1] and response to question 5 of the clarification letter.[7]
* Based on Tables 12 and 18 of the HTA Disposition and Demographics Report
† Patients with metastatic gastric or GOJ adenocarcinoma before initiating first-line treatment
AC = adenocarcinoma; BSA = body surface area; CPS = combined positive score; GC = gastric cancer; GOJ = gastro-oesophageal junction; IQR = interquartile range; OAC = oesophageal

4.2.4 Interventions and comparators

The intervention considered in the model is pembrolizumab plus doublet chemotherapy, with the comparator depending on the patient's CPS level. As the full anticipated licensed indication is for patients expressing a CPS ≥1, the two relevant comparators are doublet chemotherapy for all patients expressing a CPS ≥1 and, in patients expressing CPS ≥5, nivolumab plus doublet chemotherapy.

In the KEYNOTE-859 trial, pembrolizumab 200 mg or placebo was given IV Q3W in combination with investigator's choice of doublet chemotherapy:

- FP (continuous infusion of 5-fluorouracil [800 mg/m^2/day on days 1–5 of each cycle] plus IV cisplatin [80 mg/m^2] Q3W); or,
- CAPOX (oral capecitabine [1000 mg/m^2 BID on days 1–14 of each cycle] plus IV oxaliplatin [130 mg/m^2 on day 1 of each cycle] Q3W).

In the base-case CEA, the proportion of patients receiving each type of doublet chemotherapy regimen were informed by KEYNOTE-859 for pembrolizumab plus doublet chemotherapy and doublet chemotherapy, and CheckMate-649 for nivolumab plus doublet chemotherapy (see Table 4.5). In a scenario analysis, the proportions of patients receiving each doublet chemotherapy regimen was based on current NHS practice, as provided by clinical experts.

In addition, a scenario analysis was done changing the dosing schedule for pembrolizumab from 200 mg Q3W to 400 mg Q6W. As the company explained in their response to question B6 of the clarification letter, there is evidence to support the assumption that the dosing schedule has no impact on the safety and efficacy.[7]

Table 0.5: Proportion of patients receiving each doublet chemotherapy regimen (base-case analysis: trial data; scenario analysis: NHS practice)

Doublet chemotherapy regimen	Pembrolizumab plus doublet chemotherapy		Doublet chemotherapy	Nivolumab plus doublet chemotherapy	NHS practice (scenario analysis)
Population	CPS ≥1	CPS ≥10	CPS ≥1	CPS ≥10*	
CAPOX/XELOX	85.4%	86.7%	85.6%	51%	70%
FP	14.6%	13.3%	14.4%	-	-
FOLFOX	-	-	-	49%	25%
XP	-	-	-	-	5%

Based on Tables 26 and 45 of the HTA HECON Baseline and Efficacy Report[28]
*Data from patients in CheckMate-649 expressing CPS ≥5 used as a proxy in the absence of data from patients expressing CPS ≥10
CAPOX/XELOX = oxaliplatin and capecitabine; CPS = combined positive score; FOLFOX = folinic acid, fluorouracil and oxaliplatin; FP = cisplatin and fluorouracil; XP = capecitabine and cisplatin

4.2.5 Perspective, time horizon and discounting

The economic analyses were conducted from the perspective of the NHS and PSS perspective, in line with the NICE reference case. The model has a time horizon of 30 years which is considered appropriate as a lifetime horizon, in line with the NICE reference case, given that the average age of patients at the start of treatment is 60.1 years in the CPS ≥1 population. Costs and quality-adjusted life years (QALYs) were discounted at 3.5% as per the NICE reference case.

4.2.6 Treatment effectiveness and extrapolation

The main sources of evidence on treatment effectiveness used for the intervention is the KEYNOTE-859 trial. The primary outcome in this trial is OS, measured as the time from randomisation to any cause of death. Progression-free survival is a secondary outcome, defined as the time from randomisation to the first document DP (per RECIST 1.1 by BICR) or death, whichever comes first.

Pembrolizumab with doublet chemotherapy demonstrated statistically significant and clinically meaningful improvements in OS compared to chemotherapy alone in the ITT, CPS ≥1 and CPS ≥10 population during the pre-specified IA 1 conducted by an Independent Data Monitory Committee (Section 2.6.1 CS). The PD-L1 status was used as a stratification factor. Statistically significant and clinically meaningful improvements in PFS and ORR were also observed in the ITT, CPS ≥1 and CPS ≥10 populations, meeting all hypotheses. Therefore, IA 1 is considered the final statistical analysis. The trial will continue until reaching the specified events in the protocol, with data to be published later.

In the economic model, survival curves for pembrolizumab plus doublet chemotherapy and doublet chemotherapy were estimated using PFS and OS data from the KEYNOTE-859 trial, based on the most recent data cut-off at the first pre-specified IA 1 (3 October 2022). To estimate survival curves for nivolumab plus doublet chemotherapy in the CPS ≥10 population, the HR derived from the NMA was applied to the pembrolizumab plus doublet chemotherapy survival curves (HR of [redacted] for OS). This NMA assumed constant HRs due to a defensible PH-assumption (see Section B2.9 of the CS).

For the economic model, survival curve fitting followed NICE Decision Support Unit (DSU) guidelines. While recognising that the proportional hazard (PH) assumption is less necessary with Individual Patient Data (IPD), it was tested to determine whether separate or joint models for each arm were preferable. Statistical goodness-of-fit measures (Akaike information criterion [AIC], Bayesian

information criterion [BIC]), visual inspection, and clinical plausibility were used to choose base-case survival curves. Various standard survival distributions were assessed (exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal, Weibull), and in addition spline modelling was considered. No obvious visual hazard change was observed in the intervention and comparator curves, so a 'two-piece' approach was not pursued.

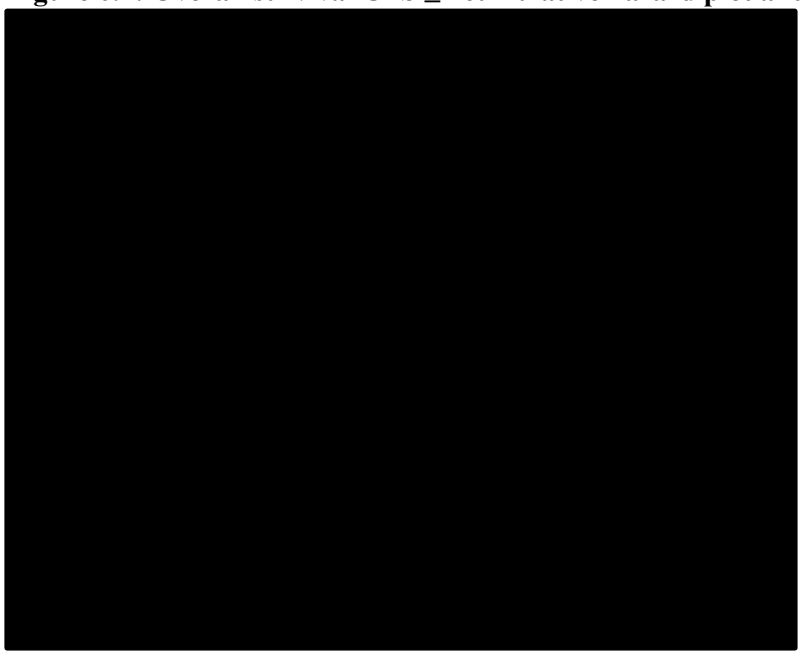
4.2.6.1 Overall survival - selection of distribution

Overall survival, CPS ≥1: Proportional hazard assessment

The PHs assumption was evaluated for the comparison between pembrolizumab plus doublet chemotherapy and chemotherapy. The company found evidence that this assumption may not hold for patients expressing CPS ≥1 during the trial period. This conclusion was based on several factors:

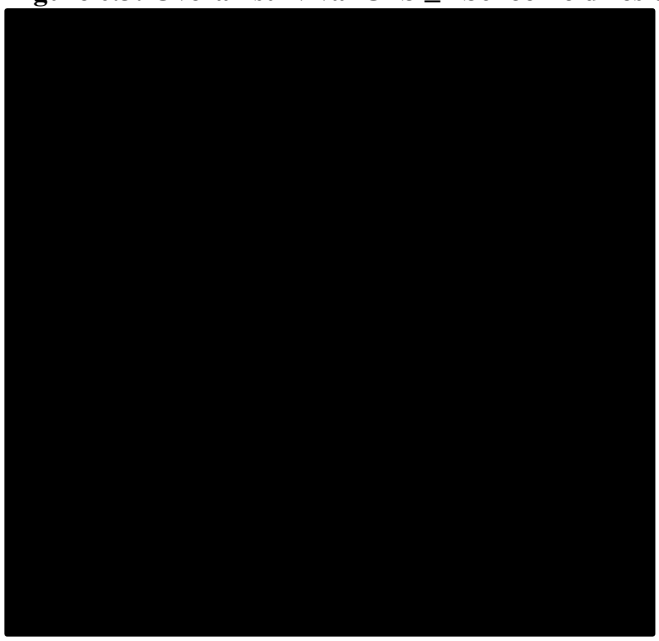
1. Visual examination of the log cumulative hazard plot and log-log plot indicate overlap of the curves at the beginning of the trial, suggesting non-PHs (Figure 4.2).
2. Flattening of the hazard curves between week 150 and 200 suggests a change in hazards, which might be due to the small number of patients remaining at risk in the trial.
3. Schoenfeld residuals plot in Figure 4.3 showed divergence from zero in the later part of the curve and the associated test was statistically significant (p=0.0248). This provides additional evidence against the PH assumption.

Figure 0.2: Overall survival CPS ≥1 cumulative hazard plot and log-log plot



Based on Figure 10 of the CS.[1]
CS = company submission

Figure 0.3: Overall survival CPS ≥1 Schoenfeld residuals plot



Based on Figure 11 of the CS.[1]
CS = company submission

Based on these, the company concluded that there is evidence to reject the PH assumption between pembrolizumab and doublet chemotherapy and doublet chemotherapy in patients expressing CPS ≥1 during the trial period. In addition, the company stated that there is a clinical argument that the PH assumption may not be valid for immune-oncology (IO) therapies versus chemotherapy comparisons, since IO therapies often show a delayed treatment effect compared to chemotherapy and can enable long-term survival in a subgroup of patients[29] are reported in Table 4.6. Of the standard parametric models, the lognormal fits the observed data best as indicated by the lowest AIC and BIC.

Table 0.6: Overall survival goodness of fit statistics CPS ≥1 (separately fitted models)

Model	Pembrolizumab plus doublet chemotherapy				Doublet chemotherapy			
	AIC	rank	BIC	rank	AIC	rank	BIC	rank
Standard parametric								
Exponential	5109.9	15	5114.1	14	5464.7	15	5469.1	15
Weibull	5105.6	14	5114.5	15	5430.8	13	5439.6	12
Log-logistic	5094.0	12	5102.9	12	5468.0	16	5476.8	16
Lognormal	**5076.0**	7	**5084.8**	1	**5421.5**	9	**5430.3**	5
Gompertz	5111.2	16	5120.1	16	5457.4	14	5466.3	14
Gamma	5100.9	13	5109.8	13	5424.5	10	5433.3	10
Generalised gamma	5087.6	11	5100.9	11	5424.6	11	5437.9	11
Spline								
1k hazard	5086.9	10	5100.2	10	5427.1	12	5440.3	13
2k hazard	**5071.3**	1	**5089.0**	2	5409.8	3	5427.5	2

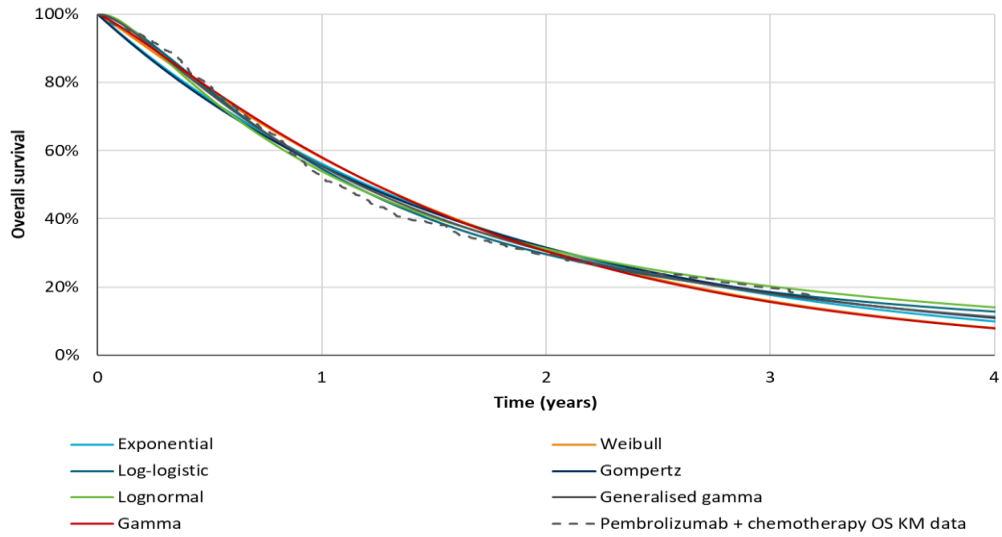
Model	Pembrolizumab plus doublet chemotherapy				Doublet chemotherapy			
	AIC	rank	BIC	rank	AIC	rank	BIC	rank
3k hazard	5073.5	4	5095.7	6	**5408.5**	1	5431.6	6
1k odds	5077.9	8	5091.2	5	5408.6	2	**5421.9**	1
2k odds	5072.2	2	5089.9	3	5410.3	5	5428.0	3
3k odds	5074.0	5	5096.2	7	5409.8	3	5432.0	7
1k normal	5084.7	9	5098.0	9	5415.6	8	5428.9	4
2k normal	5073.1	3	5090.8	4	5414.6	7	5432.3	8
3k normal	5074.1	6	5096.3	8	5410.8	6	5433.0	9

Based on Table 34 of the CS[1], ranking added by EAG.
AIC = Akaike information criterion; BIC = Bayesian information criterion; CPS = combined positive score; OS = overall survival

For pembrolizumab plus doublet chemotherapy, the company reported the lognormal and log-logistic models to be among the best statistically fitting one and argued that those two models align well with the K-M data (Figure 4.4) and the smoothed hazard plot (Figure 4.6).

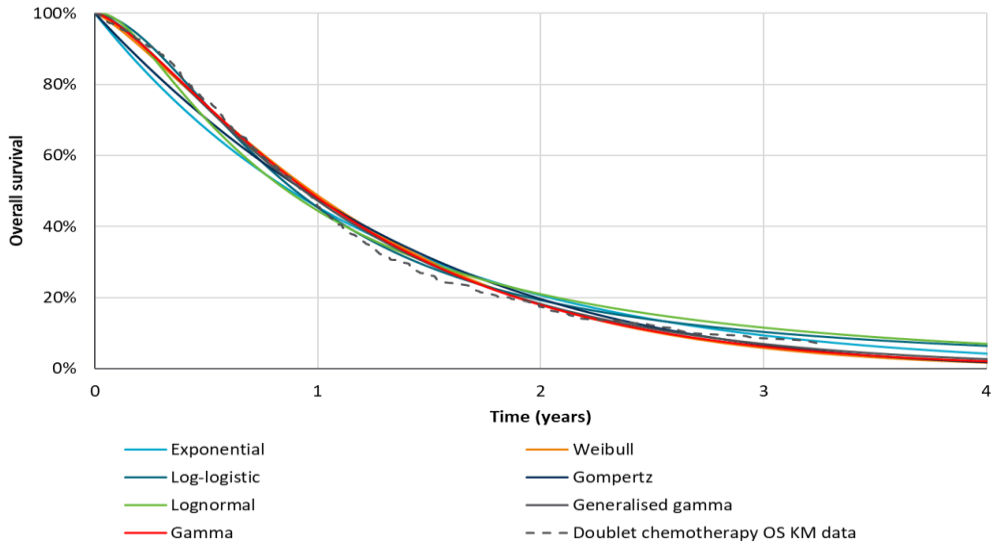
For doublet chemotherapy, the company found that the lognormal distribution the best statistically fitting, but that it overestimated the tail of the K-M data (Figure 4.5). They, therefore, preferred the log-logistic model based on visual inspection of its hazard curve as it spends more time within the 90% CI of the smoothed observed hazard plot (Figure 4.7).

Figure 0.4: Overall survival CPS ≥1 pembrolizumab plus doublet chemotherapy (separately fitted)



Based on Figure 12 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.5: Overall survival CPS ≥1 doublet chemotherapy (separately fitted)



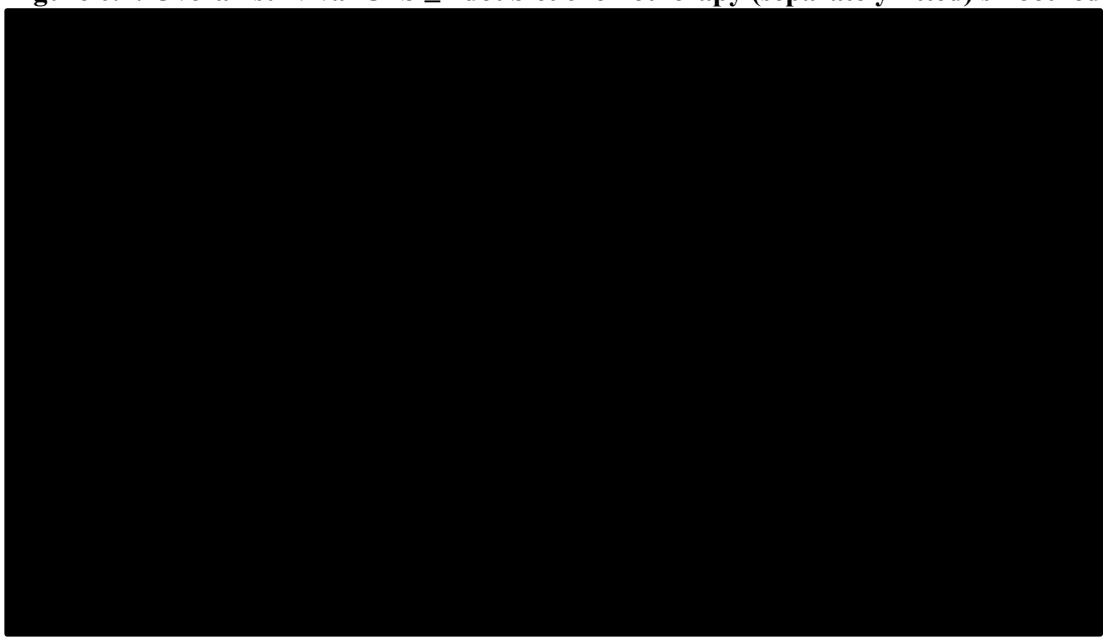
Based on Figure 13 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.6: Overall survival CPS ≥1 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards

[redacted]

Based on Figure 14 of the CS[1]
CS = company submission; CPS = combined positive score

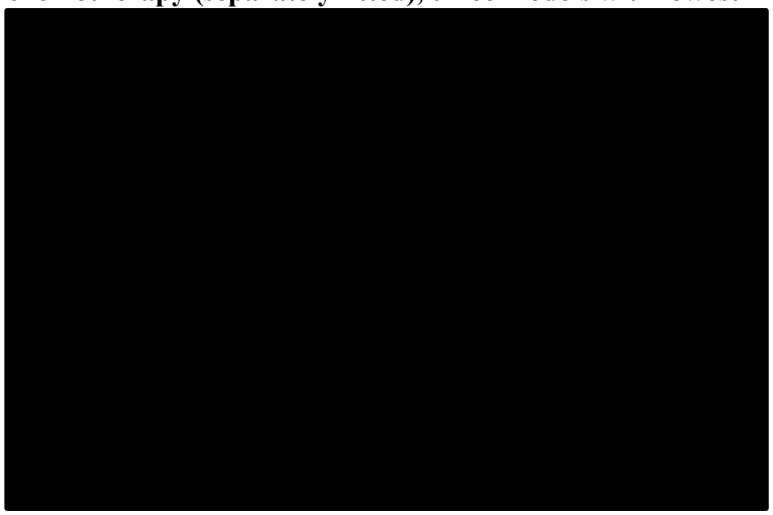
Figure 0.7: Overall survival CPS ≥1 doublet chemotherapy (separately fitted) smoothed hazards



Based on Figure 15 of the CS[1]
CS = company submission; CPS = combined positive score

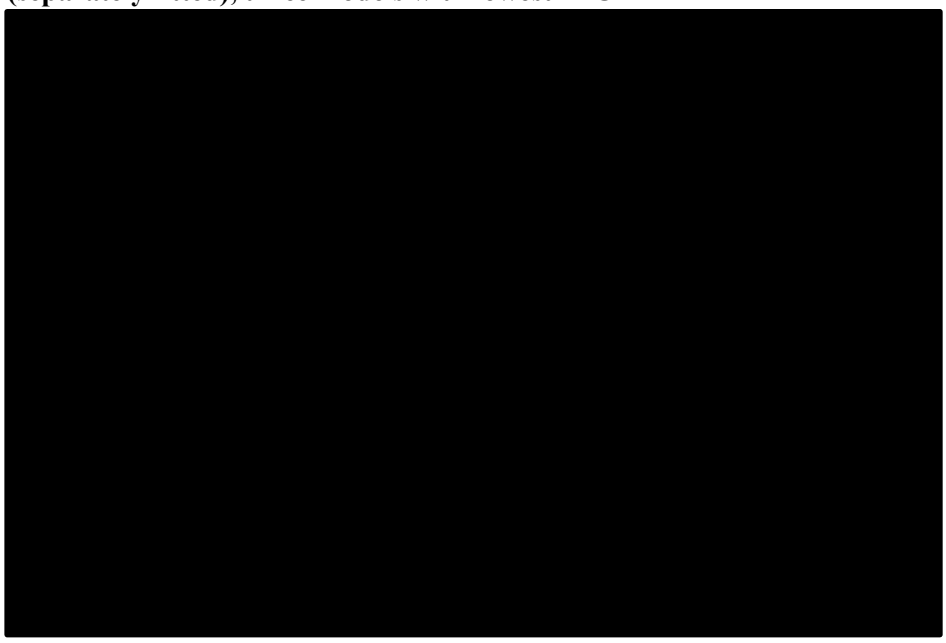
Next, the company focussed on various spline models, varying from 1 to 3 knots and the scale chosen as "hazard", "odds", or "normal". Thus, a total of nine spline models was assessed by the company. For pembrolizumab plus doublet chemotherapy, the separately fitted 2-knot hazard spline model was selected as the base-case since it has the lowest AIC and also offers a strong fit to the K-M data (Figure 4.8). The separately fitted 2-knot hazards spline was also selected for the base-case model for the doublet chemotherapy arm (Figure 4.9). The company acknowledged that the odds scale spline models had a relatively good AIC fit, but that the 2-knot hazard was preferred to the company based on visual fit. Figures 4.10 and 4.11 present the fitted 2-knot hazard spline models for both pembrolizumab plus doublet chemotherapy and doublet chemotherapy only.

Figure 0.8: Overall survival CPS ≥1 spline curves hazard profile pembrolizumab plus doublet chemotherapy (separately fitted), three models with lowest AIC



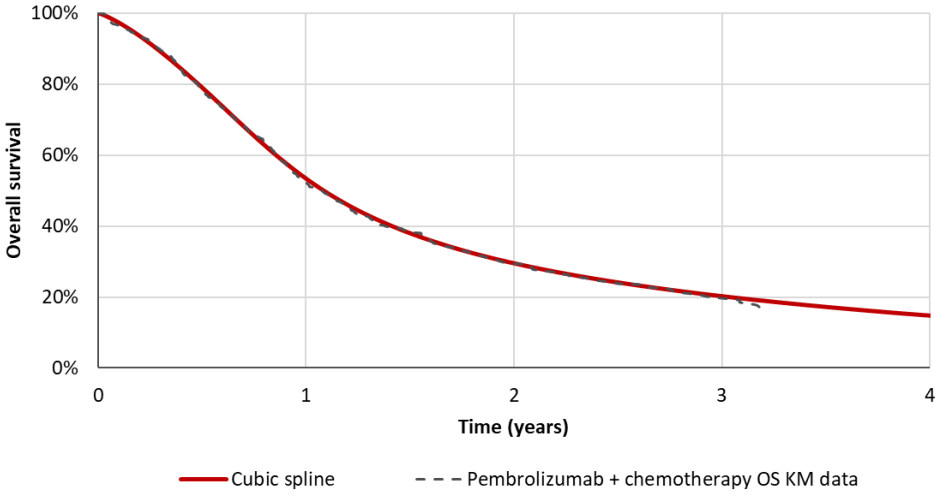
Based on Figure 16 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.9: Overall survival CPS ≥1 spline curves hazard profile doublet chemotherapy (separately fitted), three models with lowest AIC



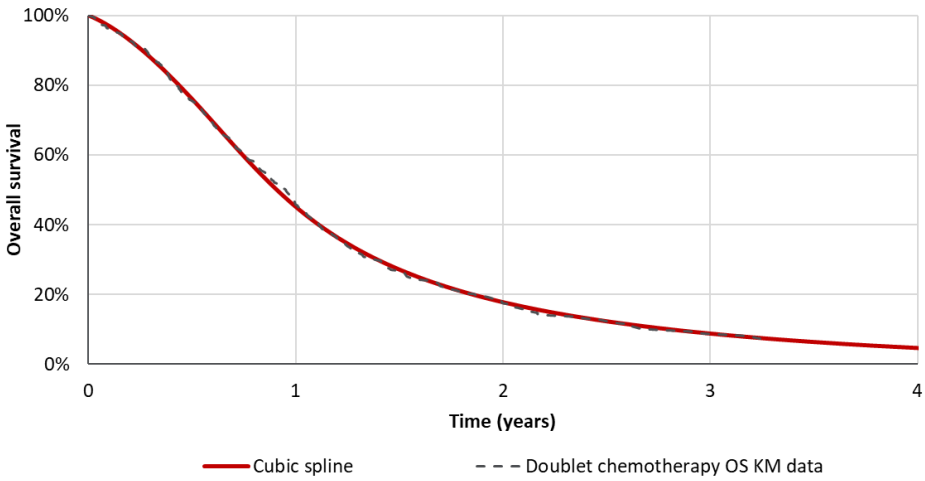
Based on Figure 17 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.10: Overall survival CPS ≥1 2-knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)



Based on Figure 18 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.11: Overall survival CPS ≥1 2-knot hazard spline doublet chemotherapy (separately fitted)



Based on Figure 19 of the CS[1]
CS = company submission; CPS = combined positive score

Overall survival, CPS ≥1: Internal and external validity

The internal validation process of the company involved comparing median OS data in weeks and months between observed and modelled KEYNOTE-859 data. As shown in Table 4.7, the modelled median OS values for both pembrolizumab plus doublet chemotherapy and doublet chemotherapy are lower compared to the observed KEYNOTE-859 data. The company concluded that this discrepancy is minimal and therefore, that the modelled and observed data show close agreement. In addition, the company compared the observed and modelled survival at fixed time points (6, 12, 18, 24, 30, 36, and 60 months, see Appendix N) showing that the discrepancy between observed and modelled is minimal over the whole range of time points. The comparison in Appendix N also included a selected few other distribution, and the company concludes that these tables consistently show that the intervention yields higher survival rates compared to the comparator across all selected models.

Table 0.7: Overall survival validation of fitted model, 2 knot hazard spline (CPS ≥1)

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	56.4	56.0	13.0	12.9
Doublet Chemotherapy	49.6	47.0	11.4	10.8

Based on Table 35 of the CS
CS = company submission; CPS = combined positive score; OS = overall survival

For the external validation, the company asked clinical experts if they knew of external data sources to validate the survival outcomes predicted by the economic model, besides CheckMate-649, but this did not yield any additional data sources. The experts shared their expectations for the proportion of patients expected to survive 2, 5 and 10 years while on doublet chemotherapy based on their experience (see Table 4.8). After seeing the results of the 10-year extrapolations, the experts found that the separately

fitted lognormal curve appeared overly optimistic. Instead, they considered the separately fitted gamma and a spline model with 2-knot hazards more plausible.

Table 0.8: Overall survival validation of fitted model (CPS ≥1)

Year	Expert A	Expert B	Expert C
2	≤ 20%	<20%	15%
5	<5 %	3 to 4%	<1%
10	0%	0%	0%

Based on Table 36 of the CS[1]
CPS = combined positive score; CS = company submission; OS = overall survival

The clinical experts had no experience using pembrolizumab plus doublet chemotherapy for the indication being appraised and therefore were unable to provide OS rate estimates. Nevertheless, the company held a discussion with the experts about the relative treatment effect by showing them the K-M data for doublet chemotherapy alongside the extrapolations for pembrolizumab plus doublet chemotherapy (up to 10 years). The experts agreed that the separately fitted 2-knot hazard spline model was a reasonable extrapolation for the base-case analysis, because they agreed that the distance between the survival curves would increase over time and that a plateau in the pembrolizumab plus doublet chemotherapy curve would be likely.

EAG comment: In general, the company has followed state-of-the-art guidance to select the optimal parametric model for OS, and thus, only two minor issues exist.

a) In the company's discussion of the best statistical fit of the standard parametric distributions, defined as lowest AIC, the lognormal and loglogistic distributions are identified as the best fit. Here the EAG misses the generalised gamma distribution in the shortlist as it has a lower AIC compared to the loglogistic distribution. To understand better why the company focussed on only the lognormal and the loglogistic distribution, the EAG asked how the company (Question B4 of the clarification letter[1]) defined optimal statistical fit. The company clarified that they focused on the lowest AIC, but that this was not used in isolation when choosing the best fitting parameter curves. Therefore, in their conclusion they already combined lowest AIC, visual inspection of survival and hazard curves, and some clinical plausibility. However, when combining these aspects, the EAG maintains that the generalised gamma distribution performs just as well as the loglogistic distribution or even better, considering the slightly lower survival at 5 years. However, as most spline models outperform the standard parametric models, the relative performance of the (generalised) gamma distribution versus the loglogistic distribution is not of great consequence.
b) In the selection of the best fitting spline model, the company focussed on the 2-knot hazard spline model for the OS model for doublet chemotherapy. However, based on AIC this function was ranked third, with the 3-knot hazard ranking first and the 1-knot odds ranking second. The EAG noticed that the 2-knot hazard spline model does not seems to have the best visual fit, based on the provided hazard curves for all cubic spline extrapolation in the clarification response from the company.[7] The EAG noticed that the 3-knot odds models seemed to have a better visual fit and this model gave the same AIC score as the 2-knot hazard model (Table 4.6). However, the 5-year survival is slightly lower with the 2-knot hazard model than with the 3-knot odds model, and as it is customary to select the same parametric model for both treatment arms (with the 2-knot hazard model ranking first for the pembrolizumab group), the selection of the 2-knot hazard spline model appears justified. The EAG explored the effect of selecting various alternative spline models, such

as the 3-knot odds model, for both the pembrolizumab plus doublet chemotherapy and doublet chemotherapy only, these results are presented in Chapter 6.

Overall survival, CPS ≥5: Population justification

In Section B2.9 of the CS, the company explain that an NMA at CPS ≥5 was not feasible at the time of writing the submission. In response to clarification, the company also explained that CPS≥5 was not a prespecified cut-off in the KEYNOTE-859 trial and no analytical validation or pathologist training was conducted for the CPS≥5 cut point, which negatively impacts the accuracy of results at the CPS≥5 level. However, the company did provide the results of an NMA at CPS≥5, with the caveats mentioned above, in their response to the clarification letter. These showed for OS an HR of [redacted] versus [redacted] for the CPS≥10 patients.

Given the caveats around the CPS≥5 NMA results, the company chose to present cost effectiveness results for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy for patients expressing CPS≥10 instead. To deal with the current uncertainty in patients expressing CPS ≥5, the company examined and compared relevant clinical effectiveness evidence.

The NICE TA857 considered results from CheckMate-649 for patient who expressed CPS ≥1 and CPS ≥5. The Opvido EMA European Public Assessment Report (EPAR) contains OS results from CheckMate-649.[16] Table 4.7 summarises the results at additional CPS levels. The company concluded that the EMA EPAR results confirm that nivolumab plus doublet chemotherapy do not show statistically significant difference compared to doublet chemotherapy at a CPS level of 5 to 9. Regardless of these results, the company stated that NICE TA857 recommends nivolumab plus doublet chemotherapy for patient expressing a CPS ≥5. Based on the results from the KEYNOTE-859, the company stated that pembrolizumab plus doublet chemotherapy show statistically significant difference compared to doublet chemotherapy at CPS levels of 1 to 9 and that the HR point estimate is lower than those from CheckMate-649 at CPS levels of 1 to 4 and 5 to 9 (0.83 versus 0.97 and 0.92, respectively). Therefore, the company would expect that pembrolizumab plus doublet chemotherapy would be an effective option versus nivolumab plus doublet chemotherapy in the CPS ≥5 population.

Table 0.9: CPS ≥1 supplementary data: KEYNOTE-859 versus CheckMate-649

CPS	KEYNOTE-859 (n=1,579)		CheckMate-649 (n=1,518)	
	n	OS HR (IO versus chemo)	N	OS HR (IO versus chemo)
1 to 4	NA		341 (22.5%)	0.97 (0.76 to 1.24)
5 to 9			187 (12.1%)	0.92 (0.66 to 1.28)
1 to 9	682 (43.2%)	0.83 (0.70 to 0.98)	NA	

Based on Table 37 of the CS[1] that cites also Higgins et al. 2022[16].
CI = confidence interval; CPS = combined positive score; HR = hazard ratio; IO = immunotherapy; NA = not applicable; OS = overall survival. n = number of patients with specified CPS

Overall survival CPS ≥10: Proportional hazard assessment

For the subgroup of patients with CPS ≥10, pembrolizumab is compared to nivolumab. As these treatments have not been compared in one single RCT, an NMA was done to assess the comparative effectiveness. The outcome of the NMA is a HR of pembrolizumab versus nivolumab. By applying this

HR to the OS model for pembrolizumab, the OS for nivolumab is estimated. This approach assumes that the PH assumption holds. The company assessed PH related to the NMA (see CS Section B2.9) and concluded that they are justified in assuming PH and therefore rely on a single HR for the entire modelled period.

Overall survival, CPS ≥10: Separately fitted models

For pembrolizumab plus doublet chemotherapy, the log-logistic and log-normal models provide the best fit for standard parametric curves based on AIC/BIC statistics (Table 4.10). The company concluded that these models also have the best visual alignment among the parametric survival models to the K-M data (Figure 4.12) and smoothed hazard plot (Figure 4.13).

From the spline models, the statistical and visual inspection showed that spline models fit the hazard data very well. The company concluded that this was better than other separately fitted parametric survival models. From the spline models, the 2-knot odds model has been selected as the base-case for the pembrolizumab plus doublet chemotherapy arm. Since there is no NMA for the PFS in this population, the company decided to use the HR from the NMA for OS as a proxy [redacted] for nivolumab plus doublet chemotherapy versus pembrolizumab plus doublet chemotherapy). They applied the HR to the OS curve for pembrolizumab plus doublet chemotherapy to generate the OS curve for nivolumab plus doublet chemotherapy.

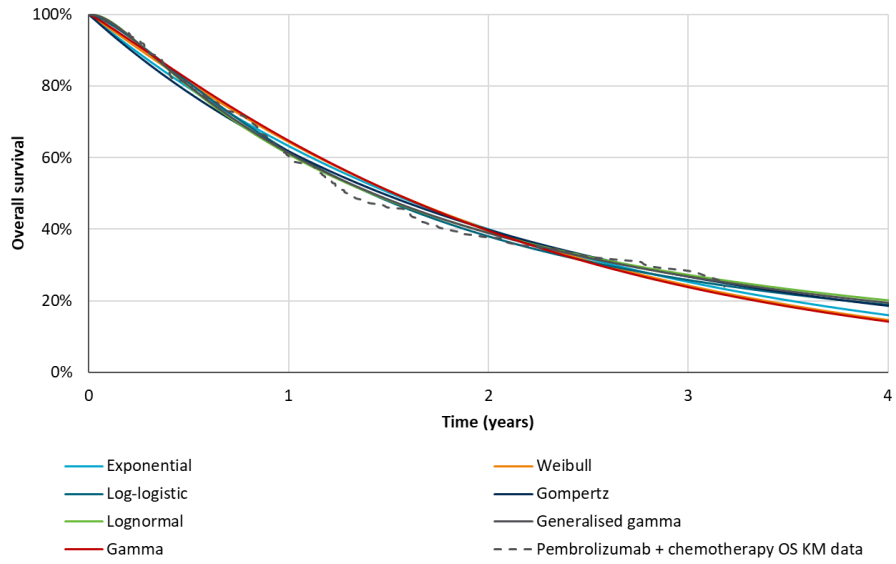
Table 0.10: Overall survival goodness of fit statistics CPS ≥10 (separately fitted models)

Model	Pembrolizumab plus doublet chemotherapy			
	AIC		BIC	
Standard parametric				
Exponential	2158.6	14	2162.2	7
Weibull	2159.7	16	2167.0	13
Log-logistic	**2147.7**	1	**2154.9**	1
Lognormal	2147.7	1	2155.0	2
Gompertz	2159.6	15	2166.8	12
Gamma	2158.4	13	2165.6	11
Generalised gamma	2149.5	8	2160.4	5
Spline				
1k hazard	2149.5	8	2160.4	5
2k hazard	2149.5	8	2164.0	8
3k hazard	2149.3	4	2167.5	14
1k odds	**2148.4**	3	**2159.3**	3
2k odds	2149.9	12	2164.4	10
3k odds	2149.4	7	2167.5	14
1k normal	2149.3	4	2160.2	4
2k normal	2149.5	8	2164.0	8
3k normal	2149.3	4	2167.5	14

Based on Table 38 of the CS[1]

Model	Pembrolizumab plus doublet chemotherapy			
	AIC		BIC	
AIC = Akaike information criterion; BIC = Bayesian information criterion; CPS = combined positive score; OS = overall survival				

Figure 0.12: Overall survival CPS ≥10 pembrolizumab plus doublet chemotherapy (separately fitted)



Based on Figure 20 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.13: Overall survival CPS ≥10 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards

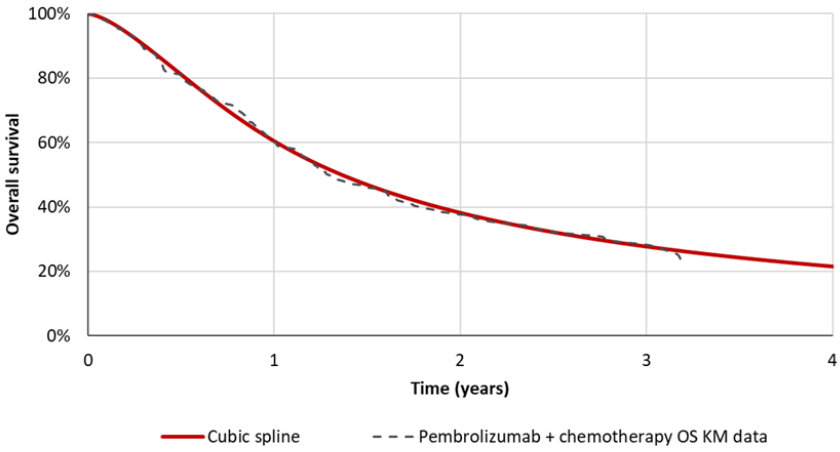
[redacted]

Based on Figure 21 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.14: Overall survival CPS ≥10 spline curve hazard profile pembrolizumab plus doublet chemotherapy (separately fitted)

Based on Figure 22 of the CS[1]
CS = company submission; CPS = combined positive score

Figure 0.15: Overall survival CPS ≥10 2-knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)



Based on Figure 23 of the CS[1]
CS = company submission; CPS = combined positive score

Overall survival, CPS ≥10: Internal and external validation

Like with the OS for CPS ≥1, internal validation of the OS in weeks and months was done by comparing the modelled data for the KEYNOTE-859 data based on the fitted survival curves with the observed KEYNOTE-859 data. Based on the data presented in Table 4.11, the company concluded that the fitted OS curve for pembrolizumab plus doublet chemotherapy fits the observed data well with minimal discrepancies. Appendix N reports the survival rate validation at different timepoints (6, 12, 18, 24, 30, 36, and 60 months).

Like the clinical expert validation for the CPS ≥1 population, clinical experts were shown extrapolations for pembrolizumab plus doublet chemotherapy (up to 10 years) alongside K-M data for doublet chemotherapy. The clinical experts agreed that curves like the Weibull are too pessimistic and curves like the separately fitted 2-knot odds spline model are more plausible.

Table 0.11: Overall survival validation of fitted model (CPS ≥10)

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	67.1	72.0	15.4	16.6

Based on Table 39 of the CS.[1]
CPS = combined positive score; CS = company submission; OS = overall survival

EAG comment: As selected by the company, the EAG noticed that the 2-knotted splines models seem to be the best choices based on visual fit compared to the 1- and 3-knots, while the AIC values do not provide any discriminating values in the comparison. However, the EAG could not discriminate regarding the odds, normal or hazard model based on the visual inspection. Therefore, the EAG explored the use of alternative models for extrapolations, as well as effect on the model results, when using a normal or hazard 2-knot model. Nonetheless, the EAG found that the changes in results are negligible to be further considered in a scenario analysis (ICER differences <£1,000/QALY).

4.2.6.2 Overall survival - treatment waning

There is no treatment waning effect assumed in the base-case analysis. The company argued that there is no clear evidence to indicate a treatment waning effect based on the independent estimation of survival curves for the intervention and comparator arms. They also described that the clinical experts concluded that the expected long-term shape of the pembrolizumab plus double chemotherapy OS curves relative to the doubled chemotherapy OS curve would diverge over time and never meet. The company also referred to TA857 and stated that a treatment waning effect was absent from the base-case analysis as there was no evidence of a treatment waning effect in the CheckMate-649 trial.

In a scenario analysis, a gradual treatment waning effect 5 year following discontinuation of pembrolizumab (7 year since treatment initiation) was applied, by gradually making the cycle specific hazard for pembrolizumab equal to that in the double chemotherapy arm over the subsequent 2 years. The company argued that the ongoing benefit of IO following cessation of treatment is further supported by addition follow-up observed in IO trials and therefore, the waning timepoints in this scenario analysis should be viewed as conservative.[30-33]

No treatment waning scenario analysis was presented for the comparison with nivolumab plus doublet chemotherapy. The company argued that this is reasonable given the comparable biological

mechanisms of action and stopping rules of nivolumab and pembrolizumab and highlighted that a scenario analysis cannot be done without additional assumptions regarding the survival that the treatment effect wanes to.

EAG comment: It is interesting to see that the company refers to TA857, as in that appraisal no treatment waning was assumed in the base-case.[23] However, in the Final Appraisal Determination (FAD) of TA857, treatment waning is discussed where the company assumed that the risk of death for the nivolumab arm would be the same as for the control group after 6.5 years, whilst the EAG assumed that the risk would be the same after 5 years. It should be noted though that around the time the FAD was published, results of CheckMate-649 after a minimum of 3 year follow-up was also published.[34] That publication presented results that clearly indicate that at that time point there were no signs (yet) of waning. When combined with the studies cited by the company (long-term follow-up in melanoma and lung cancer, with either nivolumab or pembrolizumab)[30-33] the EAG considers it reasonable to assume that the treatment effect will remain for a certain period after treatment with pembrolizumab has stopped. However, in line with the reasoning of the appraisal committee for TA857, who indicated that the treatment effect of nivolumab may not last for a person's lifetime after treatment is stopped, the EAG considers it also reasonable to limit the duration of the treatment effect.

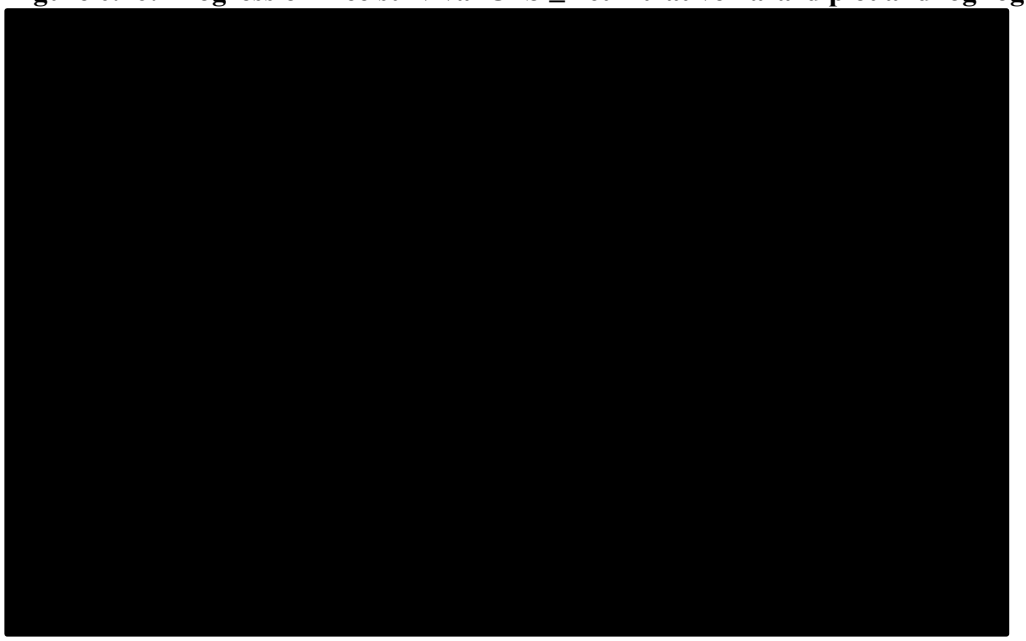
In a scenario analysis the company explored a scenario where gradual treatment waning commences 7 years after treatment initiation with pembrolizumab, indicating that they considered this scenario conservative. As this starting point of the waning is well past all long-term follow-up publications, the EAG does not agree with this assessment, and actually considers this scenario as rather optimistic. Thus, the EAG will explore an alternative assumption in Section 6 where it is assumed that treatment waning will start 5 years after treatment initiation, assuming like the company that the cycle specific hazard for pembrolizumab will become equal to that in the double chemotherapy arm over the subsequent 2 years.

4.2.6.3 Progression-free survival

Progression-free survival, CPS ≥1: Proportional hazard assessment

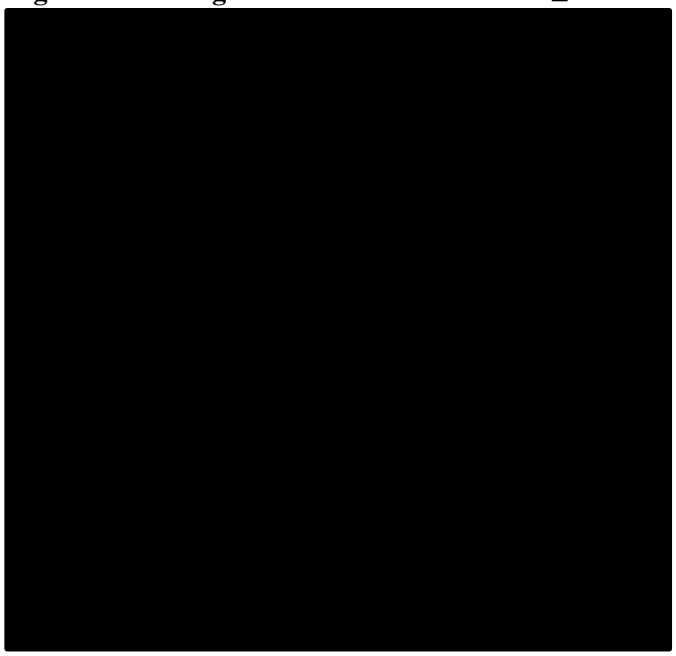
The company considered the proportional hazard assumption to be valid for the comparison of pembrolizumab plus doublet chemotherapy versus doublet chemotherapy in patient expressing CPS ≥1. This conclusion is based on the argument that the cumulative hazard plot and log-log plot (Figure 4.16) show that the curves overlap at the start of the trial, followed by a clear separation, that the Schoenfeld residuals plot (Figure 4.17) does not vary significantly from zero and that the test was found to be not significant (p=0.2072). The observed flattening curve of the cumulative hazard around week 100, suggest a change in hazard, but according to the company this is likely due to the small number of patients left at risk in the trial.

Figure 0.16: Progression free survival CPS ≥1 cumulative hazard plot and log-log plot.



Based on Figure 24 of the CS[1]
CPS = combined positive score; CS = company submission

Figure 0.17: Progression-free survival CPS ≥1 Schoenfeld residuals plot



Based on Figure 25 of the CS[1]
CPS = combined positive score; CS = company submission

Progression-free survival, CPS ≥1: Jointly fitted models

Are provided in the Appendix M of the CS.

Jointly fitted models were provided in Appendix M of the CS for reference. However, these were not further explored by the company in their submission, without giving any reason why not. This is remarkable as they had concluded the PH-assumption to be valid, and that thus joint modelling would be possible.

Progression-free survival, CPS ≥1: Separately fitted models

For the base-case analysis the 1-knot model on the hazard scale was chosen for both pembrolizumab plus doublet chemotherapy and doublet chemotherapy (Figure 4.23 and 4.24 respectively). The company stated that this was the best choice based on visual inspection (Figure 4.22), statistical fit (Table 4.12) and minimising the crossing with OS.

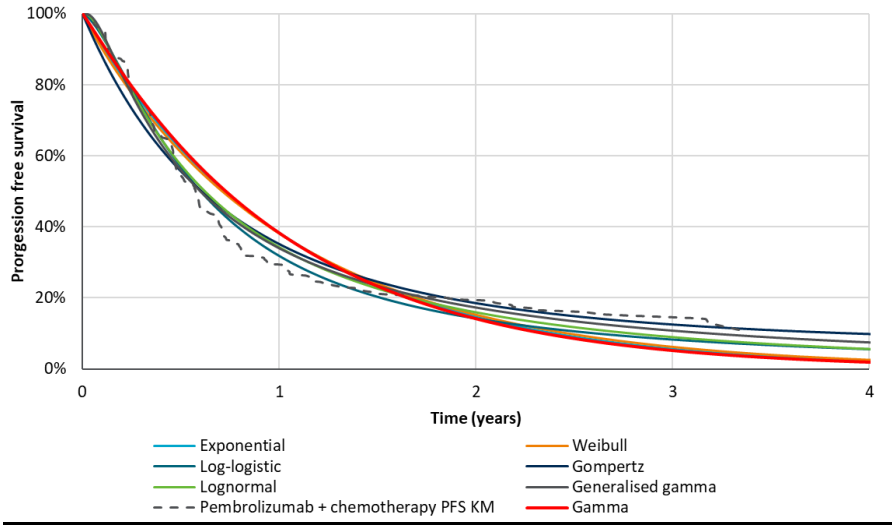
For the parametric models, the lognormal model provided the best statistical fit in both treatment arms (Table 4.12). However, the company concluded that these parametric models did not have good visual alignment to the K-M data (Figure 4.18) and smoothed hazard plot (Figure 4.20) for pembrolizumab plus doublet chemotherapy. For doublet chemotherapy, the lognormal model showed good visual alignment to the K-M data (Figure 4.19) and was one of the better visual fits in the smoothed hazard plot (Figure 4.21)

Table 0.12: Progression-free survival goodness of fit statistics CPS ≥1 (separately fitted models)

Model	Pembrolizumab plus doublet chemotherapy				Doublet chemotherapy			
	AIC	rank	BIC	rank	AIC	rank	BIC	rank
Standard parametric								
Exponential	4428.1	14	4432.5	14	4426.9	15	4431.3	15
Weibull	4429.1	15	4437.9	15	4409.3	14	4418.1	14
Log-logistic	4342.2	12	4351.0	10	4356.6	12	4365.4	11
Lognormal	**4337.9**	10	**4346.7**	9	**4330.9**	7	**4339.7**	5
Gompertz	4388.1	13	4397.0	13	4427.4	16	4436.3	16
Gamma	4429.3	16	4438.2	16	4391.3	13	4400.2	13
Generalised gamma	4338.2	11	4351.5	12	4355.1	11	4368.4	12
Spline								
1k hazard	4319.9	8	4333.2	7	4351.1	9	4364.3	9
2k hazard	4306.0	3	**4323.7**	1	4319.9	4	4337.6	4
3k hazard	4306.3	4	4328.4	6	4312.9	3	4335.0	3
1k odds	4322.5	9	4335.8	8	4332.6	8	4345.9	7
2k odds	4309.3	7	4327.0	5	4326.2	5	4343.9	6
3k odds	4303.1	2	4325.2	3	**4310.5**	1	**4332.7**	1
1k normal	4338.1	5	4351.4	11	4351.6	10	4364.9	10
2k normal	4308.4	6	4326.1	4	4329.3	6	4347.0	8
3k normal	**4302.2**	1	4324.4	2	4311.1	2	4333.2	2

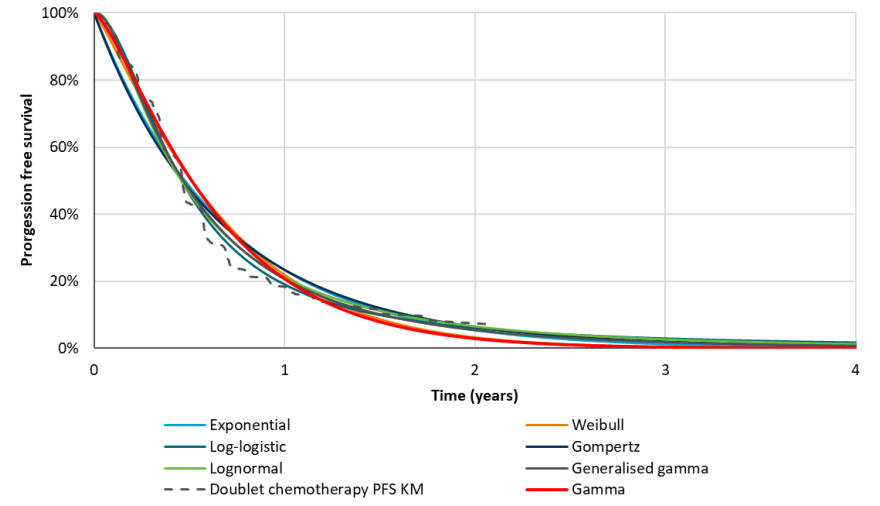
Based on Table 40 of the CS[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CPS = combined positive score; CS = company submission; PFS = progression-free survival

Figure 0.18: Progression-free survival CPS ≥1 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards



Based on Figure 26 of the CS.[1]
CPS = combined positive score; CS = company submission

Figure 0.19: PFS CPS≥1 doublet chemotherapy (separately fitted)



Based on Figure 27 of the CS[1]
CPS = combined positive score; CS = company submission

Figure 0.20: Progression-free survival CPS ≥1 pembrolizumab plus doublet chemotherapy (separately fitted) smoothed hazards

Based on Figure 28 of the CS[1]
CPS = combined positive score; CS = company submission

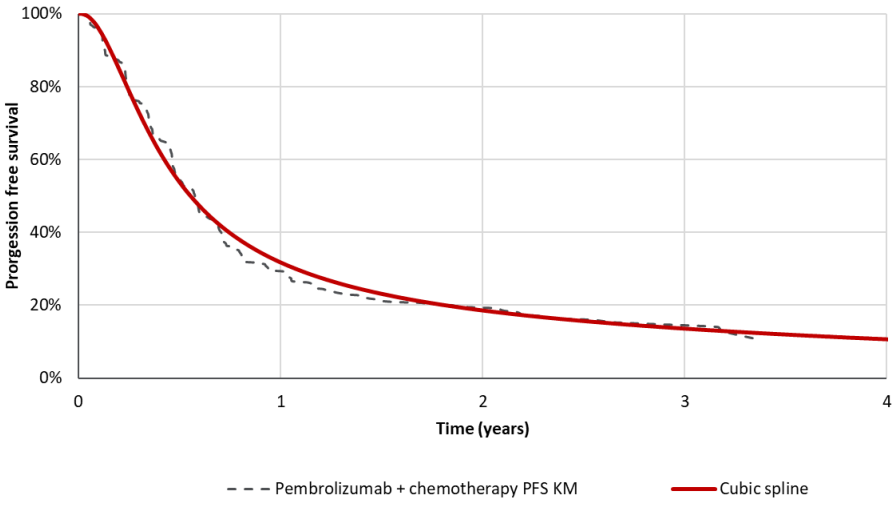
Figure 0.21: Progression-free survival CPS ≥1 doublet chemotherapy (separately fitted) smoothed hazards

Based on Figure 29 of the CS[1]
CPS = combined positive score; CS = company submission

Figure 0.22: Progression-free survival CPS ≥1 spline curve hazard profile pembrolizumab plus doublet chemotherapy (separately fitted)

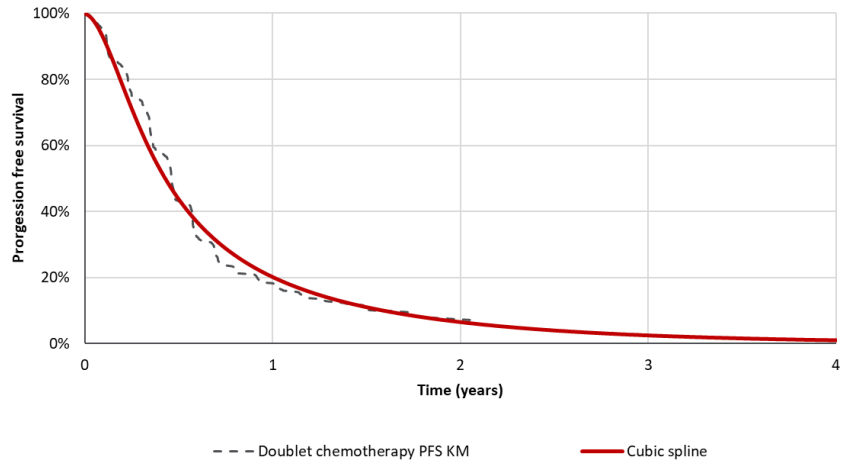
Based on Figure 30 of the CS[1]
CPS = combined positive score; CS = company submission

Figure 0.23: Progression-free survival CPS ≥1 1 knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)



Based on Figure 31 of the CS.[1]
CPS = combined positive score; CS = company submission

Figure 0.24: Progression-free survival CPS ≥1 1 knot hazard spline doublet chemotherapy (separately fitted)



Based on Figure 32 of the CS[1]
CPS = combined positive score; CS = company submission

Progression-free survival, CPS ≥1: Internal and external validation

Similar as was done for OS, the internal validation of the PFS in weeks and months was done by comparing the modelled data for the KEYNOTE-859 data based on the fitted survival curves with the observed KEYNOTE-859 data. Based on the data presented in Table 4.11, the company concluded that the fitted PFS curve for pembrolizumab plus doublet chemotherapy fits the observed data well with minimal discrepancies. Survival rate validation at different timepoints (6, 12, 18, 24, 30, 36, and 60 months) was again reported in Appendix N.

Table 0.13: Progression-free survival internal validation of fitted model (CPS ≥1)

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	30.0	28.0	6.9	6.4
Doublet Chemotherapy	24.1	22.0	5.6	5.1

Based on Table 41 of the CS[1]
CPS = combined positive score; CS = company submission; PFS = progression free survival

Apart from CheckMate-649, the clinical experts consulted by the company were not aware of any external data source that could be used to validate the survival outcomes predicted by the model. The clinical experts used their experience to provide proportions of patients they would expect to be progression free on doublet chemotherapy at 2 and 5 years (Table 4.12). They also informed the company that they expect that the majority of the patients would have already progressed at 4 years and therefore, the 5 years estimate would apply at 4 years.

Table 0.14: Progression-free survival rates for doublet chemotherapy provided by the clinical experts in NHS practice (CPS ≥1)

Year	Expert A	Expert B	Expert C
2	10%	<10%	<10%
5	≤ 1 %	≤ 1 %	0%

Based on Table 42 of the CS.[1]
CPS = combined positive score; CS = company submission; NHS = National Health Service; PFS = progression-free survival

Based on the shown extrapolation over 10 years, the experts concluded that the lognormal overpredicted survival from year 2 and that the gamma would be more reflective of long-term PFS. With the 1-knot hazard model, at 2 years about 7% of patients would still be PF, whilst at 5 years this would be below 1%.

EAG comment: The EAG noticed that the company did not provide an argument for not using the jointly fitted models, even though they concluded that the proportional hazard assumption holds. However, given the good fit provided by the spline models, the EAG considered it unlikely that the use of jointly fitted models would have a notable impact on the ICER.

A more important concern of the EAG was the decision of the company to select the 1-knot hazards spline for the base-case analysis. The company concluded that after visual inspection this model gave the best statistical fit and minimal OS crossing. Considering both the AIC values and visual inspection, the EAG does not agree with the 1-knot hazard spline model being the best fit. The EAG would conclude that the 2-knot or 3-knot spline models outperform the 1-knot values (Figure 4.22 and additional figures provided in the clarification response). In their response to clarification questions B4, the company confirmed this finding, but clarified that when using the model with the lowest AIC, the 3-knot normal, the PFS curve would exceed the OS curve between 4-5 years which is clinically implausible. To minimise the crossing of the curves, the company selected the one of the 1-knot curves with the lowest AIC (1-knot hazard). The company concluded that the choice of the PFS curve has minimal effect on the ICER. The EAG explored this and concluded that indeed, the choice of cubic spline model for the PFS curve has minimal effect on the results. Overall, the modelling choice of PFS curves seems to be mainly driven by the requirement to keep the crossing of the OS and PFS curves at minimal levels.

Progression-free survival, CPS ≥10: Proportional hazard assessment

As it was not feasible to conduct an NMA for PFS in the CPS ≥10 population, the company applied the OS HR also for PFS under the assumption that it would be justifiable to apply a single HR for the entire modelled period between nivolumab and pembrolizumab.

Progression-free survival, CPS ≥10: Separately fitted models

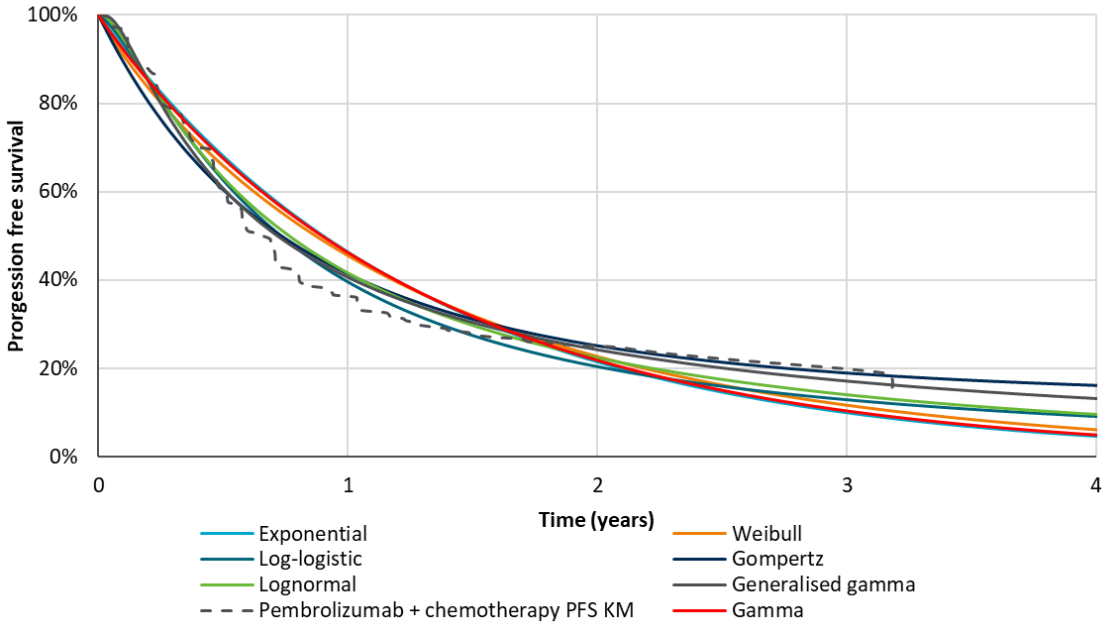
As presented in Table 4.15, the generalised gamma model provided the best parameter fit based on AIC and BIC. However, the company concluded that none of the parametric models had a good visual alignment to the K-M data (Figure 4.25) or smoothed hazard plot (Figure 4.26). The company concluded that the spline models fitted the data better, and the company selected the 1-knot odds model as the base-case for pembrolizumab plus doublet chemotherapy as it showed the best long-term fit and minimal OS crossing (Figure 4.27). The PFS curve for nivolumab plus doublet chemotherapy is generated by applying a HR of [redacted] to the PFS curve for pembrolizumab plus doublet chemotherapy.

Table 0.15: Progression free survival goodness of fit statistics CPS ≥1 (separately fitted models)

Model	Pembrolizumab plus doublet chemotherapy			
	AIC		BIC	
Standard parametric				
Exponential	1984.2	15	1987.8	14
Weibull	1983.7	14	1991.0	15
Log-logistic	1945.0	11	1952.2	11
Lognormal	1947.5	12	1954.8	12
Gompertz	1960.2	13	1967.4	13
Gamma	1986.0	16	1993.3	16
Generalised gamma	**1940.3**	**10**	**1951.2**	**10**
Spline				
1k hazard	1932.9	7	1943.8	3
2k hazard	1929.1	4	1943.6	2
3k hazard	1929.6	5	1947.8	8
1k odds	1934.9	8	1945.8	6
2k odds	1930.1	6	1944.6	4
3k odds	1927.9	2	1946.1	7
1k normal	1939.8	9	1950.7	9
2k normal	1929.0	3	**1943.5**	1
3k normal	**1927.0**	1	1945.2	5

Based on Table 43 of the CS.[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CPS = combined positive score; CS = company submission; PFS = progression-free survival

Figure 0.25: Progression free survival CPS ≥10 pembrolizumab plus doublet chemotherapy (separately fitted)



Based on Figure 33 of the CS[1]
CPS = combined positive score; CS = company submission

Figure 0.26: Progression free survival CPS ≥10 smoothed hazards pembrolizumab plus doublet chemotherapy (separately fitted)

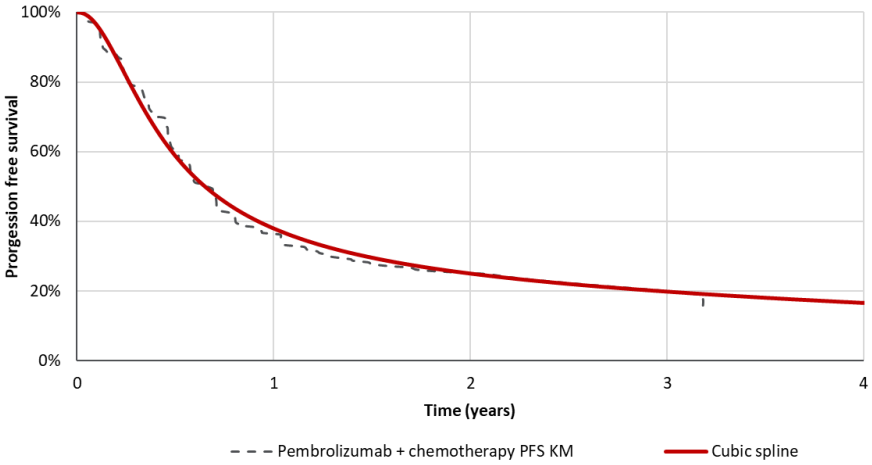
[redacted]

Based on Figure 34 of the CS[1]
CPS = combined positive score; CS = company submission

Figure 0.27: Progression free survival CPS ≥10 spline curve hazard profile pembrolizumab plus doublet chemotherapy (separately fitted)

Based on Figure 35 of the CS[1]
CPS = combined positive score; CS = company submission

Figure 0.28: Progression free survival CPS ≥10 1 knot hazard spline pembrolizumab plus doublet chemotherapy (separately fitted)



Based on Figure 36 of the CS[1]
CPS = combined positive score; CS = company submission

Progression-free survival, CPS ≥10: Internal and external validation

Like before, the internal validation of the PFS in weeks and months was done by comparing the modelled data for the KEYNOTE-859 data based on the fitted survival curves with the observed KEYNOTE-859 data. Based on the data presented in Table 4.14, the company concluded that the fitted

PFS curve for pembrolizumab plus doublet chemotherapy fits the observed data well with minimal discrepancies. Survival rate validation at different timepoints (6, 12, 18, 24, 30, 36, and 60 months) is again reported in appendix N.

Table 0.16: Progression free survival internal validation of the fitted model CPS ≥10

Treatment	Median time (weeks)		Median time (months)	
	KEYNOTE-859	Modelled	KEYNOTE-859	Modelled
Pembrolizumab plus doublet chemotherapy	35.1	34.0	8.1	7.8

Based on Table 39 of the CS[1]
CPS = combined positive score; CS = company submission; PFS = progression-free survival

4.2.6.4 Progression-free survival - treatment waning

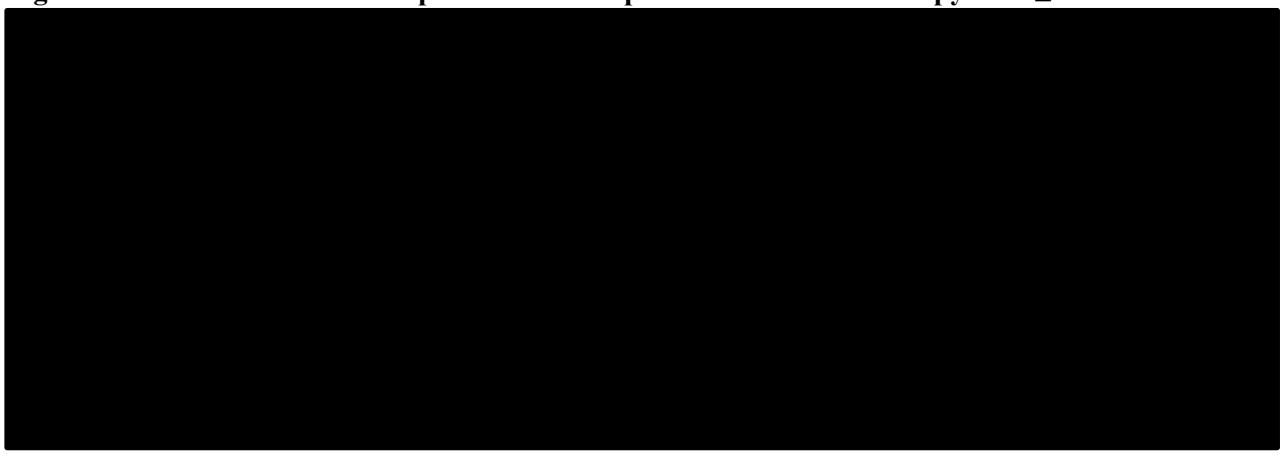
For the PFS estimates treatment, waning is not considered due to the maturity of the trial data and because most patient will have progressed before any treatment waning effect might begin. The company state that any potential treatment waning is reflected in the extrapolated curves.

4.2.6.5 Time on treatment

For all treatments in the KEYNOTE-859 trial there is relatively mature ToT data, with most patients having discontinued from the treatment in both arms at data cut-off (less than 5% remain on treatment in all treatments). Therefore, the company considered that there was no need for parametric extrapolation and the K-M data, in combination with the maximum treatment durations, is directly used in the model to inform study treatment costs for all treatments. The curves are shown in Figure 4.29, Figure 4.30 and Figure 4.31.

The ToT for nivolumab is assumed to be the same as for pembrolizumab (i.e., a HR of 1), since ToT is not an included endpoint in the NMA. The ToT on folinic acid, fluorouracil and oxaliplatin (FOLFOX) is informed by the oxaliplatin component of CAPOX and 5-FU component of cisplatin and fluorouracil from the KEYNOTE-859 trial, as FOLFOX was an option in CheckMate-649 but not in KEYNOTE-859.

Figure 0.29: Time on Treatment pembrolizumab plus doublet chemotherapy CPS ≥1



Based on Figure 37 of the CS[1]
CPS = combined positive score; CS = company submission; ToT = time on treatment; KM = Kaplan-Meyer

Figure 0.30: Time on Treatment doublet chemotherapy CPS ≥1

Based on Figure 38 of the CS[1]
CPS = combined positive score; CS = company submission; ToT = time on treatment; KM = Kaplan-Meyer

Figure 0.31: ToT pembrolizumab plus doublet chemotherapy CPS≥10

Based on Figure 39 of the CS[1]
CPS = combined positive score; CS = company submission; ToT = time on treatment; KM = Kaplan-Meyer

Treatment stopping rules

Pembrolizumab and nivolumab

For pembrolizumab the K-M data is used to directly inform the ToT and therefore no additional stopping rule is imposed on pembrolizumab in the economic model. The data shows that no patient exceeded 35 cycles of treatment, and the mean number of pembrolizumab cycles received was [redacted] and [redacted] in the populations expressing CPS ≥1 and ≥10, respectively. In the KEYNOTE-859 trial, pembrolizumab was continued until confirmed DP, unacceptable toxicity, investigator, or patient decision to withdraw from the study, noncompliance with treatment or trial procedures, or completion of 35 cycles of treatment (200mg Q3W) (approximately 2 years).

A 2-year stopping rule has been presented to NICE by NHS representatives (TA858, TA857) and this 2-year stopping rule for pembrolizumab and nivolumab is explored in a scenario analysis. The company argues that a 35-cycles stopping rule would be easier to monitor from a clinical perspective and allows for the full course of treatment in case a patient misses an administration within the 2 years.

The company stressed that in the KEYNOTE-859 trial, [redacted]

[redacted]. This means that those patients contribute to OS estimates, not PFS or ToT estimates. Because the numbers were small, the company concluded that the values did not have a meaningful contribution to the benefit or cost of pembrolizumab in the economic model. This second course would not be offered in clinical practice based on the draft summary of product characteristics.

Doublet chemotherapy

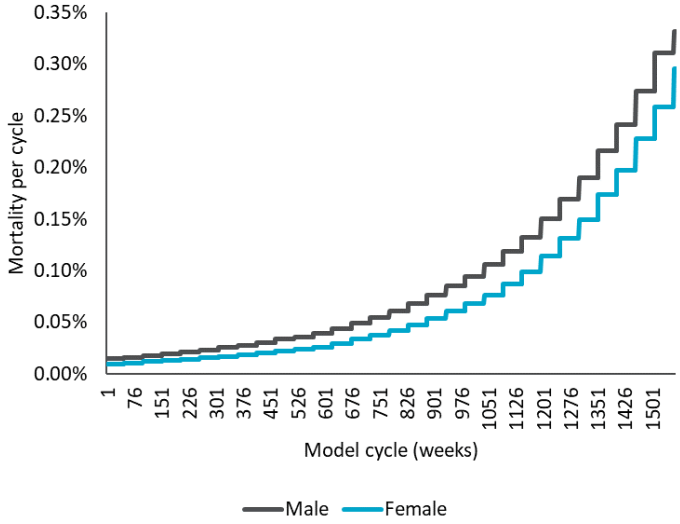
Cisplatin and oxaliplatin treatment were capped at 6 cycles in the KEYNOTE-859 trial. The company summarised that this is in line with NHS clinical practice. The clinical experts confirmed that this cap applies to all component of the regime, but that in rare cases centres may cap at 8 cycles (approximately 6 months). The base-case analysis of the model uses a maximum treatment duration of 6 cycles for all regimes (CAPOX, FP and FOLFOX). In a scenario analysis the impact of removing the cap is explored.

EAG comments: The EAG has a concern with regards to the ToT which relates to the ToT for patients receiving doublet chemotherapy. As the company explained, within the NHS these various chemotherapy treatments are capped at 6 treatment cycles (i.e., 18 weeks), whereas in the KEYNOTE-859 trial, local policy was followed regarding the maximum number of cycles. The EAG noticed that from Figures 4.29 to 4.31, it is clear that for some of these treatments the number of cycles far exceeded the NHS limit of 6 treatment cycles (12-18 weeks). In the company base-case, a cap of 6 cycles was added for all patients receiving doublet chemotherapy. However, while this cap limits the costs of the chemotherapy, it does not account for the fact the observed OS and PFS in both treatment arms of the KEYNOTE-859 trial were based on patients receiving chemotherapy for a much longer period of time than would be permitted in clinical practice in the UK. This also indicates that the observed OS and PFS curves from the KEYNOTE-859 trial may be higher than they would be observed in the UK clinical practice. The EAG is unable to assess if and how exactly this bias will affect the comparative effectiveness evidence presented in the current appraisal.

4.2.6.6 General population mortality

The economic model relies on UK mortality data from the 2017-2019 national life tables provided by the Office for National Statistics (ONS).[35] These tables were used to estimate general population mortality in the model since they do not consider the impact of the coronavirus disease 2019 (COVID-19) pandemic. Mortality for each model cycle was calculated based on the initial proportions of male and female patients (Figure 4.32).

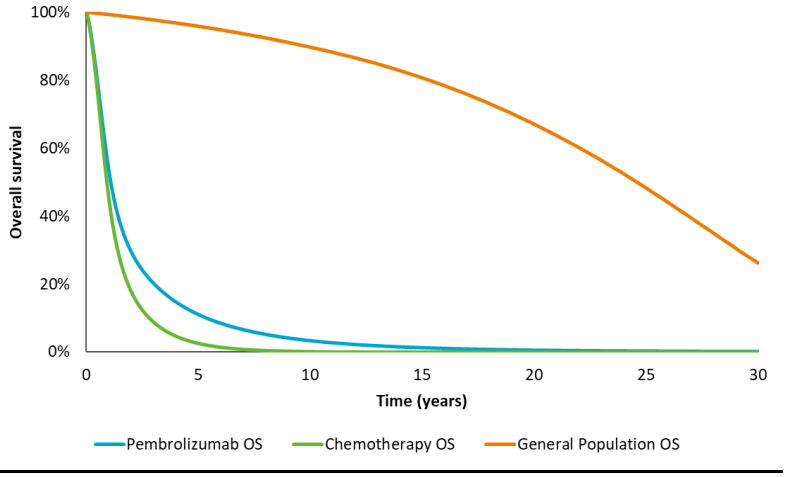
Figure 0.32: General population mortality per cycle



Based on Figure 40 of the CS[1]
CS = company submission

The company restricted OS estimates to ensure they do not exceed the general population rate in any model cycle. In the base-case analysis, this cap was not needed (Figure 4.34). Progression-free survival was not directly adjusted for general population mortality, but the company ensured that the PFS curve does not crosses the OS curve.

Figure 0.33: General population mortality versus extrapolations (CPS ≥1 population)



Based on Figure 41 of the CS[1]
CPS = combined positive score; CS = company submission

4.2.6.7 Survival analysis summary

Selected base-case survival models are summarised in Table 4.17 and illustrated in the Figures 4.35-4.41. The model provided by the company includes all aforementioned curves and could be used for scenario analysis.

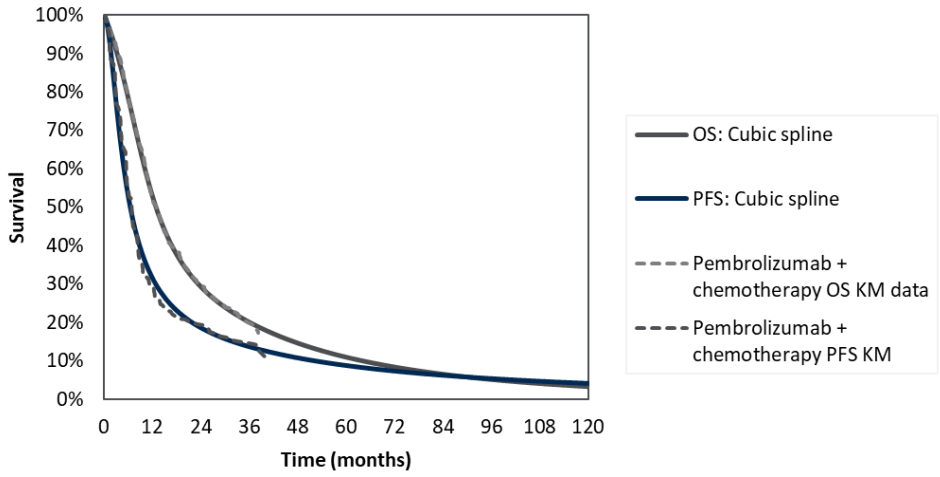
Table 0.17: Summary of the base-case extrapolations

Treatment	OS	PFS	ToT
CPS≥1			

Treatment	OS	PFS	ToT
Pembrolizumab plus doublet chemotherapy	Independent spline 2 knot hazards	Independent spline 1 knot hazards	K-M
Doublet chemotherapy	Independent spline 2 knot hazards	Independent spline 1 knot hazards	K-M
CPS≥10			
Pembrolizumab plus doublet chemotherapy	Independent spline 2 knot odds	Independent spline 1 knot hazards	K-M
Nivolumab plus doublet chemotherapy	HR of [redacted] applied to pembrolizumab plus doublet chemotherapy based on the NMA results	HR of [redacted] applied to pembrolizumab plus doublet chemotherapy based on the NMA results for OS	Assumed equal to pembrolizumab plus doublet chemotherapy (HR=1)

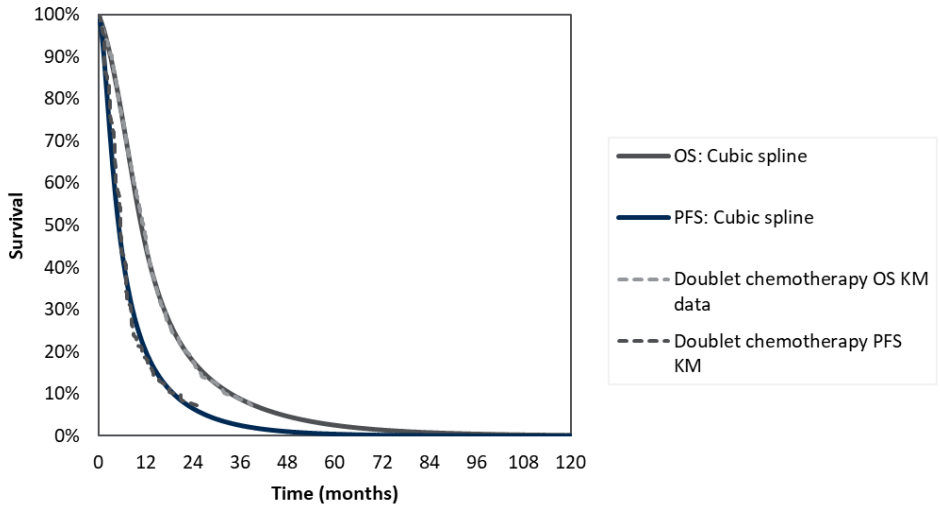
Based on Table 45 of the CS[1]
CPS = combined positive score; CS = company submission; HR = hazard ratio; K-M = Kaplan Meier; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; ToT = time-on-treatment

Figure 0.34: Survival curves: pembrolizumab plus doublet chemotherapy in CPS ≥1 population



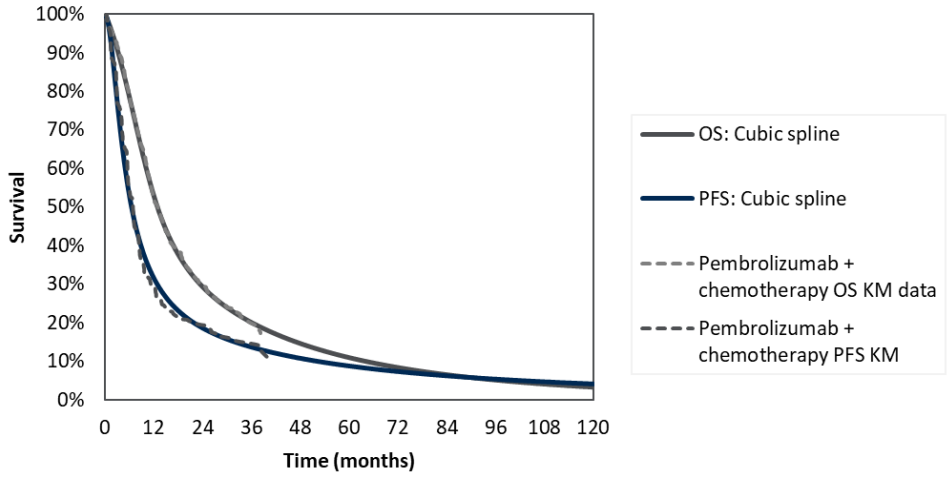
Based on Figure 42 of the CS[1]
CPS = combined positive score; CS = company submission; OS = overall survival; PFS = progression-free survival

Figure 0.35: Survival curves: doublet chemotherapy in CPS ≥1 population



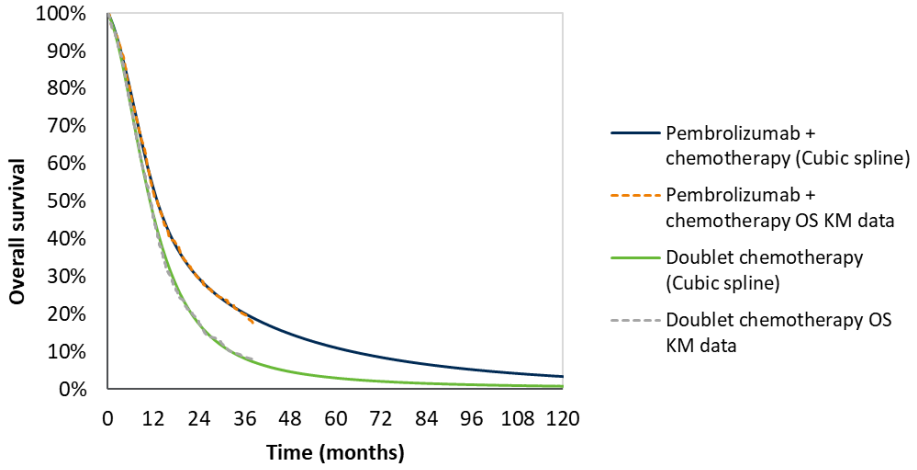
Based on Figure 43 of the CS[1]
CPS = combined positive score; CS = company submission; OS = overall survival; PFS = progression-free survival

Figure 0.36: Survival curves: pembrolizumab doublet chemotherapy in CPS ≥10 population



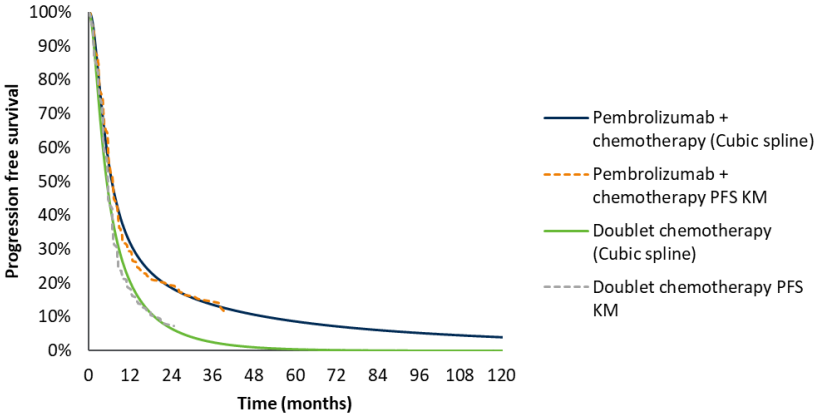
Based on Figure 44 of the CS[1]
CPS = combined positive score; CS = company submission; OS = overall survival; PFS = progression-free survival

Figure 0.37: Overall survival curves in CPS ≥1 population



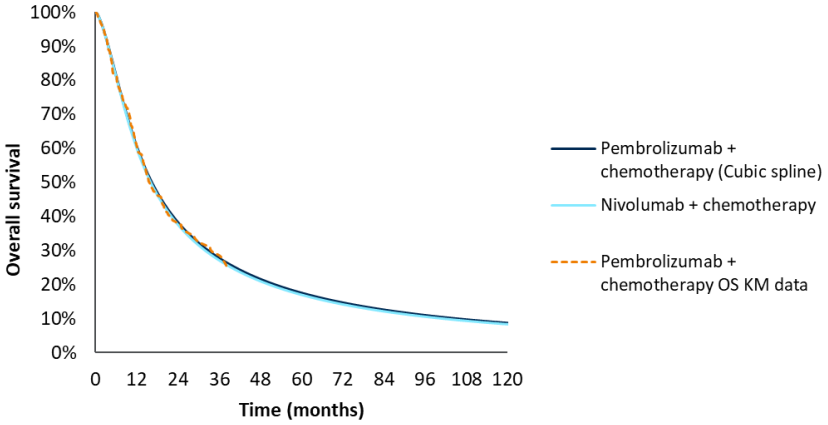
Based on Figure 45 of the CS[1]
CPS = combined positive score; CS = company submission; OS = overall survival

Figure 0.38: Progression-free survival curves in CPS ≥1 population



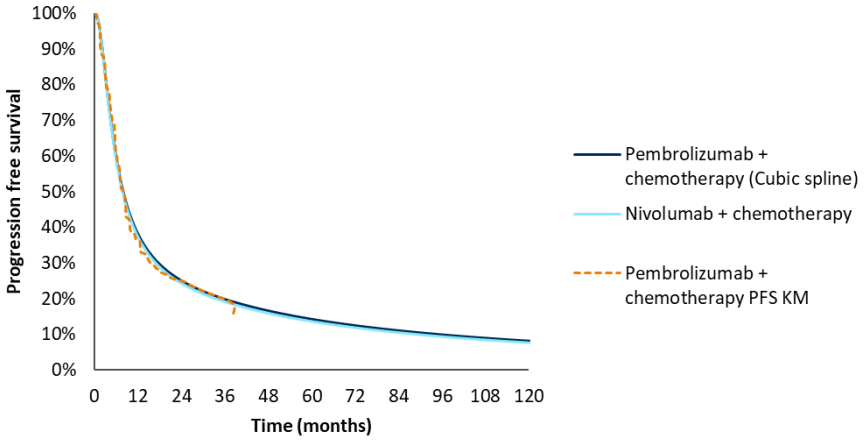
Based on Figure 46 of the CS[1]
CPS = combined positive score; CS = company submission; PFS = progression-free survival

Figure 0.39: Overall survival curves in CPS ≥10 population



Based on Figure 47 of the CS[1]
CPS = combined positive score; CS = company submission; OS = overall survival

Figure 0.40: Progression-free survival curves in CPS ≥10 population



Based on Figure 48 of the CS[1]
CPS = combined positive score; CS = company submission; PFS = progression-free survival

4.2.7 Adverse events

The main sources of evidence on treatment AE used for both the intervention and the comparator arms were the safety results of the KEYNOTE-859 and CheckMate-649 trials. The economic model includes treatment-related Grade 3+ AEs occurring in ≥3% of patients in the KEYNOTE-859 trial receiving either treatment, presented in Table 4.18. The company obtained the incidence rates from the ITT population in the KEYNOTE-859 and CheckMate-649 trials. It should be noted that these incidence rates are stated not to depend on CPS levels. The company argued that the observed differences in the probabilities of patients experiencing AEs between pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy may be largely driven by the backbone chemotherapy received in the trials. To explore the consequences of using alternative AE probabilities, the company provided a scenario analysis where the incidence of AEs for both the pembrolizumab and nivolumab arms were informed from the pembrolizumab arm.

Table 0.18: Treatment-specific AE data

Adverse events	Pembrolizumab plus doublet chemotherapy (N=785)		Doublet chemotherapy (N=787)		Nivolumab plus doublet chemotherapy (N=782)	
	Number of events	Incidence	Number of events	Incidence	Number of events	Incidence
Anaemia	69	8.8%	59	7.5%	47	6.0%
Neutropenia	82	10.4%	78	9.9%	118	15.1%
Diarrhoea	51	6.5%	40	5.1%	35	4.5%
Vomiting	39	5.0%	34	4.3%	17	2.2%
Fatigue	29	3.7%	34	4.3%	30	3.8%
Nausea	28	3.6%	31	3.9%	20	2.6%
Hypokalaemia	30	3.8%	24	3.0%	0	0.0%

Adverse events	Pembrolizumab plus doublet chemotherapy (N=785)		Doublet chemotherapy (N=787)		Nivolumab plus doublet chemotherapy (N=782)	
	Number of events	Incidence	Number of events	Incidence	Number of events	Incidence
Palmar-plantar erythrodysaesthesia syndrome	25	3.2%	14	1.8%	11	1.4%
Neuropathy peripheral	10	1.3%	25	3.2%	31	4.0%

Based on Table 30 of the clarification response, which is the adjusted version of Table 46 in the CS.[1] Main source is Table 6 of the HTA HECON Safety report[28]
AE = adverse events; CS = company submission

Decreased neutrophil count and decreased platelet count were not included in the economic model. The company stated that these are laboratory type events with low cost and impact on QoL, and therefore are different from symptoms or other disease that may occur temporally when using a medicinal product (whether considered related to the medicinal product). To support this decision the company further noted that the KEYNOTE-859 Clinical Study Report (CSR) referred to decreased neutrophil count and decreased platelet count as investigations rather than disorders or conditions and second, also TA857 did not include decreased neutrophil count and decreased platelet in the list of AEs.

Further information regarding the implementation of the AE in the economic model are provided in Section 4.2.8.

EAG comment: The main concerns of the EAG relate to:

a) The EAG is concerned about the argument that the observed difference in the AE profiles between pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy is largely driven by the backbone chemotherapy patients received in the trials. The EAG is wondering why this might not be explained by the difference between pembrolizumab and nivolumab treatment themselves. The EAG appreciated that the company provided a scenario analysis where the AE incidence rates in the nivolumab arm were assumed to be the same as for the pembrolizumab. This scenario demonstrates [redacted] (Table 79, CS). The EAG considers this ICER change worth considering and therefore the AE incidence rates a source of uncertainty for the CPS ≥10 population.

b) The decision of the company to obtain the incidence rates from the ITT population. In response to clarification question B9, the company explained that pembrolizumab modulates PD-1/PD-L1 pathways and that CPS expression is an important treatment effect modifier. However, they argued that there is no evidence or clinical rationale to suggest CPS expression modifies AE incidence rates and that the difference observed across trial populations (ITT, CPS ≥1 and CPS ≥10) do not consistently decrease or increase (see Table 31 in response to CL).[7] The EAG questioned if for consistency reasons it would not have been better to use the incidence rates observed for the CPS ≥1 population. Thus, an exploratory scenario analysis, using the CPS ≥1 population specific incidence values for pembrolizumab plus doublet chemotherapy and doublet chemotherapy was done, and this showed that the impact on the ICER was negligible (<£200).

4.2.8 Health-related quality of life

4.2.8.1 Health-related quality of life data identified in the review

According to the CS, out of the 59 included studies in the SLR, seven studies were found to report utility values for patients with untreated locally advanced unresectable gastric or GOJ cancer. Nonetheless, these studies were deemed inappropriate to inform utilities in the economic model because none of them reported utilities based on progression status or time-to-death.

Ten studies from the cost-utility analyses identified in the company's SLR for economic evaluations reported utility data according to progression status. The mean utility values in these studies varied from 0.740 to 0.836 in the progression free health state and from 0.577 to 0.600 in the PD health state. The company noted that HER2 status of the study participants was poorly reported in these studies.

The SLR for economic evaluations also led to seven HTAs. However, only the appraisal of trastuzumab for the treatment of HER2 positive metastatic GC (TA208)[24] reported unredacted utility values. In TA208, the utility value in the progression free health state was 0.7292 and increased daily by 0.000142, whereas in the PD health state, the utility value was 0.577 and this was informed from the NICE appraisal of sunitinib for the treatment of gastrointestinal stromal tumours (TA179).[36]

Considering the paucity of utility data in HER2 negative patients, in the base-case analysis, the company chose to use the utility data that were collected in the KEYNOTE-859 trial. The starting age of the model cohort was 60 years for CPS ≥1 and 61 years for CPS ≥10. Utilities were adjusted for ageing over time using the algorithm by NICE DSU.[37] The baseline general population utility was 0.8434 in patients with CPS ≥1 and 0.8401 in patients expressing CPS ≥10.

4.2.8.2 Health-related quality of life from the KEYNOTE-859 trial

Health-related quality of life data were collected in the KEYNOTE-859 trial at baseline, 3, 6, 9, 12 weeks and every 6 weeks thereafter, at the treatment discontinuation visit, and at the 30-day safety follow-up visit using the EQ-5D-5L questionnaire. Compliance at completing the EQ-5D-5L questionnaire at each treatment visit ranged from [redacted] (shown in Table 47 of the CS). The EQ-5D-5L HRQoL data was converted into UK EQ-5D-3L utilities using the NICE DSU mapping function.[38]

Utilities based on the KEYNOTE-859 trial were estimated using two different approaches in the CS. The first approach concerned a time-to-death approach, in which utility values were assumed to be dependent on patient's life expectancy (see next Section for further details). This approach was used in the company base-case analysis. The second approach assigned distinct utility values to patients in the progression free and PD health states, and this approach was used in a scenario analysis.

The utility analyses from the KEYNOTE-859 trial were conducted without adjusting for repeated measurements. The company argued that such adjustments for repeated measurements would be inappropriate as they assume that the number of measurements per patient is not correlated with the value of the measurement of interest and in presence of such correlation, biased estimates would be produced, referring to the study of Hickey et al. 2018.[39]

EAG comment: The main concerns of the EAG relate to the company's approach not to use adjustments for repeated measures when analysing the utility data from the KEYNOTE-859 trial. As questioned in the clarification response B10, the EAG was unclear on whether and how the study by Hickey et al. 2018[39] suggested that no linear mixed model should be used for unbalanced longitudinal data. The company responded that Hickey et al. 2018 was not used to exclude use of a linear mixed

models, but rather to flag that it is inappropriate to use models of repeated measures when the number of measures available per subject may be correlated with the value of the measure of interest e.g., when a higher number of utility measures is associated with a higher utility value. The company further flagged that several correlations may be present when comparing trial subjects with multiple measurements with single measurement subjects as patients with single measurements are more likely to have died shortly after the measurement, transitioned to another worse health state or being near to the point of transition to a worse health state. Nonetheless, to address the EAG's concerns the company provided an additional analysis in which utility scores were re-estimated using linear mixed models. Their analysis showed that when controlling for repeated measurements, the revised base-case ICER in patients expressing CPS ≥1 (following the clarification letter) changed by less than 1% (from [redacted] to [redacted]). The company argued the impact on ICER for patients with CPS ≥10 would be equivalent considering the output, but due to time constraints these changes were not implemented in the revised electronic model.

4.2.8.3 Utility values based on the time-to-death approach

The time-to-death approach, developed by Batty et al. 2011[40] and Hatswell et al. 2014[41], was previously used in the NICE's appraisal in advanced renal cell carcinoma (TA858).[42] This approach assumes that DP itself may not be appropriately capturing the patient's utility in that health state and that time-to-death provides a better fit to patient's utility under DP.

The time-to-death approach estimates utilities using time intervals that describe the patients' life expectancy rather than progression status. Death events can arise from both PF and PD health states. The time intervals shown below are based on the pre-specified time intervals that are used as a standard approach in the company's trials. Note that the EQ-5D assessment during baseline or before treatment start date is not included in this analysis.

- 360 or more days to death
- 180 to 359 days to death
- 30 to 179 days to death
- Less than 30 days to death
- Unknown

The unknown category includes patients in the trial who had not died at the database cut-off if the time from the date of the most recent EQ-5D assessment to the date a patient was censored for OS was less than 360 days. If the difference in time between the date of the most recent EQ-5D assessment and the date of OS censoring was greater or equal to 360 days, the patient was included in the '360 or more days to death' category. The number of patients in the 'unknown' category are provided in Table 4.19. The company noted that estimated utilities using the time-to-death approach may be underestimated as patients in the "unknown" category may live longer and therefore their utility values may be equal or higher than the utility values in the 360 or more days to death' category. Such a potential underestimation would be stronger in the pembrolizumab arm than the comparator arm, considering the number of patients in the 'unknown' category is higher in the pembrolizumab plus doublet chemotherapy arm compared to the doublet chemotherapy arm.

Table 0.19: Number of patients in the 'unknown' time-to-death category

Population	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy
CPS ≥1	[redacted]	[redacted]

Population	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy
CPS ≥10	[redacted]	[redacted]

Based on Table 48 of the CS.[1]
CPS = combined positive score; CS = company submission

The estimated time-to-death utilities from the KEYNOTE-859 trial data are presented in Table 4.20. The treatment-specific utility values are estimated per arm and therefore account for patients being on- and off-treatment in the arm they were randomised to. Although the time-to-death intervals do not fully align with the model cycle length, the company argued that this difference is expected to have a minor impact on the cost effectiveness results as the weekly cycles differ by few days from the time-to-death intervals. In the base-case analysis, utility values between the two comparator arms were pooled. [redacted] and was therefore capped at the general population utility (0.8434 in CPS ≥1 and 0.8401 CPS ≥10 patients).

Table 0.20: Utilities based on the KEYNOTE-859 trial using the time-to-death approach (mapped to EQ-5D-3L)

Time from EQ-5D assessment date to Death (days)	Pembrolizumab plus doublet chemotherapy*				Doublet chemotherapy				Pooled			
	n	m	Mean (SE)	95% CI	n	m	Mean (SE)	95% CI	n	m	Mean (SE)	95% CI
CPS ≥1												
≥360	[redacted]											
180 to 359	[redacted]											
30 to 179	[redacted]											
<30	[redacted]											
CPS ≥10												
≥360	[redacted]											
180 to 359	[redacted]											
30 to 179	[redacted]											
<30	[redacted]											

Based on Table 49 of the CS.[1]
*Nivolumab plus doublet chemotherapy utilities were assumed equal to pembrolizumab plus doublet chemotherapy
CI = confidence interval; CPS = combined positive score; CS = company submission; SE = standard error; m = number of records; n = number of participants

4.2.8.4 Utility values based on health state

In the KEYNOTE-859 trial, the patient's QoL during the PF health state was assessed based on an EQ-5D assessment that was completed either prior to the date of the first documented DP if progression occurred or prior to the censoring date of the PFS if no progression occurred.

In the KEYNOTE-859 trial, the patient's QoL following DP was assessed at the treatment discontinuation visit and at the 30-day safety follow-up visit. Responses from non-progressed patients that completed the EQ-5D assessments after the censoring date of PFS were included in the "unknown" category and were not considered in the analysis. Table 4.21 shows that patients included in the 'unknown' category are relatively low and similar between treatment arms. Similar to the time-to-death approach, the treatment-specific utility values were estimated per arm.

Table 0.21: Number of patients in the 'unknown' time-to-death category

Population	Pembrolizumab plus doublet chemotherapy	Doublet chemotherapy
CPS ≥1	[redacted]	[redacted]
CPS ≥10	[redacted]	[redacted]

Based on Table 51 of the CS.[1]
CPS = combined positive score; CS = company submission

The estimated health state utilities from the KEYNOTE-859 trial data are presented in Table 4.22. The company argued that for PD the two assessments (at the treatment discontinuation visit and at the 30-day safety follow-up visit) could possibly only capture QoL in proximity to DP rather than QoL for PD. Furthermore, the company expressed concerns that the [redacted] as compared to the values identified in the literature review [redacted] versus 0.577 to 0.600). As these values were informed by relatively fewer records and patients than the PF utility values, in the base-case analysis, the company decided to use the utility values presented in the previous Section that were estimated using the time to-death approach. The pooled health state utility values presented in Table 4.22 were instead used in the scenario analyses.

Table 0.22: Health state utilities based on the KEYNOTE-859 trial (mapped to EQ-5D-3L)

Population / Treatment	Progression free				Progressed disease			
	n	**m**	**Mean (SE)**	**95% CI**	**n**	**m**	**Mean (SE)**	**95% CI**
CPS ≥1								
Pembrolizumab plus doublet chemotherapy	[redacted]							
Doublet chemotherapy	[redacted]							
Pooled	[redacted]							

Population / Treatment	Progression free				Progressed disease			
	n	m	Mean (SE)	95% CI	n	m	Mean (SE)	95% CI
CPS ≥10								
Pembrolizumab plus doublet chemotherapy*	[redacted]							
Doublet chemotherapy	[redacted]							
Pooled	[redacted]							

Based on Table 50 of the CS.[1]
*Nivolumab plus doublet chemotherapy utilities were assumed equal to pembrolizumab plus doublet chemotherapy
CI = confidence interval; CPS = combined positive score; CS = company submission; SE = standard error; m = number of records; n = number of participants

EAG comments: The main concerns of the EAG relate to the company's decision to use the time-to-death approach to define patients' QoL in their base-case analysis instead of the health state utilities approach. The EAG asked for additional information on the reasoning of the company to use the specific time-to-death intervals in the assessment of patients' QoL. In their response to clarification question B13, the company noted that there is no available external evidence to justify the selection of these specific time-to-death intervals for the utility analysis.[7] The time-interval selection of the company was mainly driven by a consistency reasoning in specifying the intervals across the different company's trials. The company further argued that in other previous trials, some differentiation in health utility values has been observed between these different intervals (lower utilities for each successive interval closer to death). Based on these, the EAG understands that a specific evidence base to inform the time-to-death intervals in the context of this appraisal is lacking, and the company used the defined time-to-death intervals based on standardised procedures used by the company across trials. However, the EAG would consider it good practice if one or more sensitivity analyses had been done in the analysis of the utility data where alternative cut-off point had been used.

Additionally, as noted in the CS, the time-to-death approach cannot distinguish if death events arise from the PF or the PD health states. The EAG considers this may be an additional drawback of this approach as in situations in which many patients in the PF health state move quickly to the dead health state, QoL could be biased upwards as there may not be enough time to measure deterioration in patients' QoL. Unfortunately, it is not known to the EAG how many patients died in the PF health state which means that no indication can be given of the potential extent of such bias.

In order to assess the face validity of the time-to-death approach versus the commonly used health state approach, the EAG calculated the 'average' utility for both approaches, for both treatment arms. This average value was derived by dividing the undiscounted QALYs by the undiscounted LYs for each approach (see Table 4.23). These values show very little difference between the two approaches, and

also that these averages may be considered somewhat high both compared to values from the literature and compared to the utility for the general population.

Table 0.23 Average utility for each approach to include utility in model (CPS ≥1)

	Time-to-death	Health state	General population (60.1 years)
Pembrolizumab plus doublet chemotherapy	[redacted]	[redacted]	0.8434
Doublet chemotherapy	[redacted]	[redacted]	

Finally, the EAG agrees with the idea of the company that the time-to-death approach may be better in capturing the QoL for progressed patients instead of the single utility score for the progressed health state, but the cut-off values for the intervals would need to be better informed. Finally, the EAG noted that the differences in terms of economic outcomes between the two approaches (time-to-death or health state utilities) is relatively small and therefore agrees with the company base-case analysis on this matter.

4.2.8.5 Disutility values

The economic analysis considered treatment-related Grade 3+ AEs which occurred in 3% or more of patients receiving either pembrolizumab plus doublet chemotherapy or doublet chemotherapy alone in the KEYNOTE-859 trial. In the base-case analysis, the company assigned disutility values to each of the listed AEs. The company noted that including separate disutility values for AEs could potentially lead to double count as time-to-death utility values or treatment-specific health state utility values would already account for the quality of life (QoL) in patients experiencing AEs, and therefore they ran a scenario analysis in which AE disutility values were excluded from the computations.

To estimate the AEs-related disutility values based on the KEYNOTE-859 trial, the EQ-5D questionnaires completed on or after the date of initiation of AE and on or prior to the date of AE resolution were used. The disutility was then calculated as the difference between the utility value scored during AE Grade 3+ and the utility values scored once AE Grade 3+ was resolved. Therefore, a single disutility value was produced for all AEs (not type-specific). In the clarification phase (question B11), the company clarified that the pooled disutility values due to AEs from the KEYNOTE-859 trial were used to inform the company base-case (for patients expressing CPS ≥1.[7] To evaluate the impact of this approach the company presented a scenario analysis in which disutility values were informed from the sources used in the TA857 submission. The disutility values related to Grade 3+ AEs using both approaches are presented in Table 4.24.

Table 0.24: Disutilities due to AEs based on the KEYNOTE-859 trial and the literature

AE	Disutilities based on the KEYNOTE-859						Disutilities based on literature	
	CPS ≥1			CPS ≥10			Disutilities	Source
	Pembrolizumab plus doublet chemotherapy	Doublet chemo-therapy	Pooled	Pembrolizumab plus doublet chemotherapy*	Doublet chemo-therapy	Pooled		
Anaemia							-0.11500	Swinburn et al. 2010[43]
Neutropenia							-0.08973	Nafees et al. 2008[44]
Diarrhoea							-0.04680	Doyle et al. 2008[45]
Vomiting							-0.10300	Swinburn et al. 2010[43]
Fatigue							-0.11900	Lloyd et al. 2006[46]
Nausea	[redacted]	[redacted]	[redacted]^	[redacted]	[redacted]	[redacted]^	-0.10300	Swinburn et al. 2010[43]
Hypokalaemia							0.00000	Assumption
Palmar-plantar erythron dysaesthesia syndrome							-0.04320	Nafees et al. 2008[44]
Neuropathy peripheral							-0.21600	Tolley et al. 2013[47]

Based on Table 52 of the CS[1] and Table 32 of the CL.[7]

*Nivolumab plus doublet chemotherapy disutilities were assumed equal to pembrolizumab plus doublet chemotherapy.

^The pooled values were used in the company base-case and were reported in company's response to clarification question B11.[7]

AE = adverse event; CPS = combined positive score; CS = company submission; CL = clarification letter

The impact of AEs on HRQoL was implemented as a one-off loss during the first cycle of the model. The one-off loss due to AEs was calculated using the disutility values in Table 4.24 above, the treatment-specific probabilities of experiencing each AE (see Section 4.2.7) and the mean duration of each AE presented in Table 4.25.

Table 0.25: Duration of AEs based on the KEYNOTE-859 trial (ITT population)

AE	Pembrolizumab plus doublet chemotherapy*	Doublet chemotherapy	Pooled values^
Anaemia	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]

Based on Table 53 of the CS.[1]
*Nivolumab plus doublet chemotherapy AE durations assumed to equal pembrolizumab plus doublet chemotherapy
^The pooled values for duration of AEs were provided in response to EAG's question B15.[7]
AE = adverse event; CS = company submission; EAG = Evidence Assessment Group

EAG comments:

a) The EAG found the difference between the disutility values of pembrolizumab plus doublet chemotherapy versus doublet chemotherapy shown in Table 4.24 unexpectedly large for patients expressing CPS ≥1. The EAG concern was mainly driven by the fact both treatment arms receive doublet chemotherapy. In the clarification response B11[7], the company speculated that the disutility value could be lower in the pembrolizumab plus doublet chemotherapy than the doublet chemotherapy arm because the disutility score is a composite measure encompassing all types of Grade 3+ AEs whilst the incidence rate of each type of Grade 3+ AEs is different between treatment arms. To provide an example, the company flagged that peripheral neuropathy has a higher incidence in the doublet chemotherapy arm and this may impact mobility and the ability to carry out usual activities more than other types of AEs, thus having a stronger impact on the patient QoL in this arm. Whilst this appears plausible, it does not explain why peripheral neuropathy would occur more often with doublet chemotherapy alone than in doublet chemotherapy with pembrolizumab. The company also presented a scenario analysis in which treatment-specific AE disutility values from Table 4.20 were employed and the ICER in the CPS ≥1 population fell minimally from [redacted] to [redacted] per QALY gained under this scenario. The EAG has no further comments on this point.

b) The EAG queried why the Grade 3+ AE durations in Table 4.25, used to estimate disutility scores, were set to be treatment-specific while the company used pooled values for all health state utility scores. In response to clarification letter (question B15), the company provided the pooled estimates of duration and incorporated those in the new company's base-case results following the clarification phase.[7]

4.2.8.6 Utility values used in the economic model

The utility values as used by the company and the disutility due to AE in their base-case and scenario analyses are summarised in Table 4.26.

Table 0.26: Utility values used in the company base-case analysis

Treatment arm	Time to death	Utility value^	Reference in CS	Justification
CPS ≥1				
Pembrolizumab plus doublet chemotherapy	≥360 days to death	[redacted]	Section B.3.4.2.3	Time-to-death method addresses the issue with the data collection schedule (small number of PD assessments). AE disutility values are applied as a one-off QALY loss in the first model cycle to account for different AE profiles. Time-to-death utility values and AE disutility values are obtained from the KEYNOTE-859 trial to reduce heterogeneity.
	180 to 359 days to death	[redacted]		
	30 to 179 days to death	[redacted]		
	<30 days to death	[redacted]		
	One-off QALYs loss	[redacted]	Section B.3.4.3	
Doublet chemotherapy	≥360 days to death	[redacted]	Section B.3.4.2.3	
	180 to 359 days to death	[redacted]		
	30 to 179 days to death	[redacted]		
	<30 days to death	[redacted]		
	One-off QALYs loss	[redacted]	Section B.3.4.3	
CPS ≥10				
Pembrolizumab plus doublet chemotherapy	≥360 days to death	[redacted]	Section B.3.4.2.3	Time-to-death method addresses the issue with the data collection schedule (small number of PD
	180 to 359 days to death	[redacted]		
	30 to 179 days to death	[redacted]		
	<30 days to death	[redacted]		

Treatment arm	Time to death	Utility value^	Reference in CS	Justification
	One-off QALYs loss	[redacted] ([redacted])	Section B.3.4.3	assessments). AE disutility values are applied as a one-off QALY loss in the first model cycle to account for different AE profiles. Time-to-death utility values and AE disutility values are obtained from the KEYNOTE-859 trial to reduce heterogeneity.
Nivolumab plus doublet chemotherapy	≥360 days to death	[redacted]*	Section B.3.4.2.3	
	180 to 359 days to death	[redacted]*		
	30 to 179 days to death	[redacted]*		
	<30 days to death	[redacted]*		
	One-off QALYs loss	[redacted] ([redacted])	Section B.3.4.3	

Based on Table 54 of the CS.[1]
AE = adverse event; CPS = combined positive score; CS = company submission; NA = not applicable; PD = progressed disease; QALY = quality-adjusted life year; SE = standard error.
*Nivolumab plus doublet chemotherapy utilities were assumed equal to pembrolizumab plus doublet chemotherapy
^One-off QALYs loss values in the parenthesis are the ones used in the company base-case following the clarification phase

4.2.9 Resources and costs

The cost categories included in the model were treatment acquisition and administration costs, medical costs (treatment administration, monitoring and follow-up), subsequent treatment costs, costs of managing AEs, end-of-life costs and one-off costs assigned to DP.

Unit prices were based on the NHS reference prices, British National Formulary (BNF) for drug costs of branded products and the Department of Health and Social Care Drugs and pharmaceutical electronic market information tool (eMIT) for generic products. Costs sourced from the literature were inflated to 2021/22 cost year using the NHS Cost Inflation Index (NHSCII) pay and price indices.

4.2.9.1 Intervention and comparators costs

The drug acquisition costs for pembrolizumab 25 mg/mL concentrate solution are £2,630.00 per 4mL vial (i.e., one vial of 4 mL of concentrate for solution contains 100 mg of pembrolizumab), as shown in Table 4.27, indicating a cost of £5,260.00 per 200 mg dose. A Commercial Access Agreement (CAA) with a simple discount of [redacted] has been provided by the company leading to the cost of [redacted] per administration of 100 mg dose of pembrolizumab or [redacted] per administration of 200 mg dose of pembrolizumab.

Table 0.27: Drug acquisition unit costs

Drug	Unit size	Vials/tablets per pack	Cost per vial/pack	Unit cost*
Pembrolizumab	100 mg	1	£2,630.00	£2,630.00
Capecitabine (CAPOX)	150 mg	60	£6.40	£0.11
	500 mg	120	£36.49	£0.30
Oxaliplatin (CAPOX)	50 mg	1	£13.49	£13.49
	100 mg	1	£24.44	£24.44
	200 mg	1	£21.52	£21.52
5-FU (FP)	500 mg	1	£3.25	£3.25
	1,000 mg	1	£3.93	£3.93
	2,500 mg	1	£4.05	£4.05
	5,000 mg	1	£10.54	£10.54
Cisplatin (FP)	10 mg	1	£2.71	£2.71
	50 mg	1	£9.10	£9.10
	100 mg	1	£10.97	£10.97
Leucovorin (FOLFOX)	50 mg	1	£2.04	£2.04
	100 mg	1	£1.10	£1.10
	300 mg	1	£30.59	£30.59
Oxaliplatin (FOLFOX)	50 mg	1	£13.49	£13.49
	100 mg	1	£24.44	£24.44
	200 mg	1	£21.52	£21.52
5-FU (FOLFOX)	500 mg	1	£3.25	£3.25
	1,000 mg	1	£3.93	£3.93
	2,500 mg	1	£4.05	£4.05
	5,000 mg	1	£10.54	£10.54
Nivolumab	40 mg	1	£439.00	£439.00
	100 mg	1	£1,097.00	£1,097.00
	120 mg	1	£1,317.00	£1,317.00
	240 mg	1	£2,633.00	£2,633.00

Based on Table 55 in the CS.[1]
*All costs were sourced from the electronic market information tool (eMIT), apart from pembrolizumab cost which was sourced from the British National Formulary
CS = company submission; mg = milligram

Table 4.28 presents the dosing schedule for pembrolizumab plus doublet chemotherapy and doublet chemotherapy. Aligned with the dosing schedule used in the KEYNOTE-859 trial, pembrolizumab is administered by IV infusion at 200 mg Q3W combined either with cisplatin at 80 mg/m2 by IV infusion Q3W and 5-FU at 800 mg/m2/day via continuous IV infusion on days 1 to 5 (FP) or with oxaliplatin at

130 mg/m² by a 60–120-minute IV infusion on the first day of Q3W cycle treatment and oral capecitabine at 1,000 mg/m2 BID on days 1–14 of each Q3W cycle (CAPOX). As per label indication, pembrolizumab can also be administered at 400 mg, which can then be given Q6W.[4] Usage of the 400 mg dosing regimen was explored in a scenario analysis. Nivolumab plus doublet chemotherapy, aligned with the dosing schedule from the CheckMate-649 trial, is assumed to be given by IV infusion at 360 mg Q3W or 240 mg every 2 weeks (Q2W) combined either with oxaliplatin 130 mg/m² by a 60–120-minute IV infusion on the first day of Q3W cycle and oral capecitabine at 1,000 mg/m2 BID on days 1–14 of Q3W treatment cycle or with leucovorin at 400 mg/m2 on the first day of Q2W, 5-FU at 400 mg/m2 on day 1 and 1,200 mg/m2 on days 1–2 of Q2W, and oxaliplatin at 85 mg/m2 on day 1 of Q2W.

To calculate drug dosage based on body weight, a mean weight of 60.1 kg was assumed for patients with CPS ≥1 and 60.7 kg for patients with CPS ≥10 based on the KEYNOTE-859 patient population. To calculate drug dosage based on body surface area (BSA) for capecitabine, oxaliplatin, 5-FU and cisplatin, a mean BSA of 1.7 m^2 was used for both populations based on the KEYNOTE-859 trial. For drugs with multiple pack options, the pack with the lowest cost per mg was used without considering wastage costs (with vial sharing).

As CAA discount for nivolumab is confidential, cost-effectiveness outcomes for patients with CPS ≥10 comparing pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy were conducted using list prices for both drugs. The scenario analyses of the company included results based on the pembrolizumab CAA discount and 10% discount increments for the list price of nivolumab.

Finally, the base-case analysis includes a relative dose intensity (RDI) varying between [redacted] for all treatments. The RDI was defined using the actual number of doses used in the per protocol trial population, divided by the expected number of doses based on the treatment duration.

Table 0.28: Drug dosing schedules and acquisitions costs per cycle

Comparator/ Treatment	Required dose	RDI*	Doses per cycle	Cycle length (weeks)	Treatment cost without vial sharing (base-case)	Treatment cost with vial sharing (scenario analysis)
Pembrolizumab plus doublet chemotherapy						
Pembrolizumab Q3W	200 mg	[redacted]	1	3	£4,997.00	£4,997.00
Pembrolizumab Q6W	400 mg	[redacted]	1	6	£9,994.00	£9,494.00
Capecitabine (CAPOX)	1,000 mg/m^2	[redacted]	28	3	£0.93	£0.93
Oxaliplatin (CAPOX)	130 mg/m^2	[redacted]	1	3	£32.91	£22.35
5-FU (FP)	800 mg/m^2	[redacted]	5	3	£3.89	£2.12
Cisplatin (FP)	80 mg/m^2	[redacted]	1	3	£19.47	£14.47
Doublet chemotherapy						
Capecitabine (CAPOX)	1,000 mg/m^2	[redacted]	28	3	£0.94	£0.94

Comparator/ Treatment	Required dose	RDI*	Doses per cycle	Cycle length (weeks)	Treatment cost without vial sharing (base-case)	Treatment cost with vial sharing (scenario analysis)
Oxaliplatin (CAPOX)	130 mg/m^2	[redacted]	1	3	£33.26	£22.59
5-FU (FP)	800 mg/m^2	[redacted]	5	3	£3.89	£2.12
Cisplatin (FP)	80 mg/m^2	[redacted]	1	3	£19.47	£14.47
Nivolumab plus doublet chemotherapy						
Nivolumab Q2W	240 mg	[redacted]	1	2	£2,501.35	£2,501.16
Nivolumab Q3W	360 mg	[redacted]	1	3	£3,752.50	£3,751.74
Capecitabine (CAPOX)	1,000 mg/m^2	[redacted]	28	3	£0.93	£0.93
Oxaliplatin (CAPOX)	130 mg/m^2	[redacted]	1	3	£32.91	£22.35
Leucovorin (FOLFOX)	400 mg/m^2	[redacted]	1	2	£7.40	£7.19
Oxaliplatin (FOLFOX)	85 mg/m^2	[redacted]	1	2	£20.23	£14.62
5-FU (FOLFOX)	2800 mg/m^2	[redacted]	1	2	£7.78	£7.40

Based on Table 56 and Table 57 in the CS.[1]
*Nivolumab plus doublet chemotherapy RDI was assumed equal to pembrolizumab plus doublet chemotherapy
As FOLFOX was an option in CheckMate-649 and not KEYNOTE-859, the oxaliplatin component of CAPOX and 5-FU component of FP is used to inform FOLFOX RDI.
Note: BSA is set at 1.7m^2 in the CPS≥1 and CPS≥10 populations
BSA = body surface area; mg = milligram; CS = company submission; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; RDI = relative dose intensity

4.2.9.2 Drug administration costs and vial sharing

The administration costs associated with each technology have been sourced using the National Schedule of NHS reference costs 2021/22.[48]

Table 4.29 presents administration costs used in the model. All IV treatments were assumed to be delivered at the hospital. The unit cost for the administration of pembrolizumab and nivolumab, was informed from the code SB12Z in the NHS reference costs schedule 2021/22 (Deliver Simple Parenteral Chemotherapy at First Attendance). This is assumed to reflect an IV infusion time of about 30 minutes for pembrolizumab and nivolumab when administered alone, whereas when administered together with CAPOX or cisplatin and capecitabine, the total infusion time is nearly 2 hours.

The unit cost for the administration of regimens involving 5-FU (doublet chemotherapy FP comprises of 5-FU and cisplatin; FOLFOX comprises of 5-FU, leucovorin and oxaliplatin), was estimated using the unit cost code SB14Z in the NHS reference costs schedule 2021/22 (Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance). That is because 5-FU is administered over 5 days of a 21-day treatment cycle. For all other IV treatments, the unit cost code SB13Z associated with more complex parenteral chemotherapy was employed. As capecitabine is an oral treatment there were no administration costs assigned to this treatment.

Table 0.29: Drug administration costs

NHS reference code	Description	Unit cost	Treatment
SB12Z	Deliver simple parenteral chemotherapy at first attendance	£287.71	Pembrolizumab monotherapy Nivolumab monotherapy
SB13Z	Deliver more complex parental chemotherapy at first attendance	£354.64	Pembrolizumab with CAPOX Nivolumab with CAPOX CAPOX
SB14Z	Deliver complex chemotherapy including prolonged infusion treatment at first attendance	£474.94	Pembrolizumab with FP Nivolumab with FOLFOX FP FOLFOX
Based on Table 58 of the CS.[1] CAPOX = capecitabine and oxaliplatin; CS = company submission; FOLFOX = 5-FU, leucovorin and oxaliplatin; FP = 5-FU and cisplatin; FU = fluorouracil			

Wastage costs were considered in the base-case analysis. For treatments excluding vial sharing, the company used the vial combination that provided the lowest cost per dose. Wastage costs were also considered for IV drugs that were administered based on patients' BSA. No wastage costs were included for oral treatments.

4.2.9.3 Health state unit costs and resource use

Health state costs have been applied cyclically and irrespective of treatment arm throughout the duration of the model time horizon. The cost and resource use required in each health state is outlined below and summarised in Table 4.30.

For the PF health state, resource use was informed from TA857,[23] which were based on the clinical expert inputs provided in TA208.[24] Resource use in the PF health state is assumed to be dependent on whether a patient is on or off chemotherapy treatment. The total cost per patient in the PF health state was estimated at £138.90 when a patient is on chemotherapy treatment and at £54.54 when a patient if off chemotherapy treatment.

For the PD health state, resource use was also informed from TA857,[23] which were originally sourced from TA208,[24] and were based on the NICE Clinical Guideline (CG) for advanced breast cancer (CG81).[49] The total cost per patient in the PD health state was estimated at £115.33. For the PD health state, the SLR also identified the study by Gomez-Ulloa et al. 2020,[50] as an alternative source of resource use. This is a retrospective real-world evidence study compromising of 62 patients in second-line therapy for advanced gastric cancer in the UK between January 2013 and July 2015, with a mean follow-up of 6.6 months. The total cost per patient in the PD health state was estimated at £38.23 (see Table 60 of the CS)[1] when using the study by Gomez-Ulloa et al. 2020[50]. The company explained that clinical experts had concerns around both these sources used to inform resource use in the PD health state. Resource use related to hospitalisations, outpatient visits and blood and biochemistry test were deemed to be missing from TA857/TA208/CG81, while the study by Gomez-Ulloa et al. 2020[50] included resource use related to imaging tests like X-rays, ultrasound and endoscopy which were deemed unlikely to be needed for the population of interest. Ultimately, clinical experts considered the frequencies used in TA857/TA208/CG81 too high, being more representative of palliative treatments, while the frequencies reported in Gómez-Ulloa et al. 2020,[50] were considered too low.

Table 0.30: Health state costs in the base-case analysis

Health state/ Healthcare resource	Frequency per week	Reference of frequency	Unit cost	Reference of unit cost
Progression-free				
Oncologist consultation during chemotherapy	0.33 (1 per 3 weeks)	Table 48 of the TA857[23]	£363.83	National Schedule of NHS Costs 2021/22: Outpatient Care; Non-admitted face-to-face attendance, first; WF01B; Consultant led; Service code 370.
Oncologist consultation after chemotherapy	0.17 (1 per 6 weeks)		£221.48	National Schedule of NHS Costs 2021/22: Outpatient Care; Non-admitted face-to-face attendance, follow-up; WF01A; Consultant led; Service code 370.
Cardiac monitoring (MUGA)	0.08 (1 per 3 months) 0.028 (33% MUGA)		£375.99	National Schedule of NHS Costs 2021/22: MUGA Scan; RN22Z
Cardiac monitoring (echocardiogram)	0.08 1 per 3 months 0.056 (67% echocardiogram)		£130.45	National Schedule of NHS Costs 2021/22: Simple Echocardiogram, 19 years and over; RD51A.
Total cost per week during chemotherapy	**£138.90**			
Total cost per week after chemotherapy	**£54.54**			
Progressed disease (based on TA857/TA208/CG81)				
Nurse, home visit	1 (20 minutes per week)	Table 49 of the TA857[23]	£17.33	Unit Costs of Health and Social Care 2022; Table 9.3.1: Costs and unit estimations for nurses working in a GP practice nurse (Band 5); Costs.
Clinical nurse specialist	1 (1 hour per week)		£52.00	Unit Costs of Health and Social Care 2022; Table 9.3.1: Costs and unit estimations for nurses working in a GP practice nurse (Band 5); Costs.

Health state/ Healthcare resource	Frequency per week	Reference of frequency	Unit cost	Reference of unit cost
GP	0.5 (1 visit per 2 weeks)		£42.00	Unit Costs of Health and Social Care 2022; Table 9.4.2: Unit costs for a GP; Per surgery consultation lasting 9.22 minutes.
Therapist	0.5 (1 hour per 2 weeks)		£50.00	Unit Costs of Health and Social Care 2022; Table 10.3.1: Costs and unit estimations for a community occupational therapist;
Total cost per week	**£115.33**			
Based on Table 59 and Table 61 in the CS[1] CG = clinical guideline; CT = computed tomography; CS = company submission; GP = general practitioner; MUGA = multiple-gated acquisition; NA = not applicable; NHS = National Health Service; PD = progressed disease; PF = progression free				

4.2.9.4 Adverse event costs

As discussed in Section 4.2.7, only Grade 3+ AEs occurring in 3% or more of patients in either treatment arm was considered relevant for inclusion in the economic model. Table 4.31 below provides the unit costs for AEs.

Table 0.31: Adverse event unit costs

AE	Unit cost	Reference
Anaemia	£770.29	National Schedule of NHS Costs for 2021/22: Non-elective short stay; Weighted average of SA01G-K; Based on EAG comments in TA737 (weighted average preferred)
Neutropenia	£2,257.20	National Schedule of NHS Costs for 2021/22: Total HRGs; Weighted average of SA35A-E
Diarrhoea	£522.09	National Schedule of NHS Costs for 2021/22: Non-elective short stay; FD10M. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; Consistent with TA857 and TA737.
Vomiting	£522.09	National Schedule of NHS Costs for 2021/22: Assumed equal to diarrhoea.; Similar assumptions made in TA857 and TA737.
Fatigue	£780.14	National Schedule of NHS Costs for 2021/22: Non-elective short stay; SA01G. Aplasia or Other Aplastic Anaemia, with CC Score 8+; Consistent with TA737.
Nausea	£522.09	National Schedule of NHS Costs for 2021/22: Assumed equal to diarrhoea; Similar assumptions made in TA857 and TA737.
Hypokalaemia	£753.88	National Schedule of NHS Costs for 2021/22: Total HRGs. WJ11Z; Other disorders of immunity.
Palmar-plantar erythrodysaesthesia syndrome	£267.00	National Schedule of NHS Costs for 2021/22: WF01B; General Medicine, Non-Admitted Face-to-Face Attendance, First

AE	Unit cost	Reference
Neuropathy peripheral	£1,867.70	National Schedule of NHS Costs for 2021/22: Total HRGs; Weighted average of AA26C-H.
Based on Table 62 of the CS.[1] AE = adverse event; CC = complications and comorbidities; CS = company submission; EAG = Evidence Assessment Group; HRG = healthcare resource group.		

Costs related to the incidence of AEs were applied to patients in the first model cycle. This was conducted by combining the unit costs in Table 4.31 with the treatment-specific frequencies of AEs (see Section 4.2.7). This combination led to a one-off cost of £472 for pembrolizumab plus doublet chemotherapy and doublet chemotherapy alone, and one-off cost of £543 for nivolumab plus doublet chemotherapy (Table 63 of the CS).[1]

4.2.9.5 Subsequent treatment costs

The analysis included the costs of subsequent treatments that patients received after progression or treatment discontinuation. The company argued that as data from the KEYNOTE-859 trial were used to inform the model and some of these patients received subsequent lines of treatment, the impact of subsequent treatments on efficacy is accounted in the OS. Therefore, the economic impact of the subsequent lines of treatments should also be incorporated. Using a simplified approach, the company incorporated the costs due to subsequent treatments using a one-off cost upon DP.

Patients in the KEYNOTE-859 trial, which is a global trial, were eligible to also receive subsequent treatments that are not available in NHS practice. To address this issue, the company used clinical expert opinion to inform the proportion of patients who would receive subsequent treatments in the UK, the types of subsequent treatments available and the distribution of patients across these treatments. Table 4.32 below summarises these inputs, which were then used in the base-case analysis to inform the estimated one-off cost for subsequent lines of treatment. In the scenario analyses, the company explored the impact of using the 10 most common types of subsequent treatments as used in the KEYNOTE-859 trial (see Table 65 of the CS). The duration of each subsequent treatment was also taken from KEYNOTE-859 using the ITT population.

Table 0.32: Subsequent treatment distributions

Inputs	Pembrolizumab plus doublet chemotherapy*	Doublet chemotherapy
Distributions as suggested by clinical experts		
Patients receiving a subsequent treatment	70%	
Second line treatments		Pembrolizumab would be offered to MSI high patients (NICE ID4036), in place of FOLFIRI. Non-MSI high patients receive the same subsequent treatments as the pembrolizumab plus doublet chemotherapy arm, so the proportions of the other subsequent treatments are equivalent in both arms.
FOLFIRI	60%	
Paclitaxel	30%	
Irinotecan	10%	
Third line treatments		
FOLFIRI	6%	
Paclitaxel	12%	
Lonsurf	12%	

Inputs	Pembrolizumab plus doublet chemotherapy*	Doublet chemotherapy
Distributions applied in the economic model		
FOLFIRI	66%	61%
Paclitaxel	42%	42%
Irinotecan	10%	10%
Lonsurf	12%	12%
Pembrolizumab (NICE ID4036)	0%	5%^

Based on Table 64 of the CS.[1]
*For nivolumab plus doublet chemotherapy, the proportions of subsequent treatment and distributions were assumed to equal pembrolizumab plus doublet chemotherapy, in line with clinical expert opinion
^Informed by the proportion of MSI high patients in the trial, which the clinical experts considered generalisable to clinical practice. Pembrolizumab is assumed to displace FOLFIRI in this proportion of patients.
CS = company submission; MSI = microsatellite instability

To better align the costs of subsequent treatments with their contribution in the OS treatment benefit, the company explored the option of performing a cross-over adjustment. Based on this approach, the OS benefits in both treatment arms would be adjusted to better reflect the subsequent treatments received in NHS practice, by removing key non-UK treatments (e.g., pembrolizumab [non-MSI high in the doublet chemotherapy arm and all in the pembrolizumab plus doublet chemotherapy arm], ramucirumab, ramucirumab plus paclitaxel and nivolumab). However, the company did not conduct this analysis as they explained that the anticipated impact of such analysis on the ICER would be minimal considering that:

- [redacted] of patients in the pembrolizumab plus doublet chemotherapy arm received pembrolizumab as a subsequent treatment.
- The proportion of patients receiving ramucirumab plus paclitaxel in each treatment arm [redacted]
- The proportion of patients receiving nivolumab in each treatment arm [redacted]
- The QALY gain in the PD health state is [redacted] in the pembrolizumab arm ([redacted]) than the chemotherapy arm ([redacted]), with the [redacted] suggesting that QALY gains within this health state do not depend on the type of subsequent treatment received.

The one-off cost of subsequent treatments per treatment arm was then estimated using the weighted average of the proportion of patients who progressed and received a subsequent treatment, the distribution of subsequent treatments (shown in Table 4.32 above) and the acquisition and administration cost of each subsequent treatment. Drug acquisition costs for subsequent treatments were sourced from BNF and the eMIT, while administration costs were sourced from the National Schedule of NHS Costs 2021/22. RDI was set at 100% for all subsequent treatments. Table 4.33 shows the one-off cost of subsequent treatments per treatment arm used in the economic model.

Table 0.33: Subsequent treatment costs

Treatment arm	NHS practice (base-case)		Trial data (scenario analysis)	
	List prices	Including CAA price for pembrolizumab	List prices	Including CAA price for pembrolizumab
Pembrolizumab plus doublet chemotherapy*	£16,779	£16,779^	£48,060	[redacted]
Doublet chemotherapy	£35,203	[redacted]	£58,281	[redacted]

Based on Table 66 of the CS.[1]
*For nivolumab plus doublet chemotherapy, subsequent treatment costs were assumed equal to pembrolizumab plus doublet chemotherapy subsequent treatment costs
^No subsequent usage of pembrolizumab is assumed in NHS practice according to clinical experts
CAA = commercial access agreement; CS = company submission; NHS = National Health Service

EAG comments: The main concerns of the EAG relate to the company's approach on the impact of subsequent treatments. The company acknowledged that OS curves based on the KEYNOTE-859 trial may already incorporate the potential impact of subsequent treatments in terms of treatment efficacy as some patients in the trial received subsequent lines of treatment. On page 151, the company further states that '*to cost these benefits, the economic model applies a one-off cost upon progression as a simplifying assumption.*' The EAG thinks this assumption may be too simplistic to capture the impact of subsequent treatments on costs and health gains. To address uncertainties around the usage of subsequent treatments the company further suggested usage of more pessimistic OS curves in scenario analyses. However, the EAG does not think that using the more pessimistic OS curves would fully address uncertainty related to usage of subsequent treatments. That is because the uncertainty around the costs of subsequent treatments would not be captured in that respect. To highlight the impact of the one-off cost upon DP, the EAG ran a scenario analysis by completely omitting the treatment costs due to subsequent treatments from the model computations.

4.2.9.6 Miscellaneous costs

End of life costs

End of life care costs was set at £13,113 and was sourced from the 2022 Unit Costs of Health and Social Care Manual based on research carried out by the Nuffield Trust which reported cancer-specific end-of-life cost in 2021/22 prices.[51, 52]

Progression costs

To account for additional testing and imaging required to confirm DP, a one-off cost upon DP was applied in the model. The one-off cost was estimated based on the cost of one computed tomography (CT) scan at £128.84 informed from unit cost code RD25Z in the National Schedule of NHS Costs 2021/22 (Diagnostic imaging; Computerised Tomography Scan of Three Areas, without Contrast). This was grounded on the input from clinical experts in TA208 and TA857, who noted that a CT scan would be required to confirm DP. The total costs of the one-off cost upon DP were different per treatment arm due to the different number and timing of progression events.

PD-L1 testing

As pembrolizumab plus doublet chemotherapy is aimed for patients with CPS ≥1, PD-L1 testing would also be necessary to define patient eligibility. However, there were no additional costs included in the

economic model due to PD-L1 testing costs. According to the CS, that is because in NHS clinical practice, PD-L1 tests would be administered to all patients in both treatment arms (probably concurrently with HER2 testing) to proactively identify HER2 negative patients eligible for nivolumab (TA857) or pembrolizumab (TA737),[23, 53] resulting in no incremental difference between groups.

4.2.10 Disease severity

The NICE reference case stipulates that the committee will consider all QALYs as being of equal weight. However, the committee may take into account the severity of the condition, as determined by the absolute and proportional QALY shortfall (including discounting at the reference case rate), as decision modifier. Quantification of disease severity in the CEAs can then be regarded through QALY weighting, based on the absolute and proportional shortfall, as shown in Table 4.34. The severity weight will be defined based on the greater shortfall implied either by the proportional or the absolute QALY shortfall calculations. If either the proportional or absolute QALY shortfall falls exactly on the cut-off between two severity levels, the higher level will apply.[54]

Table 0.34: Quality adjusted life year weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	From 0.85 to 0.95	From 12 to 18
1.7	At least 0.95	At least 18
QALY = quality-adjusted life year		

The results of the QALY shortfall analysis presented by the company are shown in Table 4.35, where the total lifetime QALYs associated with only chemotherapy treatment were obtained from the model results of the base-case analysis, and the estimated total QALYs for the general population reflected the baseline characteristics of the KEYNOTE-859 trial and the economic analyses (29.6% female and 60.1 years for patients with CPS ≥1; 27.8% female and 60.7 years for patients with CPS ≥10). These results suggest that a QALY weight of 1.2 can be applied to patients expressing CPS ≥1, whereas a QALY weight of 1.0 can be applied to patients expressing CPS ≥10.

The company, referring to previous NICE's methods for evaluating new medicines, stated that pembrolizumab plus doublet chemotherapy would have met the end-of-life criteria in the assessment versus doublet chemotherapy based on the previous criteria and would therefore have qualified for a willingness-to-pay (WTP) threshold of £50,000/QALY. [27] The CS further argues that nivolumab for untreated HER2 negative advanced gastric, GOJ or oesophageal adenocarcinoma (TA857) met NICE's end-of-life criteria and was assessed accordingly per the previous NICE's methods.[23] Grounding their arguments on the NMA results and a visual inspection of the naïve curves OS from CheckMate 648 and KEYNOTE-859 (Figure 49 and Figure 50 in the CS), the company claimed that the same QALY weighting should also apply to the current appraisal. In addition, the company emphasised the remaining unmet need in patients expressing CPS≥1 as a reason to assign the highest QALY weight to this population. Therefore, the company implemented a QALY weighting of 1.7 in the base-case analysis for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy in patients expressing CPS ≥1 and a QALY weighting of 1.0 for patients expressing CPS ≥10. The company then used the calculated QALY weighting as shown in Table 4.35 only for a scenario analysis.

Table 0.35: Summary of company QALY shortfall analysis

Population	Expected total QALYs for the general population	Total expected QALYs for people with the condition receiving current treatment†	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
CPS ≥1					
Doublet chemotherapy	12.40	[redacted]	[redacted]	[redacted]	1.2*
CPS ≥10					
Nivolumab plus doublet chemotherapy	12.40	[redacted]	[redacted]	[redacted]	1.0

Based on Table 69 in CS.[1]
*Proportional QALY shortfall falls in the 0.85 to 0.95 category which is associated with a 1.2 QALY weight
†Includes the one-off QALY loss associated with AEs
CPS = combined positive score; CS = company submission; QALY = quality-adjusted life year

EAG comment: The QALY shortfall results presented in Table 4.36 were validated by the EAG with the Institute for Medical Technology Assessment (iMTA) Disease Burden Calculator (iDBC), an online free tool to estimate the total (and proportional) QALYs lost. In addition, the iDBC tool also estimates the likelihood of the applicable QALY weight based on the PSA results provided in the company's model, which can be used to estimate the severity adjusted probability of being cost effective.[55] The iDBC tool can be found here: https://imtamodels.shinyapps.io/iDBCv2_1/. The QALY shortfall calculations conducted by the EAG are shown in Table 4.36. These results are broadly in line with those presented by the company in Table 4.35 for both patients expressing CPS ≥1 and patients expressing CPS ≥10. The minor differences observed are likely due to using different utility sources and/or life tables to estimate expected QALYs for the total population, and due to using the PSA results of the company's model to estimate the QALYs under doublet chemotherapy for patients expressing CPS ≥1 and nivolumab plus doublet chemotherapy for patients expressing CPS ≥10. The uncertainty around the QALY weights is also presented in Table 4.36. This shows for example that, for the patients expressing CPS ≥1, a weight point estimate is 1.2, would apply in 100.0% of the simulations, indicating that there is no uncertainty around the QALY weight for this population. Finally for CPS ≥10, a weight point estimate is 1.0, would also apply in 97.2% of the simulations.

Table 0.36: Summary of EAG QALY shortfall analysis

Population	Expected total QALYs for the general population	Total expected QALYs for people with the condition receiving current treatment†	Absolute QALY shortfall	Proportional QALY shortfall	QALY Weight (probability weight applicable)
CPS≥1					
Doublet chemotherapy	12.40	[redacted]^	[redacted]	[redacted]	1.2*(100.0%)
CPS≥10					
Nivolumab plus doublet chemotherapy	12.40	[redacted]	[redacted]	[redacted]	1.0 (97.2%)

Based on iDBC tool available at: https://imtamodels.shinyapps.io/iDBCv2_1/
*Proportional QALY shortfall falls in the 0.85 to 0.95 category which is associated with a 1.2 QALY weight
†Includes the one-off QALY loss associated with AEs
^Based on the company base-case results following the clarification phase.
CPS = combined positive score; QALY = quality-adjusted life year

Furthermore, the EAG does not agree with the company's rationale for selecting a QALY weight of 1.7 for patients expressing CPS ≥1. The EAG wonders what the value of analysing and presenting results is based on the up-to-date NICE guidelines if the company in end decides to use the previous NICE guidelines. Aligned with the NICE guidelines, the EAG base-case analysis considered a QALY weight of 1.2 for patients expressing CPS ≥1 and a QALY weight of 1.0 for patients expressing CPS ≥10, considering the severity analyses results presented above.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Main results original company submission

Table 5.1 shows the company's deterministic base-case results. For patients expressing CPS ≥1, the total costs of pembrolizumab plus doublet chemotherapy treatment were estimated at [redacted] while total costs associated with doublet chemotherapy alone were estimated at [redacted], indicating that pembrolizumab treatment increases total costs by [redacted]. Note that the company's total costs include a commercial access agreement accounting for a simple discount of [redacted] for pembrolizumab. Total QALYs associated with pembrolizumab plus doublet chemotherapy treatment were estimated at [redacted] and total QALYs associated with doublet chemotherapy alone were estimated at [redacted], indicating an [redacted] QALYs increment gained with pembrolizumab treatment. Note that the company's QALYs were based on a QALY weight equal to 1.7. These values lead to a company's severity adjusted ICER for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy alone of [redacted] per QALY gained for patients expressing CPS ≥1. The QALYs in brackets in Table 5.1 are unweighted.

For patients expressing CPS ≥10, the total costs of pembrolizumab plus doublet chemotherapy treatment were estimated at [redacted] (using the list price of pembrolizumab treatment), while total costs associated with nivolumab plus doublet chemotherapy were estimated at [redacted], indicating that pembrolizumab treatment increases total costs by [redacted]. Total QALYs associated with pembrolizumab plus doublet chemotherapy treatment were estimated at [redacted] and total QALYs associated with nivolumab plus doublet chemotherapy were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained with pembrolizumab treatment. This gives an ICER for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy of [redacted] per QALY gained for patients expressing CPS ≥10. The disaggregated results are shown in Table 5.2 and Table 5.3.

Table 0.1: Company's base-case deterministic cost effectiveness results, original submission

Population/ Technologies	Total Costs^	Total LYG #	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs*	ICER (£/QALY) *
CPS ≥1							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS ≥10							
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	-			
Pembrolizumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Based on Table 71 in CS.[1]							

Population/ Technologies	Total Costs^	Total LYG #	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs*	ICER (£/QALY) *
^ For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab, whereas for patients expressing CPS ≥10 the list price of pembrolizumab has been used. # LYs are undiscounted values. *For patients with CPS ≥1, QALYs in brackets are not weighted for the severity modifier. The company's severity adjusted ICERs were based on a QALY weight equal to 1.7. CPS = combined positive score; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years							

Table 0.2: Company's disaggregated results for patients expressing CPS ≥1, original submission

Outcomes	Pembrolizumab+ Doublet chemotherapy	Doublet chemotherapy	Increment
Costs			
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Disease management (treatment related)	[redacted]	[redacted]	[redacted]
One-off progression	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Disease management (upon progression)	[redacted]	[redacted]	[redacted]
End-of life	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Health outcomes			
Life year*			
<30 days	[redacted]	[redacted]	[redacted]
30-179 days	[redacted]	[redacted]	[redacted]
180-360 days	[redacted]	[redacted]	[redacted]
360 days	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
QALYs			
<30 days	[redacted]	[redacted]	[redacted]
30-179 days	[redacted]	[redacted]	[redacted]
180-360 days	[redacted]	[redacted]	[redacted]
360 days	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]

Outcomes	Pembrolizumab+ Doublet chemotherapy	Doublet chemotherapy	Increment
Total QALYs	[redacted]	[redacted]	[redacted]

Based on Table 72, Table 74 and Table 77 of the Appendix J in CS.[1]
* LYs are undiscounted values.
CPS = combined positive score; CS = company submission; LY = life year; QALY = quality-adjusted life year

Table 0.3: Company's disaggregated results for patients expressing CPS ≥10, original submission

Outcomes	Pembrolizumab + Doublet chemotherapy	Nivolumab + Doublet chemotherapy	Increment
Costs			
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
Disease management (treatment related)	[redacted]	[redacted]	[redacted]
One-off progression	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Disease management (upon progression)	[redacted]	[redacted]	[redacted]
End-of life	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Health outcomes			
Life year*			
<30 days	[redacted]	[redacted]	[redacted]
30-179 days	[redacted]	[redacted]	[redacted]
180-360 days	[redacted]	[redacted]	[redacted]
360 days	[redacted]	[redacted]	[redacted]
Total LYs	[redacted]	[redacted]	[redacted]
QALYs			
<30 days	[redacted]	[redacted]	[redacted]
30-179 days	[redacted]	[redacted]	[redacted]
180-360 days	[redacted]	[redacted]	[redacted]
360 days	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Based on the electronic model, Table 78, Table 80 and Table 83 of the Appendix J in CS.[1]
*LYs are undiscounted values.
CPS = combined positive score; CS = company submission; LY = life year; QALY = quality-adjusted life year

5.1.2 Main results of the company after the request for clarification

Table 5.4 shows the deterministic cost effectiveness results of the updated company's base-case analysis (i.e., as provided alongside their response to request for clarification).[7] The results are quite similar to those in the original submission presented in the previous Section. Note, that for patients expressing CPS ≥1, the results include a severity QALY weight equal to 1.7 and a CAA simple discount for pembrolizumab of [redacted]. For patients expressing CPS ≥10, the results are based on a severity QALY weight equal to 1.0 and the list price of pembrolizumab.

Table 0.4: Company's base-case deterministic cost effectiveness results, after clarification

Population/ Technologies	Total Costs^	Total LYG[#]	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs	ICER (£/QALY)
CPS ≥1							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS ≥10							
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 18 in response to clarification questions.[7]
*For patients with CPS ≥1, QALYs in brackets are not weighted for the severity modifier. The company's severity adjusted ICERs were based on a QALY weight equal to 1.7.
^ For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab, whereas for patients expressing CPS ≥10 the list price of pembrolizumab has been used.
[#] LYs are undiscounted values.
CPS = combined positive score; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

5.2 Company's sensitivity analyses

The company performed and presented the results of probabilistic sensitivity analyses (PSA), deterministic sensitivity analyses (DSA) as well as scenario analyses. We will present here the analyses based on the updated version of the model after clarification.

5.2.1 Probabilistic sensitivity analysis

A PSA of 1,000 runs was conducted using the probability distributions shown in Appendix N of the CS. Table 5.5 shows the probabilistic cost effectiveness results of the updated company's base-case analysis following the clarification phase. Results of the PSA in Table 5.5 below show that probabilistic results are well aligned with the deterministic base-case. The cost effectiveness plane in Figure 5.1 shows that most of the simulations fell in the north-east quadrant for patients with CPS ≥1. For patients with CPS ≥1, based on the cost effectiveness acceptability curve (CEAC) in Figure 5.2, the probability

that pembrolizumab plus doublet chemotherapy is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted] using the company base-case assumptions.

For patients with CPS ≥10, the cost effectiveness plane in Figure 5.3 shows that most of the simulations are shared between the North-East and North-West quadrant. Based on the respective CEAC in Figure 5.4, the probability that pembrolizumab plus doublet chemotherapy is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted] using the company base-case assumptions.

Table 0.5: Company base-case probabilistic cost effectiveness results

Population/ Technologies	Total Costs^	Total LYG[#]	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
CPS ≥1 (QALY weight 1.7)							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS ≥10 (QALY weight 1.0)							
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 19 in CL.[1]
*For patients with CPS ≥1, QALYs in brackets are not weighted for the severity modifier. The company's severity adjusted ICERs were based on a QALY weight equal to 1.7.
^ For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab, whereas for patients expressing CPS≥10 the list price of pembrolizumab has been used.
[#] LYs are undiscounted values.
CPS = combined positive score; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

Figure 0.1: Probabilistic sensitivity analysis cost effectiveness plane, patient with CPS ≥1

Based on Figure 23 of the clarification response.[7]
CPS = combined positive score; ICER = incremental cost effectiveness ratio; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years; WTP = willingness-to-pay

Figure 0.2: Probabilistic sensitivity analysis cost effectiveness acceptability curve, patient with CPS ≥1

Based on Figure 22 of the clarification response.[7]
CPS = combined positive score; WTP = willingness-to-pay

Figure 0.3: Probabilistic sensitivity analysis cost effectiveness plane, patient with CPS ≥10

Based on Figure 26 of the clarification response.[7]
CPS = combined positive score; ICER = incremental cost effectiveness ratio; PSA = probabilistic sensitivity analysis; QALYs = quality-adjusted life years; WTP = willingness-to-pay

Figure 0.4: Probabilistic sensitivity analysis cost effectiveness acceptability curve, patient with CPS ≥10

Based on Figure 25 of the clarification response. [7]
CPS = combined positive score; WTP = willingness-to-pay

5.2.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was done by varying key model inputs between the upper and lower values of the 95% CIs where available. If no CI or standard error (SE) was reported, a SE of 20% of the expected value was used.

The key model inputs that were varied in the OWSA include: baseline patient characteristics, NMA results, AE incidence, utility values, AE disutility values, chemotherapy acquisition costs, RDI, disease management frequency, AE treatment costs, administration costs, disease management costs, the progression cost, the end-of-life cost and subsequent treatment proportions.

The results of the OWSA are reported as net-health benefits (NHB), with a threshold value of £30,000/QALY gained used to convert costs into QALYs.

The results in the CPS ≥1 population were most sensitive to various subsequent treatment parameters (Figure 5.5). Results in the CPS ≥10 population were most sensitive to relative efficacy (HRs) for nivolumab versus pembrolizumab and the RDI for nivolumab (Figure 5.6).

Figure 0.5 Revised OWSA: CPS ≥1 population

Based on the electronic model submitted following the clarification phase. [7]
CPS = combined positive score; IV = intravenous; NHB = net health benefit; PF = progression free; RDI = Relative dose intensity; TTD = time to treatment discontinuation; vs = versus

Figure 0.6 Revised OWSA: CPS ≥10 population

Based on the electronic model submitted following the clarification phase[7]
CPS = combined positive score; IV = intravenous; NHB = net health benefit; PF = progression free; RDI = Relative dose intensity; TTD = time to treatment discontinuation; vs = versus

5.2.3 Scenario analyses

In addition to the sensitivity analyses the company also performed scenario analyses, where key assumptions were varied.

Table 0.6: List of scenarios

Base-case	Scenario	Justification
Model set up		
Chemotherapy backbones based on trial data	Chemotherapy backbones based on clinical expert opinion	The scenario will reflect the cost of chemotherapy backbones used in NHS practice.
Chemotherapy backbones based on trial data	Nivolumab chemotherapy backbones informed by the pembrolizumab arm in KEYNOTE-859	Clinical experts did not expect the chemotherapy backbone to depend on the IO it is given in combination with.
Without half-cycle correction	With half-cycle correction	Half-cycle corrections are recommended for long cycle lengths to account for events occurring at any point during a cycle. The scenario will assess the impact of this recommendation on a short cycle length.

Base-case	Scenario	Justification
30-year time horizon	10-year time horizon	A shorter time horizon may be long enough to reflect all important differences in costs or outcomes between the treatments being compared.
30-year time horizon	20-year time horizon	A shorter time horizon may be long enough to reflect all important differences in costs or outcomes between the treatments being compared.
3.5% discount rate	1.5% discount rate	The NICE manual recommends alternative analyses using rates of 1.5% for both costs and health effects.
HRQoL		
Pooled time-to-death utility values	Pooled health state utility values	Health state utility values were also collected in the trial.
AE disutility values from KEYNOTE-859	AE disutility values from TA857	Alternative approach to estimate disutility values.
Pooled time-to-death utility values	Treatment specific time-to-death utility values	Alternative approach to account for different toxicity and administration profiles
Without general population utility adjustment	With general population utility adjustment	The impact of aging may not be inherently captured in the utility values.
Resource use and costs		
Pembrolizumab 200mg Q3W dosing schedule as per the trial	Pembrolizumab 400mg Q6W dosing schedule	Q6W schedule is more commonly used in NHS practice to reduce the burden for patients and clinic capacity.
No treatment cap for IO	2-year treatment cap for IO	The duration of treatment in the trial may overestimate the cost of treatment to the NHS. A 2-year stopping rule may apply in NHS practice.
18-week (6 treatment cycles) stopping rule for doublet chemotherapy	No treatment cap	Treatment caps in the trial depended on local standard. The scenario reflects the cost of chemotherapy used in the trial.
Include RDI	Exclude RDI (RDI=100%)	The RDI in the trial may not be reflective of NHS practice.
Include wastage costs	Exclude wastage costs	Some centres may promote vial sharing and the base-case may overestimate the acquisition cost of treatment.
PD health state costs informed by TA857/TA208/CG81	PD health state costs informed by Gómez-Ulloa *et al.* 2020	The scenario provides a more contemporary representation of clinical practice in patients with GC receiving second line treatment.
Subsequent treatment distributions based on clinical expert opinion	Subsequent treatment distributions based on KEYNOTE-859 trial data	The scenario reflects the cost and benefits of subsequent treatment received in the trial.
With one-off progression cost	Without one-off progression cost	A one-off progression cost has been excluded in previous appraisals.

Base-case	Scenario	Justification
K-M ToT curves	Parametric ToT curves	The scenario will reduce the stepped nature of K-M data.
Clinical effectiveness (survival)		
Nivolumab plus doublet chemotherapy AE data informed by CheckMate-649	Nivolumab plus doublet chemotherapy AE data informed by KEYNOTE-859	AE profile may not depend on the type of IO
HRs for nivolumab plus doublet chemotherapy versus pembrolizumab plus doublet chemotherapy based on NMA	HRs for nivolumab plus doublet chemotherapy versus pembrolizumab plus doublet chemotherapy equal to 1	[redacted]
No treatment waning effect	Gradual treatment waning effect 7 years from the start of IO treatment, where the cycle-specific hazard for the IO gradually becomes equal to that of doublet chemotherapy over the subsequent 2 years	A conservative assumption is explored in scenario analysis.
Clinical effectiveness (survival) CPS≥1		
OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot hazards	Spline 2 knot odds	Alternative extrapolation with good statistical and visual fit.
OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot hazards	Spline 2 knot normal	Alternative extrapolation with good statistical and visual fit.
OS: Doublet chemotherapy: spline 2 knot hazards	Log-logistic	Best fitting parametric model.
OS: Doublet chemotherapy: spline 2 knot hazards	Spline 2 knot odds	Alternative extrapolation with good statistical and visual fit.
PFS: Pembrolizumab plus doublet	Spline 2 knot hazards	Alternative extrapolation with good statistical and visual fit.

Base-case	Scenario	Justification
chemotherapy: spline 1 knot hazards		
PFS: Doublet chemotherapy: spline 1 knot hazards	Spline 2 knot hazards	Alternative extrapolation with good statistical and visual fit.
Clinical effectiveness (survival) CPS≥10		
OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot odds	Log-logistic	Best fitting parametric model.
OS: Pembrolizumab plus doublet chemotherapy: spline 2 knot odds	Spline 1 knot odds	Alternative extrapolation with good statistical and visual fit.
PFS: Pembrolizumab plus doublet chemotherapy: spline 1 knot hazards	Spline 2 knot odds	Alternative extrapolation with good statistical and visual fit.
Severity modifier		
Pembrolizumab plus doublet chemotherapy versus doublet chemotherapy: 1.7	1.2	The scenario analysis reflects the severity modifier calculated by the economic model.
Pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy: 1.0	1.2	An unmet need still exists with current treatments; first-line treatment of an advanced cancer should be considered a severe disease setting.
Based on Table 77 CS.[1] AE = adverse event; CPS = combined positive score; Crl = credible interval; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; IO = immunotherapy; K-M = Kaplan Meier; NHS = National Health Service; NMA = network meta-analysis; OS = overall survival; PD = progressed disease; PFS = progression-free survival; Q6W = every 6 weeks; RDI = relative dose intensity; ToT = time on treatment; TSD = Technical Support Document		

Results of the scenario analyses are provided in Table 5.7 and 5.8. In the CPS ≥1 population the results were most sensitive to assuming a severity modifier of 1.2, a treatment waning effect and alternative OS extrapolations (Table 5.7). Results in the CPS ≥10 population were most sensitive to assuming a HR of 1.0 between pembrolizumab and nivolumab for survival outcomes, a shorter time horizon and alternative OS extrapolations (Table 5.8).

Table 0.7: Revised results of scenario analysis: CPS ≥1 population (deterministic)

Scenario	ICER (CAA price)	% change from base-case
Base-case	[redacted]	[redacted]
Chemotherapy backbones: NHS practice	[redacted]	[redacted]
Half-cycle correction: Yes	[redacted]	[redacted]
Time horizon: 10-year	[redacted]	[redacted]

Time horizon: 20-year	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]
Utility source: Descriptive pooled health state utility values	[redacted]	[redacted]
Utility: General population utility adjustment	[redacted]	[redacted]
Utility: Literature-based AE disutility	[redacted]	[redacted]
Utility: Descriptive treatment-specific time to death	[redacted]	[redacted]
Pembrolizumab: 100% Q6W	[redacted]	[redacted]
Treatment administration: mean # doses	[redacted]	[redacted]
Pembrolizumab & Nivolumab: 2-year cap	[redacted]	[redacted]
RDI = 100%	[redacted]	[redacted]
Exclude wastage costs	[redacted]	[redacted]
Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
Subsequent treatment distribution: KEYNOTE-859	[redacted]	[redacted]
One-off progression cost: No	[redacted]	[redacted]
Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
Treatment waning effect: Yes	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot odds spline model	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot normal spline model	[redacted]	[redacted]
OS Doublet chemotherapy: Log-logistic	[redacted]	[redacted]
OS Doublet chemotherapy: 2-knot odds model	[redacted]	[redacted]
PFS Pembrolizumab + chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
PFS Doublet chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
Severity modifier of x1.2	[redacted]	[redacted]

Table 0.8: Results of scenario analysis: CPS ≥10 population (deterministic)

Scenario	ICER (list prices)	% change from base-case
CPS10: Base-case	[redacted]	[redacted]
CPS10: Chemotherapy backbone: NHS	[redacted]	[redacted]
CPS10: Nivolumab chemotherapy backbones: KEYNOTE-859	[redacted]	[redacted]
CPS10: Half-cycle correction: Yes	[redacted]	[redacted]
CPS10: Time horizon: 10-year	[redacted]	[redacted]
CPS10: Time horizon: 20-year	[redacted]	[redacted]
CPS10: Discount rate: 1.5%	[redacted]	[redacted]
CPS10: Utility source: Pooled health state utility values	[redacted]	[redacted]
CPS10: Utility: General population utility adjustment	[redacted]	[redacted]
CPS10: Utility: Literature-based AE disutility	[redacted]	[redacted]
CPS10: Utility: Treatment-specific time to death	[redacted]	[redacted]
CPS10: Pembrolizumab: 100% Q6W	[redacted]	[redacted]

CPS10: Treatment administration: mean # doses	[redacted]	[redacted]
CPS10: Pembrolizumab & Nivolumab: 2-year cap	[redacted]	[redacted]
CPS10: RDI = 100%	[redacted]	[redacted]
CPS10: Exclude wastage costs	[redacted]	[redacted]
CPS10: Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
CPS10: Subsequent treatment distribution: KEYNOTE-859	[redacted]	[redacted]
CPS10: One-off progression cost: No	[redacted]	[redacted]
CPS10: Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
CPS10: AEs for nivolumab = pembrolizumab	[redacted]	[redacted]
CPS10: Nivolumab versus pembrolizumab HR = 1	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-odds model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-hazard model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: log-logistic model	[redacted]	[redacted]

5.3 Model validation and face validity check

5.3.1 Clinical expert opinion

The company sought clinical input from three expert clinicians who are experienced in the management of HER2 negative advanced gastric or GOJ cancer patients in England. Thus, the company wanted to ensure that the inputs and assumptions used in the base-case analysis were relevant to UK clinical practice and to validate the clinical plausibility of the outcomes predicted by the model. The input was sought in individual consultation meetings of a two-hour duration. Topics covered in the discussions included:

- Current management of untreated HER2 negative advanced gastric or GOJ adenocarcinoma.
- The types of chemotherapy regimens offered and how long they are given for.
- The types of subsequent treatments offered and the proportion of patients who receive them.
- Use of HER2 and PD-L1 testing.
- The generalisability of the KEYNOTE-859 population to UK practice.
- The generalisability of health care resource use reported in the literature to UK practice.
- Discussion of the KEYNOTE-859 efficacy and safety results.
- Survival estimates for patients currently treated with doublet chemotherapy and nivolumab plus doublet chemotherapy, and how this compares to the survival estimates in KEYNOTE-859.

In their response to the clarification letter, the company provided the minutes of the interviews conducted with the three clinical experts.

5.3.2 Internal validation

In Sections 3.3.1 and 3.3.2 of the CS, as well as Appendix N of the CS, the company summarised validation efforts which aimed to compare OS and PFS data observed in the KEYNOTE-859 trial with modelled OS and PFS data based on the KEYNOTE-859 trial. The OS and PFS curve fittings for pembrolizumab plus doublet chemotherapy and doublet chemotherapy were compared against the observed data. Furthermore, survival rate validation at different timepoints as reported in Appendix N of the CS was conducted. For further details, see sections on OS (Section 4.2.6.1) and PFS

(Section 4.2.6.3) for thorough comparison of modelled OS and PFS versus observed data in the KEYNOTE-859 study.

Additionally, the company consulted clinical experts to identify potential external data sources that could be used to validate the survival outcomes predicted from the economic model, other than the data from the CheckMate-649 trial. In the absence of appropriate external evidence, the clinical experts who were consulted by the company also provided information on the proportion of patients they would expect to be alive on doublet chemotherapy at 2, 5 and 10 years (see Table 37 of the CS) and provided feedback on the clinical plausibility of the extrapolations predicted by the alternative parametric models.

5.3.3 Model quality checks

Besides the customary internal model quality checks done by the model developers, an independent health economist assessed the internal validity and technical accuracy using an extensive quality checklist.

5.3.4 Comparison with external trial data

The company point out that there is a lack of trials conducted in the HER2 negative advanced GC therapy area. The only relevant trial identified, i.e., CheckMate-649, was used in the company's cost effectiveness study, and thus cannot be used for external validation. The EAG did compare the incremental costs and QALYs estimated in TA737 with those in the current TA and found quite similar values.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

6.1.1 Explanation of the EAG adjustments

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case includes several changes to the original cost effectiveness model provided by the company base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and can be subdivided into three categories (derived from Kaltenthaler et al. 2016)[56]:

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong).
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to).
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred).

In the current assessment a few small errors were found by the EAG after clarification. The first relates to the LYs reported in the result tables of the PSA. Here, accidently the LYs accumulated after progression are reported instead of total LYs (see Table 5.5, where LYs are smaller than QALYs). The second relates to the scenario analysis for AE rates in patients expressing CPS ≥10, here the aim was to set the AE rates for nivolumab equal to those of pembrolizumab, but in actuality the nivolumab AE rates are set to zero for all AE. This explains the relatively large impact found of the scenario.

Errors that were found in the original model during clarification were corrected by the company in a revised electronic model. In addition, no violations were identified.

The EAG's preferences regarding alternative assumptions led to the following changes to the company base-case analysis:

- The company base-case assumed the treatment effect of pembrolizumab treatment to last for a person's lifetime even after treatment is stopped. Considering the currently available evidence from the KEYNOTE-859 trial and the studies cited by the company on the long-term follow-up in melanoma and lung cancer, with either nivolumab or pembrolizumab treatments,[30-33] the EAG considers it reasonable at this point in time to assume that the treatment effect will remain in place for a certain period but not a lifetime ongoing benefit following treatment cessation. Therefore, the EAG limits the duration of the treatment effect in the EAG base-case to 5 years from the start of treatment initiation with a gradual treatment waning over the two subsequent years assuming that the cycle specific hazard for pembrolizumab will eventually become equal to that in the doublet chemotherapy arm over the 2 -year period (see Section 4.2.6.2). For the patients expressing CPS ≥10, this scenario means that over time the cycle specific hazard of pembrolizumab and nivolumab will become equal to that of doublet chemotherapy. Note that this scenario is not the same as the company's waning scenario, as the company assumes that waning starts 7 years after treatment initiation whereas the EAG assumed that the waning starts 5 years after treatment initiation, given the currently available evidence mentioned above.
- The company used a QALY weight of 1.7 for patients expressing CPS ≥1.The EAG, aligning with the most up-to-date NICE guidelines, used a QALY weight of 1.2 for patients expressing CPS ≥1 and a QALY weight of 1.0 for patients expressing CPS ≥10. Note that the QALY weights estimated by the company were the same as the respective QALY weights estimated

by the EAG, but the company decided to use another QALY weight in their base-case analysis of patients expressing CPS ≥1 for reasons that are summarised in Section 4.2.10.

The overview of the changes and the bookmarks for the justification of the EAG changes are presented in Table 6.1.

Table 0.1: Company and EAG base-case preferred assumptions

Base-case preferred assumptions	Company	EAG	Justification for change
Treatment waning	No waning	Initiation of waning effect after 5 years and completion after 2 subsequent years (during which period the pembrolizumab hazard becomes equal to that of doublet chemotherapy)	Section 4.2.6
CPS≥1 population: QALY weight for disease severity	QALY weight of 1.7	QALY weight of 1.2	Section 4.2.10
CPS = combined positive score; EAG = Evidence Assessment Group; QALYs = quality-adjusted life years			

6.1.2 Additional scenarios conducted by the EAG

After the proposed changes were implemented in the company's model, the EAG performed the following exploratory scenario analyses to investigate the impact of alternative assumptions conditional on the EAG base-case.

Scenario 1: Alternative models for OS (Section 4.2.6.1)

The EAG explored the impact of using alternative models to fit the OS data from the KEYNOTE-859. Specifically, the EAG used the 3-knot odds and 3-knot hazards models for OS in the population of patients expressing CPS ≥1 for both the pembrolizumab plus doublet chemotherapy and doublet chemotherapy only arms. For patients expressing CPS ≥10, the EAG used the loglogistic, lognormal, 2-knots hazard and 2-knots normal models.

Scenario 2: Adverse events (Section 4.2.7)

In Section 4.2.7 the EAG noticed some differences in the observed AE profiles between pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy. The company argued this to be largely driven by the backbone chemotherapy patients received in the trials, which is possible, but the EAG is uncertain about this explanation. This, a scenario was explored where the AE incidence rates in the nivolumab arm were assumed to be the same as for the pembrolizumab arm for patients expressing CPS ≥10.

Scenario 3: Costs due to subsequent treatments (Section 4.2.9)

To account for costs due to subsequent treatments lines of treatment, the company employed a one-off cost upon progression as a simplifying assumption. The EAG found this assumption too simple as explained in the EAG comments of Section 4.2.9. Therefore, to address uncertainties around the usage of subsequent treatments, the EAG ran a scenario analysis in which the treatment costs due to subsequent treatments were omitted from the model computations and a second scenario in which costs due to subsequent treatments were equal between arms.

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG base-case was defined using the base-case of the company following the clarification phase as starting point. Table 6.2 shows the deterministic CE results of the EAG preferred base-case analysis. All results are discounted.

For patients expressing CPS ≥1, the EAG preferred severity adjusted ICER for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy alone is [redacted] per QALY gained. As with the company base-case, this analysis includes a CAA accounting for a simple discount of [redacted] for pembrolizumab and in Table 6.2 the QALYs are presented based on a QALY weight equal to 1.2 whilst the QALYs in brackets are unweighted.

For patients expressing CPS ≥10, an ICER for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy of [redacted] per QALY gained is found. Both for pembrolizumab and for nivolumab were the list prices of treatment used. No QALY weighting was applicable in this comparison.

Table 0.2: EAG preferred base-case deterministic cost effectiveness results

Population/ Technologies	Total Costs^	Total LYG #	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
CPS ≥1							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]			[redacted]	
Pembrolizumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS ≥10							
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]			[redacted]	
Pembrolizumab + Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^ For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab, whereas for patients expressing CPS≥10 the list price of pembrolizumab has been used.
# LYs are undiscounted values.
*For patients with CPS ≥1, QALYs in brackets are not weighted for the severity modifier. The EAG's severity adjusted ICERs were based on a QALY weight equal to 1.2.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

Table 6.3 shows the probabilistic cost effectiveness results of the EAG preferred base-case analysis. All results are discounted. The probabilistic results are aligned with the deterministic EAG base-case results. The cost effectiveness plane in Figure 6.1 shows that most of the simulations fell in the North-East quadrant for patients expressing CPS ≥1. Based on the CEAC in Figure 6.3, the probability that that pembrolizumab plus doublet chemotherapy is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted] using the EAG preferred base-case assumptions. For patients with CPS ≥10, the cost effectiveness plane in Figure 6.3 shows that most of the simulations are shared

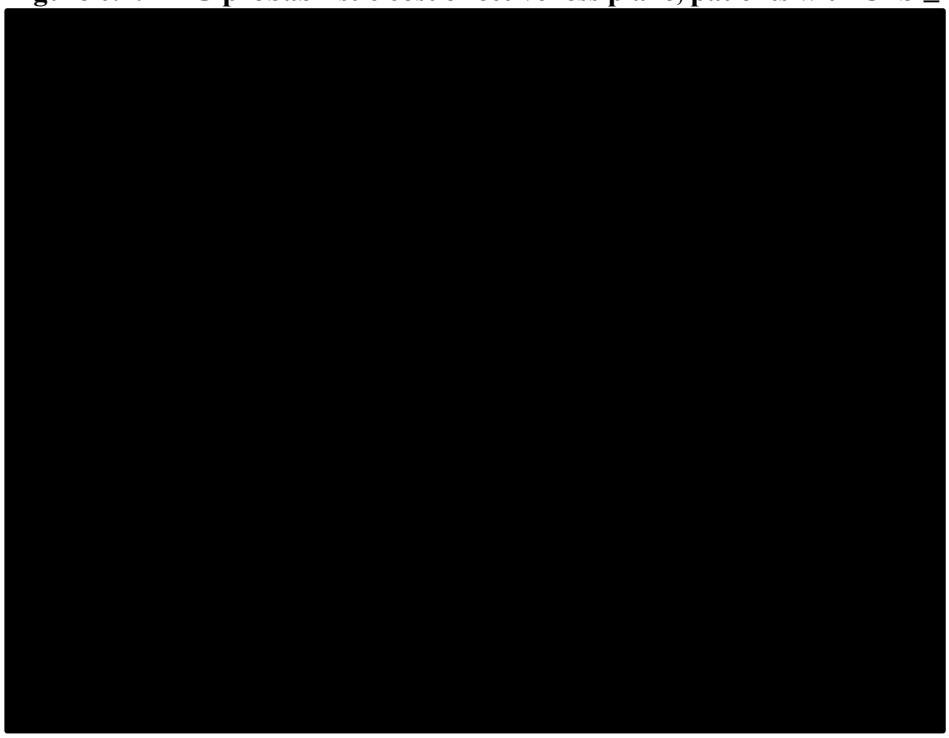
between the North-East and North-West quadrant. Based on the respective CEAC in Figure 6.4, the probability that pembrolizumab plus doublet chemotherapy is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively, for patients expressing CPS ≥10 when using the EAG preferred base-case assumptions.

Table 0.3: EAG preferred base-case probabilistic cost effectiveness results

Population/ Technologies	Total Costs^	Total LYG[#]	Total QALYs*	Inc. costs	Inc. LYG	Inc. QALYs*	ICER (£/QALY)*
CPS ≥1							
Doublet chemotherapy	[redacted]	[redacted]	[redacted]			[redacted]	
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS ≥10							
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]			[redacted]	
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

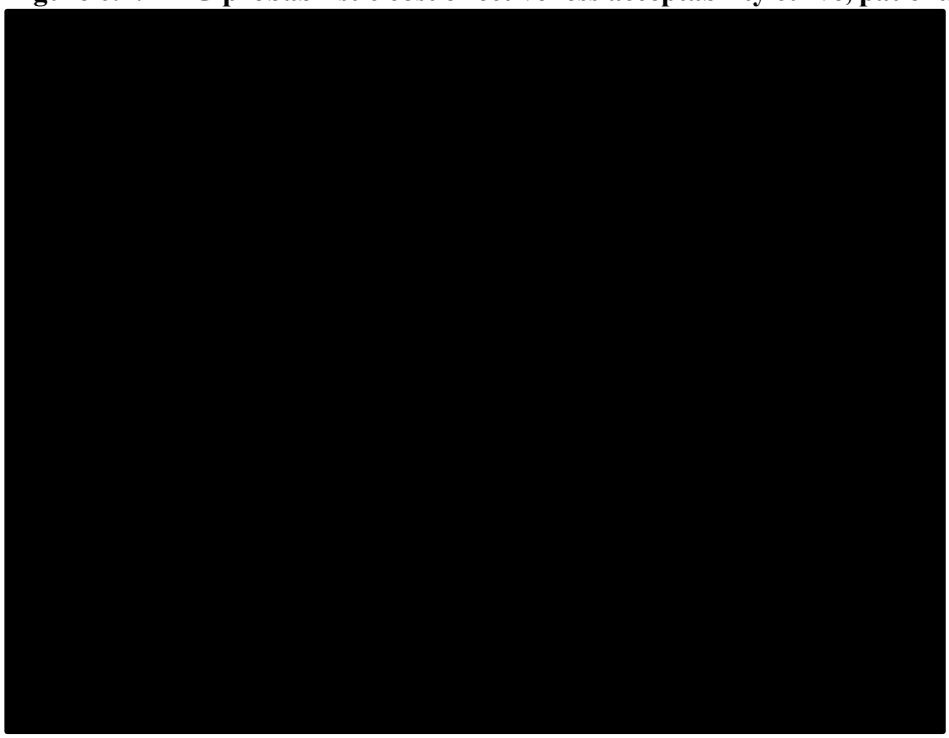
^ For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab, whereas for patients expressing CPS≥10 the list price of pembrolizumab has been used.
[#] LYs are undiscounted values.
*For patients with CPS ≥1, the EAG's severity adjusted ICERs were based on a QALY weight equal to 1.2.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years

Figure 0.1: EAG probabilistic cost effectiveness plane, patients with CPS ≥1



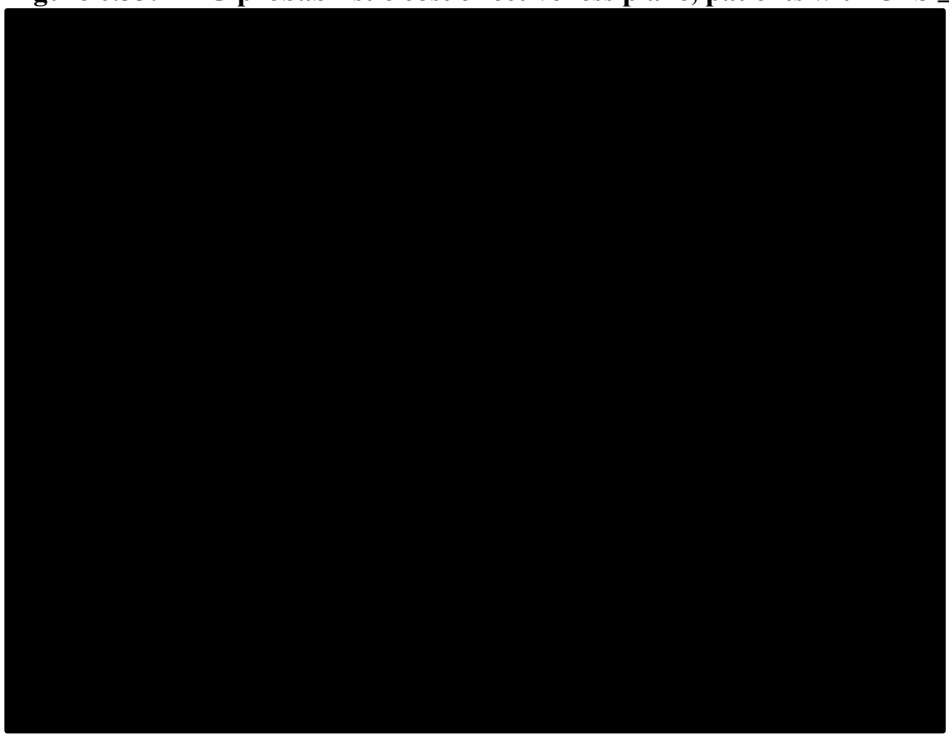
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 0.2: EAG probabilistic cost effectiveness acceptability curve, patients with CPS ≥1



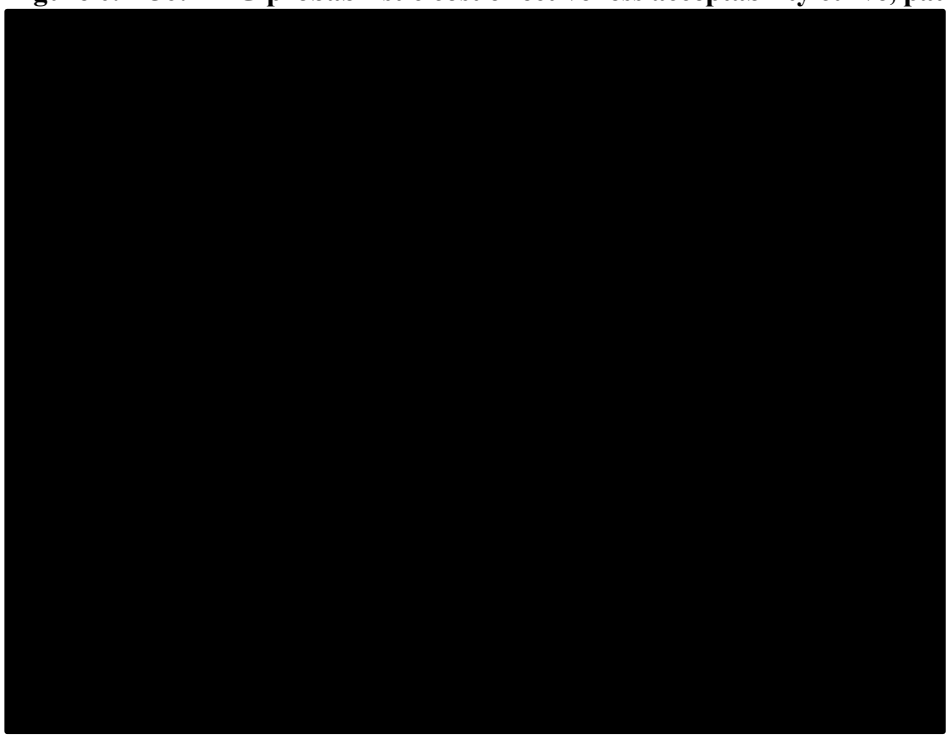
CPS = combined positive score; EAG = Evidence Assessment Group; WTP = willingness-to-pay

Figure 0.33: EAG probabilistic cost effectiveness plane, patients with CPS ≥10



CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; WTP = willingness-to-pay

Figure 0.4456: EAG probabilistic cost effectiveness acceptability curve, patients with CPS ≥10



CPS = combined positive score; EAG = Evidence Assessment Group; WTP = willingness-to-pay

In Table 6.4 and Table 6.5 it is shown how individual adjustments that were made by the EAG impact the results of the two subpopulations (i.e., patients expressing CPS ≥1 and patients expressing CPS ≥10) plus the combined effect of all adjustments simultaneously, resulting in the EAG base-case.

Table 0.4: Deterministic EAG base-case versus company base-case, patients with CPS ≥1

Technologies	Total costs^	Total QALYs*	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Doublet chemotherapy	[redacted]	[redacted]			
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS base-case following the clarification phase					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual impact on EAG base-case: Assume treatment waning					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Individual impact on EAG base-case: Use EAG preferred QALY weight					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab.
*For patients with CPS ≥1, the company's severity adjusted ICERs were based on a QALY weight equal to 1.7.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Table 0.5: Deterministic EAG base-case versus company base-case, patients with CPS ≥10

Technologies	Total costs^	Total QALYs*	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS original base-case					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]		[redacted]	

Technologies	Total costs^	Total QALYs*	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CS base-case following the clarification phase					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base-case (assume treatment waning – the only change implemented in this population)					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
^For patients expressing CPS≥10 the list price of pembrolizumab has been used. CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years					

6.3 Exploratory scenario analyses conducted by the EAG

6.3.1 EAG defined scenario analyses

The exploratory scenario analyses are presented in Table 6.6 and Table 6.7, respectively, for patients expressing CPS ≥1 and patients expressing CPS ≥10. These results are all conditional on the EAG base-case.

Table 0.6: EAG scenario analyses (conditional on EAG base-case), patients with CPS ≥1

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-knot odds model for OS					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
3-knot hazard model for OS					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs due to subsequent treatments omitted					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs due to subsequent treatments omitted set equal between comparators					
Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^For patients with CPS ≥1, company's total costs include a commercial access agreement accounting for a simple discount for pembrolizumab.
*For patients with CPS ≥1, the company's severity adjusted ICERs were based on a QALY weight equal to 1.7.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Table 0.7: EAG scenario analyses (conditional on EAG base-case), patients with CPS ≥10

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
EAG base-case					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic model for OS					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal model for OS					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knots hazard model for OS					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-knots normal model for OS					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events for nivolumab set equal to pembrolizumab					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs due to subsequent treatments omitted					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs due to subsequent treatments set equal between comparators					
Nivolumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]		
Pembrolizumab+ Doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

^For patients expressing CPS ≥10 the list price of pembrolizumab has been used.
CPS = combined positive score; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

6.3.2 Company defined scenario analyses for EAG base-case

Table 0.8: Company defined scenario analyses using EAG base-case, patients with CPS ≥1

Scenarios	ICER (£/QALY)* (pembrolizumab CAA price)	% change from base-case
EAG base-case	[redacted]	[redacted]
Chemotherapy backbones: NHS practice	[redacted]	[redacted]
Half-cycle correction: Yes	[redacted]	[redacted]
Time horizon: 10-year	[redacted]	[redacted]
Time horizon: 20-year	[redacted]	[redacted]
Discount rate: 1.5%	[redacted]	[redacted]
Utility source: Pooled health state utility values	[redacted]	[redacted]
Utility: General population utility adjustment	[redacted]	[redacted]
Utility: Literature-based AE disutility	[redacted]	[redacted]
Utility: Treatment-specific time to death	[redacted]	[redacted]
Pembrolizumab: 100% Q6W	[redacted]	[redacted]
Treatment administration: 2-year chemo cap	[redacted]	[redacted]
Pembrolizumab & Nivolumab: 2-year cap	[redacted]	[redacted]
RDI = 100%	[redacted]	[redacted]
Include wastage costs	[redacted]	[redacted]
Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
Subsequent treatment distribution: KEYNOTE-859	[redacted]	[redacted]
One-off progression cost: No	[redacted]	[redacted]
Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
Treatment waning starts at 7 years since initiation treatment	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot odds spline model	[redacted]	[redacted]
OS Pembrolizumab + chemotherapy: 2-knot normal spline model	[redacted]	[redacted]
OS Doublet chemotherapy: Log-logistic	[redacted]	[redacted]
OS Doublet chemotherapy: 2-knot odds model	[redacted]	[redacted]
PFS Pembrolizumab + chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]
PFS Doublet chemotherapy: 2-knot hazard spline model	[redacted]	[redacted]

*Note: results include a severity modifier of 1.2
AE = adverse event; EAG = Evidence Assessment Group; CPS = combined positive score; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; OS = overall survival; CAA = commercial access agreement; PFS = progression free survival; Q6W = every 6 weeks; RDI = relative dose intensity

Table 0.9: Company defined scenario analyses using EAG base-case, patients with CPS≥10

Scenarios	ICER (£/QALY) (pembrolizumab CAA price)	% change from base-case
EAG base-case	[redacted]	[redacted]
CPS10: Chemotherapy backbone: NHS	[redacted]	[redacted]
CPS10: Nivolumab chemotherapy backbones: KEYNOTE-859	[redacted]	[redacted]
CPS10: Half-cycle correction: Yes	[redacted]	[redacted]
CPS10: Time horizon: 10-year	[redacted]	[redacted]
CPS10: Time horizon: 20-year	[redacted]	[redacted]
CPS10: Discount rate: 1.5%	[redacted]	[redacted]
CPS10: Utility source: Pooled health state utility values	[redacted]	[redacted]
CPS10: Utility: General population utility adjustment	[redacted]	[redacted]
CPS10: Utility: Literature-based AE disutility	[redacted]	[redacted]
CPS10: Utility: Treatment-specific time to death	[redacted]	[redacted]
CPS10: Pembrolizumab: 100% Q6W	[redacted]	[redacted]
CPS10: Treatment administration: 2-year chemo cap	[redacted]	[redacted]
CPS10: Pembrolizumab & Nivolumab: 2-year cap	[redacted]	[redacted]
CPS10: RDI = 100%	[redacted]	[redacted]
CPS10: Exclude wastage costs	[redacted]	[redacted]
CPS10: Progressed-disease health state resource use source: Gómez-Ulloa et al. 2020	[redacted]	[redacted]
CPS10: Subsequent treatment distribution: KEYNOTE-859	[redacted]	[redacted]
CPS10: One-off progression cost: No	[redacted]	[redacted]
CPS10: Time on treatment: Best-fitting parametric curves	[redacted]	[redacted]
CPS10: Treatment waning starts at 7 years since initiation treatment	[redacted]	[redacted]
CPS10: AEs for nivolumab = pembrolizumab	[redacted]	[redacted]
CPS10: Nivolumab versus pembrolizumab HR = 1	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-odds model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: 1k-hazard model	[redacted]	[redacted]
CPS10: OS Pembrolizumab: log-logistic model	[redacted]	[redacted]

AE = adverse event; EAG = Evidence Assessment Group; CPS = combined positive score; ICER = incremental cost-effectiveness ratio; NHS = National Health Service; OS = overall survival; CAA = commercial access agreement; PFS = progression free survival; Q6W = every 6 weeks; RDI = relative dose intensity

6.4 Conclusions of the cost effectiveness section

The company developed a partition survival model in Microsoft Excel® with three health states, progression free, PD, and dead, to assess the cost effectiveness of pembrolizumab plus doublet chemotherapy in patients with locally advanced unrespectable or metastatic HER2 negative gastric or GOJ adenocarcinoma whose tumours expressing a CPS ≥1. In patients whose tumours express a CPS ≥1 the comparator for the CEA of pembrolizumab plus doublet chemotherapy was doublet chemotherapy only. For patients with a CPS ≥10 the comparator was nivolumab plus doublet

chemotherapy. This comparison deviates from the NICE scope that states that the comparison of pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy had to be done in patient with a CPS ≥5. The company decided to deviate from the scope, because the comparison for the CPS ≥5 was not feasible at the time of writing the submission. Also, CPS≥5 was not a prespecified cut-off in the KEYNOTE-859 trial and no analytical validation or pathologist training was conducted for the CPS≥5 cut point, which would negatively impact the accuracy of results at the CPS≥5 level.

The EAG considers the partition survival model suitable to answer the research questions. The CEA was performed in line with the NICE reference case in terms of perspective, lifetime time horizon, and discounting.

In the economic model, the Markov traces for the different treatments were directly informed by the fitted survival curves used to describe and extrapolate the observed data in the KEYNOTE-859 trial based on CPS level. The decision for best fitted survival model was based on statistical goodness-of-fit, statistical visual inspection of the hazard curves, and clinical plausibility. The proportion of patient in the progression free health state is represented by the PFS curve at that point in time. The proportion of patient in the PD health state at any point in time was calculated as the difference between the OS and PFS curves. The OS and PFS for nivolumab plus doublet chemotherapy was created by applying a HR of [redacted] calculated from the NMA to the OS ad PFS curves from pembrolizumab plus doublet chemotherapy, respectively. The OS and PFS were modelled independently, and to avoid illogical conclusions and the situation that PFS would exceed OS, a cap was used to prevent negative state occupancy in PD.

The EAG considers the selection of the survival model based on statistical goodness-of-fit measures, visual inspection of the smoothed hazard curve, and clinical plausibility, appropriate and values the inclusion of clinical expert opinion in the reflection on the selected models. Although all intermediate steps are reported in the CS, it was not always clear to the EAG how the combination of information led to the final decision of a selected model to fit OS or PFS data. Especially, the decision to use the 2-knot hazard model to fit the OS data of patients expressing CPS ≥1 remains uncertain. The EAG therefore, performed an exploratory analysis using the 3-knots odds and 3-knots hazard models.

There is no treatment waning effect assumed in the base-case analysis, as the company argued that there is no clear evidence to indicate a treatment waning effect exists, especially in light of additional follow-up data becoming available from various IO trials. In a scenario analysis the company assumed a gradual treatment waning effect starting 7 years following treatment initiation, with the cycle specific hazard for pembrolizumab gradually becoming equal to that in the double chemotherapy arm over the subsequent 2 years.

No treatment waning scenario analysis was presented for the comparison with nivolumab plus doublet chemotherapy. The company argued that this is reasonable given the comparable biological mechanisms of action and stopping rules of nivolumab and pembrolizumab and highlighted that a scenario analysis cannot be done without additional assumptions regarding the OS curve without IO that both treatment groups would wane to.

Based on the various studies now showing longer follow-up for IO treatments, the EAG considers it reasonable to assume that the treatment effect will remain for a certain period after treatment with pembrolizumab has stopped. However, in line with the reasoning of the appraisal committee for TA857, who indicated that the treatment effect of nivolumab may not last for a person's lifetime after treatment is stopped, and the latest publications with longer follow-up in pembrolizumab and nivolumab, the EAG

considers it reasonable to limit the duration of the treatment effect to 5 years after treatment initiation. Thus, the EAG opted to assume treatment waning for the EAG preferred base-case.

In the model, time on treatment for pembrolizumab plus doublet chemotherapy and doublet chemotherapy only was informed directly from the K-M ToT data from the KEYNOTE-859 trial for all drug components separately according to CPS level. This data could be directly used in the model considering the maturity of the K-M data. For nivolumab plus doublet chemotherapy the same ToT as for pembrolizumab plus doublet chemotherapy was used (HR of 1). This was an assumption as ToT for CPS ≥10 was not included as an endpoint in the NMA. The EAG considers this, in the absence of any data, a plausible assumption.

In the economic model, no treatment stopping rule for the immunotherapy was imposed, as the ToT observed in the KEYNOTE-859 trial was directly applied in the model, and in the trial a maximum of 35 treatment cycles with pembrolizumab could be received. This aligns with NHS clinical practice. The same was assumed for nivolumab. Treatment stopping rules were introduced for the various chemotherapy options, for each option at 6 treatment cycles, to align with NHS clinical practice. However, whilst this cap limits the costs of the chemotherapy, it does not account for the fact that the observed OS and PFS in both treatment arms of the KEYNOTE-859 trial were based on patients receiving chemotherapy for a much longer period of time than would be permitted in clinical practice in the UK. This also indicates that the observed OS and PFS curves from the KEYNOTE-859 trial may be higher than they would be observed in the UK clinical practice. The EAG is unable to assess if and how exactly this bias affects the comparative effectiveness evidence presented in the current appraisal.

Utility data from the KEYNOTE-859 trial were used to derive QALYs in the economic analysis. In that trial, the EuroQoL EQ-5D-5L questionnaire was completed by patients and utility values were calculated by mapping the fifth line descriptive system onto the third line value set.

A time-to-death approach for estimating utility was employed to address the potential limitations of the health state approach. The time-to-death approach estimates utilities using time intervals that describe the patients' life expectancy rather than progression status. Death events can arise from both progression free and PD health states. In the base-case analysis, utility values between the two comparator arms were pooled.

As a scenario, the company used utilities specific for the health states progression free and progressed.

The EAG had some concerns regarding the company's decision to use the time-to-death approach to define patients' QoL in their base-case analysis instead of the health state utilities approach. One of the issues being that there is no specific evidence base to inform the time-to-death intervals in the context of this appraisal and no sensitivity analyses had been done in the analysis of the utility data where alternative cut-off point had been used.

Additionally, the time-to-death approach cannot distinguish if death events arise from the PF, or the PD health states which could be a problem when many patients in the PF health state move quickly to the dead health state; QoL could be biased upwards as there may not be enough time to measure deterioration in patients' QoL. Unfortunately, it is not known to the EAG how many patients died in the PF health state which means that no indication can be given of the potential extent of such bias. However, the EAG agrees with the idea of the company that the time-to-death approach may better capture the QoL for progressed patients instead of the single utility score for the progressed health state. Comparing both approaches (time-to-death or health state utilities), the impact of the choice between them on the ICER is relatively small.

Adverse event disutility values were applied as a one-off QALY loss in the first model cycle to account for different AE profiles, with the disutility per AE based on the observed utilities measured when a patient was having an AE versus the utilities measured when no AE was present.

In the economic model, the following cost categories were included: drug acquisition costs, drug administration costs, AE related costs, disease management costs, subsequent treatment cost, progression costs and end-of-life costs.

The drug acquisition costs for pembrolizumab 25 mg/mL concentrate solution are £2,630.00 per 4mL vial (i.e., one vial of 4 mL of concentrate for solution contains 100 mg of pembrolizumab) dose. A CAA with a simple discount of [redacted] has been provided by the company leading to the cost of [redacted] per administration of 100 mg dose of pembrolizumab or [redacted] per administration of 200 mg dose of pembrolizumab.

As CAA discount for nivolumab is confidential, cost-effectiveness outcomes for patients with CPS ≥10 comparing pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy were conducted using list prices for both drugs.

Resource use estimates were sought from the literature identified in the SLR and previous NICE appraisals and clinical expert opinion was obtained to validate resource use estimates. Adverse event costs were applied as a one-off cost in the first model cycle.

The analysis also included the costs of subsequent treatments that patients received after progression or treatment discontinuation. Using a simplified approach, the company incorporated the costs due to subsequent treatments using a one-off cost upon DP. Patients in the KEYNOTE-859 trial were eligible to also receive subsequent treatments that are not available in NHS practice. Thus, the company used clinical expert opinion to inform the proportion of patients who would receive subsequent treatments in the UK, the types of subsequent treatments available and the distribution of patients across these treatments. In the scenario analyses, the company explored the impact of using the 10 most common types of subsequent treatments as used in the KEYNOTE-859. The duration of each subsequent treatment was also taken from KEYNOTE-859 using the ITT population.

The company used a QALY weight of 1.7 for patients expressing CPS ≥1 and a QALY weighting of 1.0 for patients expressing CPS ≥10, although they estimated that a QALY weight of 1.2 would be applicable in patients expressing CPS ≥1 based on the most up-to-date NICE guidelines. The company's decision to use another QALY weight in their base-case analysis of patients expressing CPS ≥1 was based on the assumption that pembrolizumab plus doublet chemotherapy would have met the end-of-life criteria if the previous NICE's methods for evaluating new medicines were used instead, and would therefore have been qualified for a WTP threshold of £50,000/QALY.[27] Aligning with this argumentation the company further noted that nivolumab for untreated HER2 negative advanced gastric, GOJ or oesophageal adenocarcinoma in the TA857 appraisal, similarly met NICE's end-of-life criteria and was assessed accordingly. Considering the NMA results and a visual inspection of the naïve curves OS from CheckMate 648 and KEYNOTE-859, the company claimed that the same QALY weighting should also apply to the current appraisal for patients expressing CPS ≥1. In addition, the company emphasised the remaining unmet need in patients expressing CPS≥1 as a reason to assign the highest QALY weight to this population.

The company's deterministic base-case analysis for the CPS ≥1 population (following the clarification phase) showed that the total costs associated with pembrolizumab plus doublet chemotherapy treatment

were estimated at [redacted] and total costs associated with doublet chemotherapy only were estimated at [redacted], indicating that addition of pembrolizumab to doublet chemotherapy increases total costs by [redacted]. Total QALYs associated with pembrolizumab plus doublet chemotherapy were estimated at [redacted] and total QALYs associated with doublet chemotherapy were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained for patients treated pembrolizumab plus doublet chemotherapy. These give an ICER for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy only of [redacted] per QALY gained. All results are discounted, include a severity adjusted QALY weight of 1.7, and the company include a commercial access agreement accounting for a simple discount of [redacted] for pembrolizumab.

The company's deterministic base-case analysis for the CPS ≥10 population showed that the total costs associated with pembrolizumab plus doublet chemotherapy treatment were estimated at [redacted] and total costs associated with nivolumab with doublet chemotherapy were estimated at [redacted], indicating that addition of pembrolizumab to doublet chemotherapy increases total costs by [redacted]. Total QALYs associated with pembrolizumab plus doublet chemotherapy were estimated at [redacted] and total QALYs associated with nivolumab plus doublet chemotherapy were estimated at [redacted], indicating an incremental number of [redacted] QALYs gained for patients treated pembrolizumab plus doublet chemotherapy. These give an ICER for pembrolizumab plus doublet chemotherapy versus doublet chemotherapy only of [redacted] per QALY gained. All results are discounted, include a severity adjusted QALY weight of 1.0, and for this population there is no CAA (list prices are used).

The PSA of the company showed that for the CPS ≥1 population the probability that pembrolizumab plus doublet chemotherapy is cost effective compared to doublet chemotherapy only at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted] respectively using the company base-case assumptions.

The PSA of the company showed that for the CPS ≥10 population the probability that pembrolizumab plus doublet chemotherapy is cost effective compared to nivolumab plus doublet chemotherapy at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted] respectively using the company base-case assumptions.

The EAG's preferences regarding alternative assumptions for the model let to two changes to the company base-case analysis. First, the EAG prefers to limit the duration of the treatment effect in the EAG base-case to 5 years with a gradual treatment waning over the two subsequent years assuming, in line with the scenario analysis presented by the company where the cycle specific hazard for pembrolizumab will eventually become equal to that in the double chemotherapy arm over the 2-year period. This decision is motivated by the belief of the EAG that it is reasonable at this point in time, given recent publications on longer term efficacy of pembrolizumab and nivolumab, to assume that the treatment effect will remain in place for a certain period but not a lifetime ongoing benefit following treatment cessation. Second, the EAG, aligning with the most up-to-date NICE guidelines, used a QALY weight of 1.2 for patients expressing CPS ≥1 and a QALY weight of 1.0 for patients expressing CPS ≥10. Note that the QALY weights estimated by the company were the same as the respective QALY weights estimated by the EAG, but the company decided to use another QALY weight in their base-case analysis of patients expressing CPS ≥1.

These changes in the model lead to the following EAG preferred base-case incremental cost effectiveness results. The total costs for pembrolizumab plus doublet chemotherapy amount to [redacted], versus [redacted] for doublet chemotherapy in the CPS ≥1 patient population. At the same time [redacted] and [redacted]. QALYs are accumulated, for pembrolizumab plus doublet chemotherapy and doublet chemotherapy, respectively. This leads to an ICER of [redacted] per QALY gained, which is higher than

the company ICER of [redacted] per QALY gained. The probabilistic ICER of the EAG base-case for the CPS ≥1, is [redacted] per QALY gained. The probability that that pembrolizumab plus doublet chemotherapy is cost effective at thresholds of £20,000 and £30,000 per QALY gained is respectively estimated at [redacted] and [redacted] using the EAG preferred base-case assumptions.

For the CPS ≥10 population, the total costs for pembrolizumab plus doublet chemotherapy amount to [redacted], versus [redacted] for nivolumab plus doublet chemotherapy. At the same time [redacted] and [redacted] QALYs are accumulated, for pembrolizumab plus doublet chemotherapy and nivolumab plus doublet chemotherapy, respectively. This leads to an ICER of [redacted], which is higher than the company ICER of [redacted] per QALY gained. The probabilistic ICER of the EAG base-case for the CPS ≥10, is [redacted] per QALY gained. the probability that pembrolizumab plus doublet chemotherapy is cost effective at thresholds of £20,000 and £30,000 per QALY gained is [redacted] and [redacted], respectively, for patients expressing CPS ≥10 when using the EAG preferred base-case assumptions. Several scenarios were explored, and most of these led to only small changes in the ICER. The most substantial changes occurred when cost due to subsequent treatments were omitted in the CPS ≥1 population. This scenario yielded an ICER of [redacted] per QALY gained. In the group patients expressing CPS ≥10, the results were very sensitive to changes in the HR for OS between pembrolizumab plus chemotherapy versus nivolumab plus chemotherapy. Changing the HR from of 1.02 to 1.0 leads to a very small difference in QALYs, which in turn leads to a very large ICER, of £53,110,831.

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Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Insert deadline for response** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Incorrect Table 1.1 heading

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Table 1.1 heading, page 15	It is unclear what the ID1457 in table 1.1 heading is referring to.	Please amend the ID number accordingly.	Amended.

Issue 2 Marketing authorisation wording marking

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
Marketing authorisation wording marking	Marketing authorisation wording marking can be lifted throughout the document as the marketing authorisation wording is publicly available.	No justification required.	Amended.

Issue 3 Incorrect data cut-off date

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The KEYNOTE-859 trial data cut-off date is incorrect on page 100 of the EAG report.	On page 100 of the EAG report the KEYNOTE-859 trial data cut-off date is incorrect.	The KEYNOTE-859 data cut-off date is 3 October 2022, please correct accordingly.	Amended.

Issue 4 Incorrect table number

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
There are two tables labelled as Table 6.5 and no Table 6.4.	The table on page 187 should be amended from 6.5 to 6.4. The table of tables should also be updated.	No justification required.	Amended.
There are two tables labelled as Table 1.8 and no Table 1.9.	The table on page 22 should be amended from 1.8 to 1.9. The table of tables should also be updated.		

Issue 5 Treatment waning start and end week

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
As noted in Table 5.6 of the EAG report, the treatment waning scenario provided by the company should show a waning	1. In the economic model, Efficacy!E92 and K92 should be corrected from 261 to 365.25 and Efficacy!E93 and K93 should be corrected from 365 to 469.61.	The results do not reflect the intended assumption. The ICER is negatively impacted, and this could affect decision making.	This issue is not a factual error made by the EAG, but concerns an error made by the company that they are seeking to correct at this stage. The EAG was somewhat confused during the assessment as indeed the text in the report suggests that the waning would start
	2. In Table 5.7 of the EAG report, please correct the ICER from [redacted] to [redacted] and the % change from [redacted] to [redacted].		
	3. Please amend page 181 of the EAG report, "*Therefore, the EAG limits the duration of the treatment effect in the EAG base-case to 5 years with a gradual treatment waning over the two subsequent*		

effect 7 years from the start of IO treatment, where the cycle-specific hazard for the IO gradually becomes equal to that of doublet chemotherapy over the subsequent 2 years. In the economic model, the waning effect is applied 5 years from the start of IO treatment (261 weeks in Efficacy!E92), which is incorrect. This scenario	*years assuming, in line with the scenario analysis presented by the company*" to "*Therefore, the EAG limits the duration of the treatment effect in the EAG base-case to 7 years from the start of IO treatment with a gradual treatment waning over the two subsequent years assuming, in line with the scenario analysis presented by the company*"		at 7 years after treatment initiation (see e.g. Table 33 and 77) whereas the modelled scenario assumes that waning starts 5 years after treatment initiation. The EAG attributed this discrepancy to a misalignment between those writing the submission and those working on the model, and have accepted the results of the modelled scenario (Table 78) at face value. The EAG is happy to add the intended scenario to chapter 5 in which the company results are presented. However, the EAG will keep the currently implemented scenario, where waning starts at 5 years after initiation of the
	4. Please amend Table 6.1 of the EAG report, "*Initiation of waning effect after 5 years and completion after 2 subsequent years*" to "*Initiation of waning effect 7 years from the start of IO treatment and completion after 2 subsequent years*"		
	5. Please amend page 193 of the EAG report, "*In a scenario analysis the company assumed a gradual treatment waning effect starting 5 years following treatment initiation*" to "*In a scenario analysis the company assumed a gradual treatment waning effect 7 years from the start of IO treatment"*		

is then used to inform the EAG base case, which is also incorrect.	6. Please amend page 196 of the EAG report, "*to 5 years with a gradual treatment waning over the two subsequent years assuming, in line with the scenario analysis presented by the company*" to "*to 7 years with a gradual treatment waning over the two subsequent years assuming, in line with the scenario analysis presented by the company"*		treatment, as explained in Section 4.2.6.2. However, for completeness the EAG has added the company's waning scenario to the scenarios presented in Section 6.3.2 of the EAG report. This means that for items 1, 2, and 5 the amendments have been made in the report whereas for items 3, 4, 6, 7,8, 9, and 10 they have not. Instead, at items 3 we added "*Note that this scenario is not the same as the company's waning scenario, as the company assumes that waning starts 7 years after treatment initiation whereas the EAG assumed that the waning starts 5 years after treatment initiation, given the currently available*
	7. Please amend Table 1.5 of the EAG report, "*The EAG limited the duration of the treatment effect to 5 years*" to "*The EAG limited the duration of the treatment effect to 7 years from the start of IO treatment*"		
	8. Please amend the results in and around Tables 1.8, 6.2, 6.4 and 6.6 on the EAG base-case (CPS≥1) to: [redacted] EAG scenario analysis (Tables 6.6 and 6.8) and EAG probabilistic analysis (Tables 6.3, Figures 6.1 and 6.2) on the EAG base case should also be re-run.		
	9. Please amend the results in and around Tables 1.5, 1.8 and 6.4 on the Individual impact on EAG base-case: Assume treatment waning, to:		

	[redacted] 10. Please amend the results in and around Tables 1.5, 1.9, 6.2, 6.5, 6.7 and 6.9 on the EAG base-case (CPS≥10) to: [redacted] EAG scenario analysis (Tables 6.7 and 6.9) and EAG probabilistic analysis (Tables 6.3, Figure 6.3 and 6.4) on the EAG base case should also be re-run.		*evidence mentioned above."* At item 6 we have added: *"… and the latest publications with longer follow-up in pembrolizumab and nivolumab, the EAG considers it reasonable to limit the duration of the treatment effect to 5 years after treatment initiation. Thus, the EAG opted to assume treatment waning for the EAG preferred base-case"*

Issue 6 Feasibility of CPS≥5 comparison

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
The EAG report should be amended to make it clearer that an NMA at CPS≥5 was not	Please amend Table 2.1 of the EAG report, "*A comparison between pembrolizumab CPS ≥1 and nivolumab CPS ≥5 is not currently feasible*." to	The report does now show the change in data availability over the	Amended.

feasible at the time of writing the CS. In response to clarification, an NMA was provided and its limitations were noted. For instance, CPS≥5 was not a prespecified cut-off in the KEYNOTE-859 trial and no analytical validation or pathologist training was conducted for the CPS≥5 cut point, which negatively impacts the accuracy of results at the CPS≥5 level. Thus, the company maintains that the CPS≥10 cut-off should be used to inform the comparison with nivolumab.	"*A comparison between pembrolizumab CPS ≥5 and nivolumab CPS ≥5 was not feasible at the time of writing the submission*. *In response to clarification, a post-hoc analysis was provided and the results of this analysis should be interpreted with caution*." In Table 2.1 of the EAG report please remove, "*An indirect comparison between nivolumab in CPS ≥5 and pembrolizumab in CPS ≥1 is not currently feasible*."	course of the appraisal. No corrections to the modelling approach or cost-effectiveness results are needed.	
	Please amend page 119 of the EAG report, "*In Section B2.9 of the CS, the company explain that an NMA at CPS ≥5 was not feasible and therefore the cost effectiveness results for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy were presented for patients expressing CPS ≥10 instead*". to "*In Section B2.9 of the CS, the company explain that an NMA at CPS ≥5 was not feasible at the time of writing the submission. In response to clarification, the company also explained that CPS≥5 was not a prespecified cut-off in the KEYNOTE-859 trial and no analytical validation or pathologist training was conducted for the CPS≥5 cut point, which negatively impacts the accuracy of results at the CPS≥5 level. For these reasons, cost*		The text has been amended to*:* *In Section B2.9 of the CS, the company explain that an NMA at CPS ≥5 was not feasible at the time of writing the submission. In response to clarification, the company also explained that CPS≥5 was not a prespecified cut-off in the KEYNOTE-859 trial and no analytical validation*

	effectiveness results for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet chemotherapy were presented for patients expressing CPS≥10 instead".		*or pathologist training was conducted for the CPS≥5 cut point, which negatively impacts the accuracy of results at the CPS≥5 level. However, the company did provide the results of an NMA at CPS≥5, with the caveats mentioned above, in their response to the clarification letter. These showed for OS an HR of [redacted] versus [redacted] for the CPS≥10 patients.* *Given the caveats around the CPS≥5 NMA results, the company chose to present cost effectiveness results for pembrolizumab plus doublet chemotherapy versus nivolumab plus doublet*

			chemotherapy for patients expressing CPS≥10 instead.
	Please amend page 193 of the EAG report, "*The company decided to deviate from the scope, because the comparison for the CPS ≥5 was not feasible, since the KEYNOTE-859 trial did not have a prespecified cut point of CPS ≥5".* to "*The company decided to deviate from the scope, because the comparison for the CPS ≥5 was not feasible at the time of writing the submission. Also, CPS≥5 was not a prespecified cut-off in the KEYNOTE-859 trial and no analytical validation or pathologist training was conducted for the CPS≥5 cut point, which would negatively impact the accuracy of results at the CPS≥5 level."*		Amended

Issue 7 QALY weight justification

Description of problem	Description of proposed amendment	Justification for amendment	EAG comment
As noted on page 161 of the CS, a QALY weighting of 1.7 is applied in the base case for pembrolizumab plus	On page 164 and 195 of the EAG report, please remove "*which is equivalent to a 1.7 QALY weight".*	In the CS, the company did not state a WTP threshold of	The company is correct, this statement was not made by the company, but was added by the

doublet chemotherapy versus doublet chemotherapy because of the higher decision-making threshold applied in TA857, the ability of committee to adopt a suitable approach, and the remaining unmet need in patients expressing CPS≥1.		£50,000/QALY is equivalent to a 1.7 QALY weight.	EAG to provide a logical link between the use of the EoL threshold of £50,000 for the nivolumab technology assessment, and the company's suggestion that for the current assessment a QALY weight of 1.7 should be applied. We have removed the text as requested
	In Section 4.2.10 of the EAG report, please add, "*The company also notes that committee should consider the extent of unmet health need when assessing the severity of the condition (1). 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*	The company rationale in the EAG report does not reflect the full rationale provided in the CS. For committee to make an informed decision, additional rationale should be provided.	This is not a factual error. The summaries in the EAG report are provided to refresh the readers memory about certain parts of the company submission so that it is easier to follow the EAG critique. In addition, the text suggested by the company is not text that appeared in the section

	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."		on severity (B.3.6) in the company submission. We have now added the following text to our summary, in line with the section B.3.6.: *In addition, the company emphasised the remaining unmet need in patients expressing CPS≥1 as a reason to assign the highest QALY weight to this population.*

(please cut and paste further tables as necessary)

Issue 8 Incorrect marking

<table>
<tr><th>Location of incorrect marking</th><th>Description of incorrect marking</th><th>Amended marking</th><th>EAG comment</th></tr>
<tr><td>Page 162 of the EAG report</td><td>The subsequent treatment proportions and QALYs listed in the bullets should be marked as confidential.</td><td>[redacted] of patients in the pembrolizumab plus doublet chemotherapy arm received pembrolizumab as a subsequent treatment.
The proportion of patients receiving ramucirumab plus paclitaxel in each treatment arm [redacted]
The proportion of patients receiving nivolumab in each treatment arm [redacted]
The QALY gain in the PD health state is [redacted] in the pembrolizumab arm ([redacted]) than the chemotherapy arm ([redacted]), with the [redacted] suggesting that QALY gains within this health state do not depend on the type of subsequent treatment received.</td><td>Amended</td></tr>
<tr><td>Table 4.23 on page 149 of the EAG report</td><td>Time-to-death utility values and health state utility values estimated from the KN-859 trial should be marked as confidential</td><td><table><tr><th></th><th>Time-to-death</th><th>Health state</th><th>General population (60.1 years)</th></tr><tr><td>Pembrolizumab plus doublet chemotherapy</td><td>[redacted]</td><td>[redacted]</td><td rowspan="2">0.8434</td></tr><tr><td>Doublet chemotherapy</td><td>[redacted]</td><td>[redacted]</td></tr></table></td><td>Amended</td></tr>
</table>

(Please add further lines to the table as necessary)

Please note: Besides the edits to the EAG report in conjunction with the above raised issues, the EAG made some further edits to the report regarding treatment waning in the CPS≥10 population, where pembrolizumab was compared to nivolumab. From the descriptions in the company submission the EAG had misunderstood how this scenario was implemented. Further exploration of the model after submission of the EAG report made it clear that by selecting treatment waning for both treatment groups each treatment arm would wane to the cycle specific hazard of death of doublet chemotherapy, whereas the EAG wrote in several places in the report that the pembrolizumab treatment group would wane to the nivolumab groups. Thus, the EAG deleted for example in Table 1.5 the following text:

"However, it is noteworthy that for patients expressing CPS≥10, the observed increase reflects that over time the small difference between pembrolizumab OS and nivolumab OS wanes, but not that the OS slowly reverts to the OS that would have been observed if that patient had not received an IO treatment. As also explained by the company (see Section 4.2.6.2), to appropriately incorporate treatment waning for the second comparison (i.e., CPS ≥10 patients) additional, and presumable uncertain, assumptions need to be made regarding the OS pattern without IO that both treatment groups would wane."

Similar changes have been made wherever this issue arose.

References:

1. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual: Process and methods [PMG36] 2022 [Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation.