Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Merck Sharp & Dohme:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Guts UK charity

4. **External Assessment Report** prepared by School of Health and Related Research, University of Sheffield

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

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Clinical expert, nominated by Merck Sharp & Dohme (Company)
   b. Patient expert, nominated by Guts UK Charity

8. **External Assessment Group critique of company response to technical engagement** prepared by School of Health and Related Research, University of Sheffield

9. **External Assessment Additional Scenarios** prepared by School of Health and Related Research, University of Sheffield

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 trastuzumab and chemotherapy for untreated HER2 positive advanced gastric or gastro-oesophageal junction cancer [ID3742]

Document B

Company evidence submission

May 2023

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Contents

Tables and figures

Abbreviations

Abbreviation/acronym	Definition
AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APaT	All Participants as Treated
AST	Aspartate aminotransferase
ASCT	Autologous stem cell transplant
AG	Assessment group
AUC	Area under the curve
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BL	Baseline
BMI	Body mass index
BNF	British national formulary
C1D1	Cycle 1 Day 1
CDF	Cancer drug fund
cHL	Classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CrIs	Credible Intervals
CPS	Combined positive score
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DIC	Deviance information criterion
DMC	Data monitoring committee
DOR	Duration of response
DRAE	Drug-related adverse event
DSU	Decision support unit
ECOG	Eastern cooperative oncology group performance status
EMA	European Medicine Agency
EOC	Executive oversight committee
EOL	End-of-life
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items
EQ-5D-3L	European Quality of Life Five Dimensions 3 Level Questionnaire
ESMO	European society for medical oncology
ESCC	Oesophageal squamous cell carcinoma
ESS	Effective sample size
EPAR	European public assessment report
FAS	Full analysis set
FEM	Fixed effect model

FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index disease Related Symptoms
FP	Fractional polynomial
HCHS	Hospital and community health services
HNSCC`	Head and neck squamous cell carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IFN-α	Interferon alpha
Ig	Immunoglobulin
IL-2	Interleukin-2
IO	Immuno-oncology
irRECIST	immune-related Response Evaluation Criteria in Solid Tumours
ITT	Intention-to-treat population
IV	Intravenous
KM	Kaplan Meier
MA	Marketing authorization
Mg	milligram
MSD	Merck Sharp & Dohme Ltd
N	Number of patients per treatment group
NCCN	National Comprehensive Cancer Network
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-small cell lung carcinoma
N/A	Not applicable
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease or disease progression
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	Progression-free survival
PPS	Post-progression state
PR	Partial response
PRO	Patient reported outcome
PSSRU	Personal and Social Services Research Unit
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QD	Once daily
RCT	Randomised controlled trial
RDI	Relative Dose Intensity
RECIST	Response evaluation criteria in solid tumours
REM	Random effect model
RoB	Risk of Bias
SAE	Serious adverse event
SD	Standard deviation

SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SUR	Safety update report
TA	Technology appraisal
ToT	Time on treatment
TTD	Time to true deterioration
UK	United Kingdom
WTP	Willingness-to-pay

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.
- The current first-line treatment option for patients with advanced/metastatic HER2 positive GC or GOJ adenocarcinoma is trastuzumab + chemotherapy. Over the past decade, no new first-line treatment options have come to market for this patient population. This submission aims to address the persisting unmet need in this population and potentially offers the first immuno-oncology treatment option for patients with unresectable advanced metastatic HER2 positive GC and GOJ adenocarcinoma, 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 anticipated 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	Adults with untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma	Patients with untreated locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS≥ 1.	Population is based on the proposed marketing authorisation wording.
Intervention	Pembrolizumab with trastuzumab and chemotherapy	In line with final scope	-
Comparator(s)	• Chemotherapy only, which includes: ○ doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin ○ triplet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin • Trastuzumab with cisplatin plus capecitabine or fluorouracil	Trastuzumab with cisplatin plus capecitabine or fluorouracil	KEYNOTE-811 trial results provide direct evidence between: • pembrolizumab with trastuzumab and CAPOX or FP vs. • trastuzumab plus CAPOX or FP for locally advanced unresectable or metastatic HER2 positive GC or GOJ adenocarcinoma. Based on previous appraisals in this setting, ESMO guidelines and clinical opinion received, doublet chemotherapy regimens are considered to be clinically equivalent. ESMO guidelines and clinical opinion suggest that locally advanced unresectable and metastatic GC or GOJ adenocarcinoma are treated like metastatic disease; therefore, a

			comparison versus chemotherapy without trastuzumab has not been conducted and is not presented in this submission.
Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	In line with final scope	-
Subgroups to be considered	• PD-L1 status • Locally advanced unresectable • Metastatic	• PD-L1 status	KEYNOTE-811 included less than 3% of locally advanced unresectable population which was not pre-specified subgroup of patients, therefore analysis in this subgroup of patients was not performed and not included in this submission. Clinical efficacy results in the metastatic population are available and have been provided in Appendix E.

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

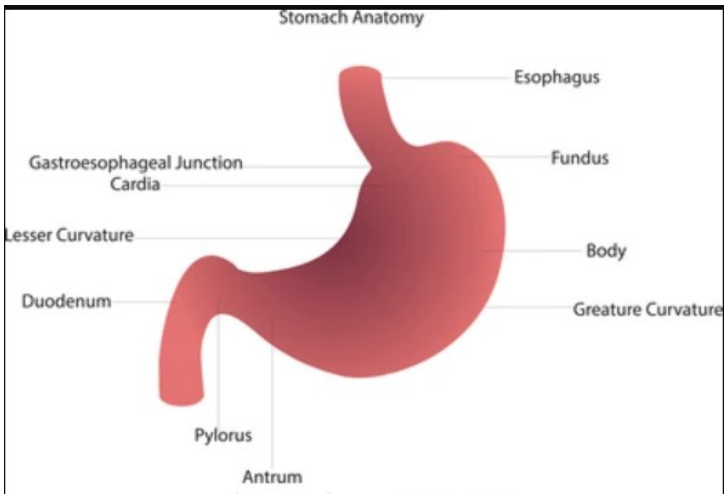
	oesophagus or HER-2 negative gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10. **Triple-negative breast cancer** • the treatment of adults with locally advanced, or early-stage triple negative breast cancer at high risk of recurrence. • the treatment of 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.
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 trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS≥1 in adults.
Method of administration and dosage	• Pembrolizumab 200 mg* every three weeks (Q3W); intravenous (IV) infusion (up to a maximum duration of 35 cycles). • Cisplatin (80 mg/m^2 administered on Day 1 of each treatment cycle, Q3W) plus 5-FU (800 mg/m2/day administered from Day 1 to Day 5 of each treatment cycle Q3W, 120 hours or per local standard). • Oxaliplatin 130 mg/m2 on Day 1 of each cycle (Q3W) over 2 hours plus capecitabine 1000 mg/m2 twice daily (BID) on Days 1-14 of each cycle (Q3W). • Trastuzumab 8 mg/kg loading dose and then 6 mg/kg maintenance thereafter (Q3W).
Additional tests or investigations	Not applicable (both HER2 testing and PD-L1 testing are established in the 1L gastric cancer 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 Patient Access Scheme (PAS) is available for pembrolizumab. The discount is [redacted], leading to a net price of [redacted] per vial.

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

Health condition

Although often reported as a single entity, gastric cancers (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 [2]. 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



The most used GC histological classifications 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 [3].

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 [4].

The most common method for diagnosing GC is via a specific type of endoscopy, called gastroscopy [3].

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 [5]. 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 [6]. Excess mortality from this cancer is high, with approximately 800 000 deaths globally [7].

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) [8]. 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 Black people, then White people, and least common in Asian people [8].

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 [8].

Dietary factors increase risk; foods preserved by salting, low fruit intake, alcohol consumption and active tobacco smoking are established risk factors [9]. 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. [10] Other factors, such as smoking and diet may increase the risk of *H. pylori* leading to cancer [11].

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 [11].

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. [12] 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 [13], [14]. For stage 1-3 GC, surgical resection of the affected section of the stomach (gastrectomy) is the usual course of treatment [15]. 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 [16], [17]. 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 [15]. 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 [18].

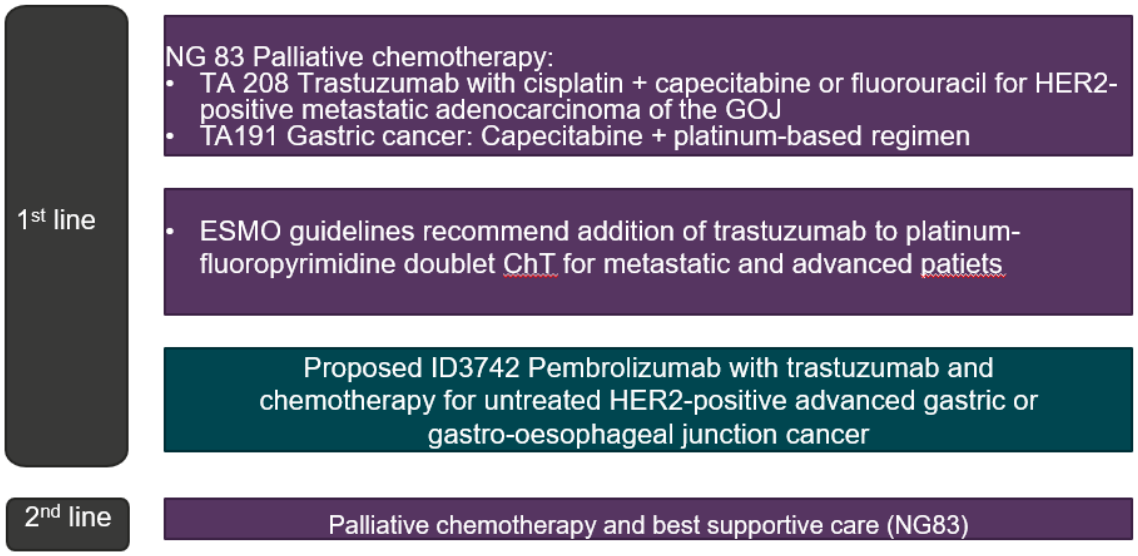
Treatment pathway

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 trastuzumab in combination with cisplatin and capecitabine or 5-fluorouracil as a treatment option to people with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction (GOJ) in line with NICE TA208 recommendation [19], [20].

European Society for Medical Oncology (ESMO) guidelines also recommend platinum–fluoropyrimidine doublet chemotherapy with trastuzumab as a standard of care in patients with advanced metastatic HER2 positive GC or GOJ adenocarcinoma [21].

ESMO guidelines and clinical opinion suggest that doublet chemotherapies (cisplatin and oxaliplatin; 5FU and capecitabine) are clinically equivalent [22], [23], [24]. Triplet chemotherapy regimens do not have a role in treating HER2 positive metastatic or locally advanced GC or GOJ adenocarcinoma due to increased toxicity and lack of added clinical effect [21].

Figure 2: GC treatment pathway and proposed pembrolizumab positioning



Abbreviations: NG, NICE guidance; TA, Technology appraisal; ESMO, European Society for Medical Oncology; HER2; human epidermal growth factor receptor; GOJ, gastroesophageal junction

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], [21], [25]. 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. There is mounting evidence of the role of HER2 overexpression in patients with gastric cancer, and it has been correlated to poor outcomes and a more aggressive disease [26]. This appraisal focusses on HER2 positive 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 gastric cancer to tailor first-line treatment in combination with chemotherapy [21]. Following publication of NICE guidance TA208 [19] and TA857 [27], 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

Patients with HER2 positive locally advanced unresectable or metastatic GC or GOJ adenocarcinoma have not benefitted from any new treatment options for over a decade. In 2010, NICE published TA208 which recommends trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, as an option for the treatment of people with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction since 2010 [19]. However, since then, patients with HER2 positive GC and GOJ adenocarcinoma have had no new effective treatment options come to market. Numerous HER2-targeting drugs such as the tyrosine kinase inhibitor lapatinib [28], [29] the antibody-drug conjugate trastuzumab-emtansine [30] and the addition of pertuzumab [31] to trastuzumab failed to demonstrate an improvement in OS in phase III studies in metastatic HER2 positive GC; therefore high unmet still persists in this patient population [32]. Addition of pembrolizumab to trastuzumab and doublet chemotherapy is already recommended in the USA based on KEYNOTE-811 IA1 data [33]. This submission aims to address this ongoing unmet need and potentially offers the first immuno-oncology (IO) treatment option for patients with unresectable advanced metastatic HER2 positive GC and GOJ adenocarcinoma, thereby broadening the available treatment options for clinicians to use for these patients.

Under NICE's previous methods for evaluating new medicines [34] and based on the poor prognosis associated with locally advanced unresectable or metastatic GC or GOJ adenocarcinoma, pembrolizumab with trastuzumab plus 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 [27] and oesophageal cancer [35], [36] 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 trastuzumab and platinum-based chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2 positive GC or GOJ adenocarcinoma in adults.

B.2 Clinical effectiveness

Summary of key clinical effectiveness information

Randomised controlled trial:

- An SLR was conducted (search date of January 2023) with eligibility criteria aligned with the decision problem with.
- KEYNOTE–811 is a phase III, randomised, double-blind trial comparing trastuzumab plus chemotherapy and pembrolizumab with trastuzumab plus chemotherapy and placebo as first-line treatment in participants with HER2 positive advanced gastric or gastroesophageal junction adenocarcinoma (NCT03615326). 698 participants from 20 countries were randomised, including 29 patients from the UK.
- KEYNOTE –811 trial results presented in this submission are based on a data cut from the second interim analysis of this study (IA2) conducted in May 2022.
- In line with the anticipated regulatory indication wording, this submission is focussed on the results of the PD-L1 CPS≥1 subgroup (n=594 [85.1%]) of patients and for the purpose of HTA, more specifically on a post-hoc analysis of the CPS≥1 non-Asia region subgroup, which is considered more generalisable to patients in England and Wales than the Global cohort. Median duration of follow up was 15.4 months.
- Post-hoc analysis in Asia vs non-Asia region populations shows that geographical region appears to be an effect modifier and given patient characteristics, clinical pathway differences and compatibility with previous trials in HER2 positive GC or GOJ adenocarcinoma, the non-Asia region results look to be more generalisable to UK clinical practice.
- Results of post-hoc analyses based on the subgroup of patients with CPS≥1 from the non-Asia geographic region (considered most generalisable to CPS≥1

patients in England and Wales) show that pembrolizumab in combination with trastuzumab and chemotherapy demonstrated a clinically meaningful improvement in PFS per RECIST 1.1 as assessed by BICR and OS, compared with SoC, for the first-line treatment of patients with HER2 positive locally advanced or metastatic GC or GOJ adenocarcinoma with PD-L1 tumour expression of CPS≥1:

  - The PFS HR was 0.62 ([95% CI: 0.49; 0.78], p = 0.1449) and OS HR was 0.67 ([95% CI: 0.52; 0.85], p = 0.0257) in favour of pembrolizumab plus SoC. These results represent a 38% reduction in the risk of disease progression and a 33% reduction in the risk of death when treated with pembrolizumab plus SoC vs. SoC alone.

- For completeness, clinical efficacy results are also presented for the CPS≥1 subgroup (irrespective of geographic region) at IA2; these demonstrate that pembrolizumab in combination with standard of care (SoC) provided a clinically meaningful improvement in PFS per RECIST 1.1 as assessed by BICR and in OS when compared with SoC.

  - The PFS HR was 0.70 ([95% CI: 0.58, 0.85], p = 0.0001), in favour of pembrolizumab plus SoC and consistent with the PFS HR for the ITT population.

  - Median PFS was longer in the pembrolizumab plus SoC group compared with the SoC group (10.8 months [95% CI: 8.5, 12.5] vs 7.2 months [95% CI: 6.8, 8.4]).

  - The OS HR was 0.79 ([95% CI: 0.64, 0.98], p = 0.0143).

  - Median OS was longer in the pembrolizumab plus SoC group compared with the SoC group (20.5 months [95% CI: 18.2, 24.3] vs 15.6 months [95% CI: 13.5, 18.6]).

- The KM curves for PFS and OS separated early and remained separated throughout the evaluation period in favour of pembrolizumab plus SoC.
- The confirmed ORR per RECIST 1.1 based on BICR was higher in the pembrolizumab plus SoC group compared with the SoC group (73.2% vs 58.4%), reflecting a 14.7% difference (95% CI: 7.1, 22.2, p = 0.00008).
- The median DOR per RECIST 1.1 based on BICR was longer in the pembrolizumab plus SoC group compared with the SoC group (11.3 vs 9.5 months) and extended response durations were higher in the in the pembrolizumab plus SoC group compared with the SoC group beginning at ≥6 months and extending beyond 24 months.

- In the PD-L1 CPS ≥1 population, pembrolizumab plus SoC was generally consistent with the individual safety profiles of either SoC regimen alone or pembrolizumab monotherapy. No new safety concerns were identified.

Network meta-analysis:

- An NMA is required to compare pembrolizumab +trastuzumab +CAPOX/FP against trastuzumab + XP in the metastatic setting and against CAPOX/FP/XP in locally advanced unresectable settings.
- The trials included in the NMA were identified via the SLR described previously.
- The feasibility assessment concluded that NMA was feasible only under an assumption of doublet chemotherapy equivalence, and the results mirror the KEYNOTE–811 trial results. An NMA versus doublet chemotherapy without trastuzumab for the locally advanced unresectable population was not feasible due to a low number of locally advanced patients included in both trials.

Clinical effectiveness conclusions

- Efficacy results show that pembrolizumab plus SoC provide a clinically meaningful improvement in both PFS and OS compared with SoC in previously untreated

participants with locally advanced unresectable or metastatic HER2 positive GC or GOJ adenocarcinoma whose tumours express PD-L1 CPS≥1.

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 trastuzumab and chemotherapy and relevant comparators (as per final scope described in Table 1) in patients with locally advanced unresectable or metastatic HER2 positive GC or GOJ adenocarcinoma.

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

In total, two RCTs were identified [37], [38]: one trial reporting evidence for the relevant comparators and one reporting evidence for pembrolizumab in combination with trastuzumab and chemotherapy: KEYNOTE-811 [37].

Please refer to Table 3 for a summary of the evidence coming from the pivotal clinical trial KEYNOTE-811.

Table 3: Clinical effectiveness evidence

Study	• Janjigian YY, Kawazoe A, Yañez P, Li N, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature. 2021 Dec;600(7890):727-730. [37] • Chung HC, Bang YJ, S Fuchs C, Qin SK, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer:

	KEYNOTE-811. Future Oncol. 2021 Feb;17(5):491-501.[39]
Study design	Phase III Randomised, Double-Blind, Placebo-Controlled Clinical Trial
Population	Human epidermal growth factor receptor 2 (HER2) positive participants with advanced gastric or GOJ adenocarcinoma
Intervention(s)	Trastuzumab and pembrolizumab plus either cisplatin plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX)
Comparator(s)	Trastuzumab and 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-811 clinical trial design and results. The expected final marketing authorisation is for a subgroup of the KEYNOTE-811 ITT population: those with PD-L1 CPS ≥ 1, therefore we report the results for the CPS ≥ 1 ITT subgroup. MSD also reports results for the PD-L1 CPS ≥1 subgroup specifically based on non-Asia geographic region. We provide rationale below (see sections B.2.6 and B.3.3) and we consider the non-Asia population results to be generalisable to UK patients.

Summary of the methodology of the KEYNOTE-811 study

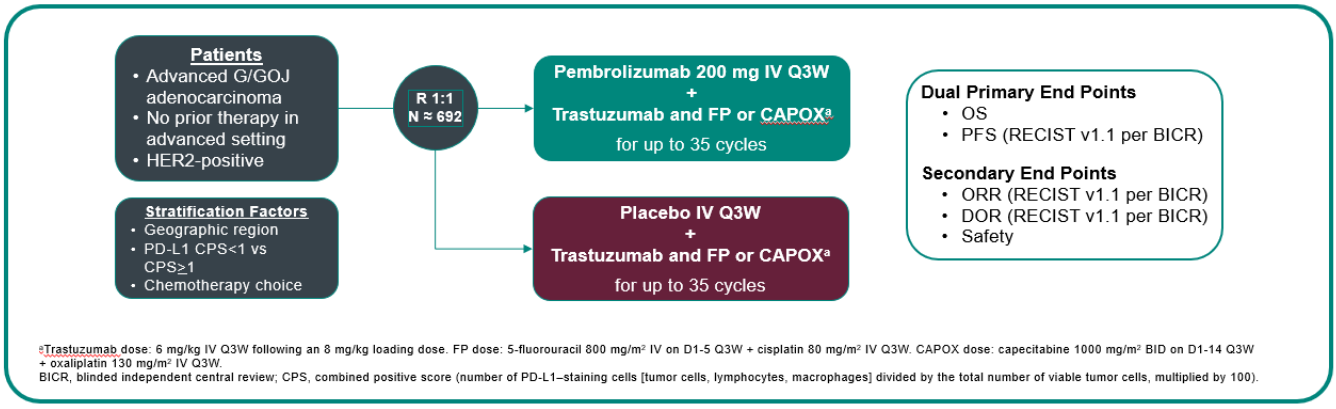
Trial design

KEYNOTE-811 [37, 39] is a phase 3, randomised, placebo-controlled, multi-site, double-blind study in participants diagnosed with previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma.

Approximately 692 participants were randomised in the global cohort in a 1:1 ratio to receive pembrolizumab or placebo each in combination with chemotherapy plus trastuzumab. The investigator had two chemotherapy regimen choices, cisplatin plus 5 fluorouracil (FP) or capecitabine/oxaliplatin (CAPOX), which had to be chosen prior to randomisation in the trial. All participants received trastuzumab. Participants continued on the fluoropyrimidine and platinum chosen prior to randomisation throughout the study.

Participants were stratified by geographic region, PD-L1 status, and chemotherapy treatment prior to randomisation.

Figure 3: Schematic of KEYNOTE–811



Abbreviations: CAPOX = capecitabine/oxaliplatin; FP = cisplatin plus 5 fluorouracil; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed cell death ligand 1; R = randomisation.

Assignment, randomisation, and blinding

All eligible participants were randomly allocated and received a treatment/randomisation number. The treatment/randomisation number identified the participant for all procedures occurring after treatment allocation/randomisation. Once

a treatment/randomisation number was assigned to a participant, it could never be re-assigned to another participant, and a single participant could not be assigned more than 1 treatment/randomisation number.

The investigator had to decide the choice of intervention and provide the rationale prior to randomisation. Treatment allocation/randomisation occurred centrally using an interactive response technology (IRT) system. There were 2 study treatment arms. Participants were assigned randomly in a 1:1 ratio to pembrolizumab and placebo, respectively.

Treatment allocation/randomisation were stratified according to the following factors:

- Geographic region (Global Cohort only)
    - Europe/Israel/North America/Australia
    - Asia
    - Rest of the World (including South America)
- PD-L1 status (positive versus negative)
- Chemotherapy regimen (FP or CAPOX) Japan-specific SOX cohort

A double-blinding technique was used. Study medications were prepared and/or dispensed according to the specifications in the pharmacy manual. The participant and the investigator who were involved in the study treatment administration of clinical evaluation of the participants were unaware of the group assignments.

Eligibility criteria

Criteria

Male and female participants with previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma of at least 18 years of age were enrolled in this trial.

Inclusion criteria:

- Histologically or cytologically confirmed diagnosis of previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma. HER2 positive defined as either immunohistochemistry (IHC) 3+ or IHC 2+ in combination with in-situ hybridization positive (ISH+) or fluorescent in-situ hybridization (FISH), as assessed by central review on primary or metastatic tumour
- Has measurable disease as defined by RECIST 1.1 as determined by the site investigator
- Male participants must agree to use approved contraception
- Female participants who are not pregnant or breastfeeding, and who are either not a woman of childbearing potential (WOCBP), or are a WOCBP who agrees to use approved contraception
- Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale
- Has a life expectancy of greater than 6 months
- Has adequate organ function.

Exclusion Criteria:

- Previously received neoadjuvant or adjuvant therapy for locally advanced or metastatic disease (as long as it was completed ≥6 months before randomisation without disease progression)
- Major surgery, open biopsy or significant traumatic injury ≤28 days before randomisation, or anticipated need for major surgery during the study treatment period
- Radiotherapy within14 days of randomisation

- Known additional malignancy that is progressing or has necessitated active treatment within the past 5 years (except BCC or SCC of the skin that has undergone potentially curative treatment or in situ cervical cancer)
- Known active CNS metastases and/or carcinomatous meningitis (patients with previously treated brain metastases may be eligible if disease is radiologically and clinically stable)
- Active autoimmune disease that has necessitated systemic treatment (other than replacement therapy) in the past 2 years
- Diagnosis of immunodeficiency or receiving long-term systemic steroid therapy (≥10 mg/day prednisone equivalent) or any other form of immunosuppression therapy within 7 days before the first dose of study treatment
- History of (non-infectious) pneumonitis treated with steroids or current pneumonitis
- History of active tuberculosis
- Active infection necessitating systemic therapy
- Poorly controlled diarrhoea
- Accumulation of pleural, ascitic or pericardial fluid necessitating drainage or diuretic drugs ≤2 weeks before enrolment
- History or current evidence of any condition, therapy, or laboratory abnormality that might confound the study results or interfere with study participation
- Peripheral neuropathy grade >1
- Psychiatric or substance abuse disorder that could impede cooperation with study requirements

- Positive urine pregnancy test ≤72 hours before randomisation (females of childbearing potential)
- Pregnant or breastfeeding or expecting to conceive or father children within the projected study duration
- Active or clinically significant cardiac disease
- Known history of HIV, HBV or HCV infection
- Known hypersensitivity (grade ≥3) to any of the study drugs or their excipients
- Active infection necessitating systemic therapy
- Allogeneic tissue or solid organ transplant
- Previous treatment with anti-PD-1, anti-PD-L1 or anti-PD-L2, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA4, OX40 and CD137)
- Immunized with live vaccine ≤30 days before first dose of study treatment
- Participation in study of investigational agent or device ≤4 weeks before the first dose of study treatment.

Settings and locations where the data were collected

The KEYNOTE-811 study was conducted at 92 centres in 19 countries: Australia, Brazil, Chile, China, France, Germany, Guatemala, Ireland, Israel, Italy, Japan, New Zealand, Poland, Russia, South Korea, Spain, Turkey, UK, Ukraine, USA. 29 subjects from 10 UK centres participated in the KEYNOTE-811 study.

Trial drugs and concomitant medications

Trial drugs

Study medications used in this trial are outlined below.

Table 4: Trial treatments

Arm Name	Intervention Name	Unit Dose Strength(s)[c]	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period/ Vaccination Regimen
Pembrolizumab	Pembrolizumab (MK-3475)	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle (Q3W)
Placebo	Placebo	N/A	N/A	IV Infusion	Day 1 of each cycle (Q3W)
FP[a]	Cisplatin[b]	1 mg/mL	80 mg/m^2	IV Infusion	Day 1 of each cycle (Q3W)
	5-FU[b]	25 mg/mL 50 mg/mL	800 mg/m^2	IV Infusion	Continuous on Days 1 to 5 of each cycle (Q3W) (120 hours, or per local standard)
CAPOX[d]	Oxaliplatin[b]	5 mg/mL	130 mg/m^2	IV Infusion	Day 1 of each cycle (Q3W) over 2 hours
	Capecitabine[b]	150 mg or 500 mg	1000 mg/m^2	Oral	BID on Days 1 to 14 of each cycle (Q3W)

FU=5 fluorouracil; BID=twice daily; BSA=body surface area; CAPOX=capecitabine/oxaliplatin; CR=complete response; FP=cisplatin plus 5 fluorouracil; IV=intravenous; Q3W=every 3 weeks;
Pembrolizumab/trastuzumab was administered until disease progression, completion of 35 cycles, or other discontinuation criteria were met.
Participants had the option to receive up to 1 additional year of trastuzumab and capecitabine or 5-FU beyond 35 administrations of pembrolizumab/placebo at the discretion of the investigator and after Sponsor consultation. Pembrolizumab/placebo treatment was not allowed beyond 35 administrations in the initial treatment course.
Participants who stopped pembrolizumab/placebo treatment after 35 administrations, for reasons other than disease progression or intolerability, or participants who attain a CR and stop trial treatment, may be eligible for up to 17 additional administrations of pembrolizumab upon experiencing disease progression if they were randomised to the pembrolizumab arm.
a FP: Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines; however, treatment with 5-FU may continue per protocol.
b Chemotherapy options and trastuzumab are used in both the experimental and placebo arms.
c The strength of treatment may vary depending on the source. The table captures the current available strengths but could vary depending on availability.
d CAPOX: duration of oxaliplatin may be capped at 6 or 8 cycles as per local country guidelines; however, treatment with capecitabine may continue per protocol.

Study treatment in both arms began on Day 1 of each 3-week dosing cycle. Treatments were administered in the following order:

Pembrolizumab and Placebo

Pembrolizumab or placebo were administered as a 30-minute IV infusion Q3W on day 1 of each 3-week cycle for up to 35 cycles after all procedures/assessments have been completed.

FP

Cisplatin 80 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 for up to 6 cycles.

5-FU 800 mg/m^2/day was administered as a continuous IV infusion from Day 1 to Day 5 (120 hours) of each treatment cycle, after completion of all procedures and assessments according to the schedule of assessments. 5-FU could be administered up to 1 additional year beyond 35 administrations.

CAPOX

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

Capecitabine was administered as a 1000 mg/m^2 dose bid Days 1 to 14 Q3W. The evening dose of capecitabine should be taken approximately 12 hours after the morning dose and should be taken with food, or within 30 minutes after food/meal, with approximately 200 mL of water. Capecitabine could be administered up to 1 additional year beyond 35 administrations of pembrolizumab/placebo.

Trastuzumab

Trastuzumab was administered as an IV 8 mg/kg loading dose, and then 6 mg/kg maintenance thereafter Q3W on Day 1 of every treatment cycle. Trastuzumab could be administered up to 1 additional year beyond 35 administrations of pembrolizumab/placebo.

Trial blinding

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.

Acceptable Concomitant Medications

All treatments that the investigator considered necessary for a subject's welfare were permitted to be administered at the discretion of the investigator in keeping with the community standards of medical care.

Prohibited concomitant medication

Subjects were prohibited from receiving the following therapies during screening to the end of treatment of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic aetiology or for cisplatin or 5-FU supportive care. The use of physiologic doses of corticosteroids were approved after consultation with the Sponsor.
- Brivudine, sorivudine analogues, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase were not to be administered with 5-FU therapy.

Subjects who, in the assessment of the investigator, required the use of any of the aforementioned treatments for clinical management were to be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

Concomitant medications which were permitted to be used with caution

- Cimetidine, metronidazole, and interferons may increase levels of 5-FU.
- Phenytoin should not be started with cisplatin therapy.
- Subjects who were taking phenytoin in conjunction with 5-FU were to be examined regularly due to a potential elevation in phenytoin plasma levels.
- Hepatotoxic effects (i.e., rise in alkaline phosphatase, transaminase, or bilirubin levels) are commonly observed under the treatment with 5-FU and levamisole.
- For 5-FU and cisplatin, protocol specified to refer to the product labels or local standards of care for further information regarding concomitant medications to be used with caution.

Subjects who, following the assessment by the investigator, required additional anti-cancer treatments were discontinued from study treatment but continued survival follow-up. Subjects who, following the assessment by the investigator, required any other prohibited medications for the assigned study treatment for long-term clinical management, were discontinued from trial treatment but continued disease assessments and survival follow-up.

The exclusion criteria describe other medications or vaccinations that were specifically prohibited in KEYNOTE-811.

Outcomes used in the economic model or specified in the scope, including primary outcome

KEYNOTE–811 objectives were pre-specified. In male and female adult subjects (≥18 years of age) with locally advanced/metastatic HER2 positive gastric cancer and GOJ adenocarcinoma, the objectives were as follows:

Primary objective(s)

- To compare progression-free survival (PFS) per RECIST 1.1 assessed by BICR between treatment groups

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

- To compare overall survival (OS) between treatment groups

OS was defined as the time from randomisation to death due to any cause. OS will be determined for each treatment arm.

Secondary objective(s)

- To compare overall response rate (ORR) between treatment groups.
- To estimate duration of response (DOR), per RECIST 1.1 as assessed by BICR for each treatment group.
- To assess the safety and tolerability of pembrolizumab in combination with trastuzumab plus chemotherapy by proportion of adverse events (AEs).

ORR was defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).

For subjects who demonstrated CR or PR, DOR was defined as the time from first documented evidence of CR or PR until disease progression per RECIST 1.1 based on assessments by BICR or death due to any cause, whichever occurs first.

Exploratory objectives

1. To compare the change from baseline in health-related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-STO22 among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.

2. To characterise utilities using EQ-5D-5L among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.

3. To evaluate the genetic and genomic correlates of treatment in pre- and post-treatment blood samples where available.

4. 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

5. To compare PFS and ORR using modified RECIST 1.1 for immune-based therapeutics (iRECIST), as assessed by the investigator, following administration of pembrolizumab versus placebo when each is combined with chemotherapy

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

Trial number (acronym)	KEYNOTE–811 • Janjigian, Y.Y., Kawazoe, A., Yañez, P. et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. Nature 600, 727–730 (2021)[a] [37]. • Chung HC, Bang YJ, S Fuchs C, Qin SK, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. Future Oncol. 2021 Feb;17(5):491-501[b] [39].
Location	This study was conducted at 192 centres in 19 countries: Australia, Brazil, Chile, China, France, Germany, Guatemala, Ireland, Israel, Italy, Japan, New Zealand, Poland, Russia, South Korea, Spain, Turkey, Ukraine, the United Kingdom, and the United States
Trial design	Phase III, randomised, double-blind trial comparing pembrolizumab and placebo, both in combination with trastuzumab plus chemotherapy as first line treatment in participants with HER2 positive advanced gastric or GOJ adenocarcinoma Participants were randomised in a 1:1 ratio to the experimental arm and the control arm.

Eligibility criteria for participants	Key inclusion criteria: • Male or female • Age ≥18 years • Previously untreated histologically or cytologically confirmed locally advanced unresectable or metastatic gastric or GOJ adenocarcinoma • HER2 positive disease, defined as either IHC 3+ or IHC 2+ in combination with ISH+ (or FISH), as assessed by BICR on primary or metastatic tumour • Measurable disease per RECIST v1.1 by site investigator • ECOG PS 0 or 1 • Life expectancy ≥6 months • Willing to provide a tumour tissue sample adequate for PD-L1 and MSI biomarker analysis • Adequate cardiac function, defined as left ventricular ejection fraction ≥55% as determined by MUGA scan or ECHO and QT interval calculated according to the Fridericia method (≤470 ms for men and ≤480 ms for women) • Adequate hematologic function, defined as ANC ≥1500/µl, platelet count ≥100,000/µl and hemoglobin ≥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 levels 1.5 × ULN, ALT/AST levels ≤2.5 × ULN or ≤5 × ULN for those with liver metastases, and albumin ≥2.5 g/dl • Adequate coagulation function, defined as INR ≤1.5 × ULN, unless the patient is receiving anticoagulant therapy with PT or aPTT/PTT is within the therapeutic range
Settings and locations where the data were collected	The study was run in specialist oncology departments. Patients received treatment as out-patients.
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed	**Intervention: n=350** Pembrolizumab + trastuzumab + FP or CAPOX **Pembrolizumab** 200 mg Q3W **Trastuzumab** 8 mg/kg loading dose and then 6 mg/kg maintenance thereafter (Q3W). **FP** • Cisplatin (80 mg/m^2 administered on Day 1 of each treatment cycle, Q3W) plus 5-FU (800 mg/m^2/day administered from Day 1 to Day 5 of each treatment cycle Q3W, 120 hours or per local standard). **CAPOX** • Oxaliplatin 130 mg/m^2 on Day 1 of each cycle (Q3W) over 2 hours plus capecitabine 1000 mg/m^2 twice daily (BID) on Days 1-14 of each cycle (Q3W).

concomitant medication	**Comparator: n=348** • Placebo + trastuzumab + FP or CAPOX (dose and method of administration same as in the intervention arm) Participants were prohibited from receiving the following during KEYNOTE–811: Antineoplastic systemic chemotherapy, biologic therapy, immunotherapy, other investigational agents given while on treatment or before study entry during screening (unless allowed per protocol)
Primary outcomes (including scoring methods and timings of assessments)	1) Progression-free survival (PFS) per RECIST 1.1 assessed by BICR 2) Overall survival (OS)
Other outcomes used in the economic model/specified in the scope	N/A
Pre-planned subgroups	Randomisation is stratified by geographic region (Australia/Europe/Israel/North America versus Asia versus rest of world), PD-L1 combined positive score (≥1 versus <1), and investigator's choice of chemotherapy (FP or CAPOX)
[a] *this publication relates to the results from IA1* [b] *this publication covers the design and rationale of this study*	

Pre-planned subgroups

To determine whether the treatment effect is consistent across various 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 each subgroup. The following are examples of classification variables:

- Age category: <65 versus ≥65 years
- Sex: female versus male
- Race: Asian versus non-Asian
- Region: Europe/Israel/North America/Australia versus Asia versus Rest of World (including South America)
- PD-L1: positive (CPS ≥1) versus negative (CPS <1)

- MSI status: microsatellite instable high or microsatellite stable
- Primary location: stomach versus GOJ
- Histological subtype: diffuse versus intestinal versus indeterminate
- Tumour burden: ≥median versus <median
- Number of metastases: ≤2 versus ≥3
- Prior Gastrectomy: yes versus no

In addition, MSD performed post-hoc analyses of based on geographical region (Asia vs. non-Asia cohorts) of the CPS ≥1 subgroup for the co-primary endpoints of PFS and OS. Results from the non-Asia subgroup is considered to be more generalisable to patients in England and Wales (see section 2.6).

Baseline characteristics of trial participants

PD-L1 CPS≥1 population

Baseline characteristics of the PD-L1 CPS≥1 subgroup irrespective of geographic region and of the CPS≥1 non-Asia region subgroup are summarised in Table 6 and Table 7 respectively. The baseline demographic and disease characteristics of participants for the two groups were generally well balanced and representative of a patient population with locally advanced unresectable or metastatic GC. Most participants were male (80.3%) in PD-L1 CPS≥1 and (79.1%) in non-Asia region patients, 42.9% of PD-L1 CPS≥1 patients and 40.8% of non-Asia region patients were 65 years of age and above.

Table 6: Participant Baseline Characteristics by Treatment Group (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population)

	Pembrolizumab + SoC		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	298		296		594	
Sex						

Male	240	(80.5)	237	(80.1)	477	(80.3)
Female	58	(19.5)	59	(19.9)	117	(19.7)
Age (Years)						
< 65	174	(58.4)	165	(55.7)	339	(57.1)
>= 65	124	(41.6)	131	(44.3)	255	(42.9)
Mean	60.6		61.4		61.0	
SE	0.7		0.6		0.5	
Median	63.0		63.0		63.0	
Range	19 to 85		32 to 85		19 to 85	
Race						
American Indian Or Alaska Native	5	(1.7)	6	(2.0)	11	(1.9)
Asian	97	(32.6)	97	(32.8)	194	(32.7)
Black Or African American	2	(0.7)	2	(0.7)	4	(0.7)
Multiple	5	(1.7)	4	(1.4)	9	(1.5)
White	188	(63.1)	184	(62.2)	372	(62.6)
Missing	1	(0.3)	3	(1.0)	4	(0.7)
Ethnicity						
Hispanic Or Latino	36	(12.1)	41	(13.9)	77	(13.0)
Not Hispanic Or Latino	259	(86.9)	249	(84.1)	508	(85.5)
Not Reported	1	(0.3)	5	(1.7)	6	(1.0)
Unknown	2	(0.7)	1	(0.3)	3	(0.5)
Age Group (Years)						
18-39	16	(5.4)	12	(4.1)	28	(4.7)
40-49	34	(11.4)	27	(9.1)	61	(10.3)
50-59	59	(19.8)	86	(29.1)	145	(24.4)
60-69	118	(39.6)	92	(31.1)	210	(35.4)
70-79	67	(22.5)	73	(24.7)	140	(23.6)
>=80	4	(1.3)	6	(2.0)	10	(1.7)
Age Group 2 (Years)						
< 65	174	(58.4)	165	(55.7)	339	(57.1)
65 - 74	101	(33.9)	104	(35.1)	205	(34.5)
75 - 84	22	(7.4)	26	(8.8)	48	(8.1)
85+	1	(0.3)	1	(0.3)	2	(0.3)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	97	(32.6)	96	(32.4)	193	(32.5)
Asia	96	(32.2)	96	(32.4)	192	(32.3)
Rest of the World	105	(35.2)	104	(35.1)	209	(35.2)
ECOG Performance Scale						
0	127	(42.6)	121	(40.9)	248	(41.8)
1	171	(57.4)	174	(58.8)	345	(58.1)
Missing	0	(0.0)	1	(0.3)	1	(0.2)
Primary Location at Diagnosis						

Adenocarcinoma of the gastroesophageal junction	97	(32.6)	99	(33.4)	196	(33.0)
Adenocarcinoma of the stomach	201	(67.4)	197	(66.6)	398	(67.0)
Current Disease Overall Stage						
IIB	1	(0.3)	0	(0.0)	1	(0.2)
IIIA	2	(0.7)	1	(0.3)	3	(0.5)
IIIB	5	(1.7)	1	(0.3)	6	(1.0)
IIIC	0	(0.0)	3	(1.0)	3	(0.5)
IV	290	(97.3)	291	(98.3)	581	(97.8)
Disease Status						
Locally advanced	8	(2.7)	6	(2.0)	14	(2.4)
Metastatic	290	(97.3)	290	(98.0)	580	(97.6)
Number of Metastatic Sites						
0-2	149	(50.0)	172	(58.1)	321	(54.0)
>=3	149	(50.0)	124	(41.9)	273	(46.0)
Histological Subtype (Lauren classification)						
Diffuse	56	(18.8)	49	(16.6)	105	(17.7)
Intestinal	169	(56.7)	158	(53.4)	327	(55.1)
Indeterminate	73	(24.5)	89	(30.1)	162	(27.3)
Prior Gastrectomy/Esophagectomy						
Yes	36	(12.1)	48	(16.2)	84	(14.1)
No	262	(87.9)	248	(83.8)	510	(85.9)
PD-L1 Status (CPS≥1)						
Positive	298	(100.0)	296	(100.0)	594	(100.0)
Tumor Burden						
< Median	139	(46.6)	139	(47.0)	278	(46.8)
>= Median	147	(49.3)	146	(49.3)	293	(49.3)
Missing	12	(4.0)	11	(3.7)	23	(3.9)
HER2 Status						
IHC 1+	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Equivocal	0	(0.0)	1	(0.3)	1	(0.2)
IHC 2+ ISH Negative	1	(0.3)	1	(0.3)	2	(0.3)
IHC 2+ ISH Positive	51	(17.1)	68	(23.0)	119	(20.0)
IHC 3+	245	(82.2)	225	(76.0)	470	(79.1)
MSI Status						
MSI High	6	(2.0)	2	(0.7)	8	(1.3)
non-MSI-High	282	(94.6)	280	(94.6)	562	(94.6)
Unknown	10	(3.4)	14	(4.7)	24	(4.0)
Chemotherapy Regimen						
CAPOX	251	(84.2)	253	(85.5)	504	(84.8)
FP	47	(15.8)	43	(14.5)	90	(15.2)
Body Surface Area (m^2)						
Participants with data	298		295		593	
Mean	1.8		1.8		1.8	
SD	0.2		0.2		0.2	
SE	0.0		0.0		0.0	
Median	1.8		1.8		1.8	

Range	1.3 to 2.8		1.2 to 2.5		1.2 to 2.8	
Weight (kg)						
Participants with data	298		296		594	
Mean	68.4		68.1		68.2	
SD	15.6		15.5		15.5	
SE	0.9		0.9		0.6	
Median	67.0		65.7		66.0	
Range	37.0 to 162.0		30.2 to 125.0		30.2 to 162.0	
Body Mass Index (kg/m^2)						
Participants with data	298		295		593	
Mean	23.9		24.0		24.0	
SD	4.6		4.4		4.5	
SE	0.3		0.3		0.2	
Median	23.5		23.5		23.5	
Range	14.9 to 57.4		11.9 to 39.5		11.9 to 57.4	
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification. *Database Cut-off Date: 25 May 2023*						

Participants from CPS≥1 non-Asia region subgroup (Post-hoc analysis)

Table 7: Participant Baseline Characteristics by Treatment Group (CPS≥1 Participants) (Global Cohort - Participants from non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SoC		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	202		200		402	
Sex						
Male	160	(79.2)	158	(79.0)	318	(79.1)
Female	42	(20.8)	42	(21.0)	84	(20.9)
Age (Years)						
< 65	121	(59.9)	117	(58.5)	238	(59.2)
>= 65	81	(40.1)	83	(41.5)	164	(40.8)
Mean	59.7		60.6		60.2	
SE	0.9		0.8		0.6	
Median	62.0		61.0		61.5	
Range	19 to 85		32 to 82		19 to 85	
Race						
American Indian Or Alaska Native	5	(2.5)	6	(3.0)	11	(2.7)
Asian	1	(0.5)	1	(0.5)	2	(0.5)
Black Or African American	2	(1.0)	2	(1.0)	4	(1.0)
Multiple	5	(2.5)	4	(2.0)	9	(2.2)

White	188	(93.1)	184	(92.0)	372	(92.5)
Missing	1	(0.5)	3	(1.5)	4	(1.0)
Ethnicity						
Hispanic Or Latino	36	(17.8)	41	(20.5)	77	(19.2)
Not Hispanic Or Latino	163	(80.7)	153	(76.5)	316	(78.6)
Not Reported	1	(0.5)	5	(2.5)	6	(1.5)
Unknown	2	(1.0)	1	(0.5)	3	(0.7)
Age Group (Years)						
18-39	13	(6.4)	12	(6.0)	25	(6.2)
40-49	28	(13.9)	18	(9.0)	46	(11.4)
50-59	38	(18.8)	65	(32.5)	103	(25.6)
60-69	79	(39.1)	53	(26.5)	132	(32.8)
70-79	41	(20.3)	48	(24.0)	89	(22.1)
>=80	3	(1.5)	4	(2.0)	7	(1.7)
Age Group 2 (Years)						
< 65	121	(59.9)	117	(58.5)	238	(59.2)
65 - 74	65	(32.2)	62	(31.0)	127	(31.6)
75 - 84	15	(7.4)	21	(10.5)	36	(9.0)
85+	1	(0.5)	0	(0.0)	1	(0.2)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	97	(48.0)	96	(48.0)	193	(48.0)
Rest of the World	105	(52.0)	104	(52.0)	209	(52.0)
ECOG Performance Scale						
0	91	(45.0)	79	(39.5)	170	(42.3)
1	111	(55.0)	120	(60.0)	231	(57.5)
Missing	0	(0.0)	1	(0.5)	1	(0.2)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	81	(40.1)	79	(39.5)	160	(39.8)
Adenocarcinoma of the stomach	121	(59.9)	121	(60.5)	242	(60.2)
Current Disease Overall Stage						
IIB	1	(0.5)	0	(0.0)	1	(0.2)
IIIA	2	(1.0)	1	(0.5)	3	(0.7)
IIIB	5	(2.5)	1	(0.5)	6	(1.5)
IIIC	0	(0.0)	2	(1.0)	2	(0.5)
IV	194	(96.0)	196	(98.0)	390	(97.0)
Disease Status						
Locally advanced	8	(4.0)	5	(2.5)	13	(3.2)
Metastatic	194	(96.0)	195	(97.5)	389	(96.8)
Number of Metastatic Sites						
0-2	108	(53.5)	114	(57.0)	222	(55.2)
>=3	94	(46.5)	86	(43.0)	180	(44.8)
Age Group 2 (Years)						
< 65	121	(59.9)	117	(58.5)	238	(59.2)
65 - 74	65	(32.2)	62	(31.0)	127	(31.6)

75 - 84	15	(7.4)	21	(10.5)	36	(9.0)
85+	1	(0.5)	0	(0.0)	1	(0.2)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	97	(48.0)	96	(48.0)	193	(48.0)
Rest of the World	105	(52.0)	104	(52.0)	209	(52.0)
ECOG Performance Scale						
0	91	(45.0)	79	(39.5)	170	(42.3)
1	111	(55.0)	120	(60.0)	231	(57.5)
Missing	0	(0.0)	1	(0.5)	1	(0.2)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	81	(40.1)	79	(39.5)	160	(39.8)
Adenocarcinoma of the stomach	121	(59.9)	121	(60.5)	242	(60.2)
Current Disease Overall Stage						
IIB	1	(0.5)	0	(0.0)	1	(0.2)
IIIA	2	(1.0)	1	(0.5)	3	(0.7)
IIIB	5	(2.5)	1	(0.5)	6	(1.5)
IIIC	0	(0.0)	2	(1.0)	2	(0.5)
IV	194	(96.0)	196	(98.0)	390	(97.0)
Disease Status						
Locally advanced	8	(4.0)	5	(2.5)	13	(3.2)
Metastatic	194	(96.0)	195	(97.5)	389	(96.8)
Number of Metastatic Sites						
0-2	108	(53.5)	114	(57.0)	222	(55.2)
>=3	94	(46.5)	86	(43.0)	180	(44.8)
Median	1.8		1.8		1.8	
Range	1.3 to 2.8		1.3 to 2.5		1.3 to 2.8	
Weight (kg)						
Participants with data	202		200		402	
Mean	71.9		72.0		72.0	
SD	16.7		16.0		16.3	
SE	1.2		1.1		0.8	
Median	70.2		70.0		70.0	
Range	39.0 to 162.0		39.5 to 125.0		39.0 to 162.0	
Body Mass Index (kg/m^2)						
Participants with data	202		199		401	
Mean	24.7		25.1		24.9	
SD	5.1		4.5		4.8	
SE	0.4		0.3		0.2	
Median	23.9		24.8		24.3	
Range	14.9 to 57.4		14.5 to 39.5		14.5 to 57.4	

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
Participants from Non-Asia region are defined as participants from the geographical location of Western Europe/Israel/North America/Australia and Rest of the World.
Database Cut-off Date: 25 May 2023

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-811 study

This section reports the relevant statistical methodology of KEYNOTE-811.

Objectives, hypotheses, and endpoints

Table 8: Keynote-811 study objectives, hypotheses, and endpoints

Objective/Hypothesis	Endpoint
Primary	
Objective: To compare PFS between treatment groups. Hypothesis (H1): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone in terms of PFS per RECIST 1.1 as assessed by blinded independent central review (BICR).	PFS: The time from randomisation to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: To compare OS between treatment groups. Hypothesis (H2): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone in terms of OS.	OS: The time from randomisation to death due to any cause.
Secondary	
Objective: To compare ORR between treatment groups. Hypothesis (H3): Pembrolizumab in combination with trastuzumab plus chemotherapy is superior to trastuzumab plus chemotherapy alone per RECIST 1.1 as assessed by BICR in terms of ORR.	Objective Response (OR): Complete response (CR) or partial response (PR)
Objective: To estimate DOR, per RECIST 1.1 as assessed by BICR for each treatment group.	DOR: The time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first.
Objective: To assess the safety and tolerability of pembrolizumab in combination with trastuzumab plus chemotherapy by proportion of adverse events (AEs).	Adverse events Discontinuation of study treatment due to AEs
Tertiary/Exploratory	

Objective: To compare the change from baseline in health-related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-STO22 among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.	EORTC QLQ-C30 and EORTC QLQ-STO22 score.
Objective: To characterise utilities using EQ-5D-5L among participants when treated with pembrolizumab in combination with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone.	Health utility scores assessed from the EQ-5D-5L
Objective: To evaluate the genetic and genomic correlates of treatment in pre- and post-treatment blood samples where available.	Expression of PD-1, PD-L1 and PD-L2 by IHC or ribonucleic acid (RNA) sequencing. Genetic alterations in PD-1, PD-L1 and PD-L2 on chromosome 9p24.1 by fluorescent in-situ hybridization (FISH).
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	Germline genetic variation, genetic (DNA) mutations from tumour, tumour and blood RNA variation, proteomics and IHC, and other biomarkers
To compare PFS and ORR using modified RECIST 1.1 for immune-based therapeutics (iRECIST), as assessed by the investigator, following administration of pembrolizumab versus placebo when each is combined with chemotherapy	PFS using iRECIST ORR using iRECIST

Analysis populations

Efficacy analysis population

The Intention-to-Treat (ITT) population served as the population for primary efficacy analysis (PFS, OS, and ORR). All randomised participants, whether or not treatment was administered, were included in this population. Any participant who received a randomisation number was considered to have been randomised. Participants were included in the treatment group to which they were randomised.

The ITT population excluding MSI-H participants served as the sensitivity analysis for the endpoints of PFS per RECIST 1.1 by BICR, OS, and ORR per RECIST 1.1 per BICR.

Safety analysis population

The all participants as treated (APaT) population was used for the analysis of safety data in this study. The APaT population consisted of all randomised participants who received at least one dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this was the treatment group to which they are randomised.

Statistical methods

Table 9: Summary of KEYNOTE-811 study statistical methods

Study Design Overview	Phase III, randomised, double-blind trial comparing pembrolizumab and placebo, both in combination with trastuzumab plus chemotherapy as first- line treatment in participants with HER2 positive advanced gastric or GOJ adenocarcinoma [37, 39]
Treatment Assignment	Participants were randomised in a 1:1 ratio to the experimental arm and the control arm.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT) Patients were stratified by PD-L1 status (CPS≥1 or CPS<1).
Primary Endpoints	Progression-free survival (PFS) per RECIST 1.1 assessed by BICR Overall survival (OS)
Key Secondary Endpoint	Objective response rate (ORR) per RECIST 1.1 assessed by BICR
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses on PFS and OS were evaluated by comparing the experimental arm to the control arm 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 Kaplan-Meier method. The stratified Miettinen and Nurminen method [40] with sample size weights was used for analysis of ORR.
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 Miettinen and Nurminen method [40].
Interim Analyses	Three interim analyses (IA) were planned to be performed in this study based on current projection of enrolment and event accrual rates. IA1: Timing: performed when ~ 260 participants have been followed up for ~ 8.5 months. Primary purpose: efficacy analysis for ORR (hypothesis testing). IA2[a]:

	Timing: performed after ~ 542 PFS events have occurred AND ~ 9 months after last participant randomised. Primary purpose: efficacy analysis for PFS and OS. IA3 [a]: Timing: performed when ~ [redacted] after the last participant has been randomised AND approximately [redacted] have been observed. This is the final PFS analysis. Primary purpose: efficacy analysis for PFS and OS. Final analysis[a]: Timing: to be performed when ~ [redacted] after the last participant has been randomised AND ~ [redacted] have occurred. Primary purpose: efficacy analysis for OS. [a] *Note for IA2, IA3, and FA, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to 3 additional months of follow-up than the minimal follow-up as described above, or when the specified number of events are observed, whichever comes first.*
Multiplicity	The overall type I error over the primary endpoints (PFS and OS) and the key secondary endpoint (ORR) was strongly controlled at 2.5% (1-sided), with initially 0.2% allocated to ORR, 0.3% to PFS and 2% to OS. By using the graphical approach of Maurer and Bretz [41], if 1 hypothesis was rejected, the alpha was shifted to other hypotheses.
Sample Size and Power	The planned sample size was ~ 692 participants. For ORR, with sample size of ~ 260 at IA1, the study has ~ 90% power for detecting a 25% difference in ORR (73% vs 48%) at an initially assigned 0.002 (1-sided) significance level. For PFS, there was ~ 606 events at the PFS final analysis. With 606 PFS events, the study has ~ 95% power for detecting a HR of 0.7 at an initially assigned 0.003 (1-sided) significance level. For OS, there will be ~ [redacted] at the OS final analysis. With [redacted], the study has ~ 90% power for detecting a HR of 0.75 at an initially assigned 0.020 (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 10: Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method†	Analysis Population	Missing Data Approach

Primary Endpoints			
PFS per RECIST 1.1 by BICR	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Primary censoring rule Sensitivity analysis 1 Sensitivity analysis 2
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the last known alive date
Key Secondary Endpoint			
ORR per RECIST 1.1 by BICR	Test and Estimation: Stratified M&N method with sample size weights††	ITT	Participants without assessments are considered non-responders and conservatively included in the denominator
Abbreviations: PFS = Progression-free survival; OS = Overall survival; ORR = Objective response rate; ITT = Intention to treat. *† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomisation (Protocol Section 6.3.1.1) will be applied to the analysis. Small strata will be combined in a way specified by a blinded statistician prior to the analysis.* *†† Miettinen and Nurminen method*			

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 11.

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. The study protocol specified that based on an examination of the appropriateness of the data to the assumptions required by recognised methods, exploratory analyses to adjust for the effect of crossover to other PD-1 therapies on OS may be performed based on recognised methods (e.g., the Rank Preserving Structural Failure Time model proposed by Robins and Tsiatis, 2-stage model, etc.,) [42].

Table 11: 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 anti-cancer therapy[a], 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 anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer 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 treatment or completed study treatment.
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 *a New anti-cancer therapy: excluding curative surgical resections*			

The proportional hazards (PH) assumption for PFS was examined using both graphical and analytical methods if warranted.

Three interim analyses were permitted to be performed in this study based on projection of enrolment and the purpose of each analysis are summarised in Table 12.

Table 12: Summary of Interim and Final Analyses Strategy

Analyses	**Timing**	**Estimated Time after First Participant Randomised**	**Primary Purpose of Analysis**
IA1	The first 260 participants with at least 8.5 months follow-up.	~22.5 months	Efficacy analysis of ORR (hypothesis testing)
IA2 [a]	At least 542 PFS events have occurred and ~ 9 months after the last participant has been randomised.	~37 months	Efficacy analysis for PFS and OS

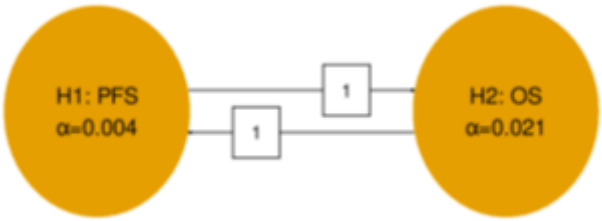
IA3 [a]	At least [redacted] after the last participant has been randomised AND at least [redacted] events have been observed. This is final PFS analysis.	~[redacted]	Efficacy analysis for PFS and OS
Final Analyses [a]	Final OS analysis to be performed until at least [redacted] after the last participant has been randomised AND at least ~[redacted] have occurred.	~[redacted]	Efficacy analysis for OS

[a]Note for IA2, IA3, and FA, if the events accrue slower than expected, the Sponsor may conduct the analysis with up to 3 additional months of follow-up than the minimal follow-up as described above, or when the specified number of events are observed, whichever comes first.
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 [41] 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-811



Subgroup Analyses

The estimate of the between-group treatment effect (with a nominal 95% CI) for the dual 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

2.5.1 & 2 Summary of quality assessment

Quality Assessment of KEYNOTE-811 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. A tabulated summary of the quality assessment results is presented below in Table 13.

Table 13: Quality assessment results for KEYNOTE-811

Type of bias	Review authors' judgement	Support for judgement
Bias arising from the randomization process	Low risk	Double blind study; randomization was performed using an interactive voice/web response system and pembrolizumab or placebo assignment was masked to patients and investigators.
Bias due to deviations from intended interventions	Low risk	Double blind; no deviations from the intended interventions arose because of the trial context

Bias due to missing outcome data	Low risk	Data for outcomes available for all or nearly all randomised participants
Bias in measurement of the outcome	Low risk	Appropriate method used to measure outcomes
Bias in selection of the reported result	Low risk	Analysis was in accordance with a pre-specified analysis plan that was finalised before the outcome data were available for analysis
Overall bias	Low risk	Low risk of bias across all domains

B.2.6 Clinical effectiveness results of the relevant studies

B 2.6.1. KEYNOTE-811 results

Early results are presented from the KEYNOTE-811 study, based on the interim analysis 2 (IA2), which had a data cut-off date of 25 May 2022. 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. Efficacy analyses were conducted using the ITT population. The median duration of follow-up in the ITT population was 15.4 months (range: 0.3 to 41.6 months).

The study enrolment period was divided into 2 periods: Global Cohort and Japan specific SOX cohort. The results of only the Global cohort are presented in this submission and henceforth referred to as the Global cohort. 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-811 had tumours with CPS ≥1 (594 [85.1%]) including 298 and 296 participants from the pembrolizumab plus SoC and SoC groups, respectively.

The pre-specified subgroup analyses of the PD-L1 CPS≥1 population in KEYNOTE-811 highlighted a distinct difference in the efficacy of pembrolizumab plus trastuzumab and FP/CAPOX based on geographic region (Asia versus non – Asia). A post-hoc analysis of Asia vs non-Asia population shows that region appears to be an effect

modifier. Given patient characteristics, clinical pathway differences between the regions and compatibility with previous trials in HER2 positive GC or GOJ adenocarcinoma (results from the ToGA trial demonstrated differing outcomes for the Asia vs non-Asia regions, suggesting [38] a regional effect modifier in this population is not limited to KEYNOTE-811), the non-Asia region results are considered to be more generalisable to patients in England and Wales (discussed in more detail in section B3.3).

Results in both the full ITT population and the subgroup of patients with metastatic GC or GOJ adenocarcinoma are provided in an Appendix M. KEYNOTE-811 results show that disease stage is not an effect modifier in HER2 positive GC or GOJ adenocarcinoma.

Interim analysis 2 – data-cut 25 May 2022

IA2 was planned to be performed after approximately 542 PFS events had occurred and approximately 9 months after the last participant was randomised, however IA2 was triggered at slightly more than 9 months after last patients in with 484 PFS events. For IA2, IA3, and FA, per protocol, if the events accrued slower than expected, the sponsor was permitted to conduct the analysis with up to 3 months of additional follow-up or when the specified number of events were observed, whichever occurred first.

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

A total of 594 participants with PD-L1 CPS≥1 were randomised across 192 global study sites in 19 countries. 27 patients were recruited across 10 sites in the UK. A total of 593 randomised participants received at least 1 dose of study medication (pembrolizumab plus SoC: 298; SoC: 296). The participant flow and subject disposition from KEYNOTE-811 are provided in Appendix D.

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

At IA2, KEYNOTE-811 efficacy results showed that pembrolizumab plus SoC provided a clinically meaningful improvement in both PFS and OS compared with SoC in previously untreated participants with locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma. As of the data cut-off date (25 May 2022) for IA2 CPS≥1 population, the median duration of follow up was 17 months (0.6 to 41.6 months) in the pembrolizumab plus SoC group and 13.9 months (0.3 to 41.2 months) in the SoC group.

The pre-specified subgroup analyses from the PD-L1 CPS≥1 population in KEYNOTE-811 (further described in section B.2.7) highlighted a distinct difference in the efficacy of pembrolizumab plus trastuzumab and FP/CAPOX based on geographic region (Asia versus non–Asia). The results show that patients with unresectable locally advanced or metastatic HER2 positive GC or GOJ adenocarcinoma in the Asia region do not respond as favourably to treatment with pembrolizumab plus trastuzumab and FP/CAPOX as patients from the non-Asia region, and the SoC arm performs better in the Asia region. Countries included in non-Asia region analysis are Germany, Poland, France, Ireland, Italy, Spain and UK, Brazil, Chile, Guatemala, Russian Federation, Turkey, Ukraine, United States, Australia and Israel. Countries included in Asia region cohort are Japan (excluding Japan specific cohort), Republic of Korea and China.

It is unclear whether the differences in PFS and OS results between these two regions could be attributable to variations in treatment practices. MSD believes that the results in the non-Asia region cohort better represent the effectiveness of pembrolizumab plus trastuzumab and chemotherapy in NHS practice in England and Wales and is presenting additional post-hoc analyses specifically focusing on the efficacy and safety results for the non–Asia region CPS≥1 subgroup, in addition to the overall CPS≥1 population of KEYNOTE-811.

Progression free survival – post-hoc analysis in Asia vs non-Asia region PD-L1 CPS ≥1 population

At IA2, pembrolizumab in combination with trastuzumab and chemotherapy demonstrated a clinically meaningful improvement in PFS per RECIST 1.1 as assessed by BICR compared with SoC for the first-line treatment of non-Asia region patients with HER2 positive locally advanced or metastatic GC or GOJ adenocarcinoma whose tumours express PD-L1 CPS≥1.

- The PFS HR was 0.62 ([95% CI: 0.49; 0.78], p = 0.1449) in favour of pembrolizumab plus SoC (Table 14), representing a 38% reduction in the risk of disease progression when treated with pembrolizumab plus SoC vs. SoC alone.
- The median PFS was 9.86 months (95% CI: 8.31; 11.34) for the pembrolizumab plus SoC group vs 6.31 months (95% CI: 5.59; 7.26) for the SoC group (Table 14).
- In the pembrolizumab plus SoC group, the PFS rates at 6, 12, 18 and 24 months were higher compared with the SoC group.
- The KM curves for PFS separated early and remained separated throughout the evaluation period in favour of pembrolizumab plus SoC (Figure 5).

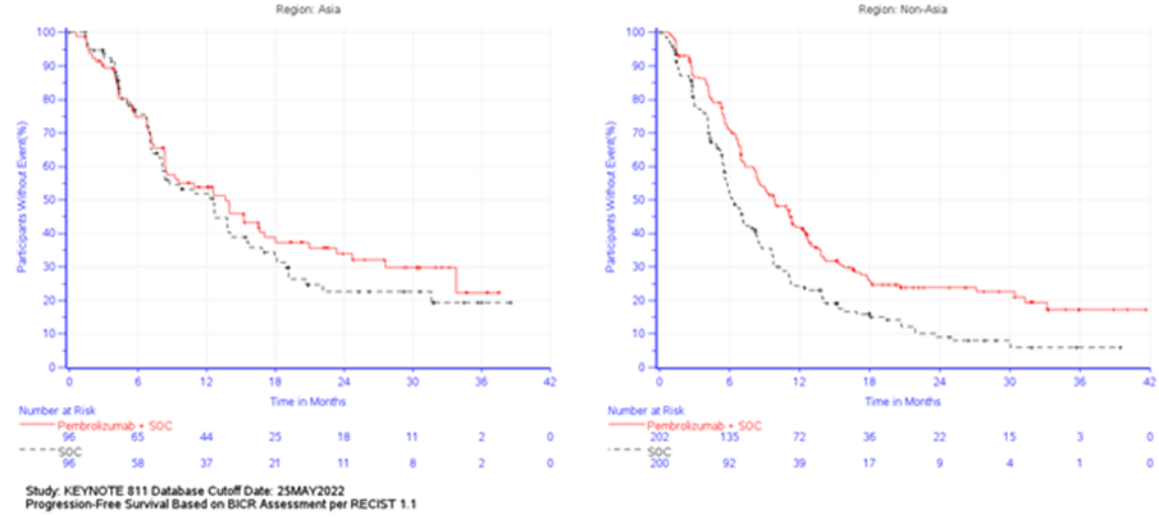
Table 14: Analysis of Progression-Free Survival (Primary Censoring Rule) for Region Subgroup (Asia vs non-Asia) (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population)

	Pembrolizumab + SoC			SoC			Pembrolizumab + SoC vs. SoC	
Progression-Free Survival (Primary Censoring Rule)	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value for Interaction Test[d]
Region								
Asia	96	58 (60.4)	13.63 [8.35; 17.02]	96	59 (61.5)	12.52 [8.08; 14.06]	0.85 [0.59; 1.22]	0.1449

Non-Asia	202	141 (69.8)	9.86 [8.31; 11.34]	200	156 (78.0)	6.31 [5.59; 7.26]	0.62 [0.49; 0.78]	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model with treatment as a covariate using Wald confidence interval
d: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
Database Cut-off Date: 25 May 2023
CI: Confidence Interval

Figure 5: Kaplan-Meier Curves of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population) Region (Asia vs non-Asia)



Progression-Free survival per RECIST 1.1 by BICR – PD-L1 CPS ≥1 population

At IA2, pembrolizumab in combination with chemotherapy demonstrated a clinically meaningful improvement in PFS per RECIST 1.1 as assessed by BICR compared with SoC for the first-line treatment of patients with HER2 positive locally advanced or metastatic gastric or GOJ adenocarcinoma whose tumours express PD-L1 CPS ≥1.

- The PFS HR was 0.70 ([95% CI: 0.58, 0.85], p = 0.0001) in favour of pembrolizumab plus SoC (Table 15), representing a 30% reduction in the risk of disease progression when treated with pembrolizumab plus SoC vs. SoC alone. The results are consistent with the PFS HR for the ITT population (reported in appendix M).

- The median PFS was 10.8 months (95% CI: 8.5, 12.5) for the pembrolizumab plus SoC group vs 7.2 months (95% CI: 6.8, 8.4) for the SoC group (Table 15).

- In the pembrolizumab plus SoC group, the PFS rates at 6, 12, 18 and 24 months were higher compared with the SoC group.

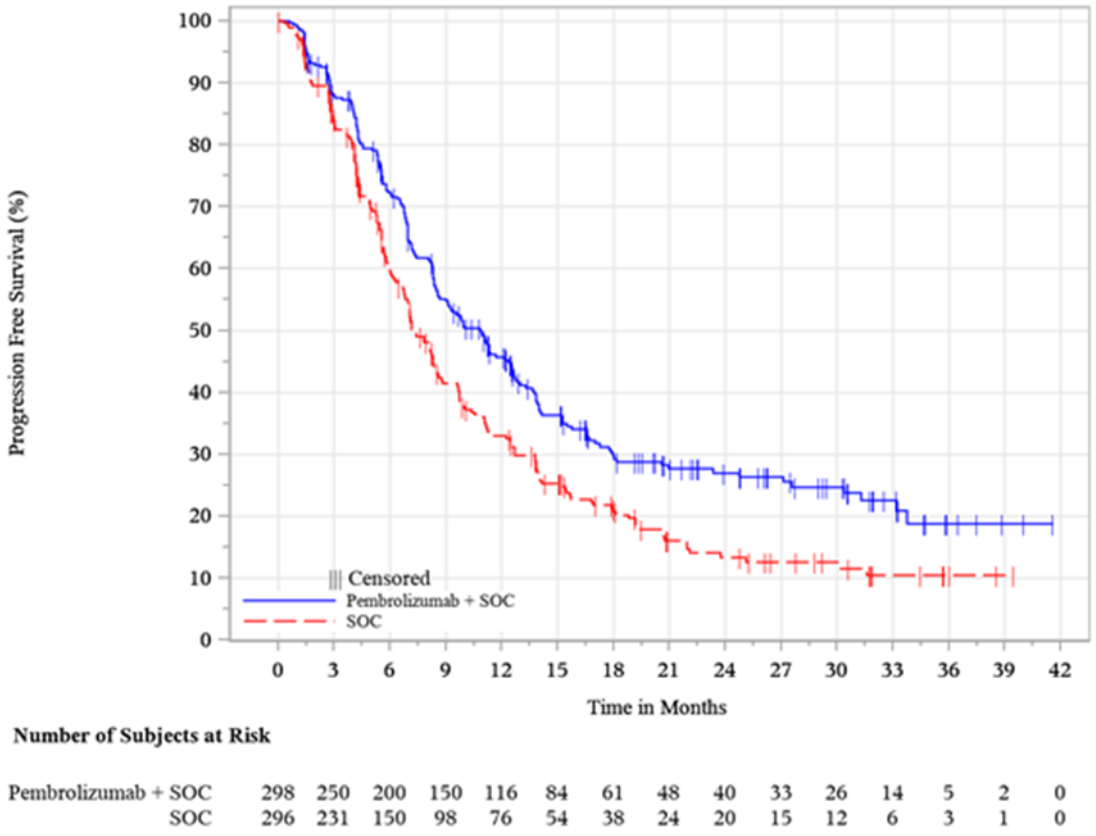
- The KM curves for PFS separated early and remained separated throughout the evaluation period in favour of pembrolizumab plus SoC (Figure 6).

Table 15: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS≥1 Participants)

	Pembrolizumab + SoC (N=298)	**SoC (N=296)**
Number of Events (%)	199 (66.8)	215 (72.6)
DEATH	29 (9.7)	30 (10.1)
DOCUMENTED PROGRESSION	170 (57.0)	185 (62.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	10.8 (8.5, 12.5)	7.2 (6.8, 8.4)
[Q1, Q3]	[5.6, 27.6]	[4.3, 15.2]
Person-months	3530.2	2644.1
Event Rate / 100 Person-months	5.6	8.1
vs SoC		
Hazard Ratio (95% CI)[b]	0.70 (0.58, 0.85)	
p-value[c]	0.0001	
PFS Rate at month 6 (%) (95% CI)	72.3 (66.7, 77.1)	59.9 (53.7, 65.5)
PFS Rate at month 12 (%) (95% CI)	45.7 (39.7, 51.5)	32.9 (27.2, 38.8)
PFS Rate at month 18 (%) (95% CI)	29.8 (24.2, 35.6)	20.7 (15.7, 26.2)
PFS Rate at month 24 (%) (95% CI)	27.0 (21.5, 32.8)	13.3 (9.0, 18.5)

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.
c One-sided p-value based on log-rank test. BICR = Blinded Independent Central Review.
Database Cut-off Date: 25 May 2023

Figure 6: Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS≥1 Participants)



Database Cut-off Date: 25 May 2022

Overall survival – post-hoc analysis in Asia vs non-Asia region PD-L1 CPS ≥1 population

At IA2, pembrolizumab in combination with chemotherapy demonstrated a clinically meaningful improvement in OS compared with SoC for the first-line treatment of patients in the non-Asia region with HER2 positive locally advanced or metastatic gastric or GOJ adenocarcinoma whose tumours express PD-L1 CPS ≥1.

- The OS HR was 0.67 ([95% CI: 0.52; 0.85], p = 0.0257) (Table 16), representing a 33% reduction in the risk of death when treated with pembrolizumab plus SoC vs. SoC alone.

- The median OS was 18.83 months (95% CI: 15.47; 24.28) for the pembrolizumab plus SoC group vs 12.62 months (95% CI: 11.14; 14.85) for the SoC group (Table 16).

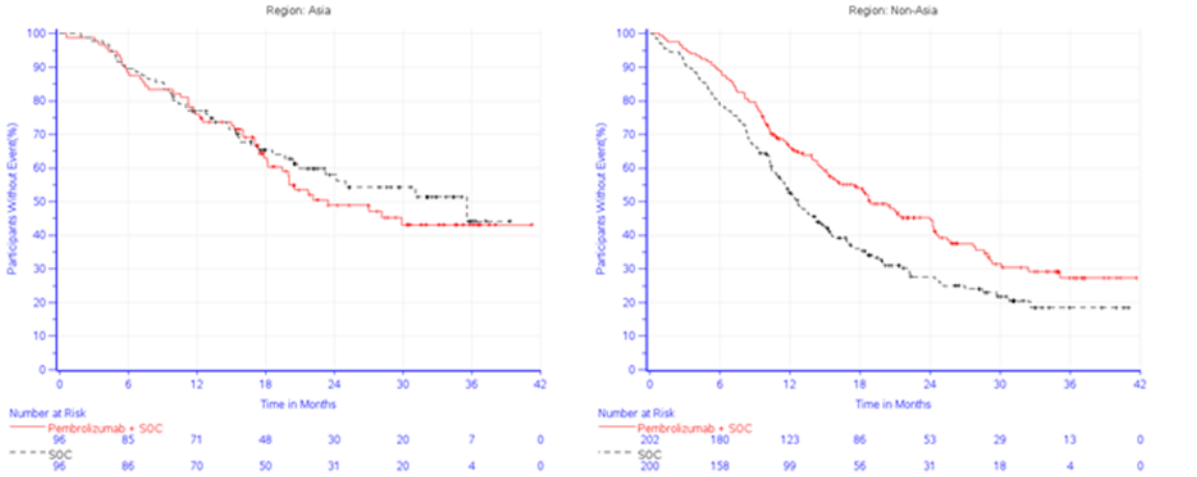
- The KM curves for OS separated early in favour of pembrolizumab plus SoC and were sustained (Figure 7).

Table 16: Analysis of Overall Survival for Region Subgroup (Asia vs Non-Asia) (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population)

Study: KEYNOTE-811	Pembrolizumab + SoC			SoC			Pembrolizumab + SoC vs. SoC	
Overall Survival	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value for Interaction Test[d]
Region								
Asia	96	47 (49.0)	23.43 [18.20; -]	96	41 (42.7)	35.58 [20.76; -]	1.15 [0.76; 1.76]	0.0257
Non-Asia	202	120 (59.4)	18.83 [15.47; 24.28]	200	142 (71.0)	12.62 [11.14; 14.85]	0.67 [0.52; 0.85]	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model with treatment as a covariate using Wald confidence interval
d: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
Database Cut-off Date: 25 May 2022
CI: Confidence Interval

Figure 7: Kaplan-Meier Curves of Overall Survival (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population) Region (Asia vs non-Asia)



Database Cut-off Date: 25 May 2022

Overall survival - PD-L1 CPS≥1 population

At IA2, pembrolizumab in combination with chemotherapy demonstrated a clinically meaningful improvement in OS compared with SoC for the first-line treatment of patients with HER2 positive locally advanced or metastatic gastric or GOJ adenocarcinoma whose tumours express PD-L1 CPS ≥1.

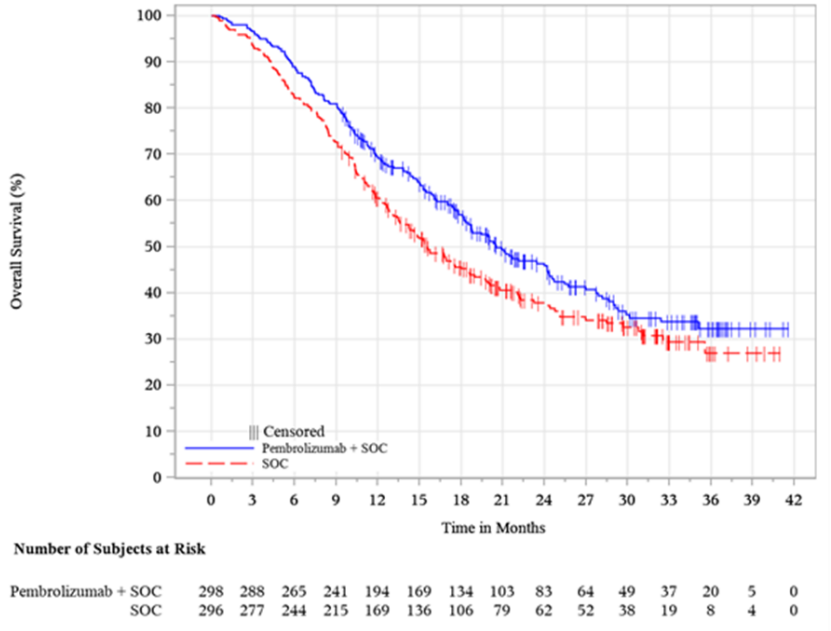
- The OS HR was 0.79 ([95% CI: 0.64, 0.98], p = 0.0143) (Table 17), representing a 21% reduction in the risk of death when treated with pembrolizumab plus SoC vs SoC alone.
- The median OS was 20.5 months (95% CI: 18.2, 24.3) for the pembrolizumab plus SoC group vs 15.6 months (95% CI: 13.5, 18.6) for the SoC group (Table 17).
- The OS rates were higher in the pembrolizumab plus OS group at 6, 12, 18 and 24 months compared with the SoC group (Table 17).
- The KM curves for OS separated early in favour of pembrolizumab plus SoC and were sustained (Figure 8).

Table 17: Analysis of Overall Survival (CPS≥1 Participants)

	Pembrolizumab + SoC (N=298)	SoC (N=296)
Number of Events (%)	167 (56.0)	183 (61.8)
DEATH	167 (56.0)	183 (61.8)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	20.5 (18.2, 24.3)	15.6 (13.5, 18.6)
[Q1, Q3]	[10.3,]	[8.4,]
Person-months	5383.7	4684.2
Event Rate / 100 Person-months	3.1	3.9
vs SoC		
Hazard Ratio (95% CI)[b]	0.79 (0.64, 0.98)	
p-value[c]	0.0143	
OS Rate at month 6 (%) (95% CI)	88.9 (84.8, 92.0)	82.4 (77.6, 86.3)
OS Rate at month 12 (%) (95% CI)	69.2 (63.6, 74.1)	60.6 (54.7, 65.9)
OS Rate at month 18 (%) (95% CI)	56.9 (50.9, 62.5)	45.6 (39.7, 51.4)
OS Rate at month 24 (%) (95% CI)	45.8 (39.5, 51.8)	37.8 (31.8, 43.8)

a From product-limit (Kaplan-Meier) method for censored data.
b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on log-rank test. NR = Not reached.
Database Cut-off Date: 25 May 2022

Figure 8: Kaplan-Meier Estimates of Overall Survival (CPS≥1 Participants)



Database Cut-off Date: 25 May 2022

Secondary endpoints

Objective response rate and duration of response

Pembrolizumab in combination with chemotherapy demonstrated a clinically meaningful improvement in ORR compared with SoC for the first-line treatment of patients with HER2 positive locally advanced or metastatic gastric or GOJ adenocarcinoma whose tumours express PD-L1 CPS ≥1.

The ORR and median DOR as determined by BICR per RECIST 1.1 were consistent between the CPS ≥1 subgroup and the ITT population (Appendix M).

- The confirmed ORR per RECIST 1.1 based on BICR was higher in the pembrolizumab plus SoC group compared with the SoC group (73.2% vs 58.4%) (95% CI: 7.1, 22.2, nominal p-value = 0.00008) (Table 18).
- The CR and PR rates were higher in the pembrolizumab plus SoC group compared with the SoC group (14.1% vs 9.8% and 59.1% vs 48.6%, respectively) (Table 19).
- The median DOR per RECIST 1.1 based on BICR was longer in the pembrolizumab plus SoC group compared with the SoC group (11.3 vs 9.5 months) (Table 19).
- By KM estimation, extended response duration was higher in the pembrolizumab plus SoC group compared with the SoC group beginning at ≥6 months (74.5% vs 67.3%) and continuing for ≥12 months (Figure 9).
- The percentage of participants who were censored and the most frequently reported reason for censoring of ongoing response in both intervention groups was consistent with the ITT population.

Table 18: Analysis of Objective Response with Confirmation Based on BICR Assessment per RECIST 1.1 (CPS≥1 Participants)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + SoC vs. SoC	
				Estimate (95% CI)[a]	p-Value[b]

Pembrolizumab + SoC	298	218	73.2 (67.7, 78.1)	14.7 (7.1, 22.2)	0.00008
SoC	296	173	58.4 (52.6, 64.1)		

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 Cut-off Date: 25 May 2022.

Table 19: Summary of Objective Response with Confirmation Based on BICR Assessment per RECIST 1.1 (CPS≥1 Participants)

	Pembrolizumab + SoC			SoC		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Subjects in Population	298			296		
Complete Response (CR)	42	14.1	(10.4, 18.6)	29	9.8	(6.7, 13.8)
Partial Response (PR)	176	59.1	(53.2, 64.7)	144	48.6	(42.8, 54.5)
Overall Response (CR+PR)	**218**	**73.2**	**(67.7, 78.1)**	**173**	**58.4**	**(52.6, 64.1)**
Stable Disease (SD)	55	18.5	(14.2, 23.3)	83	28.0	(23.0, 33.5)
Disease Control (CR+PR+SD)	**273**	**91.6**	**(87.9, 94.5)**	**256**	**86.5**	**(82.1, 90.2)**
Progressive Disease (PD)	16	5.4	(3.1, 8.6)	22	7.4	(4.7, 11.0)
Not Evaluable (NE[a])	1	0.3	(0.0, 1.9)	5	1.7	(0.6, 3.9)
No Assessment[b]	8	2.7	(1.2, 5.2)	13	4.4	(2.4, 7.4)

Responses are based on BICR assessment per RECIST 1.1. BICR = Blinded independent central review.
Stable disease includes SD, Non-CR/Non-PD, and NED.
NED: No lesions were identified at baseline assessment and there remained no lesions at post baseline assessment(s).
aNE: post-baseline assessment(s) available however not being evaluable.
bNo Assessment: no post-baseline assessment available for response evaluation. Database Cut-off Date: 25 May 2022.

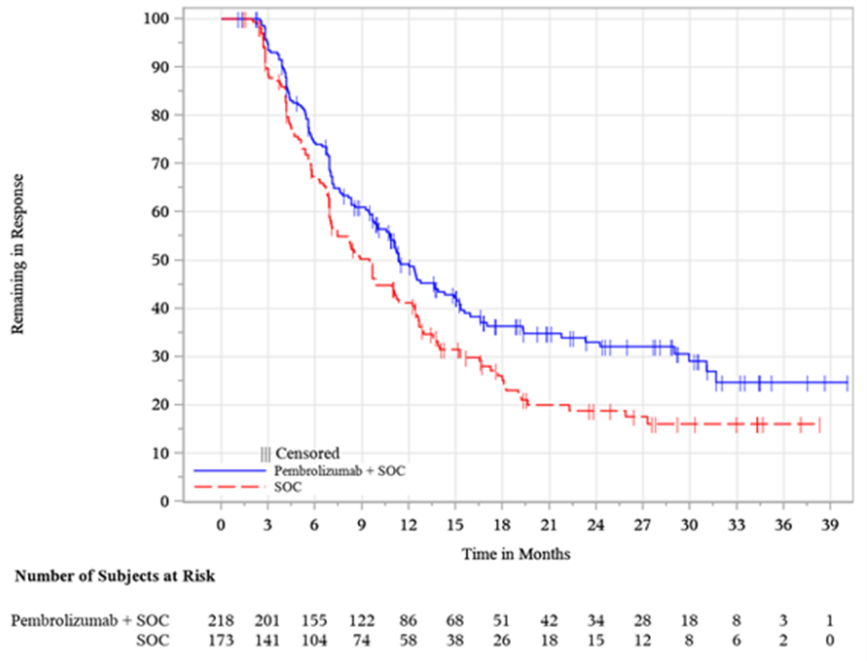
Table 20: Summary of Time to Response and Duration of Response Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response (CPS≥1 Participants)

	Pembrolizumab + SoC (N=298)	SoC (N=296)
Number of participants with response[a]	218	173
Time to Response (months)		
Mean (SD)	1.9 (1.4)	1.9 (1.1)
Median (Range)	1.4 (0.9-15.2)	1.5 (1.0-7.0)
Response Duration[b] (months)		
Median (Range)	11.3 (1.1+ - 40.1+)	9.5 (1.4+ - 38.3+)

Number (%[b]) of Participants with Extended Response Duration:		
≥3 months	201 (93.9)	141 (89.1)
≥6 months	155 (74.5)	104 (67.3)
≥9 months	122 (60.9)	74 (50.2)
≥12 months	86 (49.2)	58 (41.2)

a Includes participants with best objective response as confirmed 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 Cut-off Date: 25 May 2022

Figure 9: Kaplan-Meier Estimates of Duration of Response Based on BICR Assessment per RECIST 1.1 (CPS≥1 Participants)



Database Cut-off Date: 25 May 2022

Exploratory endpoints

PRO Compliance Rate and Completion Rate – IA 2 May 2022 data-cut

PROs were analysed in the PRO FAS population, which consisted of participants who received at least 1 dose of study medication and completed at least 1 PRO assessment. All PROs for both arms were performed at Cycles 1 to 9. After Cycle 9 (Week 24), PROs were administered every 3 cycles. Compliance rates for all the PROs were high at baseline and Week 24 in both treatment groups. As expected,

completion rates generally decreased at each time point as more participants discontinued the study treatment.

In the PRO FAS population, the compliance and completion for the EQ-5D at baseline was 94.5% for the pembrolizumab plus SoC and 95.5% for the SoC groups. Compliance at week 24 was 88% for the pembrolizumab plus SoC group and 79.5% for the SoC group. Completion at week 24 was 67.6% for the pembrolizumab plus SoC group and 53.4% for the SoC group. There were no clinically meaningful differences from baseline to week 24 in the EQ-5D-VAS health status/QoL score for participants in both the pembrolizumab plus SoC group and the SoC group based on data from the May 2022 data-cut (Table 21). Changes from baseline to week 24 were generally similar between the treatment groups at week 24 (Table 21).

EQ-5D-VAS Health Status/Quality of Life change from baseline to Week 24: IA May 2022 data-cut

Table 21: Analysis of Change from Baseline in EQ-5D-5L VAS to Week 24 (CPS≥1 Participants) (Global Cohort)

Treatment	Baseline		Week 24		Change from Baseline to Week 24	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + SoC	277	76.48 (17.19)	198	78.89 (14.90)	292	1.20 (-0.81, 3.21)
SoC	278	75.45 (18.45)	155	79.54 (14.66)	290	1.36 (-0.81, 3.53)

Pairwise Comparison	Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + SoC vs. SoC	-0.16 (-2.84, 2.51)	0.9049

† 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)).
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
For baseline and Week 24, 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: 25 May 2022

B.2.7 Subgroup analysis

Subgroup analyses were pre-specified in the KEYNOTE-811 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 population are presented in Appendix E.

As discussed previously, post-hoc analyses were conducted and are presented for the non-Asia cohort of the CPS ≥ 1 subgroup, which is considered to be more generalisable to patients in England and Wales (see section B.2.6.1).

PFS by Subgroup: IA2 May 2022 data-cut

The improvement in PFS for pembrolizumab plus SoC compared with SoC (based on the May 2022 data-cut) was observed across all subgroups and sub-populations analysed (Appendix E.) Subgroup analyses of PFS for the ITT population covered by the other co-primary endpoints of KEYNOTE-811 are presented in Appendix E.

OS by Subgroup: IA2 May 2022 data-cut

The improvement in OS for pembrolizumab plus chemotherapy compared with SoC in all subjects (based on the May 2022 data-cut) was consistent across the majority of subgroups and sub-populations analysed (Appendix E). Subgroup analyses of OS for the ITT population covered by the other co-primary endpoints of KEYNOTE-811 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 trastuzumab and chemotherapy compared with a relevant comparator, in our specific population of interest (patients with patients with locally advanced or metastatic HER2 positive GC or GOJ adenocarcinoma): KEYNOTE-811 [37]. Therefore, it was not possible to conduct a meta-analysis.

B.2.9 Indirect and mixed treatment comparisons

Summary of key NMA results:

- An NMA would be required to compare pembrolizumab + trastuzumab + CAPOX/FP against trastuzumab + XP in the metastatic setting. Although clinical opinion and ESMO guideline suggest that locally advanced unresectable patients are treated as per metastatic patients in clinical practice as explained in section B.1.3, investigation was conducted to assess the feasibility of presenting NMA results for pembrolizumab + trastuzumab + CAPOX/FP versus CAPOX/FP/XP in locally advanced unresectable setting.
- The trials included in the NMA were identified via the SLR described previously.
- The feasibility assessment concluded that an NMA was feasible only under the assumption of doublet chemotherapy equivalence, and the results mirror the KEYNOTE-811 trial results.

Please refer to Appendix D for full details of the methodology used for the SLR.

Pembrolizumab in combination with trastuzumab and CAPOX or FP have only been compared head-to-head to placebo plus trastuzumab and CAPOX or FP in metastatic or locally advanced unresectable HER2 positive GC or GOJ adenocarcinoma in the KEYNOTE-811 study. An indirect treatment comparison is needed to obtain estimates of the relative efficacy and safety of pembrolizumab + trastuzumab + CAPOX/FP

versus other regimens relevant to the UK context, including trastuzumab plus XP in the metastatic setting, and a feasibility assessment was undertaken accordingly. With regards to the locally advanced population, clinical opinion and ESMO guideline suggest that these patients are treated as per metastatic patients in clinical practice (see section B.1.3); an assumption supported by clinical expert opinion and ESMO guidelines (see section B.1.3). Nevertheless, MSD undertook an assessment to ascertain the feasibility of conducting an indirect treatment comparison for pembrolizumab + trastuzumab + CAPOX/FP versus doublet chemotherapy without trastuzumab (CAPOX, FP, XP) in the locally advanced setting (Figure 10).

Results from the feasibility assessments demonstrated that due to a lack of common comparator between the studies, performing a network meta-analysis (NMA) of pembrolizumab plus trastuzumab chemotherapy versus competing interventions was not feasible.

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 22. An overview of the patients' characteristics in all included studies is provided in Appendix D.

Table 22: Summary of the trials of relevance identified through the SLR

Trial Name/ Author Year	Author	Year	Title
KEYNOTE-811	Janjigian et al	2021	The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer
	Janjigian et al	2021	Initial data from the phase 3 KEYNOTE-811 study of trastuzumab and chemotherapy with or without pembrolizumab for HER2-positive metastatic gastric or gastroesophageal junction (G/GEJ) cancer
	Merck and Co., Inc.	2023	MK-3475: Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants With HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-811)

ToGA	Bang et al	2010	Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial
	Sawaki et al	2012	Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the Trastuzumab for Gastric Cancer (ToGA) study
	Satoh et al	2014	Quality of Life in the Trastuzumab for Gastric Cancer Trial
	CT000299	--	ToGA Study - A Study of Herceptin (Trastuzumab) in Combination With Chemotherapy Compared With Chemotherapy Alone in Patients With HER2-Positive Advanced Gastric Cancer

Feasibility assessment

Metastatic setting

Both RCTs (ToGA and KEYNOTE – 811) identified through the SLR were included in feasibility assessment evaluated a predominantly metastatic (≥97%) population. For NMA relevant to a metastatic population, the comparison between pembrolizumab + trastuzumab + CAPOX/FP and trastuzumab + CAPOX/FP is available via direct evidence from the KEYNOTE-811 trial, rendering an NMA unnecessary for this comparison. A comparison between pembrolizumab + trastuzumab + CAPOX/FP from KEYNOTE 811 and trastuzumab + XP from ToGA is of interest for the metastatic population.

Both trials allowed for administration of a mix of fluoropyrimidine and platinum doublet agents, either alone or in combination with pembrolizumab and/or trastuzumab. Although there was some overlap in the specific fluoropyrimidine and platinum doublets administered (i.e. FP), KEYNOTE-811 also allowed for receipt of CAPOX, while ToGA allowed for receipt of XP. Without complete overlap in the fluoropyrimidine and platinum doublets evaluated, the trials do not share a common comparator and thus, a connected evidence network for the purposes of NMA does not exist, rendering NMA infeasible for the comparison with trastuzumab plus XP in the metastatic setting. As evidence and clinical opinion suggest that doublet chemotherapies (XP, FP, CAPOX) are considered clinically equivalent, [24], [22], [23] the inability to conduct an NMA to inform this specific comparison does not appear to be a significant limitation.

Figure 10: Illustration of specific fluoropyrimidine and platinum doublet therapies being considered equivalent and pooled into a single node for the purposes of the NMA

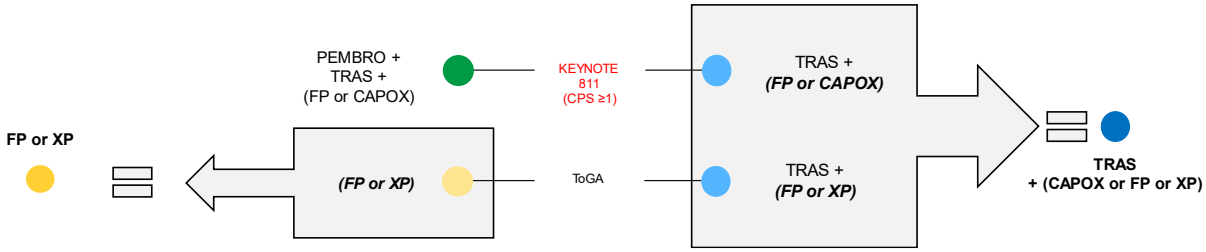
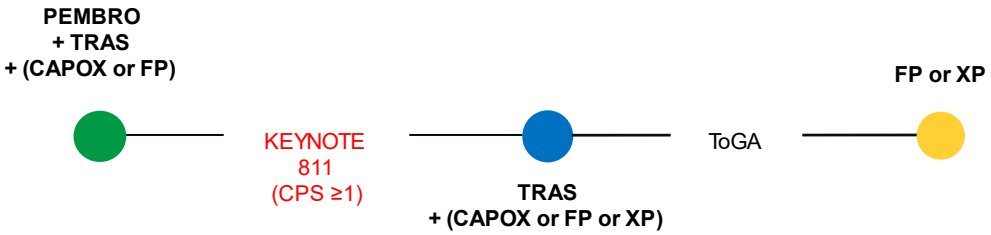


Figure 11: Network of available evidence for OS and PFS, equivalence between CAPOX, FP, and XP



Locally advanced setting

As described in section B.1.3, clinical opinion and ESMO guideline suggest and as demonstrated by KEYNOTE – 811 subgroup analysis, locally advanced unresectable GC or GOJ adenocarcinoma patients are treated as per metastatic patients in clinical practice. Consequently, an indirect comparison between pembrolizumab + trastuzumab + CAPOX/FP and CAPOX/FP/XP is not required for the decision problem; nevertheless, MSD assessed the feasibility of performing such analysis for completeness. The results from the feasibility assessment demonstrated that an indirect comparison would only be possible using an assumption of doublet chemotherapy equivalence (Figure 11). However, the data informing this comparison reflect a population where almost all participants (>97%) have metastatic disease. Although it may be possible to conduct scenario analyses using data restricted to the locally advanced patients from both trials, these would represent populations of very small sample size (<3% of the population in each trial) and analysis using these subgroup data would result in imprecise point estimates of the relative treatment effects within each trial, leading to NMA results with large margins of error.

Uncertainties in the indirect and mixed treatment comparisons

Only the KEYNOTE-811 trial reported subgroup data for a PD-L1 CPS ≥1 population; an NMA of these trials would need to utilise data for this subgroup from the KEYNOTE-811 trial and data for a population not restricted by PD-L1 CPS ≥1 status from the ToGA trial. Doing so is only reasonable under the assumption that PD-L1 CPS status does not act as an effect modifier for the relative treatment effects between trastuzumab + FP/XP and FP/XP. Although minimal evidence was identified either supporting or refuting the assumption, the mechanisms of action for the treatments evaluated in the ToGA trial do not rely on the PD-L1 pathway, as they do for pembrolizumab, and therefore it is a reasonable assumption to make.

For patients with metastatic disease, relevant comparisons to pembrolizumab + trastuzumab + CAPOX/FP include:

i) broadly, trastuzumab + CAPOX/FP/XP and

ii) more specifically, trastuzumab + XP.

Given that the first comparison was informed by direct evidence from the KEYNOTE-811 RCT, an NMA was unnecessary; and the second comparison was otherwise not possible. For patients with locally advanced disease, the only comparison of potential interest was between pembrolizumab + trastuzumab + CAPOX/FP and CAPOX/FP/XP. Since direct evidence was not available for the comparison, an indirect comparison via NMA would only be theoretically feasible under the assumption of equivalence between CAPOX, FP, and XP in order to create a common comparator node and form a connected network of evidence. Such an assumption was supported by observational evidence indicating that there is no significant difference in efficacy between various fluoropyrimidine and platinum doublet treatments [22], [23], [24]. However, the data informing the comparison between pembrolizumab + trastuzumab + CAPOX/FP and FP/XP still represented a population where the majority of individuals had metastatic disease; hence an NMA for the locally advanced population is also considered infeasible. The limitation of being unable to conduct an NMA focused on the locally advanced population has a low impact for the decision problem

given locally advanced patients are treated as per metastatic patients in clinical practice (section B.1.3).

B.2.10 Adverse reactions

Summary of adverse events information

- The percentage of participants that experienced AEs, drug-related AEs, Grade 3 to 5 AEs, drug-related Grade 3 to 5 AEs, SAEs, drug-related SAEs, discontinuation due to AEs, and discontinuations due to SAEs were similar between treatment groups.
- 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 SoC, and no new safety concerns were identified.

The primary safety analyses of IA2 were based on data from the All Participants as Treated (APaT) population of 593 participants as of the cut-off date of 25 May 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 SoC group compared with the SoC group (12.0 vs 9.7 months) (Table 23). However, the mean exposure and mean number of cycles received was higher in the pembrolizumab plus SoC group compared with the SoC group. Participants in the pembrolizumab plus SoC group (41.9%) remained on treatment for ≥12 months compared with the SoC group (28.8%). The rate of drug-related AEs was similar between the groups (Table 24).

Table 23: Summary of Drug Exposure (CPS≥1 Participants)

	Pembrolizumab + SoC	SoC
	(N=298)	(N=295)
Number of Months on Therapy (months)		
n	298	295
Mean (SD)	12.0 (8.8)	9.7 (8.0)
Median	10.2	7.1
Range	0.3 to 36.6	0.0 to 36.1
Number of Cycles		
n	298	295
Mean (SD)	16.4 (11.8)	13.4 (10.8)
Median	14.0	9.0
Range	1.0 to 51.0	1.0 to 49.0
Database Cut-off Date: 25 May 2022		

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

Table 24: Exposure by Duration (CPS≥1 Participants)

	Pembrolizumab + SoC			SoC		
	(N=298)			(N=295)		
	n	(%)	Person-months	n	(%)	Person-months
Duration of Exposure						
> 0 m	298	(100.0)	3,576.9	295	(100.0)	2,870.6
≥ 1 m	284	(95.3)	3,568.3	281	(95.3)	2,865.2
≥ 3 m	254	(85.2)	3,506.0	236	(80.0)	2,774.4

≥ 6 m	203	(68.1)	3,271.5	171	(58.0)	2,481.1
≥ 12 m	125	(41.9)	2,578.8	85	(28.8)	1,753.7

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: 25 May 2022

Table 25: Estimated Median and Mean Time on Treatment (CPS≥1 Participants)

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 + SoC	298	238 (79.9)	10.35 (8.81, 11.99)	13.4 (0.6)	(12.2, 14.6)
SoC	295	259 (87.8)	7.06 (6.24, 8.08)	10.3 (0.5)	(9.3, 11.2)

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 (not including second course).
Number of Events is defined as number of participants who had discontinued or completed treatment at the database Cut-off date.
Database Cut - off Date: 25 May 2022

Adverse events

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

The incidences of AEs were generally similar in the pembrolizumab plus SoC group and the SoC 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 SoC group and the SoC group.

The number of participants with AEs resulting in death was similar in the pembrolizumab plus SoC (22 [6.3%] participants) and SoC group (20 [5.8%] participants). Four AEs resulting in death in the pembrolizumab plus SoC group were

considered drug-related by the investigator: pneumonitis, hepatitis, sepsis, and cerebral infarction. Three AEs resulting in death in the SoC group were considered drug-related by the investigator: myocarditis, pulmonary embolism, and cholangitis. 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 SoC group than in the SoC 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 four participants died due to an AEOSI: three (1.4%) participants in the pembrolizumab plus SoC group (two participants due to pneumonitis and one participant due to hepatitis) and 1 (0.5%) participant in the SoC group (due to myocarditis).

The most frequently reported AEOSIs in the pembrolizumab plus SoC group were infusion reactions, hypothyroidism, and pneumonitis, while the most frequently reported AEOSI in the SoC 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 SoC group were generally consistent with those previously reported for pembrolizumab monotherapy or for the SoC.

The proportion of participants who experienced Grade 3 to 5 AEs of cardiac disorders were generally similar in both intervention groups. Incidence of LVEF <50% and ≥10% decrease from baseline was low and generally similar in both intervention groups.

Table 26: Adverse Event Summary AEOSI (CPS≥1 Participants)

	Pembrolizumab + SoC		SoC	
	n	(%)	n	(%)
Participants in population	298		295	
with one or more adverse events	112	(37.6)	68	(23.1)
with no adverse event	186	(62.4)	227	(76.9)

with drug-related[a] adverse events	104	(34.9)	64	(21.7)
with toxicity grade 3-5 adverse events	31	(10.4)	10	(3.4)
with toxicity grade 3-5 drug-related adverse events	29	(9.7)	10	(3.4)
with serious adverse events	30	(10.1)	14	(4.7)
with serious drug-related adverse events	27	(9.1)	14	(4.7)
who died	3	(1.0)	1	(0.3)
who died due to a drug-related adverse event	2	(0.7)	1	(0.3)
discontinued any drug due to an adverse event	21	(7.0)	12	(4.1)
discontinued pembrolizumab or placebo	13	(4.4)	6	(2.0)
discontinued trastuzumab	8	(2.7)	4	(1.4)
discontinued any chemotherapy	17	(5.7)	10	(3.4)
discontinued all drugs	7	(2.3)	4	(1.4)
discontinued any drug due to a drug-related adverse event	20	(6.7)	12	(4.1)
discontinued pembrolizumab or placebo	12	(4.0)	6	(2.0)
discontinued trastuzumab	7	(2.3)	4	(1.4)
discontinued any chemotherapy	16	(5.4)	10	(3.4)
discontinued all drugs	6	(2.0)	4	(1.4)
discontinued any drug due to a serious adverse event	15	(5.0)	6	(2.0)
discontinued pembrolizumab or placebo	12	(4.0)	6	(2.0)
discontinued trastuzumab	8	(2.7)	4	(1.4)
discontinued any chemotherapy	12	(4.0)	4	(1.4)
discontinued all drugs	7	(2.3)	4	(1.4)
discontinued any drug due to a serious drug-related adverse event	14	(4.7)	6	(2.0)
discontinued pembrolizumab or placebo	11	(3.7)	6	(2.0)
discontinued trastuzumab	7	(2.3)	4	(1.4)
discontinued any chemotherapy	11	(3.7)	4	(1.4)
discontinued all drugs	6	(2.0)	4	(1.4)

a Determined by the investigator to be related to the drug.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.
NCI CTCAE version 4.03.
Database Cut-off Date: 25 May 2022

B.2.11 Ongoing studies

The KEYNOTE-811 [39] study is ongoing, with an estimated study completion date of December 2024. There are no other ongoing clinical trials for pembrolizumab in this indication other than KEYNOTE-811.

B.2.12 Interpretation of clinical effectiveness and safety evidence

KEYNOTE-811 demonstrated clinically meaningful improvements across both of its primary endpoints of OS and PFS, as well as its key secondary endpoint of ORR, where a continued improvement with durable responses was also observed. The results from the IA2 of KEYNOTE-811 provide evidence that treatment with pembrolizumab plus trastuzumab and chemotherapy is superior to SoC alone for patients with untreated, unresectable locally advanced or metastatic GC or GOJ adenocarcinoma. Results for the ITT population (Appendix M) show that the benefit across the key endpoints is driven by the CPS≥1 subgroup, which comprises the majority of the study population and is the population of relevance to the anticipated marketing authorisation (regulatory review currently underway). Pembrolizumab in combination with trastuzumab and chemotherapy has generally acceptable safety profile. The safety results from KEYNOTE-811 showed the combination of pembrolizumab plus SoC to be comparable with the existing SoC regimen and reflective of AEs expected for trastuzumab, chemotherapy (FP/CAPOX), and pembrolizumab. Thus, pembrolizumab plus SoC provides an improved treatment option for patients with locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma.

Efficacy

Post-hoc analyses of populations from the Asia versus non–Asia geographic regions show that pembrolizumab in combination with trastuzumab and chemotherapy demonstrated a clinically meaningful improvement in PFS per RECIST 1.1 as assessed by BICR and OS, compared with SoC, for the first-line treatment of patients from the non-Asia region who have HER2 positive locally advanced or metastatic GC or GOJ adenocarcinoma with PD-L1 tumour expression of CPS≥1. The PFS HR was

0.62 ([95% CI: 0.49; 0.78], p = 0.1449) and OS HR was 0.67 ([95% CI: 0.52; 0.85], p = 0.0257) in favour of pembrolizumab plus SoC which represents a 38% reduction in the risk of disease progression and a 33% reduction in the risk of death, respectively, when treated with pembrolizumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy alone.

In participants with CPS≥1 (based on pre-specified PD-L1 CPS≥1 subgroup analyses), pembrolizumab plus SoC is superior to SoC in participants with previously untreated, locally advanced unresectable or metastatic HER2 positive GC or GOJ adenocarcinoma:

- Clinically meaningful improvements in PFS, OS, and ORR were observed
- Confirmed ORR and DOR (per RECIST 1.1 by BICR) is higher in the pembrolizumab plus SoC group compared with the SoC group and is consistent with the ITT population.

Safety

The safety profile of pembrolizumab in combination with trastuzumab plus chemotherapy:

- Is generally consistent with the individual profiles of either SoC 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 SoC.
- Showed no new indication-specific immune-mediated AEs.

Patient-reported Outcomes Results Summary

- LS mean changes from baseline at Week 24 were similar between the pembrolizumab plus SoC and SoC groups for all scales analysed.

- Median TTD was not reported for both the pembrolizumab plus SoC and SoC groups for all scales analysed.

- At Week 24, the proportion of participants with “improved/stable” or “improved” pain symptom was, respectively, 82.0% and 40.0% in the pembrolizumab plus SoC group compared with 78.2% and 32.1% in the SoC group. For other scales analysed, the proportion of participants who “improved/stable” or “improved” were similar between groups.

It was not feasible to conduct an indirect treatment comparison between pembrolizumab and other non-trial treatment regimens of relevance to the UK population (trastuzumab + XP in metastatic setting and doublet chemotherapy without trastuzumab in locally advanced population) due to study differences and a lack of connected network between the studies identified in the SLR (see section B.2.9).

Internal validity

KEYNOTE-811 is a robust, multi-centre, randomised, double-blind, placebo controlled phase III trial of pembrolizumab plus trastuzumab and chemotherapy versus trastuzumab plus chemotherapy in patients with locally advanced unresectable or metastatic HER2 positive 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 endpoints were to compare OS and PFS (per RECIST 1.1 as assessed by BICR) in subjects treated with pembrolizumab plus trastuzumab and chemotherapy versus trastuzumab plus 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 PFS in KEYNOTE-811 followed an established response evaluation criterion (RECIST 1.1), in line with European Guidance [43].

HRQoL was explored under exploratory endpoints in the KEYNOTE-811 study, with changes from baseline in patients treated with pembrolizumab plus trastuzumab and chemotherapy compared to trastuzumab plus 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-OES18.

KEYNOTE-811 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-811 is a global study conducted in 192 centres in 19 countries, including 56 sites in Europe. Of the patients participating in the study, 189 were enrolled at sites in Europe, including 29 from the UK.

Baseline characteristics of patients enrolled in KEYNOTE-811 were as expected for patients with locally advanced unresectable or metastatic HER2 positive GC or GOJ adenocarcinoma. Most patients were male, 32.7% of participants were Asian and 62.6% were white, median age of the participants was 63 years. The treatment arms were generally well balanced by all baseline characteristics.

KEYNOTE–811 pre-specified subgroup analysis shows that patients from the non-Asia regions (Western Europe, Israel, North America and rest of the world) respond more favourably to treatment with pembrolizumab in combination with trastuzumab and chemotherapy compared with patients from the Asia region. Similar results in an Asian population were observed in ToGA trial HR 0.82; 95% CI (0.61–1.11) [38]. Post-hoc analyses conducted by MSD demonstrate that the efficacy in the non–Asia region subgroup of patients favours pembrolizumab in combination with trastuzumab and chemotherapy in both PFS and OS. The reason for these findings is unclear, but it could be impacted by variations in treatment practices across the geographic regions or other biologic or physiological specifics of Asia population. MSD considers that the results in the non-Asia population which includes Western Europe, North America, South America and Eastern Europe are more representative of the population in

England and Wales; hence subgroup analyses for this subpopulation has been presented in section B 2.6.

The observed safety profile of pembrolizumab plus trastuzumab and chemotherapy in KEYNOTE-811 reflects the known safety profiles of the components i.e. generally well-tolerated. The types and severity of adverse events observed in the pembrolizumab plus trastuzumab 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–811 results.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

In line with the NICE guide to the methods of technology appraisal, an SLR was conducted, to identify relevant cost-effectiveness studies from published literature.[44] The search was conducted on April 16 2023.

No cost-effectiveness studies evaluating pembrolizumab in combination with trastuzumab in the specified population were identified. However, a previous NICE appraisal of trastuzumab for the treatment of patients with HER2 positive metastatic gastric cancer (TA208) was identified.[19] Details of the appraisal are presented in Table 27 below. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

Table 27: Summary list of published cost-effectiveness studies

Intervention	Comparator	Model structure	Key clinical trials	Treatment stopping rule	Utility values	Drug acquisition cost calculations	Drug administration costs	Disease management costs	Subsequent treatments	End of life costs	End of life criteria	Subgroups
Trastuzumab, in combination with cisplatin and capecitabine or 5-FU. Roche anticipates that, in the UK, patients with HER2 positive metastatic adenocarcinoma of the stomach or GOJ will receive trastuzumab at the same time as their chemotherapy as per the treatment regimen in the registration trial (ToGA). In this regimen, trastuzumab was administered as an IV infusion as follows: an initial loading dose of 8 mg/kg body	Triple regimens used in UK clinical practice: ECF, EOX, ECX. The manufacturer assumed no difference in effect between these triple regimens and the comparator regimen in the ToGA trial." The comparator in the ToGA trial was CX/F (the choice of capecitabine or 5-FU was at the discretion of the clinician). According to committee UK clinical practice is normally a triplet regimen that includes an anthracycline,	Markov model with 3 health states: PFS, PD and death. Cycle length of 1 month and 8-year time horizon (considered lifetime). An AUC model was used to estimate the disease progression and was calculated from PFS and OS estimates from ToGA.	ToGA trial - phase 3 RCT. Changes in the understanding of HER2 testing during the ToGA trial resulted in HER2 positive being defined as tumours that were IHC2 positive and FISH positive, or IHC3 positive. From the full population of 594 in the ToGA trial, 446 people (75%) had tumours that met this narrower definition. The European marketing authorisation was granted for	NA	Baseline utility of 0.7292 estimated from the EQ-5D data collected in the ToGA trial. This increased daily by 0.000142 during PFS. Utiltiy for PD of 0.577 taken from TA179 (sunitinib for gastrointestinal stromal tumours). AE disutilities not included. The ERG suggested that it would be more appropriate to apply a small decrease in utility values over time (0.003503 per year) to reflect the change in	Where the cost per mg differed depending on the vial size the weighted average price per mg was used. The duration of treatment, average dose and subsequent total cost of each of the trastuzumab containing regimens was based upon that observed within the ToGA study. RDI per cycle for the comparator regimens was obtained from the appendix of the	It was assumed that the delivery cost per visit of 5-FU monotherapy would be the same as for trastuzumab and that the combination of trastuzumab and 5-FU would cost 20% more than this. Administration of HCF involves a continuous infusion over 5 days whereas ECF requires a 21 day continuous infusion. The unit cost for hospital administration of trastuzumab was also taken from Ward and colleagues (Ward 2006).	Monitoring during PFS consisted of routine consultations with an oncologist and additional cardiac monitoring. Cardiac monitoring was assumed to be done using a MUGA scan or an echocardiogram and to take place once every cycle for people treated with epirubicin and once every 3 months for people treated with trastuzumab, in accordance with the SPC. The committee heard from the clinical specialists that people on epirubicin	It was assumed that there was no difference in the use of second line treatments between the treatment regimens. This was based on similar proportions of patients receiving second line treatment and the mix of drugs between the treatment arms in ToGA	NR	The committee was persuaded that the criterion for short life expectancy was met. On balance the committee was persuaded that the addition of trastuzumab to chemotherapy would provide an extension to life of more than 3 months. The committee considered that 7000 was at the upper end of the population size for which it understood the supplementary advice to apply.	The committee discussed the clinical effectiveness of trastuzumab for the IHC3-positive subgroup, who in clinical practice would not require a confirmatory FISH test. It noted the efficacy in the trial was greater for the subgroup than for the whole population. The committee discussed the biological plausibility of greater benefit in the IHC3-positive subgroup

weight on day one of the first cycle (3weekly cycles); followed by 6 mg/kg body weight repeated Q3W. The planned duration of treatment of trastuzumab is until PD.	a platinum agent and a fluoropyrimidine. The committee concluded that the comparator in the ToGA trial did not represent current practice in the UK.		this population (referred to as the EMA subgroup). The HR for OS in the EMA subgroup was 0.65 (0.51 to 0.83) corresponding to a median survival for the trastuzumab plus chemotherapy group of 16 months compared with 11.8 months for the chemotherapy alone group.		utility over time for an equivalent group of people from UK general population norms for EQ-5D. The ERG also considered using a ceiling utility value equal to general population utility value estimates. The committee was persuaded that an increase in utility was plausible. However, it accepted the ERG comments that such increases should be capped so that they did not go above those of the general population of a comparable age.	REAL-2 study. total drug costs included an amount for wastage based on an assumption that 80% of centres using trastuzumab to treat GC would also use it to treat breast cancer and would share vials, thereby implying no wastage.	Other chemo administrations: SB14Z: Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance.	treatment were not necessarily given cardiac monitoring this often in the UK. It heard that in current practice people were tested before starting epirubicin treatment and this was only repeated when treatment levels made it necessary or if cardiac toxicity was suspected during treatment. Supportive care costs were included for patients in the progressive disease state. The cost of supportive care (£542 per month) was obtained from the NICE advanced breast cancer guideline (CG81).			However, the Committee concluded overall that applying the supplementary advice on end-of-life was appropriate.	and considered that greater effectiveness may be experienced with higher levels of HER2. The committee concluded it was an appropriate subgroup and discussed the clinical evidence. A new economic analysis based on a subgroup of people who tested IHC3 positive (that is, people with very high levels of HER2) was provided by the manufacturer.

Abbreviations: AE, adverse event; AUC, area under the curve; ECF, epirubicin plus cisplatin and 5-fluorouracil; ECX, epirubicin plus cisplatin and capecitabine; EMA, European medicines agency; EOX, epirubicin plus oxaliplatin and capecitabine; ERG, Evidence Review Group; FISH, fluorescence in situ hybridization; GC, gastric cancer; GOJ, gastroesophageal; HCF, trastuzumab in combination with cisplatin and 5-FU; HER2, human Epidermal growth factor Receptor 2; HR, hazard ratio; IHC, Immunohistochemistry; IV, intravenous; MUGA, multiple-gated acquisition; NA, not applicable; NR, not reported; OS, overall survival; Q3W, every 3 weeks; PD, progressed disease; PFS, progression free survival; RCT, randomised controlled trial; RDI, Relative dose intensity; SPC, summaries of product characteristics

B.3.2 Economic analysis

A published cost-effectiveness analysis that met the relevant inclusion criteria for this submission was not identified by the systematic review. This led to the development of a *de novo* cost-effectiveness model to assess the cost-effectiveness of pembrolizumab in combination with trastuzumab compared with the relevant comparators. Key features of the economic analysis are presented in Table 28. Further details are provided in subsequent sections.

Table 28: Summary of the economic analysis

Specification	Details	Justification
Patient population	Adult patients with untreated locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS≥1 (based on non-Asia region cohort)	Aligned with the anticipated licensed indication for pembrolizumab in combination with trastuzumab and informed by the trial population that is representative of NHS patients.
Treatment arms within model	*Intervention arm:* Pembrolizumab plus trastuzumab plus chemotherapy (CAPOX/FP) *Comparator arm:* Trastuzumab plus chemotherapy (CAPOX/FP/XP)	In line with KEYNOTE-811 intervention arm and appropriate comparators for untreated locally advanced unresectable or metastatic HER2 positive gastric or GOJ adenocarcinoma, expressing a CPS≥1%, informed by clinical expert opinion. This input confirmed that unresectable locally advanced patients are treated similar to metastatic patients, hence the trial comparator is appropriate for both patient subgroups. As outlined in section B.2.3, the chemotherapy regimens received in the trial were CAPOX and FP. These regimens are included in the base case analysis, as per the trial proportions. A scenario where XP is also administered, based on TA208 and clinical expert opinion, is presented.[19]

Analytical method	Partitioned survival model	The choice of modelling approach aligns with the approaches used in TA208 in HER2 positive advanced GC.[19] This approach is the most prevalent model structure for advanced or metastatic cancer appraisals reviewed by NICE.
Model structure	Three-health states (progression-free disease, progressed disease, and death)	This structure is consistent with approaches accepted in previous NICE technology appraisals in oncology and utilises the co-primary endpoints (PFS, OS) of the KEYNOTE-811 trial.
Time horizon	Lifetime (40 years)	The time horizon for estimating clinical and cost effectiveness is sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared. Patients enter the model aged 60 years (in line with the KEYNOTE-811 non-Asia region population) hence it allows patients to potentially live until 100 years. The model results indicate the final patient dies in both arms after approximately 39 years.
Cycle length	1 week	The chosen cycle length ensures that the model can consider the different dosing schedules across the comparator arms, while also being the common denominator for all treatment cycles, for both the intervention and comparators. Longer cycle lengths would increase the risk of over- or under-predicting costs or QALYs when averaging across cycles.
Discounting options	Costs and health outcomes at 3.5% per annum	In line with NICE reference case[44]
Perspective	NHS and PSS	In line with NICE reference case[44]
Health effects	QALYs LYs	In line with NICE reference case[44]
Clinical efficacy and safety	Data were sourced from: • KEYNOTE-811 trial • Published clinical evidence	The KEYNOTE-811 trial is the primary source of evidence for the efficacy and safety of pembrolizumab in combination with trastuzumab and chemotherapy treatment, in the first-line HER2 positive GC setting.

	• UK population general mortality	
Costs and resource use	Costs include: • Drug acquisition • Drug administration • Disease management • AE management • Terminal care Unit costs were sourced from: • BNF or eMIT for drug acquisition costs[45, 46] • National Schedule of NHS Costs[47] • Unit costs of Health and Social Care[48] • Previous HTA appraisals within GC Resource use was sourced from: • A systematic review of published studies • Previous HTA appraisals within GC	In line with NICE reference case[44] and clinical expert opinion
HRQOL	HRQoL was measured using the EQ-5D-5L by patients in the KEYNOTE-811 trial. Utility values were calculated by mapping the 5L descriptive system	In line with NICE reference case[44]

	data onto the 3L value set. Utility values were derived according to time-to-death and progression status. The disutility values associated with adverse events were also estimated.	

Abbreviations: BNF, British National Formulary; CPS, Combined Positive Score; eMIT, electronic market information tool; GC, gastric cancer; HER, Human Epidermal Growth Factor Receptor; HRQoL, health-related quality of life; HTA, Health technology assessment; LY, life year; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PFS, Progression-free survival; PSS, Prescribed Specialised Services; PSSRU, Personal Social Services Research Unit; QALY, Quality-adjusted life year; RCC, Renal cell carcinoma

Patient population

The patient population included in the economic evaluation base case consisted of non-Asia region patients with untreated HER2 positive unresectable locally advanced or metastatic gastric or GOJ adenocarcinoma, expressing a CPS≥1. This is narrower than the patient population included in the final scope issued by NICE, which did not restrict by CPS expression or by patient region.[49] However, the patient population of focus in this submission is aligned with the anticipated licence indication as per the European regulatory filing. As discussed previously in section B.2.6.1, MSD believes the non-Asia region patients in the trial to be representative of the England and Wales population and hence these data inform the economic evaluation base case.

As discussed previously in section B.1.3, clinical expert opinion indicates that HER2 positive NHS patients with unresectable locally advanced gastric or GOJ adenocarcinoma are treated with a consistent approach to patients whose cancer has metastasised i.e. with trastuzumab as their first-line treatment. This approach aligns with ESMO guidelines.[21] Furthermore, subgroup analysis of the metastatic cancer participants in KEYNOTE-811 indicate that cancer stage is not an effect modifier for the intervention's clinical benefit, with the result for metastatic patients consistent with that of the combined population (results are presented in Appendix M). In addition, an indirect treatment comparison versus doublet chemotherapy without trastuzumab (CAPOX, FP, XP) in the locally advanced setting was infeasible (see section B.2.9).

The baseline patient characteristics in the model base case reflect those reported for the non-Asia region patients expressing a CPS≥1 in the KEYNOTE-811 trial and are presented in Table 29 below.[37]

Table 29: Baseline patient characteristics of base case model cohort (non-Asia CPS≥1 patients)

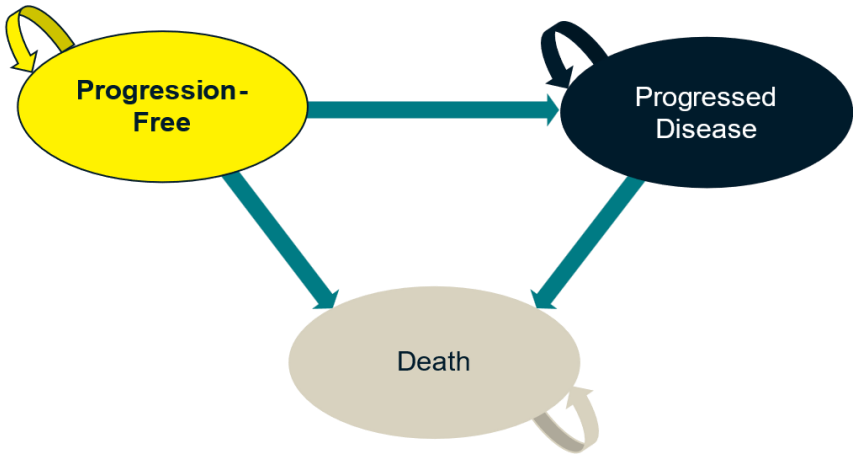
Characteristics	CPS≥1 (non-Asia region)
Age (years), mean	60.2
Male (%)	79.1
Body weight (kg), mean	72.0
Body weight (kg), standard deviation	16.3
BSA (m^2), mean	1.8
BSA (m^2), standard deviation	0.2
Abbreviations: BSA, body surface area; CPS, combined positive score. *Source: KEYNOTE-811 (database cut-off date: May 25, 2022).*	

Model structure

Consistent with economic models developed for recent NICE oncology submissions in advanced GC and oesophageal cancer (TA208, TA737, TA857, TA707, TA865),[19, 27, 35, 36, 50] a *de novo* partitioned survival cohort simulation model was developed to estimate health outcomes and costs for pembrolizumab in combination with trastuzumab and chemotherapy and the comparator regimen in the target patient population. This model structure utilises the co-primary endpoints (PFS, OS) of the KEYNOTE-811 trial and includes three mutually exclusive health states (see Figure 12 below):

- Progression-free, which is the starting health state, with patients staying in this state until disease progression or death
- Progressed disease, which includes patients alive after progression and before death
- Death, which is an absorbing health state.

Figure 12: Cost-effectiveness model structure

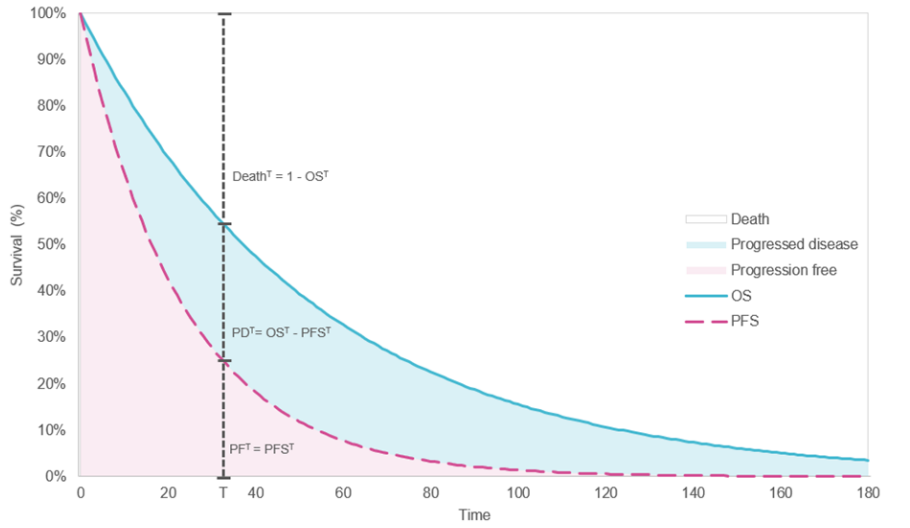


Patients enter the model in the pre-progression health state. At the end of each weekly cycle, patients may remain in the state, transition to the post-progression health state or to death; patients who are in the post-progression state may remain in that state or die at the end of each cycle. Patients cannot transition to an improved health state (i.e., from post-progression to pre-progression).

The partitioned survival model differs from a Markov model, in which transition probabilities between health states are needed, as the proportions of patients in each health state at each time point is directly estimated.

Partitioned survival modelling uses two survival curves (OS and PFS) to estimate state membership. The state membership of the death state is estimated using the OS curve (Death=1-OS); the area underneath the OS curve represents the proportion of patients that are still alive (both in pre-progression and post-progression) at different points in time, while the proportion of patients in the pre-progression state is represented by the patients located underneath the PFS curve. In this model progression is defined by the primary censoring rule in KEYNOTE-811,[51] i.e. assessment by BICR per RECIST 1.1.[52] Hence, the area between the PFS and the OS curves represents the proportion of post-progression patients, i.e., those who are in the 'post-progression' health state (PD=OS-PFS) (see Figure 13).

Figure 13: Health state occupancy at time T in a partitioned survival model



Abbreviations: PFS, progression-free survival; OS, overall survival

For each health state, a specific cost and quality-of-life adjustment weight (i.e., utility) can be assigned within each cycle for calculating the cumulative costs and cumulative QALYs over the modelled time horizon. Costs and QALYs are discounted with an annual rate of 3.5%, as stipulated by the NICE reference case.[44] A half-cycle correction was not applied in the base case due to the short cycle length (1 week).

Comparison of chosen methods to previous appraisals

A comparison of methods selected for this appraisal and the approaches adopted in the previous appraisal in HER2 positive advanced GC (TA208) is presented in Table 30.[19]

Table 30: Features of previous and the current economic analysis

	Previous evaluations	Current evaluation	
Factor	**TA208**	**Chosen values**	**Justification**
Appraisal	Trastuzumab for the treatment of HER2 positive metastatic GC	Pembrolizumab in combination with trastuzumab and chemotherapy for untreated HER2 positive advanced gastric or gastro-oesophageal cancer	NA

	Previous evaluations	Current evaluation	
Factor	**TA208**	**Chosen values**	**Justification**
Time horizon	8	40	Lifetime time horizon required to capture long-term outcomes of treatment. Model outcomes indicate final patient alive does not die until almost 40 years. 8 years was deemed to be not long enough to capture all benefits of this intervention.
Half-cycle correction	Yes (cycle length: 1 month)	No	Not applied due to short cycle length. It is implicitly assumed that all patient transitions, health outcomes and costs occur at the beginning of each cycle
Health effects measure	QALYs	QALYs	Consistent with NICE reference case[44]
Discount rate	3.5%	3.5%	Consistent with NICE reference case[44]
Perspective (NHS/PSS?)	Yes	Yes	Consistent with NICE reference case[44]
Source of utilities	Utilities for PF were estimated from the EQ-5D collected in the ToGA trial, but the baseline value was used for the PF state. Utilities for PD were taken from a previous NICE evaluation of sunitinib for gastrointestinal stromal tumours (TA179)[38, 53]	Utility values estimated from the EQ-5D collected in the KEYNOTE-811 trial[51]	Consistent with NICE reference case[44]

	Previous evaluations	Current evaluation	
Factor	**TA208**	**Chosen values**	**Justification**
Source of costs	BNF, NHS reference costs, PSSRU, UK published literature	TA208, BNF, eMIT, National Schedule of NHS Costs, Unit Costs of Health and Social Care, UK published literature[19, 45, 46, 48, 54, 55]	Consistent with previous appraisal in this population; alignment with NICE reference case[44]
Treatment waning effect?	No	Explored within scenario analysis	Due to the fixed treatment duration of pembrolizumab, the treatment benefit duration is explored through a waning scenario

Abbreviations: BNF, British National Formulary; eMIT; electronic market information tool; GC, gastric cancer; HER, human epidermal growth factor; LY, life year; NA, not applicable; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; OS, overall survival; PD, progressed disease; PF, Progression-free; PSSRU, Personal Social Services Research Unit; QALY, Quality-adjusted life year

Intervention technology and comparators

In the model base case, the intervention (pembrolizumab in combination with trastuzumab and chemotherapy) was included as per the proposed licensed dosing regimen i.e., pembrolizumab administered intravenously at a fixed dose of 200 mg over 30 minutes Q3W combined with trastuzumab 8mg/kg loading dose followed by 6mg/kg thereafter (Q3W) and a choice of CAPOX or FP, as per the KEYNOTE-811 trial. It should be noted that a label update also permits the administration of pembrolizumab 400mg Q6W,[56] and administration using this longer interval is modelled in a scenario analysis. The chemotherapy doses have been previously reported in section B.2.3 (Table 4).

In the base case analysis, the proportion of patients receiving each chemotherapy regimen aligns with those observed for non-Asia region patients in the trial (presented in Table 31). Clinical expert opinion indicated that the majority of UK patients receive the XP regimen, with a minority receiving FP (if they experience swallowing difficulties, which would preclude them from receiving capecitabine tablets) or CAPOX (as oxaliplatin is more suitable than cisplatin for patients with impaired kidney function, cardiac issues or hearing issues). To align with the trial, XP is not included in the base

case analysis, however a scenario analysis explores the impact of its inclusion. As discussed in section B.1.3, doublet chemotherapies are considered clinically equivalent when combined with trastuzumab in HER2 positive patients.

Table 31: Proportion of non-Asia region patients receiving each chemotherapy regimen in KEYNOTE-811

Chemotherapy regimen	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy
CAPOX	77.2%	78.5%
FP	22.8%	21.5%

The trial protocol permitted pembrolizumab and trastuzumab to be administered until PD or unacceptable toxicities or for a maximum of 35 doses (approximately two years). Cisplatin and oxaliplatin are subject to a maximum duration of 6 cycles in NHS practice, and clinical expert opinion confirmed that this treatment cap applies to all components of the regimen. Hence all regimens in the model (CAPOX, FP, XP) are subject to a maximum treatment duration of 6 cycles in the model base case, without adjustment for efficacy. The treatment caps were not imposed in KEYNOTE-811 and the mean number of cycles administered in the trial are presented in Table 32 below.[57] These values represent all CPS≥1 patients. The impact of administering cycles above the cap as per the trial is explored in scenario analysis.

Table 32: Mean number of chemotherapy cycles administered in KEYNOTE-811

	Pembrolizumab with trastuzumab plus chemotherapy; mean (SD)	Trastuzumab plus chemotherapy; mean (SD)
Capecitabine (in CAPOX)	13.4 (10.6)	10.9 (9.5)
Oxaliplatin (in CAPOX)	7.0 (4.4)	6.6 (4.4)
Cisplatin (in FP)	5.2 (1.8)	5.6 (1.9)
5-FU (in FP)	9.4 (6.7)	11.2 (9.5)

Abbreviations: SD, standard deviation

A summary of the model intervention and comparators is presented in Table 33 below.

Table 33: Intervention and comparators included in cost-effectiveness model

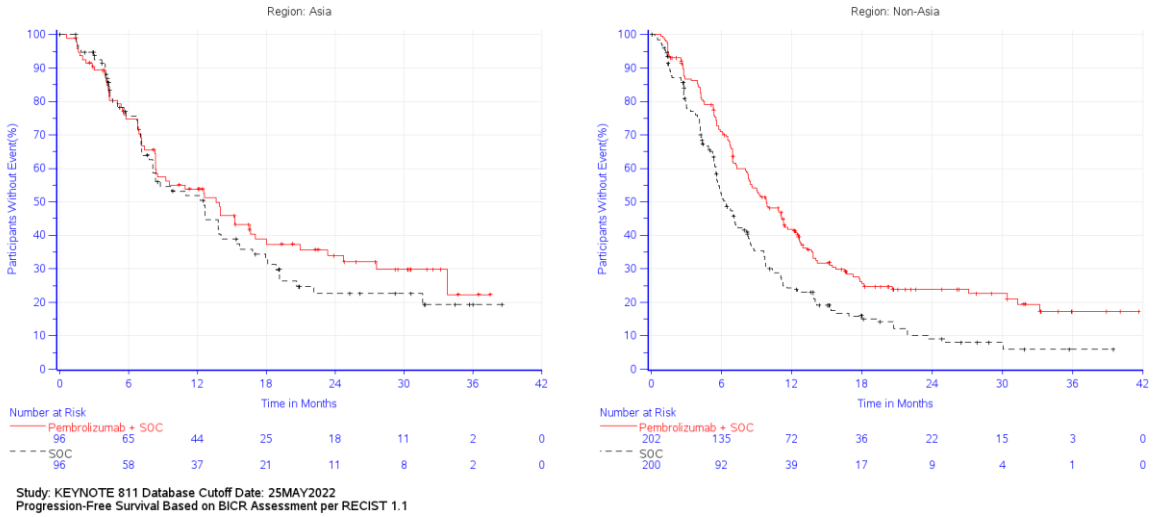
Population	Intervention and comparators	Clinical evidence derived from:
Adults with untreated locally advanced unresectable or metastatic HER2 positive gastric or gastro-oesophageal junction adenocarcinoma expressing a CPS≥1 (based on non-Asia region)	Pembrolizumab plus trastuzumab plus chemotherapy (CAPOX/FP/XP)	KEYNOTE-811 intervention arm (assumption of equivalent efficacy between doublet chemotherapy arms when combined with pembrolizumab and trastuzumab, based on clinical expert opinion and committee findings in TA208).
	Trastuzumab plus chemotherapy (CAPOX/FP/XP)	KEYNOTE-811 comparator arm (assumption of equivalent efficacy between doublet chemotherapy arms when combined with trastuzumab, based on clinical expert opinion, committee findings in TA208: *"trastuzumab plus cisplatin and either capecitabine or 5-fluorouracil provided a 4.2-month gain in overall survival and a 2.1-month gain in progression-free survival."*)[19]
Abbreviations: CPS, combined positive score; HER, human epidermal growth factor; TA, technology appraisal		

B.3.3 Clinical parameters and variables

The data used to inform the clinical parameters within the economic analysis are primarily informed by the results for the non-Asia region CPS≥1 population from the KEYNOTE-811 study, where available.

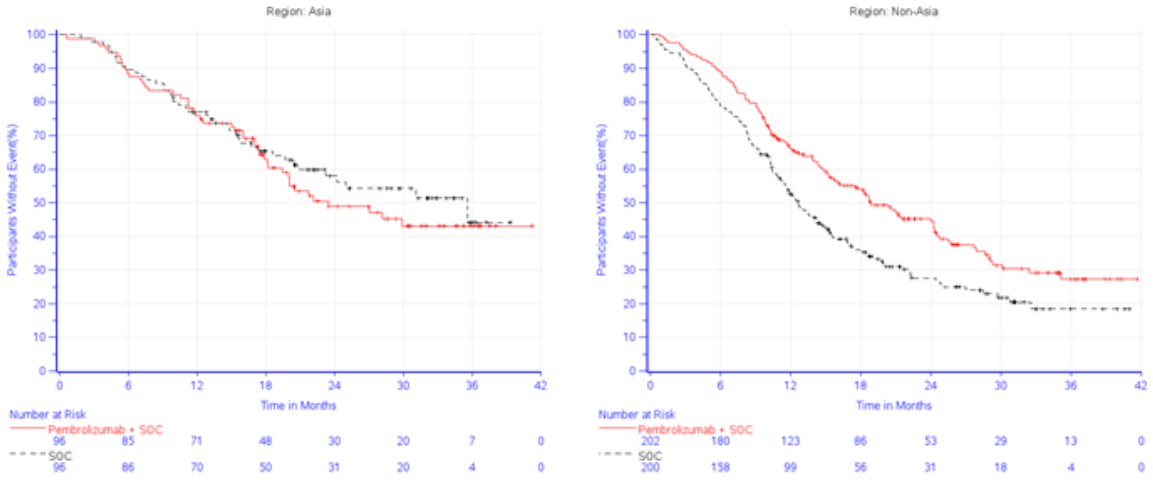
Upon examination of the trial data, the strikingly divergent shapes of the survival curves between patients in the Asia and non-Asia regions (presented in Figure 14 and Figure 15 below) led to consideration of the appropriateness of using the curves for CPS≥1 patients in the economic analysis.

Figure 14: KM curves of PFS for Asia vs. non-Asia (region) CPS≥1 patients



Abbreviations: BICR, Blinded Independent Central Review; CPS: combined positive score; PFS, progression-free survival

Figure 15: KM curves of OS for Asia vs. non-Asia (region) CPS≥1 patients



Abbreviations: CPS: combined positive score; OS, overall survival

The results from the Asia region are subject to a high level of censoring, lower patient numbers and lack statistical significance, as described by HRs which cross unity and wide confidence intervals: PFS HR (95% CI): 0.85 (0.59, 1.22), OS HR (95% CI): 1.15 (0.76, 1.76). Differing outcomes for the Asia region have been previously reported in

a study of HER2 positive metastatic GC patients suggesting a regional effect modifier in this population is not limited to the current study.[38]

The survival rates observed for patients treated with trastuzumab plus chemotherapy in the ToGA trial and the JACOB trial,[31] which used a similar control arm to KEYNOTE-811, indicate the SoC results for all CPS≥1 patients to be an outlier (e.g., 2-year OS rate in KEYNOTE-811 vs. approximately 25% and 30% in ToGA and JACOB respectively, based in visual inspection of KM curves.[38] The non-Asia region OS curve presented in Figure 15 presents survival rates more consistent with what has been previously reported for the SoC arm. Furthermore, discussions with UK clinical experts estimated a reasonable survival rate at 2 years in this population to range from 10-20% in practice. The non-Asia region CPS≥1 results from KEYNOTE-811 appear to be a more plausible outcome.

In KEYNOTE-811, the baseline characteristics of the patient subgroups were investigated to detect clinically meaningful differences between those enrolled in the Asia region compared to other participants. The characteristics have been presented previously in Table 7.

The Asia and non-Asia region participants are noted to differ in terms of the following:

- Diffuse histological subtype (Lauren classification) is twice as prevalent among non-Asia participants (20.9%) compared to among Asia participants (10.9%)
- A primary tumour location in the GOJ is more than twice as prevalent among non-Asia participants (39.8%) compared to among Asia participants (18.8%)

Subgroup analysis of the KEYNOTE-811 results indicates differential results dependent on histological subtype and primary tumour location (see Appendix E). Marked imbalances in these effect modifiers between the participants in these regions speak to a challenge in combining the results from these populations. The Asia region enrolled a higher proportion of patients aged >65 years (47.4% compared to 40.8% in the non-Asia region); see Table 6 and Table 7. Based on clinical expert opinion, patients in Asia tend to typically be fitter with an earlier age of diagnosis and less

tumour burden, hence the Asia region trial cohort may have been living with the cancer for a longer period of time. Established use of screening programmes in Asian countries is likely to be linked to this earlier age at diagnosis, with screening reported to take place in adults aged 40 years and over.[58] In contrast, screening is not routinely performed in the UK. This may have an impact on the benefit offered by the combination of an immunotherapy and HER2-targeted treatment.

Furthermore, an examination of the subsequent therapies administered in KEYNOTE-811 reflect noteworthy treatment pathway differences between the regions. A greater proportion of patients in the Asia region received a subsequent therapy (i.e. any) and imbalances were observed in the proportions receiving individual therapies, underscoring a trend of a more heavily treated population in the Asia region. The impact of this on trial efficacy outcomes is uncertain but highlights the heterogeneity between these trial populations. A summary of selected subsequent therapy administered is presented in Table 34, and the full details of the subsequent therapies are presented in the subsequent treatments report.[57]

Table 34: Summary of subsequent therapy administration for Asia, non-Asia region CPS≥1 patients

Subsequent therapy	**Asia region**		**Non-Asia region**	
	Pembrolizumab with trastuzumab plus chemotherapy: n (%)	Trastuzumab plus chemotherapy: n (%)	Pembrolizumab with trastuzumab plus chemotherapy: n (%)	Trastuzumab plus chemotherapy: n (%)
With one or more subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
With no subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
Selected subsequent therapies				
Ramucirumab	[redacted]	[redacted]	[redacted]	[redacted]
Trastuzumab deruxtecan	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: CPS, combined positive score				

Finally, notably different utility values were reported by the Asia and non-Asia region populations in the trial (further details are provided in section B.3.4), indicating a further challenge for combining these populations in an economic analysis.

The data reported for the non-Asia region participants in KEYNOTE-811 are deemed to be more generalisable of NHS patients in England and Wales, and the base case economic analysis uses these non-Asia region data. While the inconsistent survival curve shapes may not be fully explained by the imbalance in clinical characteristics or differences in treatment pathways discussed above, there is a clear difference by geography that appears to identify the Asia region results to not be generalisable to NHS patients.

Approach to modelling PFS and OS

PFS and OS are the co-primary endpoints in KEYNOTE-811 and the trial data inform the modelling of these endpoints for patients treated with the intervention and comparator described in the previous section.

The PFS and OS KM data from KEYNOTE-811 were used to estimate survival curves. The most recent pre-specified interim analysis was IA2 (data cut-off May 25 2022).

The survival curve fitting was carried out in line with NICE Decision Support Unit (DSU) guidelines.[59] Whilst acknowledging that Technical Support Document (TSD) 14 outlines that the reliance on the proportional hazards assumption is reduced when individual patient data (IPD) are available, the proportional hazards assumption was nonetheless tested. Both separately fitted and jointly fitted curves were evaluated.

Statistical goodness-of-fit statistics based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), visual inspection (comparing fitted SoC 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 choice of base case OS extrapolations were informed by discussions with UK clinical experts about plausible survival estimates for the SoC arm.

For the pembrolizumab with trastuzumab plus chemotherapy and trastuzumab plus chemotherapy arms, OS and PFS curves were extrapolated by fitting survival models to time-to-event endpoints of patient-level data from the KEYNOTE-811 trial.

Estimated survival data is applied in the model using parametric survival curves fitted to the KM data in a “one-piece” approach i.e. extrapolating based on the complete data. Spline modelling was also investigated. With this approach, a Royston-Parmar spline model splits the KM data into multiple sections, fits a parametric curve onto the data in each section, and connects the curves at each intersection, or “knot”.[60] A “two-piece” approach was not considered because no visually obvious change in the hazards early in the KM curves was observed, at time points where a sample size was sufficient thereafter to fit parametric survival curves.

The standard survival distributions (Exponential, Gamma, Generalised Gamma, Gompertz, Log-logistic, Log-normal, Weibull) were all assessed for goodness-of-fit and the most representative survival distributions were selected based on clinical plausibility of the results. The survival curves are used to extrapolate the survival estimates beyond the follow-up period of observed data. The format of the following sections is a discussion of the proportional hazards assumption assessment followed by a description of the extrapolation methods and choice. In these sections, SoC is defined as trastuzumab in combination with chemotherapy.

Overall Survival

Assessment of proportional hazards

The assessment was conducted for all CPS≥1 patients in the trial. The Schoenfeld residuals plot for OS did not vary significantly from zero as the p-value is 1.000 (see Figure 16). The proportional hazards assumption during the trial period for those treated with pembrolizumab + SoC versus SoC. Furthermore, the log cumulative hazards in OS over time for the pembrolizumab + SoC and SoC arms are approximately parallel to the y-axis for most of the trial period, with the tail-end of the KM curves appearing to converge at the end of the curve with heavy censoring (see

Figure 17). Overall, there is insufficient information to reject the proportional hazards assumption based on the log cumulative hazards plot. Given the plausibility of proportional hazards, an approach was taken which independently fitted an extrapolated curve to the SoC arm and then applied a constant HR to this curve to estimate the intervention arm survival. The OS HR applied is that reported for the non-Asia region CPS≥1 patients i.e. 0.67 (95% CI: 0.52, 0.85). Both one-piece and spline models were investigated.

Figure 16: Plot of KM curve and Schoenfeld residual for graphical diagnosis of proportional hazards in overall survival between groups treated with Pembrolizumab + SoC versus SoC

Abbreviations: SoC: standard of care
Source: KEYNOTE-811 (Database cut-off May 25 2022)

Figure 17: Comparison in cumulative hazard in overall survival over time between groups treated with pembrolizumab + SoC versus SoC

Abbreviations: SoC: standard of care
Source: KEYNOTE-811 (Database cut-off May 25 2022)

Independently-fitted one-piece models

The standard survival distributions listed above were fit to the trial data and the results of the goodness-of-fit assessment is presented in Table 35.

Table 35: Fit statistics of OS extrapolation: trastuzumab plus chemotherapy arm, independently fitted one-piece models

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	2092.7	6	2096.4	5
Generalized gamma	2083.2	3	2094.3	3
Gompertz	2094.7	7	2102.1	7
Log-logistic	**2078.4**	**1**	**2085.8**	**1**
Log-normal	2082.9	2	2090.3	2
Weibull	2090.1	5	2097.5	6
Gamma	2087.8	4	2095.2	4

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

Log-logistic is the statistically best-fitting curves based on AIC/BIC in the SoC arm. For trastuzumab plus chemotherapy, log-logistic has a reasonable visual fit regarding the hazard plot (higher in the tail, but still within the 95% confidence interval; see Figure 18) and log-logistic has a good visual fit to its KM curve (see Figure 19).

Figure 18: Plot of OS hazard function for trastuzumab plus chemotherapy, independently fitted one-piece models

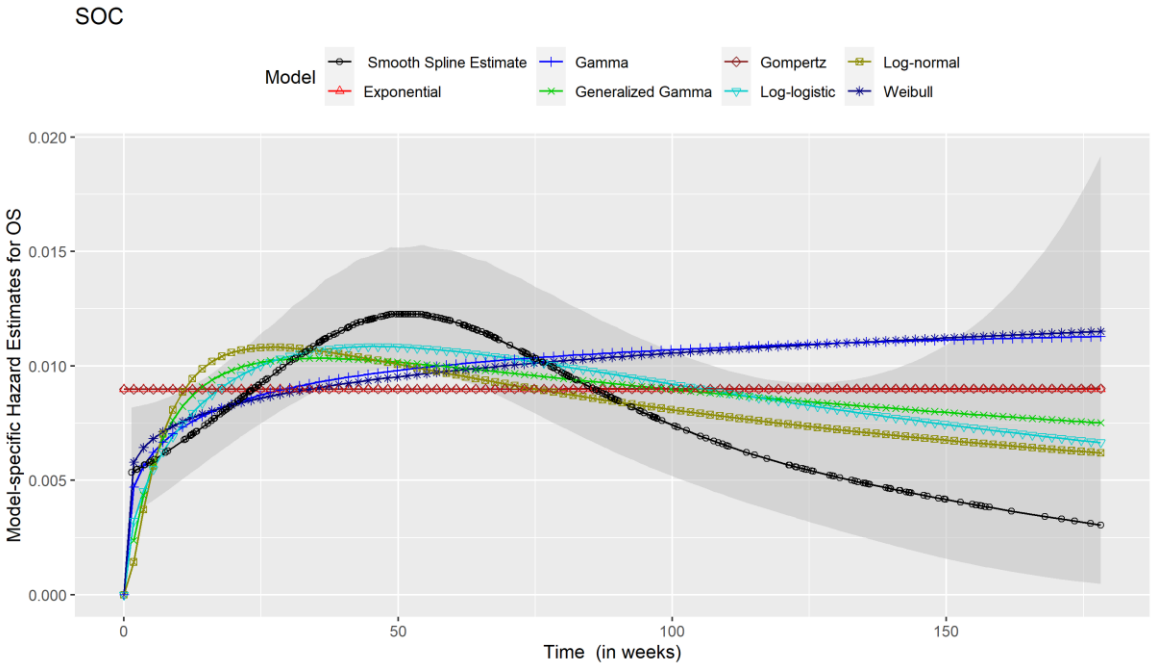
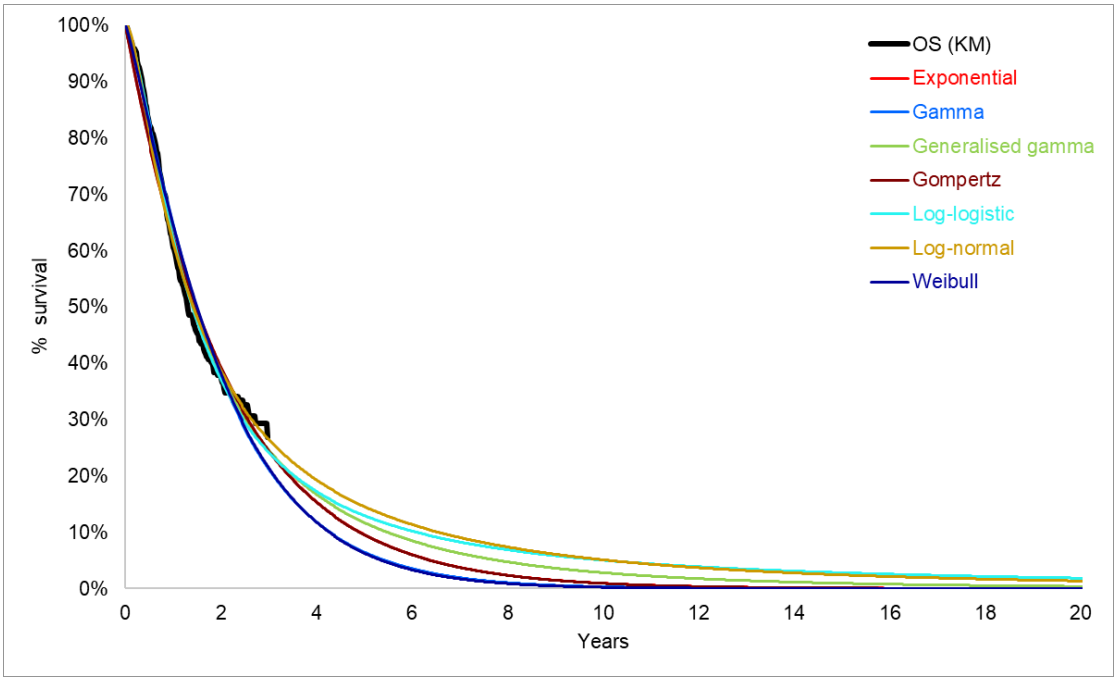


Figure 19: OS for trastuzumab plus chemotherapy, independently fitted one-piece models



Predicted survival

The OS HR reported for the non-Asia region population in the trial was applied to the independently fitted [redacted] SoC curve at all time points, in accordance with the outcome of the proportional hazards assumption. The KM curves and extrapolated curves for both arms are presented in Figure 20.

Figure 20: Overall survival, independently fitted one-piece model with non-Asia region HR applied

Independently-fitted spline models

The standard survival distributions listed above were fit to the trial data and the results of the goodness-of-fit assessment is presented in Table 36.

Table 36: Fit statistics of OS extrapolation: trastuzumab plus chemotherapy, independently fitted spline models

Distribution	AIC	AIC rank	BIC	BIC rank
Hazards, 1 knot	2082.9	9	2094.0	6
Hazards, 2 knots	**2077.0**	**1**	**2091.8**	**2**
Hazards, 3 knots	2078.7	6	2097.1	9
Odds, 1 knot	2080.0	7	2091.1	1
Odds, 2 knots	**2077.6**	**2**	**2092.3**	**3**
Odds, 3 knots	2078.6	5	2097.0	8
Normal, 1 knot	2082.4	8	2093.5	5
Normal, 2 knots	2077.9	3	2092.7	4
Normal, 3 knots	2078.3	4	2096.8	7

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

For trastuzumab plus chemotherapy, the 2 knots, hazard model and 2 knots, odds models are the best-fitting curves based on AIC and BIC. Visual fit indicates the 2 knots, odds to be the better fitting to the data. All 3 knots models do not have good AIC or BIC. 2 knots, hazard model and 2 knots, odds model have a good visual fit according to the hazard plot. All 1 knot models do not have good visual fit to the KM curves (see Figure 21 and Figure 22).

Figure 21: Plot of OS hazard function for trastuzumab plus chemotherapy, independently fitted spline models

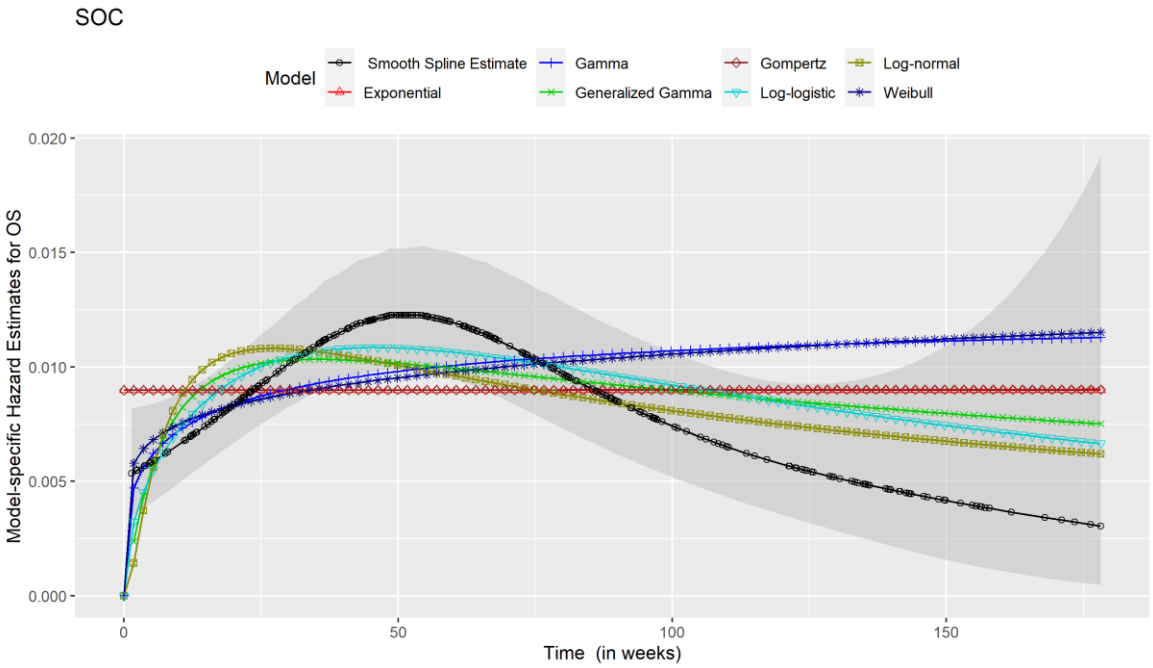
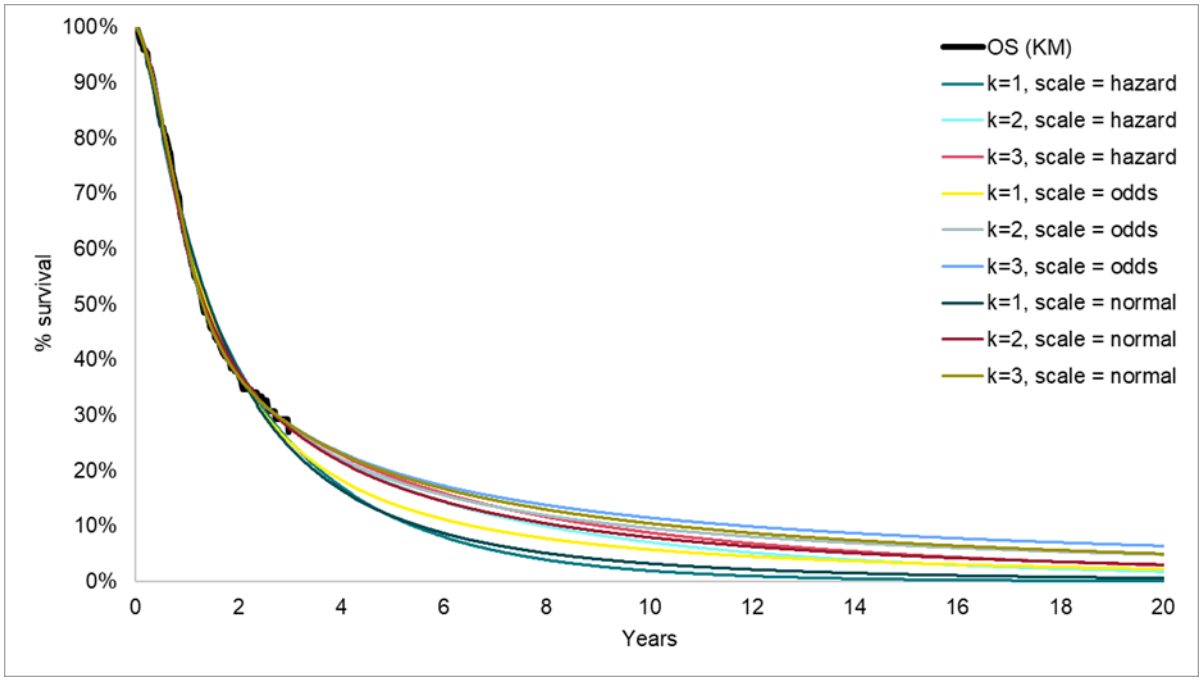


Figure 22: OS for trastuzumab plus chemotherapy, independently fitted spline models



Predicted survival

The OS HR reported for the non-Asia region population in the trial was applied to the independently fitted SoC spline curve (2 knots, odds) at all time points, in accordance with the outcome of the proportional hazards assumption. This survival is presented alongside the KM curve and extrapolated curve for the SoC arm in Figure 23.

Figure 23: Overall survival, independently fitted spline model with non-Asia region HR applied

Base case selection

A visual comparison between the one-piece and spline models (i.e. Figure 20 vs. Figure 23) indicates the independently fitted spline model to be a better fit to the KM data, hence this was selected for the base case analysis.

Treatment waning

Based on the independent estimation of survival curves for the intervention an comparator arms, the length of the follow-up period and the immunotherapy precedent, there is no clear evidence to indicate a treatment waning. 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 five years following discontinuation of pembrolizumab for all patients (i.e. seven years since treatment initiation), where the cycle-specific hazard for the pembrolizumab plus SoC arm gradually becomes equal to that in the comparator arm over the subsequent two years.

Progression-free Survival

Assessment of proportional hazards

The assessment was conducted for all CPS≥1 patients in the trial. The Schoenfeld residuals plot is predominantly linear and p-value =1.000 (Figure 24). The evidence

suggested that the proportional hazards assumption may be valid for BIRC-assessed PFS over time for those between the groups treated with pembrolizumab + SoC and SoC. The log-cumulative hazards are non-parallel during the first part of the trial period through approximately 20 weeks, likely due to the protocol-driven tumor assessment schedules in the early part of the trial. Thereafter, log-cumulative hazards are approximately parallel for the remainder of the trial (see Figure 25). Based on this, there is insufficient evidence to reject the proportional hazards assumption. As with OS, given the plausibility of proportional hazards, an approach was taken which independently fitted an extrapolated curve to the SoC arm and then applied a constant HR to this curve to estimate the intervention arm survival. The PFS HR applied is that reported for the non-Asia region CPS≥1 patients i.e. 0.62 (95% CI: 0.49, 0.78). As with OS, both one-piece and spline models were investigated.

Figure 24: Plot of KM curve and Schoenfeld residual for graphical diagnosis of proportional hazards in BIRC-assessed progression-free survival between groups treated with Pembrolizumab + SoC versus SoC

Figure 25: Comparison in cumulative hazard in BIRC-assessed Progression-free Survival over time between groups treated with Pembrolizumab + SoC versus SoC

Independently-fitted one-piece models

The standard survival distributions listed above were fit to the trial data and the results of the goodness-of-fit assessment is presented in Table 37.

Table 37: Fit statistics of PFS extrapolation: trastuzumab plus chemotherapy arm, independently fitted one-piece models

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	2143.1	6	2146.7	5
Generalized gamma	2113.7	3	2124.7	3
Gompertz	2144.1	7	2151.5	7
Log-logistic	**2109.6**	**1**	**2117.0**	**1**
Log-normal	2111.7	2	2119.1	2

Weibull	2139.9	5	2147.2	6
Gamma	2134.2	4	2141.6	4
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival				

For the SoC arm, log-logistic is the statistically best-fitting curve based on AIC/BIC. Log-logistic has a reasonable visual fit to a hazard plot (within the 95% confidence interval; see Figure 26) and a good visual fit to the control arm's KM curve (see Figure 27).

Figure 26: Plot of PFS hazard function for trastuzumab plus chemotherapy, independently fitted one-piece models

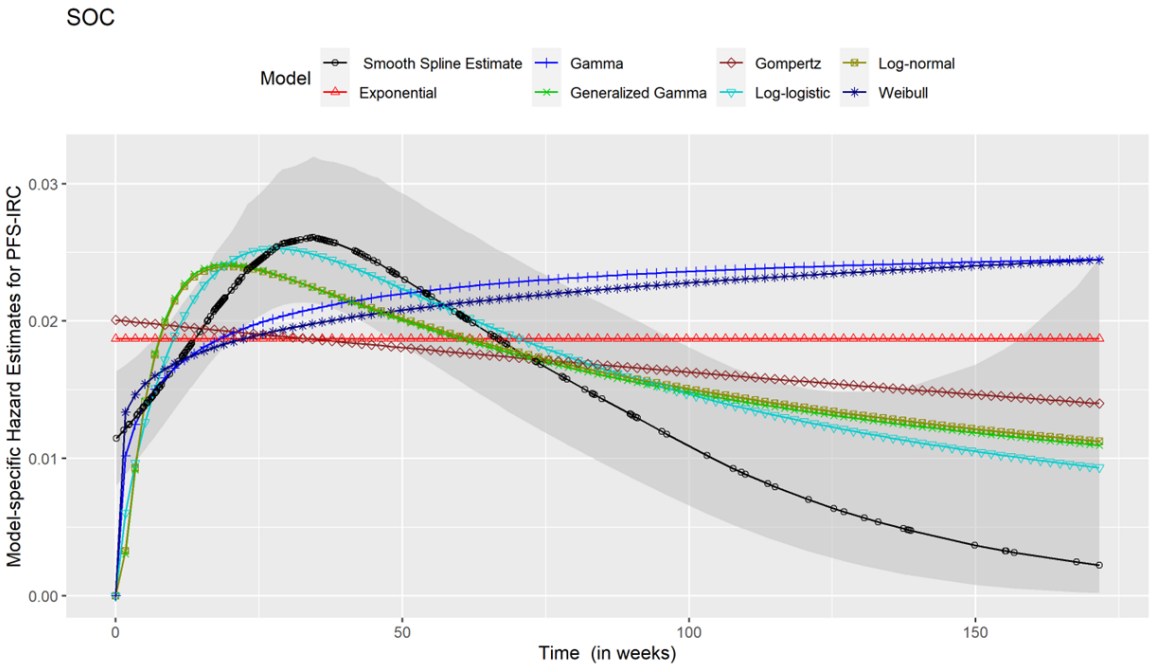
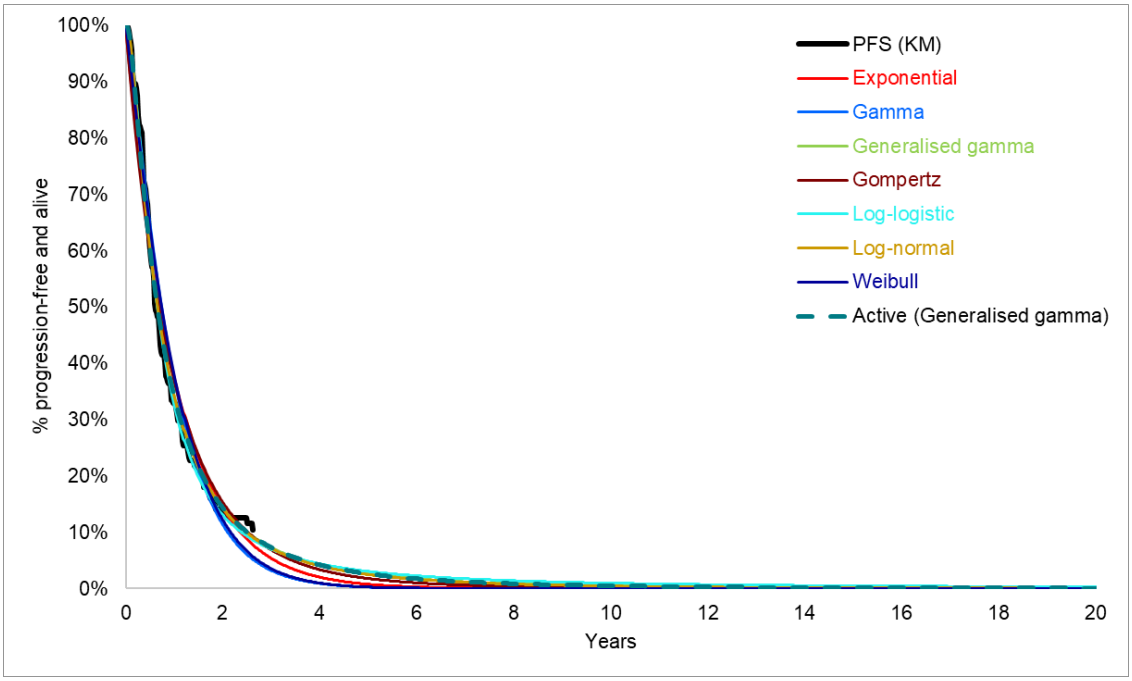


Figure 27: PFS for trastuzumab plus chemotherapy, independently fitted one-piece models



Predicted survival

The PFS HR reported for the non-Asia region population in the trial was applied to the independently fitted [redacted] SoC curve at all time points, in accordance with the outcome of the proportional hazards assumption. This survival is presented alongside the KM curve and extrapolated curve for the SoC arm in Figure 28.

Figure 28: Progression-free survival, independently fitted one-piece model with non-Asia region HR applied

Independently-fitted spline models

The standard survival distributions listed above were fit to the trial data and the results of the goodness-of-fit assessment is presented in Table 38.

Table 38: Fit statistics of PFS extrapolation: trastuzumab plus chemotherapy, independently fitted spline models

Distribution	AIC	AIC rank	BIC	BIC rank
Hazards, 1 knot	2112.6	6	2123.7	2
Hazards, 2 knots	2110.5	3	2125.3	5
Hazards, 3 knots	2112.7	7	2131.2	8
Odds, 1 knot	**2110.4**	**1**	**2121.4**	**1**
Odds, 2 knots	2110.9	4	2125.6	6
Odds, 3 knots	2112.9	8	2131.3	9
Normal, 1 knot	2113.7	9	2124.7	3
Normal, 2 knots	**2110.4**	**2**	**2125.1**	**4**
Normal, 3 knots	2112.1	5	2130.6	7

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

For trastuzumab plus chemotherapy, the 2 knots hazard model is a relatively well-fitting curve based on AIC and BIC. It has a good visual fit to the hazard plot (see Figure 29) and a good visual fit to the KM curve (see Figure 30).

Figure 29: Plot of PFS hazard function for trastuzumab plus chemotherapy, independently fitted spline models

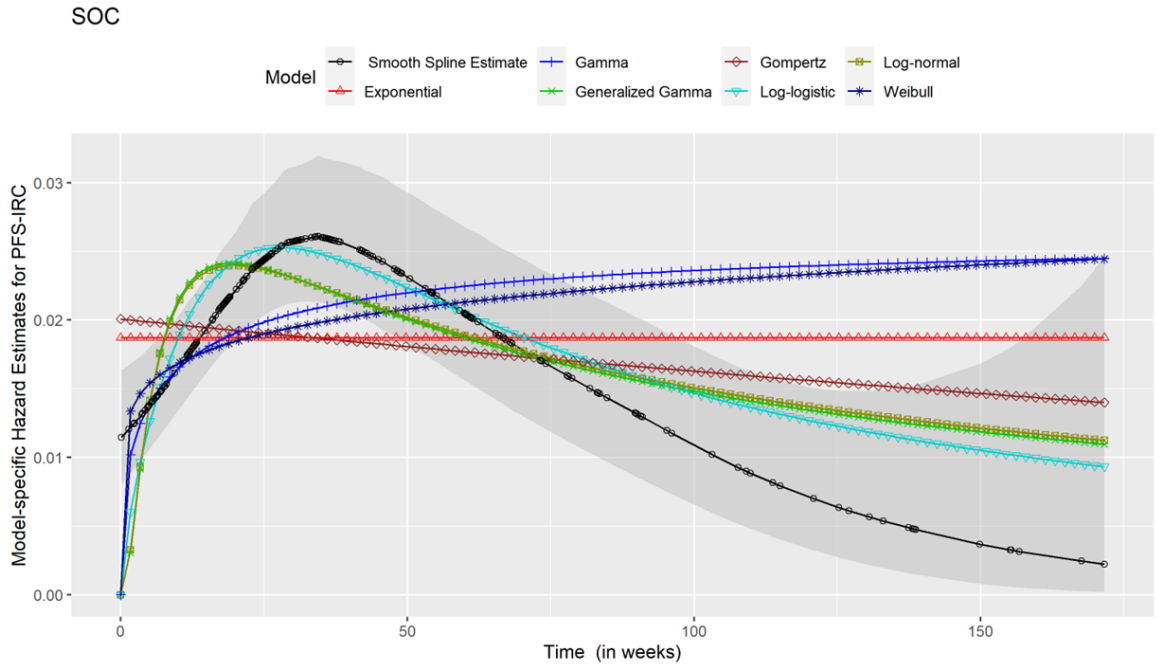
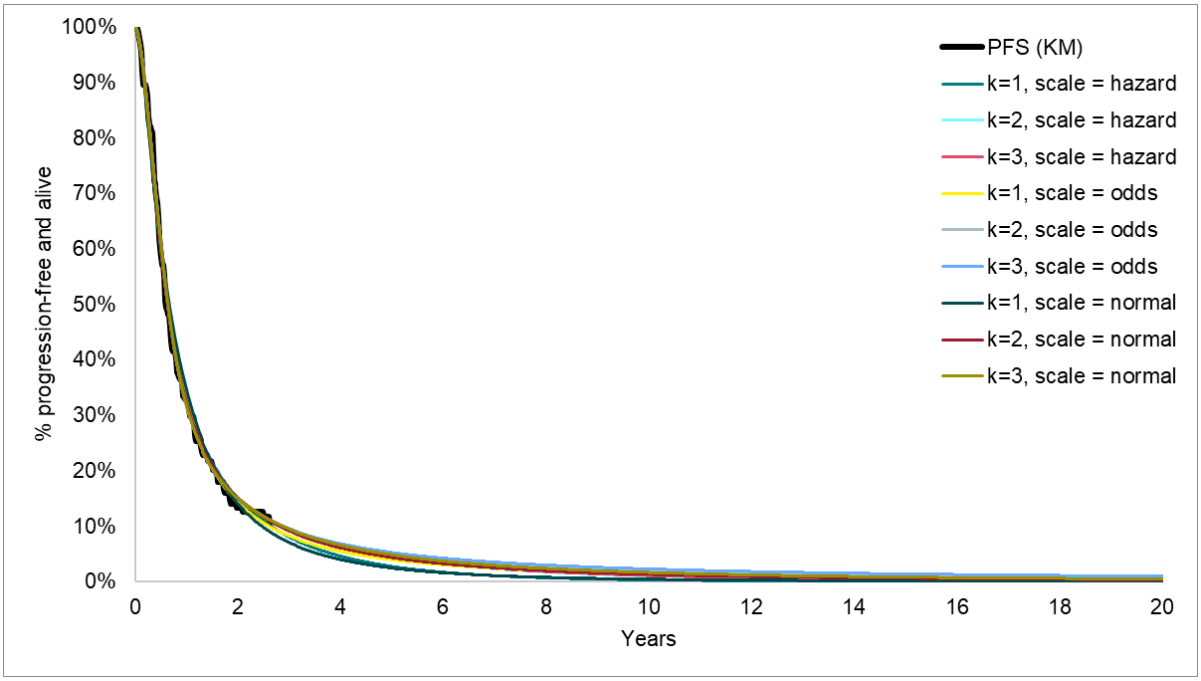


Figure 30: PFS for trastuzumab plus chemotherapy, independently fitted spline models



Predicted survival

The PFS HR reported for the non-Asia region population in the trial was applied to the independently fitted SoC spline curve (2 knots, hazard) at all time points, in accordance with the outcome of the proportional hazards assumption. This survival is presented alongside the KM curve and extrapolated curve for the SoC arm in Figure 31.

Figure 31: Progression-free survival, independently fitted spline model for trastuzumab plus chemotherapy

Base case selection

A visual comparison between the one-piece and spline models (i.e. Figure 28 and Figure 31) indicates the independently fitted spline model to be a better fit to the KM data, hence this was selected for the base case analysis.

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 in the intervention arm before any treatment waning effect might begin, hence any potential waning effect is reflected in the extrapolated curves.

Time to treatment discontinuation

Time-on-treatment (ToT) data was recorded in the KEYNOTE-811 study for all drug components separately. ToT KM data for all CPS≥1 patients is presented for each drug from Figure 32 to Figure 37.

Figure 32:ToT KM data for pembrolizumab (CPS≥1 patients)

Abbreviations: CPS, combined positive score; KM, Kaplan-Meier; ToT, time-on-treatment

Figure 33: ToT KM data for trastuzumab (CPS≥1 patients)

Abbreviations: CPS, combined positive score; KM, Kaplan-Meier; ToT, time-on-treatment

Figure 34: ToT KM data for capecitabine (CPS≥1 patients)

Abbreviations: CPS, combined positive score; KM, Kaplan-Meier; ToT, time-on-treatment

Figure 35: ToT KM data for oxaliplatin (CPS≥1 patients)

Abbreviations: CPS, combined positive score; KM, Kaplan-Meier; ToT, time-on-treatment

Figure 36: ToT KM data for 5-FU (CPS≥1 patients)

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; KM, Kaplan-Meier; ToT, time-on-treatment

Figure 37: ToT KM data for cisplatin (CPS≥1 patients)

Abbreviations: CPS, combined positive score; KM, Kaplan-Meier; ToT, time-on-treatment

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 10% remain on-treatment for all drugs). Hence KM data is directly used in the model to inform study treatment costs for all treatments without parametric extrapolation, which would introduce additional uncertainty to a dataset which is deemed reasonably informative.

Furthermore, in the base case, all treatments are subject to a treatment cap (35 cycles for pembrolizumab and trastuzumab, in line with the trial protocol, and 6 cycles for all chemotherapy regimens, in line with NHS clinical practice, as confirmed by clinical expert opinion). Survival models struggle to appropriately account for stopping rules due to the sudden change in the shape of the curve at the point of the stopping rule. Therefore, due to the maturity of the data and the implementation of stopping rules, parametric extrapolation of ToT was not included in the base case analysis.

Summary of approach to clinical parameters used in the model

For the key clinical parameters used in the economic model, the settings used in the base case analysis are presented in Table 39.

Table 39: Summary of OS, PFS, ToT approach in base case

	Pembrolizumab with trastuzumab plus chemotherapy	**Trastuzumab plus chemotherapy**
Overall survival	Non-Asia region HR applied at all time points	Independently fitted spline model (2 knots, odd)
Progression-free survival	Non-Asia region HR applied at all time points	Independently fitted spline model (2 knots, hazard)
Time-on-treatment	KEYNOTE-811 KM data	KEYNOTE-811 KM data
Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; ToT, time-on-treatment		

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life studies

Relevant health-related quality-of-life data were identified via a SLR described in Appendix H. The health-state utility values reported for the ToGA trial in TA208 are 0.7292 for progression-free and 0.577 for progressed disease.[19, 38] The ToGA trial baseline utility value was used as representative of the PF state. The value for progressed disease was sourced externally from a previous oncology appraisal (TA179).[53]

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

Utility values in the economic model are based on EQ-5D-5L data collected from all non-Asia region patients expressing a CPS≥1 enrolled in the KEYNOTE-811 trial. In the trial, the EQ-5D-5L questionnaire was administered at each of the first five treatment cycles, then every two cycles thereafter (every 6 weeks) for up to a year or end of treatment. The EQ-5D-5L was also administered at a treatment discontinuation visit and at the 30-day post-treatment safety follow-up visit, implying a paucity of values for patients in the progressed disease health state.

As data was gathered using the EQ-5D-5L descriptive system, utility values for this UK analysis were calculated by mapping the 5L descriptive system data onto the 3L value set. The mapping function developed by the Decision Support Unit, using the 'EEPRU dataset' (Hernández Alava et al. 2020), was employed.[61]

All utility analyses were conducted descriptively, without adjustment for repeated measurements, which may have occurred if a trial participant 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.[62]

Patients with multiple measurements spending longer time in a health state should receive proportionately greater weight for their health utilities than those with a single measurement, as they account for relatively more of the time and QALYs spent in that state within the model and are more representative of that health state experience. Descriptive utility analyses preserve real differences in patient characteristics between individuals experiencing different health states and hence were deemed more appropriate for informing the economic model.

Base case approach: time-to-death utility

In the time-to-death utility approach, utility values are specified for the following intervals of time-to-death based on KEYNOTE-811 EQ-5D data:

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

This approach reflects the accepted decline in cancer patients' quality of life during the terminal phase of the disease, defining health state utilities based on time to death. The approach was developed by Batty et al. 2011 and Hatswell et al. (2014).[63, 64] Hatswell et al. noted 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.[65] Furthermore, due to the post-progression data collection schedule in this trial, data were collected for newly progressed patients but not for those whose condition had deteriorated further (see schedule above). 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 intervals outlined above were pre-specified in order to avoid bias upon availability of the trial data. Furthermore, previous trial analyses have indicated these intervals to differentiate from each other in measuring patient utility (i.e. lower utility values for each successive interval closer to death).

EQ-5D scores collected from patients within each time interval were used to estimate mean utility for that category. The analyses of the intervals related to time-to-death less than 360 days focused on patients with observed death dates. For patients

whose death dates were censored (i.e., death date unknown), some have utility assessments for which time to censoring date is less than 360 days. In these cases, the corresponding utility assessments were classified to the 'unknown' time-to-death category because their EQ-5D values could not be linked to a known time-to-death ≤360 days category. This comprises a relatively small proportion of the PRO Full Analysis Set population for the trial cohort with almost 75% of participants from the PRO Full Analysis Set population either having a recorded death date or having all of their utility assessments in the ≥360 days before censoring date (and hence ≥360 days before days before death) category.

In the model, utilities were applied based on the distribution of patients across different categorisations of time to death in each weekly cycle. In a given weekly cycle, the proportion of patients within each time to death category was estimated based on the modelled OS within each treatment arm.

The time-to-death utility values analysed from the trial data are presented in Table 40.[66] It was noted that the values reported for the Asia region population in the trial (Table 41) are implausibly high in most categories for patients with this advanced cancer, further underscoring the issue of generalisability of results for those patients to NHS practice.

Table 40: Base case utility values (time-to-death approach), non-Asia region

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

Abbreviations: N, number of participants with non-missing score; SE, standard error
Source: MK3475_prot811_PEM_EQ5D_Report_v3.0, Table 118

Table 41: Utility values (time-to-death approach), Asia region

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

Abbreviations: N, number of participants with non-missing score; SE, standard error
Source: MK3475_prot811_PEM_EQ5D_Report_v3.0, Table 117

Scenario analysis: Progression-based approach

This approach, commonly employed in oncology economic modelling literature, defines health states based on time relative to disease progression, and hence generates results that can be used in a partitioned survival model by health state.

Using the mapped 3L values from the KEYNOTE-811 trial, the mean EQ-5D scores associated with each health state (progression-free and progressed disease) were estimated. The date of progression was determined based on RECIST Version 1.1 using BICR, as per the primary censoring rule applied to the PFS curve. The EQ-5D scores collected at all post-baseline visits prior to the date of the first documented disease progression if progression occurred before the progression date are used to estimate the utility for the progression-free state, and EQ-5D scores collected at all visits after the progression date to estimate the utility for the progressed disease state. As noted previously, the trial collection schedule means that there are relatively fewer values available for the PD health state (approximately 50% of those collected for the PF heath state). The descriptive utility values analysed from the trial data are reported in Table 42.[66] As with time-to-death, it was noted that the values reported for the Asia region population in the trial (Table 43) are implausibly high in most categories for patients with this advanced cancer, further underscoring the issue of generalisability of results for those patients to NHS practice.

The values estimated for both health states are much higher than those used in the TA208 economic analysis (see earlier paragraph), however it should be noted that neither of the values used in that appraisal were reported for the population they were associated with (i.e. baseline value for PF, and a value from another trial in patients with a different cancer receiving a different treatment for PD). The scenario analysis values presented below are the means of values for non-Asia region patients in the KEYNOTE-811 trial. A further scenario analysis follows the TA208 approach of using

the baseline utility value for PF and maintaining the quantitative relationship between the PF and PD values that was observed in the trial.

Table 42: Scenario analysis utility values (progression-based approach), non-Asia region

Health state	N	Utility value (mean)	SE
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of participants with non-missing score; SE, standard error
Source: MK3475_prot811_PEM_EQ5D_Report_v3.0, Table 114

Table 43: Utility values (progression-based approach), Asia region

Health state	N	Utility value (mean)	SE
Progression-free	[redacted]	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]	[redacted]

Abbreviations: N, number of participants with non-missing score; SE, standard error
Source: MK3475_prot811_PEM_EQ5D_Report_v3.0, Table 113

Adverse reactions

The negative impact AEs can have on patients' HRQoL was accounted for in the economic model as a one-off QALY loss in the first model cycle, consistent with the approach taken in TA737.[35] The model considers treatment-related Grade ≥3 AEs occurring in ≥3% of all CPS≥1 patients receiving either treatment. These AEs are relevant to the economic model as they are expected to have an impact in terms of resource use or HRQoL. AE rates are sourced from the KEYNOTE-811 trial.

The one-off QALY loss was calculated in each treatment arm as a function of:

- Treatment-specific AE rate (see section B.2.10)
- Mean duration of AEs per affected patient in KEYNOTE-811
- Estimated disutility associated with AE based on analyses of EQ-5D data from the KEYNOTE-811 trial. The disutility is calculated as the difference between the “During Grade 3+ AE” value and the “without AE value”, and hence reflects the impact on HRQoL of experiencing such an event. These values are not treatment-specific as the patient impact of experiencing an

AE is assumed to be independent of treatment arm. The difference between arms were observed to be negligible. Based on this assumption and to preserve a larger sample size, disutility values for the pooled population (both arms) are calculated.

The disutility and duration data for each AE is presented in Table 44 below. These values are assumed to be equivalent across treatment arms. The impact of removing this one-off QALY loss is explored in a scenario analysis.

Table 44: Disutility and duration of adverse events

Grade 3+ adverse event	Disutility		Duration (days)	
	Mean	SE	Mean	SE
Anaemia	[redacted]	[redacted]	157.17	31.5
Neutropenia	[redacted]	[redacted]	69.18	23.5
Thrombocytopenia	[redacted]	[redacted]	73.59	36.6
Diarrhoea	[redacted]	[redacted]	43.02	13.8
Nausea	[redacted]	[redacted]	112.55	43.7
Vomiting	[redacted]	[redacted]	45.20	14.4
Asthenia	[redacted]	[redacted]	210.40	82.5
Fatigue	[redacted]	[redacted]	136.88	68.7
Neutrophil count decreased	[redacted]	[redacted]	21.84	5.1
Platelet count decreased	[redacted]	[redacted]	101.75	34.0
Decreased appetite	[redacted]	[redacted]	115.53	33.1
Hypokalaemia	[redacted]	[redacted]	14.15	3.8
Peripheral sensory neuropathy	[redacted]	[redacted]	432.26	67.7

Abbreviations: SE, standard error
Source of disutility values: MK3475_prot811_PEM_EQ5D_Report_v3.0, Table 116

Table 45 presents the resulting one-off QALY loss applied to each treatment arm. Given the equivalence of disutility and duration values, the between-arm differences in the QALY loss are attributable to their differing AE rates.

Table 45: Adverse event QALY loss applied in the model

Regimen	QALY loss applied in Cycle 1
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]
Trastuzumab plus chemotherapy	[redacted]

Abbreviations: QALY, quality-adjusted life year

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

Table 46: Summary of HRQOL data applied in the cost-effectiveness analysis

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
360 or more days to death	[redacted]	Section B.3.4 , page 132	Utility values elicited from KEYNOTE-811; more accurately captures the patient experience as they approach death, uses values from both PF and PD health states, addresses imbalance in volume of available values between health states; values capped at those of general population
180 to 359 days to death	[redacted]		
30 to 179 days to death	[redacted]		
Less than 30 days to death	[redacted]		
Death	0		
One-off QALY loss due to AEs: Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	Section B3.4, page 134	Differential values applied due to arm-specific AE rates; equivalent disutility and duration per event assumed
One-off QALY loss due to AEs: Trastuzumab plus chemotherapy	[redacted]		

Abbreviations: AE, adverse event; PD, progressed disease; PF, progression-free; QALY, quality-adjusted life year

Age-related disutility

Age is a significant covariate for utility in the general UK population; therefore, age-related utility decrements are included in the model base case to account for the natural decline in quality of life. Furthermore, when extrapolating beyond the duration of the clinical trial, TSD12 recommends to supplement the health state utility values used to account for potential changes due to factors such as age and increasing numbers of comorbidities, by using data from the general population as the baseline.[67] The general population baseline utility was first determined using the

algorithm by NICE DSU, based on the model starting patient age and proportion of male patients, resulting in a baseline general population utility of 0.842 The equivalent general population utility value was then estimated at each model cycle. The multiplier applied in each cycle throughout the model time horizon was based on the relative decline in general population utility values at each model cycle time point versus the model baseline.[61] The impact of removing this disutility is explored in a scenario analysis.

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

A SLR was conducted to identify relevant cost and health care resource use data associated with the first-line treatment and management of patients with advanced GC, for the purpose of populating the economic model. Full details of the SLR search strategy, study selection process and results are presented in Appendix I.

The costs included in the model comprise:

1. Treatment-related costs (study treatment)
    a. Acquisition costs
    b. Administration costs
2. Subsequent treatment costs
    a. Acquisition costs
    b. Administration costs
3. Disease management costs
4. Adverse-event costs
5. End-of-life care costs
6. PD-L1 testing costs

Disease management costs differ according to progression status. Costs are sourced from the National Schedule of NHS Costs or the Unit Costs of Health and Social Care were obtained from the most recent publication.[47, 48] All other costs were inflated to a 2021/22 cost year as necessary using the NHS Cost Inflation Index (NHSCII) pay and prices indices.

Intervention and comparators' costs and resource use

Study treatment drug acquisition costs

Table 47 presents the list prices of drugs, sourced from the UK British National Formulary (BNF) online database (accessed 27 February 2023)[45] for branded products and the Department of Health and Social Care Drugs and pharmaceutical electronic market information tool (eMIT) for generic products,[46] last updated on March 22 2023.

Drug acquisition costs are applied in line with the dosing schedules for each treatment detailed in Table 48. A simple relative dose intensity (RDI) is applied to all treatments - RDI is expressed as a proportion (mg) of the planned dose a patient receives, these are presented for all drugs in Table 49. The RDI is defined as the actual number of doses divided by the expected number of doses and then multiplied by 100, and is based on an analysis of all CPS≥1 patients in the trial. 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. A commercial access agreement is currently in place, as discussed in section B.1.2. It is assumed that trastuzumab does not currently have a commercial access agreement, due to loss of exclusivity, and a generic biosimilar price has been used in the model.

For the intravenously administered drugs dosed by patient weight, wastage costs are assumed in the base case. This implies that the contents of vial which are incompletely administered are discarded and the cost of this surplus drug is included in the drug acquisition cost. The impact of vials being shared is explored in a scenario analysis, where wastage costs are excluded. In the base case, method of moments is applied to calculate an average number of vials received. This method accounts for the distribution of a patient population's weight, as opposed to a point estimate, and works by fitting a log-normal distribution to weight data. It also assumes that patients only receive whole vials (no vial sharing), therefore accounting for drug wastage. The variation in weight was obtained from the KN-811 trial CPS≥1 population in the non-Asia region in the base case. The drugs for which method of moments was used are

summarised in Table 50. It is assumed there are no wastage costs associated with treatments that are administered orally.

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).

Table 47: List prices of intervention and comparator drugs

Drug name	Drug form	Strength per unit (mg)	Units in packet	Price per pack (£)
Pembrolizumab	Vial	100	1	2,630.00
Trastuzumab	Vial	150	1	366.65
Capecitabine	Tablet	150	60	6.40
		300	60	31.17
		500	120	36.49
Oxaliplatin	Vial	100	1	24.44
		200	1	21.52
		50	1	13.49
5-FU	Vial	1000 mg	1	3.93
		2500 mg	1	4.05
		2500 mg	1	4.78
		500 mg	1	3.25
		500 mg	10	63.97
		5000 mg	1	10.54
Cisplatin	Vial	100	1	10.97
		50	1	9.10
Abbreviations: 5-FU, fluorouracil; IV, intravenous				

Table 48: Dosing schedules

Regimen	Drug	Frequency	Dosage	Maximum treatment cycles	Source for dosage
	Pembrolizumab	Q3W	200mg IV	35[51]	SmPC[56]
Loading dose	Trastuzumab	NA	8 mg/kg IV on Day 1	35[51]	NICE TA208[19]
Maintenance dose		Q3W	6 mg/kg IV on Day 1		
CAPOX	Capecitabine	Q3W	1000 mg/m^2 orally BID on Days 1–14	6	KEYNOTE-811[37]
	Oxaliplatin		130 mg/m^2 IV on Day 1	6	
FP	5-FU	Q3W	800 mg/m^2 IV on Days 1–5	6	

	Cisplatin		80 mg/m^2 IV on Day 1	6	
XP	Capecitabine	Q3W	1000 mg/m^2 orally BID on Days 1–14	6	NICE Guideline NG83[20]
	Cisplatin		80 mg/m^2 IV on Day 1	6	

Abbreviations: 5-FU, fluorouracil; BID, twice daily; IV, intravenous; NA, not applicable; NICE, National Institute for Health and Care Excellence; Q2W, ever 2 weeks; Q3W, every 3 weeks; SmPC, summary of product characteristics.
Note: all chemotherapy regimens are capped at a maximum of 6 cycles based on UK clinical expert opinion

Table 49: RDI applied in model base case

Comparator	Regimen	Treatment	Treatment cycle (weeks)	RDI
Pembrolizumab with trastuzumab plus chemotherapy	Pembrolizumab	200mg, Q3W	3	[redacted]
	Trastuzumab	Loading dose	3	[redacted]
		Maintenance dose	3	[redacted]
	CAPOX	Capecitabine	3	[redacted]
		Oxaliplatin	3	[redacted]
	FP	5-FU	3	[redacted]
		Cisplatin	3	[redacted]
	XP	Capecitabine	3	[redacted]
		Cisplatin	3	[redacted]
Trastuzumab plus chemotherapy	Trastuzumab	Loading dose	3	[redacted]
		Maintenance dose	3	[redacted]
	CAPOX	Capecitabine	3	[redacted]
		Oxaliplatin	3	[redacted]
	FP	5-FU	3	[redacted]
		Cisplatin	3	[redacted]
	XP	Capecitabine	3	[redacted]
		Cisplatin	3	[redacted]

Abbreviations: 5-FU, fluorouracil; CAPOX, capecitabine and oxaliplatin; FP, 5-FU and cisplatin; IV, intravenous; RDI, Relative Dose intensity; Q3W, every 3 weeks; Q3W, every 3 weeks; XP, capecitabine plus cisplatin.

Note: Source of RDI is KN-811, except in the XP regimen which was assumed to have an equivalent RDI to the corresponding drug in the FP and CAPOX regimens in the trial.

Table 50: Calculated average doses for drugs used in method of moments analysis

Drug name	Regimen amount per dose	Calculated drug amount per dose (no wastage) mg	Method of moments calculated drug amount (with wastage) mg*
Trastuzumab	8 mg/kg	576.00	664.85
	6 mg/kg	432.00	518.17
Oxaliplatin	130 mg/m2 (CAPOX)	234.00	384.36
5 FU	800 mg/m2 (FP)	1440.00	2500.00
Cisplatin	80 mg/m2	144.00	200.10

Abbreviations: 5-FU, fluorouracil; CAPOX, capecitabine and oxaliplatin; FP, 5-FU and cisplatin; kg, kilogram; mg, milligram

**drug amount is then rounded up to next full unit for costing*

Time-on-treatment

As per KEYNOTE-811, patients treated with pembrolizumab or trastuzumab are treated until disease progression or unacceptable toxicities or for a maximum of 35 doses (two years). A stopping rule has been implemented in the model for the intervention arm whereby patients do not receive pembrolizumab or trastuzumab treatment beyond 24 months (35 doses or 18 doses if using Q6W dosing). As discussed previously, a treatment cap of 6 cycles is applied to all chemotherapy regimens in order to reflect clinical practice in England and Wales, based on clinical expert opinion. For this reason, the KM data from KEYNOTE-811 was used directly in the model to estimate time-on-treatment, as data for all treatments is deemed to be complete. KM data for each treatment within a combination are considered separately, and the KM curves have previously been presented in section B.3.3. Parametric extrapolation was not employed in the base case analysis.

Study treatment drug administration costs

Administration costs per dose for the intervention and comparators are presented in Table 51. For IV drugs, it was assumed that patients would receive treatment in a hospital setting at each administration. Values were taken from the most recent National Schedule of NHS Costs (2021/22).[47] For administrations of regimens involving 5-FU (i.e. FP), which is administered over 5 days each cycle, the tariff for "Deliver complex chemotherapy, including prolonged infusion treatment, at first

attendance" (SB14Z) is employed. For administrations involving all other combinations of treatments, the tariff for "Deliver more complex parenteral chemotherapy at first attendance" (SB13Z) is employed. The oral therapy, capecitabine, is co-administered with IV therapies (i.e. as part of CAPOX and XP), hence no additional cost to the NHS is assumed.

Table 51: Drug administration costs

Treatment	In combination with	Reference code	Description	Administration cost (£)
Pembrolizumab	Trastuzumab + CAPOX	SB13Z	Deliver more complex parenteral chemotherapy at first attendance	353.64
	Trastuzumab + FP	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	474.94
	Trastuzumab + XP	SB13Z	Deliver more complex parenteral chemotherapy at first attendance	353.64
	Trastuzumab (i.e. beyond 6 cycles)	SB13Z	Deliver more complex parenteral chemotherapy at first attendance	353.64
Trastuzumab	CAPOX	SB13Z	Deliver more complex parenteral chemotherapy at first attendance	353.64
	FP	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	474.94
	XP	SB13Z	Deliver more complex parenteral chemotherapy at first attendance	353.64
	Monotherapy (i.e. beyond 6 cycles)	SB13Z	Deliver more complex parenteral chemotherapy at first attendance	353.64
Abbreviations: 5-FU, fluorouracil; CAPOX, capecitabine and oxaliplatin; FP, 5-FU and cisplatin				

Health-state unit costs and resource use

A comprehensive literature search was conducted on April 16 2023, to identify costs and resource use in the treatment of, and ongoing management of, unresectable locally advanced and metastatic GC. Please see Appendix I for details of the search strategy and literature identified.

Resource use is assumed to be linked to the health state rather than to the treatment arm. Patients incur disease management costs whilst in the PF and PD health states. For the PF health state, the previous NICE appraisal in this population (TA208) was used to inform the resource use. Disease management resource use in the progressed disease health state reflect those reported by Gomez-Ulloa et al. 2020,[54] a retrospective real-world evidence study of resource use in patients receiving second-line therapy for advanced GC 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 an accurate and more contemporary representation of the current treatment practice in PD than that presented in TA208. The number and percentage of patients using each key healthcare resource was informed by the study, and the results only included non-medicines resources that >5% of patients have used during the follow-up period. presents the resource use and unit costs for monitoring and disease management in both states. The frequency per year is calculated for each resource based on the mean follow-up period, and this assumes that patients use the resource once during the follow-up period.

Table 52 and Table 53 present the disease management costs for the PF and PF health states respectively, rounded to the nearest whole pound.

Table 52: Resource use (Progression-free health state)

Resource	Frequency (per week)	Source: frequency	Unit cost (£)	References
Non-admitted face-to-face attendance, first	0.33	TA208[19]	364	National Schedule of NHS Costs 2020/21. WF01B. Service code 370.
Non-admitted face-to-face attendance, follow-up	0.17		221	National Schedule of NHS Costs 2020/21. WF01A. Service code 370.
Cardiac monitoring	0.08		212	Weighted average of MUGA scan (RN22Z), echocardiogram (RD51C), as per TA208
Total cost per week (£)	**176**			
Total cost per month (£)	**764**			
Abbreviations: NHS, National Health Service; TA, technology appraisal				

Table 53: Resource use (Progressed disease health state)

Resource	Frequency (per year)	Source: frequency	Unit cost (£)	References
Hospitalization/inpatient stay	0.59	Gomez-Ulloa et al. 2020[54]	2,152	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		174	Emergency Care. Emergency Medicine, Category 3 Investigation with Category 1-3 Treatment. VB03Z.

Outpatient (visit for follow-up)	1.47		221	Consultant led. Currency description: Non-Admitted Face-to-Face Attendance, Follow-up. Currency code: WF01A. Service description: Medical oncology. Service code: 370
Blood cell count	1.79		5	Directly accessed pathology. Currency description: Phlebotomy. Currency code: DAPS08. This cost will also include liver and renal function test which are assessed via blood test
Biochemistry test	1.79		2	Directly accessed pathology Currency description: Clinical biochemistry Currency code: DAPS04
Liver function test	1.67		0	Covered by blood cell count
Renal function test	1.64		0	Covered by blood cell count
Blood pressure test	1.44		0	Assumed to incur no cost
Electrocardiogram	0.41		223	Outpatient procedures. Currency description: Electrocardiogram Monitoring or Stress Testing. Currency code: EY51Z. Service description: Medical oncology. Service code: 370

X-ray	0.29		38	Directly accessed diagnostic services. Currency description: Direct Access Plain Film. Currency code: DAPF
Ultrasound (non-obstetric)	0.26		58	Diagnostic imaging. Direct Access. Ultrasound Scan with duration of less than 20 minutes, without Contrast, RD40Z
CT scan	1.58		129	Diagnostic imaging. Currency description: Computerised Tomography Scan of Three Areas, without Contrast. Currency code: RD25Z
Endoscopy	0.15		220	Outpatient procedures. Currency description: Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over. Currency code: FE22Z. Service code: 106
Total cost per year (£)	**2,132**			
Total cost per month (£)	**178**			
Abbreviations: CT, computerised tomography; HRG, healthcare resource group				

End-of-life costs

A cost for end-of-life care is applied in the analysis upon death. The cost was sourced from NICE TA522, which assessed pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin was unsuitable.[55] Based on the acceptance of that cost, the cost was deemed to be applicable to this

appraisal. The appraisal reported a cost of £7,253 (2015/2016 value) to estimate the cost of hospital care in the last three months of life. This estimate was inflated to 2021/22 values and the current value of £8,169 is applied as a one-off cost to patients who die in each model cycle.

Adverse reaction unit costs and resource use

The safety results of the trial are presented in section B.2.10. The model includes the costs of managing Grade ≥3 AEs that occurred in ≥3% of all CPS≥1 patients in either treatment arm as these AEs were expected to have an important impact on costs. The approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in B.3.4.

The unit costs, informed by NHS reference costs for 2021/22, associated with the resolution of each AE event, are presented in Table 54 below, rounded to the nearest whole pound.

Table 54: Adverse event unit costs

Adverse event	Unit cost (£)	Notes
Anaemia	770	Weighted average of SA01G-K non-elective short stay: based on ERG criticism in TA737
Neutropenia	2,257	Weighted average of SA35A-E; note that TA208 currency codes for febrile neutropenia have been discontinued
Thrombocytopenia	993	Weighted average of SA12G-K: consistent with TA857
Diarrhoea	522	FD10M non-elective short stay; consistent with TA857, TA208 codes have been discontinued
Nausea	522	Assumed equal to diarrhoea
Vomiting	522	Assumed equal to diarrhoea
Asthenia	780	Assumed equal to fatigue
Fatigue	780	SA01G - Aplasia or Other Aplastic Anaemia, with CC Score 8+. Non-elective short stay (consistent with TA737). NR in TA208
Neutrophil count decreased	445	Non-elective short stay. WJ11Z Other disorders of immunity (consistent with TA737). NR in TA208
Platelet count decreased	993	Assumed equivalent to thrombocytopenia
Decreased appetite	561	Weighted average of Non-elective short stay FD04B-E; NR in TA208
Hypokalaemia	2,257	Assumed equivalent to neutropenia

Peripheral sensory neuropathy	607	Weighted average of AA26C-H, Acute setting
Abbreviations: ERG, Evidence Review Group; NR, not reported; TA, technology appraisal		

A one-off AE-related cost per first-line treatment arm were applied at the first model cycle, consistent with the approach taken in TA737[35] and were calculated based on the unit costs for managing each AE (Table 54) and the proportion of patients experiencing AEs for each arm presented in Table 55 below. Table 56 presents the one-off AE costs for the intervention and control arms. This approach allocates AE-related costs to all patients who have the potential to experience (i.e. all those treated) and provides a simplified method for estimating the cost.

Table 55: Estimation of adverse events proportions that occurred per treatment arm

Adverse event	% of patients experiencing the event		Mean number of events per patient		Adjusted % of patients experiencing the event*	
	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy
Anaemia	5.4%	5.4%	1.25	1.13	6.7%	6.1%
Neutropenia	7.4%	4.1%	1.45	1.17	10.7%	4.8%
Thrombocytopenia	3.4%	2.0%	1.10	1.00	3.7%	2.0%
Diarrhoea	9.7%	7.8%	1.14	1.09	11.1%	8.5%
Nausea	4.4%	4.7%	1.15	1.00	5.0%	4.7%
Vomiting	4.4%	3.4%	1.15	1.00	5.0%	3.4%
Asthenia	1.7%	3.1%	1.20	1.00	2.0%	3.1%
Fatigue	3.4%	2.0%	1.00	1.00	3.4%	2.0%
Neutrophil count decreased	8.1%	9.2%	1.75	1.41	14.1%	12.9%
Platelet count decreased	7.0%	5.4%	1.14	1.25	8.0%	6.8%
Decreased appetite	3.0%	2.7%	1.00	1.00	3.0%	2.7%
Hypokalaemia	3.0%	2.4%	1.00	1.57	3.0%	3.7%
Peripheral sensory neuropathy	4.0%	2.4%	1.00	1.00	4.0%	2.4%
*defined as the Total number of AE episodes (considering that some patients experienced multiple AE episodes) divided by the Total patient number						

Table 56: One-off AE costs applied in the model first cycle

	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy
One-off AE costs	£734	£540
Abbreviations: AE, adverse event		

Miscellaneous unit costs and resource use

Costs associated with subsequent therapies received by patients after treatment discontinuation

In the advanced GC pathway, first-line patients can progress to subsequent lines of treatment and the cost of this care is included in the economic analysis of first-line treatments, given that divergent treatment patterns per treatment arm were observed in KEYNOTE-811. It is noted that the trial administered subsequent treatments which are not approved in England and Wales, hence the cost and benefits of these treatments are not generalisable to current clinical practice. Clinical expert opinion was sought on the approach to treating HER2 positive patients following discontinuation of trastuzumab plus chemotherapy, and it is estimated that 50% of patients receive a subsequent treatment, which is typically split in equal proportions between those treated with docetaxel and platinum re-challenge.

In the model, subsequent treatments are assumed to affect cost only and are not associated with any adjustments to efficacy as the impact of subsequent treatment is assumed to be implicitly included in the modelled OS estimates. Therefore, the base case contains costs which are not incurred by NHS practice. A scenario analysis is presented using the proportions informed by clinical expert opinion.

The costs of subsequent treatments, following progression and cessation of initial treatment, are applied as a one-off cost in the cycle of progression as a simplifying assumption. The one-off cost is estimated as a weighted average based on the patients receiving a subsequent treatment (total across all lines) as a proportion of patients who completed or discontinued from the study treatment. The model included

the treatments most commonly administered to the CPS≥1 population. This is a conservative approach, as more patients in the Asia region cohort received subsequent treatments than in the non-Asia cohort (see Table 34), hence the analysis slightly overestimates the subsequent treatment costs in a base case which reflects the non-Asia region. The proportions receiving other treatments were distributed amongst those more common treatments. The treatments and their use amongst in both treatment arm cohorts in the model are presented in Table 57. Ramucirumab is intentionally excluded from the base case analysis due to the negative recommendation issued by NICE TA378.[68]

Table 57: Proportion of CPS≥1 patients receiving subsequent treatments

Subsequent Treatment (across all arms)	Proportions per arm	
	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The subsequent treatment cost is a weighted average of the costs for each treatment, weighted according to the distribution above, and incorporating the mean treatment duration observed for each treatment and the weekly acquisition cost. Consistent with first-line drug unit costs, the list prices of subsequent treatment drugs were also sourced from BNF and the eMIT, meaning that applicable confidential discounts available to the NHS were not accounted for. RDI were assumed to be 100% for all subsequent treatment drugs.

Administration costs were also applied to subsequent treatments, with a consistent approach to that of first-line treatments. A one-off weighted administration cost was estimated and applied alongside the drug acquisition cost. These estimates are presented in Table 58, rounded to the nearest whole pound.

Table 58: Summary of subsequent treatment costs used in the model

Treatment arm	Subsequent treatment acquisition costs	Subsequent treatment administration costs
Pembrolizumab with trastuzumab plus chemotherapy	£7,062	£1,221
Trastuzumab plus chemotherapy	£7,252	£1,297

PD-L1 testing cost

[redacted], the administration of PD-L1 testing is required to identify eligible patients. Patients with advanced GC also receive a HER2 test as standard in line with TA208, as the point at which they are deemed incurable. Clinical expert opinion indicates that in current NHS practice, these tests are administered at the same time, in order to proactively identify HER2-negative patients eligible for the available immunotherapy (in line with TA857[27]), pending the outcome of the HER2 test. Therefore, PD-L1 tests are administered to all patients in both treatment arms of the model, in order to align with NHS practice, leading to no incremental difference. Hence this testing cost is excluded from the base case analysis.

B.3.6 Severity

As discussed in section B.3.1, patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS≥1 experience a profound worsening in both their expected length of life and their quality of life. The economic evaluation assessed the severity of the condition, defined as the future health lost by people living with the condition with standard care in the NHS (including use of other available treatments, diagnostics, or best supportive care).[44] The QALY shortfall calculator developed by Schneider et al. 2022 was used to generate absolute and proportional QALY shortfall estimates using the reference case HRQoL norms (HSE 2017-18 EQ-5D-5L mapped to EQ-5D-3L using the Hernandez Alava et al. algorithm).[61, 69, 70] Patient characteristics used in the shortfall estimation were consistent with those informing the base-case economic analysis i.e. those from the non-Asia region previously presented in Table 29. These results were then used to assign a QALY weighting to

both treatment arms. In this analysis of HER2 positive patients, trastuzumab plus chemotherapy is considered to be representative of standard of care and the results for this arm were used to estimate the shortfall.

Table 59: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Proportion male (%)	79.10	B.3.2, Patient population
Starting age	60.20	B.3.2, Patient population

The only previous NICE appraisal in this population - TA208[19] - was consulted to investigate alternative QALY shortfall estimates (Table 60). General population QALY estimates were derived using the patient characteristics considered in this economic evaluation (Table 59), with total QALYs for trastuzumab plus chemotherapy extracted from the ERG report for TA208. It is noted that the median patient age for the TA208 population (59.0-61.0) is similar to the mean values in the KEYNOTE-811 non-Asia region; gender split was not identified. The total QALYs for trastuzumab differed according to the chemotherapy in combination; as a conservative assumption, the higher QALY outcome (i.e. in combination with FP) was selected. This indicated a proportional shortfall of over [redacted], supporting the allocation of a 1.2 QALY weighting. It is noted that this intervention met the previous end-of-life criteria and qualified for the higher WTP threshold, and pembrolizumab in combination with trastuzumab and chemotherapy would also qualify for a WTP of £50,000/QALY if those criteria currently applied to decision making.

Table 60: Summary list of QALY shortfall from previous evaluations

TA	Expected Total QALYs for the general population	Expected Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
TA208	12.277	0.980	11.297	92.0%
Abbreviations: QALY, quality-adjusted life year ***Source:*** *TA208; ERG report Table 23, page 90 – results for HCF (trastuzumab + FP)*				

The QALY shortfall estimates for the current evaluation are presented in Table 61. To calculate estimates of total QALYs expected with current treatment, health state utilities consistent with those used in the base case were applied (Table 62).

Table 61: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment*	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
12.277	[redacted]	[redacted]	[redacted]	1.0
Abbreviations: QALY, quality-adjusted life year **Includes the QALY loss (-0.010) associated with treatment-related adverse events*				

Table 62: Summary of health state benefits and utility values for QALY shortfall analysis

State	Mean utility	Undiscounted LYs	Discounted QALYs
360 or more days to death	[redacted]	2.981	[redacted]
180 to 359 days to death	[redacted]	0.365	[redacted]
30 to 179 days to death	[redacted]	0.374	[redacted]
Less than 30 days to death	[redacted]	0.076	[redacted]
AE disutility	[redacted]	-	[redacted]
Total		3.796	[redacted]
Abbreviations: AE, adverse event; LY, life year; QALY, quality-adjusted life year **One-off QALY loss accounts for the duration of each AE and the incidence associated with current treatment*			

The updated NICE manual and corresponding materials suggest that the committee adopt a suitable approach with respect to the QALY shortfall analysis based on the requirements of each appraisal.[44] The approach used in this evaluation was to estimate QALY shortfall estimates for this population, based on the SoC used in the economic analysis and associated QALY norms for the general population. This estimate of the QALY shortfall results in a 1.0 QALY modifier weight. However, this estimation is based on the SoC arm informed by data from all CPS≥1 patients in the trial, which as discussed previously, is not considered to be representative of NHS patients. An examination of the KM curve for the non-Asia region population indicates a lower survival curve for the SoC arm relative to all CPS≥1, indicating a reduced survival for these SoC patients, and it is implausible that NHS patients with this

condition would not incur a proportional shortfall of less than 85%. The QALY weight for the intervention arm has been adjusted to 1.2 in the base case analysis. Weighted cost-effectiveness results for the overall indication presented in Section B.3.10 include this QALY weight.

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 structural assumptions made within the economic model. The key areas of uncertainty in the economic analysis are considered to be the following:

- There is a paucity of longer-term survival data for trastuzumab plus chemotherapy in HER2 positive advanced GC patients. Since the publication of the ToGA trial, there have been limited data-based opportunities to understand the longer-term effects of treatment with the standard of care. As a result, clinical expert opinion was sought to inform plausible survival predictions for the standard of care arm, based on their clinical experience.

- The average starting age in the economic model reflected that of the non-Asia region PD-L1 CPS≥1 cohort in the KEYNOTE-811 trial, however input from clinical experts indicated the typical average age in UK practice in this setting to be higher (approximately 68 years was estimated). The impact of this younger age profile in the trial and model results is uncertain.

- Subjects in KEYNOTE-811 were offered a range of subsequent treatments following discontinuation from the study treatments. Discussions with UK clinical experts indicate there to be a lack of effective treatments available following trastuzumab plus chemotherapy i.e. fewer options in routine UK practice than in the trial. The efficacy results were not adjusted to reflect this, hence the impact of receiving the broader selection in the trial is uncertain. The scenario analysis for subsequent treatments adjusted treatment costs only.

- The economic evaluation follows the precedent from previous appraisals[35] where the QALY loss and cost associated with adverse events are applied as one-off impacts at the beginning of the model time horizon. This approach assumes that similar disutility is experienced, independent of both AE type and treatment arm. It is plausible that individual AEs may differ in HRQoL impact and according to which treatment is administered. However, it is expected the impact of using the base case approach on cost-effectiveness to be minor.

- The model base case reflects the distribution of chemotherapies administered in the trial, with the majority of patients receiving trastuzumab in combination with CAPOX. TA208 recommends the chemotherapy to be co-administered is XP or FP[19], and clinical expert opinion indicates the more commonly used regimen in clinical practice to be XP. This divergence between trial and practice is a potential source of uncertainty, however clinical expert opinion indicates doublet chemotherapies to be clinically equivalent when combined with trastuzumab in this population. Furthermore, the cost differentials between regimens are minor so the impact for cost-effectiveness of switching chemotherapy is expected to be limited.

- In order 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 practice. These maximum durations were not applied in KEYNOTE-811, hence there is uncertainty over whether continuing to administer chemotherapy beyond 6 cycles is associated with clinical benefit. The impact was investigated in scenario analysis.

- In KEYNOTE-811, subjects in both arms received up to a maximum of 35 cycles of trastuzumab. TA208 does not impose a maximum treatment duration[19] and was based on the ToGA trial, which permitted administration until disease progression. Clinical expert opinion confirmed the treatment cap in the trial is not replicated in clinical practice, hence the generalisability of the standard of care arm to practice is uncertain. However, it was also confirmed that the number of cycles received in practice is typically much lower than 35.

B.3.8 Managed access proposal

Given the maturity of the dataset available from KEYNOTE-811 and the limited number of pre-specified data cuts remaining in the trial, MSD believe 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.

MSD propose that the primary area of clinical uncertainty with a potential for resolution through interrogation of real-world evidence would be the representativeness of the non-Asia region data from KEYNOTE-811 for the population receiving the intervention in England and Wales.

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

Summary of base-case analysis inputs

The full list of variables used in the cost-effectiveness analysis is presented in Table 63 below.

Table 63: Summary of variables applied in the economic model

Parameter label	Varied in OWSA?	Varied in PSA?	Mean	Distribution	Lower Limit*	Upper Limit*	Section in CS
Discount rates							
Discount rate (costs)	No	No	3.50%	-	-	-	B.3.2
Discount rate (LYs)	No	No	3.50%		-	-	
Discount rate (QALYs)	No	No	3.50%	-	-	-	
Patient characteristics							

Age at model start	Yes	Yes	60.20	Normal	59.02	61.38	B.3.2
Proportion male	Yes	Yes	79.10%	Beta	43.8%	98.5%	
Weight, mean	Yes	Yes	72.00	Log-Normal	70.45	73.59	
BSA, mean	Yes	Yes	1.80	Log-Normal	1.78	1.82	
Proportion of different chemo backbones							
Pembrolizumab with trastuzumab plus CAPOX	No	No	77.2%	Dirichlet	-	-	B.3.2
Pembrolizumab with trastuzumab plus FP	No	No	22.8%	Dirichlet	-	-	
Pembrolizumab with trastuzumab plus XP	No	No	0.0%	Dirichlet	-	-	
Pembrolizumab with trastuzumab plus FOLFOX	No	No	0.0%	Dirichlet	-	-	
Trastuzumab plus CAPOX	No	No	78.5%	Dirichlet	-	-	
Trastuzumab plus FP	No	No	21.5%	Dirichlet	-	-	
Trastuzumab plus XP	No	No	0.0%	Dirichlet	-	-	
Trastuzumab plus FOLFOX	No	No	0.0%	Dirichlet	-	-	
Proportion of different dosing schedules of pembrolizumab							
Pembrolizumab 200mg Q3W % used	No	No	100.0%	Beta	100.0%	100.0%	B.3.2
Clinical inputs							
OS – Trastuzumab plus chemotherapy	No	No	Independently fitted spline (2k, odd)		-	-	B.3.3
PFS – Trastuzumab plus chemotherapy	No	No	Independently fitted spline (2k, hazard)		-	-	
OS HR – Pembrolizumab with trastuzumab plus chemotherapy	Yes	No	0.67	-	0.52	0.85	
PFS HR – Pembrolizumab with trastuzumab plus chemotherapy	Yes	No	0.62	-	0.49	0.78	
ToT – Pembrolizumab	No	No	Pembrolizumab ToT KM		-	-	
ToT Trastuzumab	No	No	Trastuzumab ToT KM		-	-	
ToT capecitabine	No	No	Capecitabine ToT KM		-	-	
ToT oxaliplatin	No	No	Oxaliplatin ToT KM		-	-	
ToT cisplatin	No	No	Cisplatin ToT KM		-	-	
ToT 5-FU	No	No	5-FU ToT KM		-	-	
Drug administration costs							
Cost per administration: Oral	Yes	Yes	£217	Normal	£140.37	£309.82	B.3.5
Cost per administration: Deliver simple parenteral chemotherapy at first attendance	Yes	Yes	£287	Normal	£185.54	£409.54	
Cost per administration: Deliver more complex parenteral chemotherapy at first attendance	Yes	Yes	£354	Normal	£228.85	£505.13	
Cost per administration: Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance	Yes	Yes	£475	Normal	£307.36	£678.41	
Cost per administration: Deliver subsequent elements of a chemotherapy cycle	Yes	Yes	£368	Normal	£238.44	£526.29	

Relative dose intensity							
Pembrolizumab with trastuzumab plus chemotherapy - Pembrolizumab, 200mg Q3W	Yes	Yes	[redacted]	Beta	42.8%	100.0%	B.3.5
Pembrolizumab with trastuzumab plus chemotherapy - Pembrolizumab, 400mg Q6W	Yes	Yes	[redacted]	Beta	42.8%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Trastuzumab (loading dose)	Yes	Yes	[redacted]	Beta	42.6%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Trastuzumab	Yes	Yes	[redacted]	Beta	42.6%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Capecitabine (CAPOX)	Yes	Yes	[redacted]	Beta	43.5%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Oxaliplatin (CAPOX)	Yes	Yes	[redacted]	Beta	42.6%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - 5-FU (FP)	Yes	Yes	[redacted]	Beta	42.8%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Cisplatin (FP)	Yes	Yes	[redacted]	Beta	50.1%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Capecitabine (XP)	Yes	Yes	[redacted]	Beta	43.5%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Cisplatin (XP)	Yes	Yes	[redacted]	Beta	50.1%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Leucovorin (FOLFOX)	Yes	Yes	[redacted]	Beta	42.8%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - 5-FU (FOLFOX)	Yes	Yes	[redacted]	Beta	42.8%	100.0%	
Pembrolizumab with trastuzumab plus chemotherapy - Oxaliplatin (FOLFOX)	Yes	Yes	[redacted]	Beta	42.6%	100.0%	
Trastuzumab plus chemotherapy - Trastuzumab (loading dose)	Yes	Yes	[redacted]	Beta	42.7%	100.0%	
Trastuzumab plus chemotherapy - Trastuzumab	Yes	Yes	[redacted]	Beta	42.7%	100.0%	
Trastuzumab plus chemotherapy - Capecitabine (CAPOX)	Yes	Yes	[redacted]	Beta	43.5%	100.0%	
Trastuzumab plus chemotherapy - Oxaliplatin (CAPOX)	Yes	Yes	[redacted]	Beta	42.6%	100.0%	
Trastuzumab plus chemotherapy - 5-FU (FP)	Yes	Yes	[redacted]	Beta	43.1%	100.0%	
Trastuzumab plus chemotherapy - Cisplatin (FP)	Yes	Yes	[redacted]	Beta	53.1%	100.0%	
Trastuzumab plus chemotherapy - Capecitabine (XP)	Yes	Yes	[redacted]	Beta	43.3%	100.0%	
Trastuzumab plus chemotherapy - Cisplatin (XP)	Yes	Yes	[redacted]	Beta	43.3%	100.0%	
Trastuzumab plus chemotherapy - Leucovorin (FOLFOX)	Yes	Yes	[redacted]	Beta	43.3%	100.0%	
Trastuzumab plus chemotherapy - 5-FU (FOLFOX)	Yes	Yes	[redacted]	Beta	43.3%	100.0%	
Trastuzumab plus chemotherapy - Oxaliplatin (FOLFOX)	Yes	Yes	[redacted]	Beta	43.3%	100.0%	

Distribution of subsequent treatments used among patients who progressed: Pembrolizumab with trastuzumab plus chemotherapy							
Paclitaxel + Ramucirumab	No	No	[redacted]	-	-	-	B.3.5
Paclitaxel	No	No	[redacted]	-	-	-	
Trastuzumab Deruxtecan	No	No	[redacted]	-	-	-	
Irinotecan	No	No	[redacted]	-	-	-	
Calcium Folinate + Fluorouracil + Irinotecan	No	No	[redacted]	-	-	-	
Docetaxel	No	No	[redacted]	-	-	-	
Nivolumab	No	No	[redacted]	-	-	-	
Trastuzumab	No	No	[redacted]	-	-	-	
Capecitabine + Oxaliplatin	No	No	[redacted]	-	-	-	
Distribution of subsequent treatments used among patients who progressed: Trastuzumab plus chemotherapy							
Paclitaxel + Ramucirumab	No	No	[redacted]	-	-	-	B.3.5
Paclitaxel	No	No	[redacted]	-	-	-	
Trastuzumab Deruxtecan	No	No	[redacted]	-	-	-	
Irinotecan	No	No	[redacted]	-	-	-	
Calcium Folinate + Fluorouracil + Irinotecan	No	No	[redacted]	-	-	-	
Docetaxel	No	No	[redacted]	-	-	-	
Nivolumab	No	No	[redacted]	-	-	-	
Trastuzumab	No	No	[redacted]	-	-	-	
Capecitabine + Oxaliplatin	No	No	[redacted]	-	-	-	
Subsequent treatment duration (weeks)							
Paclitaxel + Ramucirumab	Yes	Yes	[redacted]	Normal	10.51	24.05	B.3.5
Paclitaxel	Yes	Yes	[redacted]	Normal	6.32	14.48	
Trastuzumab Deruxtecan	Yes	Yes	[redacted]	Normal	11.80	27.02	
Irinotecan	Yes	Yes	[redacted]	Normal	6.58	15.06	
Calcium Folinate + Fluorouracil + Irinotecan	Yes	Yes	[redacted]	Normal	12.54	28.72	
Docetaxel	Yes	Yes	[redacted]	Normal	3.48	7.96	
Nivolumab	Yes	Yes	[redacted]	Normal	3.38	7.74	
Trastuzumab	Yes	Yes	[redacted]	Normal	9.15	20.95	
Capecitabine + Oxaliplatin	Yes	Yes	[redacted]	Normal	12.77	29.23	
Subsequent treatment acquisition costs							
Pack cost: Paclitaxel (1 units, strength = 100)	No	No	£8.49	Gamma	£5.50	£12.13	B.3.5
Pack cost: Paclitaxel (1 units, strength = 150)	No	No	£12.93	Gamma	£8.37	£18.47	
Pack cost: Paclitaxel (1 units, strength = 300)	No	No	£19.85	Gamma	£12.85	£28.35	
Pack cost: Paclitaxel (1 units, strength = 30)	No	No	£4.78	Gamma	£3.10	£6.83	
Pack cost: Trastuzumab Deruxtecan (1 units, strength = 100)	No	No	£1,455.00	Gamma	£941.60	£2,078.33	
Pack cost: Irinotecan (1 units, strength = 100)	No	No	£5.87	Gamma	£3.80	£8.39	
Pack cost: Irinotecan (1 units, strength = 300)	No	No	£13.71	Gamma	£8.87	£19.58	

Pack cost: Irinotecan (1 units, strength = 40)	No	No	£4.08	Gamma	£2.64	£5.82	
Pack cost: Irinotecan (1 units, strength = 500)	No	No	£19.03	Gamma	£12.31	£27.18	
Pack cost: Calcium Folinate (1 units, strength = 100)	No	No	£10.18	Gamma	£6.59	£14.55	
Pack cost: Calcium Folinate (1 units, strength = 300)	No	No	£30.59	Gamma	£19.80	£43.70	
Pack cost: Calcium Folinate (10 units, strength = 50)	No	No	£6.50	Gamma	£4.21	£9.29	
Pack cost: Fluorouracil (1 units, strength = 1000)	No	No	£3.93	Gamma	£2.54	£5.62	
Pack cost: Fluorouracil (1 units, strength = 2500)	No	No	£4.05	Gamma	£2.62	£5.78	
Pack cost: Fluorouracil (1 units, strength = 2500)	No	No	£4.78	Gamma	£3.09	£6.83	
Pack cost: Fluorouracil (1 units, strength = 500)	No	No	£3.25	Gamma	£2.10	£4.64	
Pack cost: Fluorouracil (10 units, strength = 500)	No	No	£63.97	Gamma	£41.40	£91.38	
Pack cost: Fluorouracil (1 units, strength = 5000)	No	No	£10.54	Gamma	£6.82	£15.06	
Pack cost: Docetaxel (1 units, strength = 160)	No	No	£15.67	Gamma	£10.14	£22.39	
Pack cost: Docetaxel (1 units, strength = 20)	No	No	£3.57	Gamma	£2.31	£5.10	
Pack cost: Docetaxel (1 units, strength = 80)	No	No	£8.18	Gamma	£5.29	£11.68	
Pack cost: Nivolumab (1 units, strength = 240)	No	No	£2,633.00	Gamma	£1,703.94	£3,760.99	
Pack cost: Trastuzumab (1 units, strength = 150)	No	No	£366.65	Gamma	£237.28	£523.72	
Pack cost: Capecitabine (60 units, strength = 150)	No	No	£6.40	Gamma	£4.14	£9.15	
Pack cost: Capecitabine (60 units, strength = 300)	No	No	£31.17	Gamma	£20.17	£44.53	
Pack cost: Capecitabine (120 units, strength = 500)	No	No	£36.49	Gamma	£23.62	£52.12	
Pack cost: Oxaliplatin (1 units, strength = 100)	No	No	£24.44	Gamma	£15.82	£34.91	
Pack cost: Oxaliplatin (1 units, strength = 200)	No	No	£21.52	Gamma	£13.93	£30.74	
Pack cost: Oxaliplatin (1 units, strength = 50)	No	No	£13.49	Gamma	£8.73	£19.27	
Subsequent treatment relative dose intensity							
Paclitaxel	No	No	100%	Beta	100%	100%	B.3.5
Ramucirumab	No	No	100%	Beta	100%	100%	
Paclitaxel	No	No	100%	Beta	100%	100%	
Trastuzumab Deruxtecan	No	No	100%	Beta	100%	100%	
Irinotecan	No	No	100%	Beta	100%	100%	
Calcium Folinate	No	No	100%	Beta	100%	100%	
Fluorouracil	No	No	100%	Beta	100%	100%	
Irinotecan	No	No	100%	Beta	100%	100%	
Docetaxel	No	No	100%	Beta	100%	100%	
Nivolumab	No	No	100%	Beta	100%	100%	
Trastuzumab	No	No	100%	Beta	100%	100%	

Capecitabine	No	No	100%	Beta	100%	100%	
Oxaliplatin	No	No	100%	Beta	100%	100%	
Cost per adverse event							
Anaemia	Yes	Yes	£770	Normal	£498.49	£1,100.28	B.3.5
Neutropenia	Yes	Yes	£2,257	Normal	£1,460.74	£3,224.19	
Thrombocytopenia	Yes	Yes	£993	Normal	£642.86	£1,418.93	
Diarrhoea	Yes	Yes	£522	Normal	£337.87	£745.75	
Nausea	Yes	Yes	£522	Normal	£337.87	£745.75	
Vomiting	Yes	Yes	£522	Normal	£337.87	£745.75	
Asthenia	Yes	Yes	£780	Normal	£504.87	£1,114.36	
Fatigue	Yes	Yes	£780	Normal	£504.87	£1,114.36	
Neutrophil count decreased	Yes	Yes	£445	Normal	£287.91	£635.48	
Platelet count decreased	Yes	Yes	£993	Normal	£642.86	£1,418.93	
Decreased appetite	Yes	Yes	£561	Normal	£362.94	£801.09	
Hypokalaemia	Yes	Yes	£2,257	Normal	£1,460.74	£3,224.19	
Peripheral sensory neuropathy	Yes	Yes	£607	Normal	£392.78	£866.95	
Adverse event utility decrements							
Anaemia	No	No	[redacted]	-	-0.0758	-0.0522	B.3.4
Neutropenia	No	No	[redacted]	-	-0.0758	-0.0522	
Thrombocytopenia	No	No	[redacted]	-	-0.0758	-0.0522	
Diarrhoea	No	No	[redacted]	-	-0.0758	-0.0522	
Nausea	No	No	[redacted]	-	-0.0758	-0.0522	
Vomiting	No	No	[redacted]	-	-0.0758	-0.0522	
Asthenia	No	No	[redacted]	-	-0.0758	-0.0522	
Fatigue	No	No	[redacted]	-	-0.0758	-0.0522	
Neutrophil count decreased	No	No	[redacted]	-	-0.0758	-0.0522	
Platelet count decreased	No	No	[redacted]	-	-0.0758	-0.0522	
Decreased appetite	No	No	[redacted]	-	-0.0758	-0.0522	
Hypokalaemia	No	No	[redacted]	-	-0.0758	-0.0522	
Peripheral sensory neuropathy	No	No	[redacted]	-	-0.0758	-0.0522	
Adverse event durations (days)							
Anaemia	Yes	Yes	157.17	Normal	95.43	218.91	B.3.4
Neutropenia	Yes	Yes	69.18	Normal	23.12	115.24	
Thrombocytopenia	Yes	Yes	73.59	Normal	1.86	145.32	
Diarrhoea	Yes	Yes	43.02	Normal	15.97	70.07	
Nausea	Yes	Yes	112.55	Normal	26.90	198.20	
Vomiting	Yes	Yes	45.20	Normal	16.98	73.42	
Asthenia	Yes	Yes	210.40	Normal	48.70	372.10	
Fatigue	Yes	Yes	136.88	Normal	2.23	271.53	
Neutrophil count decreased	Yes	Yes	21.84	Normal	11.84	31.84	
Platelet count decreased	Yes	Yes	101.75	Normal	35.11	168.39	
Decreased appetite	Yes	Yes	115.53	Normal	50.66	180.40	
Hypokalaemia	Yes	Yes	14.15	Normal	6.70	21.60	
Peripheral sensory neuropathy	Yes	Yes	432.26	Normal	299.57	564.95	

Adverse event events per participant: Pembrolizumab with trastuzumab plus chemotherapy							
Anaemia	No	No	1.25	Gamma	1.06	1.45	B.3.5
Neutropenia	No	No	1.45	Gamma	0.92	2.09	
Thrombocytopenia	No	No	1.10	Gamma	0.91	1.30	
Diarrhoea	No	No	1.14	Gamma	0.95	1.34	
Nausea	No	No	1.15	Gamma	0.96	1.35	
Vomiting	No	No	1.15	Gamma	0.96	1.35	
Asthenia	No	No	1.20	Gamma	0.84	1.62	
Fatigue	No	No	1.00	Gamma	0.65	1.43	
Neutrophil count decreased	No	No	1.75	Gamma	1.21	2.39	
Platelet count decreased	No	No	1.14	Gamma	0.95	1.34	
Decreased appetite	No	No	1.00	Gamma	0.65	1.43	
Hypokalaemia	No	No	1.00	Gamma	0.65	1.43	
Peripheral sensory neuropathy	No	No	1.00	Gamma	0.65	1.43	
Adverse event events per participant: Trastuzumab plus chemotherapy							
Anaemia	No	No	1.13	Gamma	0.94	1.33	B.3.5
Neutropenia	No	No	1.17	Gamma	0.98	1.37	
Thrombocytopenia	No	No	1.00	Gamma	0.65	1.43	
Diarrhoea	No	No	1.09	Gamma	0.90	1.29	
Nausea	No	No	1.00	Gamma	0.65	1.43	
Vomiting	No	No	1.00	Gamma	0.65	1.43	
Asthenia	No	No	1.00	Gamma	0.65	1.43	
Fatigue	No	No	1.00	Gamma	0.65	1.43	
Neutrophil count decreased	No	No	1.41	Gamma	1.05	1.83	
Platelet count decreased	No	No	1.25	Gamma	1.06	1.45	
Decreased appetite	No	No	1.00	Gamma	0.65	1.43	
Hypokalaemia	No	No	1.57	Gamma	1.04	2.21	
Peripheral sensory neuropathy	No	No	1.00	Gamma	0.65	1.43	
***Adverse event frequency: Pembrolizumab with trastuzumab plus chemotherapy*, % of patients who had the adverse event**							
Anaemia	Yes	Yes	5.37%	Beta	3.1%	8.2%	B.3.5
Neutropenia	Yes	Yes	7.38%	Beta	4.7%	10.6%	
Thrombocytopenia	Yes	Yes	3.36%	Beta	1.6%	5.7%	
Diarrhoea	Yes	Yes	9.73%	Beta	6.6%	13.3%	
Nausea	Yes	Yes	4.36%	Beta	2.4%	7.0%	
Vomiting	Yes	Yes	4.36%	Beta	2.4%	7.0%	
Asthenia	Yes	Yes	1.68%	Beta	0.5%	3.4%	
Fatigue	Yes	Yes	3.36%	Beta	1.6%	5.7%	
Neutrophil count decreased	Yes	Yes	8.05%	Beta	5.2%	11.4%	
Platelet count decreased	Yes	Yes	7.05%	Beta	4.4%	10.2%	
Decreased appetite	Yes	Yes	3.02%	Beta	1.4%	5.2%	
Hypokalaemia	Yes	Yes	3.02%	Beta	1.4%	5.2%	
Peripheral sensory neuropathy	Yes	Yes	4.03%	Beta	2.1%	6.5%	
***Adverse event frequency: Trastuzumab plus chemotherapy*, % of patients who had the adverse event**							

Anaemia	Yes	Yes	5.42%	Beta	3.1%	8.3%	B.3.5
Neutropenia	Yes	Yes	4.07%	Beta	2.1%	6.6%	
Thrombocytopenia	Yes	Yes	2.03%	Beta	0.8%	3.9%	
Diarrhoea	Yes	Yes	7.80%	Beta	5.0%	11.1%	
Nausea	Yes	Yes	4.75%	Beta	2.6%	7.4%	
Vomiting	Yes	Yes	3.39%	Beta	1.6%	5.7%	
Asthenia	Yes	Yes	3.05%	Beta	1.4%	5.3%	
Fatigue	Yes	Yes	2.03%	Beta	0.8%	3.9%	
Neutrophil count decreased	Yes	Yes	9.15%	Beta	6.1%	12.7%	
Platelet count decreased	Yes	Yes	5.42%	Beta	3.1%	8.3%	
Decreased appetite	Yes	Yes	2.71%	Beta	1.2%	4.8%	
Hypokalaemia	Yes	Yes	2.37%	Beta	1.0%	4.4%	
Peripheral sensory neuropathy	Yes	Yes	2.37%	Beta	1.0%	4.4%	
Healthcare resource use (progression-free)							
Non-admitted face-to-face attendance, first: unit cost	Yes	Yes	£364	Normal	£235	£520	B.3.5
Non-admitted face-to-face attendance, follow-up: unit cost	Yes	Yes	£221	Normal	£143	£316	
Cardiac monitoring: unit cost	No	No	£199	Normal	£129	£284	
Multigated acquisition (MUGA) scan: unit cost	Yes	Yes	£338	Normal	£219	£483	
Simple echocardiogram, 19+ years: unit cost	Yes	Yes	£130	Normal	£84	£186	
Healthcare resource use (progression-free)							
Non-admitted face-to-face attendance, first: frequency of use (per week)	Yes	Yes	0.33	Gamma	£0	£0	B.3.5
Non-admitted face-to-face attendance, follow-up: frequency of use (per week)	Yes	Yes	0.17	Gamma	£0	£0	
Cardiac monitoring: frequency of use (per week)	Yes	Yes	0.08	Gamma	£0	£0	
Healthcare resource use (progressed)							
Hospitalization/inpatient stay: unit cost	Yes	Yes	£2,180	Normal	£1,411	£3,115	B.3.5
Emergency room visit: unit cost	Yes	Yes	£174	Normal	£113	£249	
Outpatient (visit for follow-up): unit cost	Yes	Yes	£221	Normal	£143	£316	
Blood cell count: unit cost	Yes	Yes	£5	Normal	£3	£7	
Biochemistry test: unit cost	Yes	Yes	£2	Normal	£1	£2	
Liver function test: unit cost	Yes	Yes	£0	Normal	£0	£0	
Renal function test: unit cost	Yes	Yes	£0	Normal	£0	£0	
Blood pressure test: unit cost	Yes	Yes	£2	Normal	£1	£2	
Electrocardiogram: unit cost	Yes	Yes	£223	Normal	£144	£318	
X-ray: unit cost	Yes	Yes	£38	Normal	£25	£55	
Ultrasound (non-obstetric): unit cost	Yes	Yes	£58	Normal	£38	£83	
CT scan: unit cost	Yes	Yes	£129	Normal	£83	£184	
Endoscopy: unit cost	Yes	Yes	£220	Normal	£142	£314	
Healthcare resource use (progressed)							

Hospitalization/inpatient stay: frequency of use (per year)	Yes	Yes	0.59	Gamma	0.38	0.84	B.3.5
Emergency room visit: frequency of use (per year)	Yes	Yes	0.21	Gamma	0.14	0.30	
Outpatient (visit for follow-up): frequency of use (per year)	Yes	Yes	1.47	Gamma	0.95	2.10	
Blood cell count: frequency of use (per year)	Yes	Yes	1.79	Gamma	1.16	2.56	
Biochemistry test: frequency of use (per year)	Yes	Yes	1.79	Gamma	1.16	2.56	
Liver function test: frequency of use (per year)	Yes	Yes	1.67	Gamma	1.08	2.39	
Renal function test: frequency of use (per year)	Yes	Yes	1.64	Gamma	1.06	2.34	
Blood pressure test: frequency of use (per year)	Yes	Yes	1.44	Gamma	0.93	2.06	
Electrocardiogram: frequency of use (per year)	Yes	Yes	0.41	Gamma	0.27	0.59	
X-ray: frequency of use (per year)	Yes	Yes	0.29	Gamma	0.19	0.41	
Ultrasound (non-obstetric): frequency of use (per year)	Yes	Yes	0.26	Gamma	0.17	0.37	
CT scan: frequency of use (per year)	Yes	Yes	1.58	Gamma	1.02	2.26	
Endoscopy: frequency of use (per year)	Yes	Yes	0.15	Gamma	0.10	0.21	
End of life cost							
EOL Cost: NICE TA522	Yes	Yes	£7,253	Gamma	£4,694	£10,360	
Utility values - descriptive statistics approach - health state specific							
PFS	Yes	Yes	[redacted]	Beta	0.812	0.828	B.3.4
PD	Yes	Yes	[redacted]	Beta	0.718	0.761	
Utility values - descriptive statistics approach - time-to-death specific							
Utility values <30 days to death	Yes	Yes	[redacted]	Beta	0.416	0.611	B.3.4
Utility values [30, 180) days to death	Yes	Yes	[redacted]	Beta	0.720	0.763	
Utility values [180, 360) days to death	Yes	Yes	[redacted]	Beta	0.786	0.814	
Utility values ≥ 360 days to death	Yes	Yes	[redacted]	Beta	0.829	0.845	
Abbreviations: BSA, body surface area; CT, computerised tomography; EOL, end of life; HR, hazard ratio; LY, life year; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life year; Q3W, every 3 weeks; ToT, time-on-treatment **if SE data is unavailable, a 20% variance has been assumed*							

Assumptions

Table 64 presents the assumptions adopted in the base case analysis.

Table 64: List of assumptions used in the economic model

Category	Assumption made for base case analysis	Justification/reason
Model structure	A partitioned survival model is appropriate for use in this setting.	Established modelling precedent in the disease area; uses trial co-primary endpoints

Time horizon	40 years	Deemed appropriate and sufficient to capture all relevant and important differences in the future costs or outcomes among the modeled treatment arms
Perspective	NHS and PSS	2022 NICE manual reference case[44]
Discount rates	3.5% for costs and benefits	2022 NICE manual reference case[44]
WTP	£30,000	2022 NICE manual reference case[44]
Intervention OS	Non-Asia region HR applied at all time points	Proportional hazards assumption is not rejected
Comparator OS	Independently fitted spline model (2 knots, odd)	Goodness-of-fit, visual inspection
Intervention PFS	Non-Asia region HR applied at all time points	Proportional hazards assumption is not rejected
Comparator PFS	Independently fitted spline model (2 knots, hazard)	Goodness-of-fit, visual inspection
Intervention ToT	KM applied directly	KM data is mature
Comparator ToT	KM applied directly	KM data is mature
Treatment waning	No	No evidence to indicate a treatment waning, curves fit independently
Drug wastage costs	Drug wastage costs (no vial sharing)	Conservative assumption
Relative dose intensity	An adjustment is applied, based on the quantity administered in KEYNOTE-811.	To estimate the true cost to the NHS
Treatment stopping rules	Maximum cycle numbers of 35 (for pembrolizumab and trastuzumab) and 6 cycles (for chemotherapy) applied	To align with KN811 trial protocol (for pembrolizumab and trastuzumab) and NHS clinical practice (for chemotherapy) i.e. to align with expectations for how pembrolizumab would be used in clinical practice
Treatment administration	A single administrative cost for prolonged administration of complex chemotherapy covers the entirety of both intervention and comparator administration	National Schedule of NHS Costs presents up-to-date costs per episode[47]
Healthcare resource use	Disease management costs in progression-free and progressed disease health states are assumed to be the same for the intervention and comparator arms	Disease management costs assumed to be independent of treatment arm
AE costs	One-off application	Aligned with previous NICE TA737[35]
Utilities	The base case uses a time-to-death utility approach,	It is expected that health-related quality of life deteriorates as the

	applying an incremental utility value to each patient dependent upon the numbers of days until death, instead of a health state utility approach.	patient nears death. Also data collection in the trial provided more robust data for this approach.
AE QALY loss	One-off application	Aligned with previous NICE TA737[35]
Subsequent treatment costs	Subsequent treatments are assumed to be used after progression and are based on those administered in the KEYNOTE-811 trial	In the event patients do not respond to the intervention and disease progresses, they receive subsequent treatment to manage their condition
End-of-life costs	A one-off cost of death sourced from the literature is applied to the proportion of patients who die in each model cycle per treatment arm	This condition is a terminal disease; the approach is consistent with previous oncology appraisals
Abbreviations: AE, adverse event; KM, Kaplan-Meier; NHS, National Health Service; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; TA: technology assessment; ToT, time-on-treatment; WTP, willingness-to-pay		

B.3.10 Base-case results

The deterministic results of the base case analysis are presented in Table 65 below. The chemotherapy regimens used in both treatment arms reflect those administered in KEYNOTE-811, in the proportions reported from the trial.

In the base case analysis, using the non-Asia region PD-L1 CPS≥1 cohort, the estimated mean overall survival was [redacted] years with pembrolizumab with trastuzumab plus chemotherapy and [redacted] years with SoC (discounted life years). Patients treated with pembrolizumab with trastuzumab plus chemotherapy accrued [redacted] QALYs compared to [redacted] among patients in the SoC cohort. As discussed in section B.6.6, these QALY estimates for both arms have been weighted by a factor of 1.2. This gives an incremental life year gain of [redacted] years and an incremental QALY gain of [redacted] QALYs. MSD considers this to be a substantial and clinically meaningful improvement in both LYs gained, and QALYs gained, considering the unmet need within this patient population, and the absence of innovation in the treatment of this population in over a decade. The results show pembrolizumab with trastuzumab plus chemotherapy to be

cost-effective compared to SoC when considering a willingness to pay threshold of £30,000/QALY.

The net health benefit (NHB) is presented in Table 66 for WTP thresholds of £20,000/QALY and £30,000/QALY. A [redacted] NHB is observed at the higher threshold and a [redacted] NHB at the lower threshold.

The estimates of the clinical outcomes included in the cost-effectiveness analysis (compared with the clinical trial results) and the tabulated, disaggregated results for the base case are presented in Appendix J.

Table 65: Base-case discounted results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	4.94	[redacted]	-	-	-	
Trastuzumab plus chemotherapy	[redacted]	3.03	[redacted]	[redacted]	1.91	[redacted]	[redacted]

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

Table 66: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £20,000	NHB at £30,000
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	[redacted]	-	-		
Trastuzumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALYs, quality-adjusted life years
**Inclusive of x1.2 weighting*

B.3.11 Exploring uncertainty

Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-effectiveness 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 Table 63.

PSA results for the base case analysis are summarised in Table 67, inclusive of QALY weights. These results show that the mean PSA ICER is highly congruent to the deterministic base case ICER presented in Table 65. The mean PSA ICER appears robust to additional PSA draws, as illustrated by the convergence plot presented within the cost-effectiveness model. The corresponding cost-effectiveness plane is presented in Figure 38. This demonstrates that almost every PSA iteration estimates offers an incremental QALY benefit for pembrolizumab versus SoC at a positive incremental cost.

Table 67: Incremental cost-effectiveness results based on PSA vs. SoC

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	[redacted]	-	-	-
Trastuzumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 38: Cost-effectiveness plane for PSA (1,000 simulations) vs. SoC

The cost-effectiveness acceptability curve is presented in Figure 39 to demonstrate the probability of pembrolizumab being cost-effective versus SoC at increasing

willingness-to-pay thresholds. The analysis indicates that, when adjusting for severity-of-disease modifiers, the addition of pembrolizumab is cost-effective in approximately [redacted] of probabilistic iterations at the WTP threshold of £30,000/QALY.

Figure 39: Cost-effectiveness acceptability curve (1,000 simulations) vs. SoC

Abbreviations: SoC, standard of care

Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were conducted for multiple key variables using the lower and upper bounds of the 95% confidence intervals for the variables except when it is indicated otherwise. The key variables and their variance are presented in Table 63.

The results of the DSA for pairwise comparisons of pembrolizumab combination vs. SoC are presented in Figure 40 below.

The tornado diagram below shows the parameters the ICER is most sensitive to; the most impactful parameter is the OS HR applied to the SoC arm curve at all time points to generate the survival estimates for the intervention arm, particularly when set at or near the upper bound of its confidence interval. For the other parameters featuring in the top ten most impactful, there is movement in the ICER estimate, however this is modest and relatively stable. This list of parameters includes the PFS HR applied to the SoC arm curve at all time points.

Scenario analysis

Alternative scenarios were tested to assess uncertainty regarding structural and methodological assumptions in the cost-effectiveness analysis. A summary of the deterministic results is presented in Table 68, ranked in descending order from the most impactful scenario. This was the scenario which employed a time horizon of 8

years, as in the TA208 base case. The base case horizon of 40 years is considered more appropriate in order to capture all costs and benefits of the intervention arm.

A scenario which implemented a treatment waning from 7 years to 9 years to investigate the effect of pembrolizumab stopping rule also increased the ICER. With additional follow-up observed in immunotherapy trials, the ongoing benefit of immunotherapy following treatment stopping is further supported, and the waning timepoints above should be viewed as conservative.

Figure 40: Tornado diagram presenting the results of the deterministic sensitivity analysis for the ten most sensitive variables vs. SoC

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival, PFS, progression-free survival, RDI, relative dose intensity; SoC, standard of care

Table 68: Scenario analyses results (deterministic) vs. SoC

Rank	Scenario Name	Incremental Costs	Incremental QALYs	ICER	Difference vs. base case
1	Time horizon = 8 years	[redacted]	[redacted]	[redacted]	[redacted]
2	0% discounting	[redacted]	[redacted]	[redacted]	[redacted]
3	OS – gradual treatment waning between 7 & 9 years	[redacted]	[redacted]	[redacted]	[redacted]
4	1.5% discounting	[redacted]	[redacted]	[redacted]	[redacted]
5	Time horizon = 20 years	[redacted]	[redacted]	[redacted]	[redacted]
6	Progression-based utility approach with PFS value = baseline and PD value = 0.706	[redacted]	[redacted]	[redacted]	[redacted]
7	Progression-based utilities	[redacted]	[redacted]	[redacted]	[redacted]
8	Exclude age-related gen pop utility multiplier	[redacted]	[redacted]	[redacted]	[redacted]
9	Exclude RDI for 1L drugs	[redacted]	[redacted]	[redacted]	[redacted]
10	Pembrolizumab administration: 100% of patients on Q6W pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
11	% subsequent treatments adjusted by % patients who progressed	[redacted]	[redacted]	[redacted]	[redacted]
12	Exclude drug wastage (i.e. assume vial sharing)	[redacted]	[redacted]	[redacted]	[redacted]
13	UK subsequent treatments costs distribution – informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
14	Exclude terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]
15	UK chemotherapy regimen distribution - informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
16	Chemotherapy mean number of cycles as observed in trial	[redacted]	[redacted]	[redacted]	[redacted]
17	Include half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; SoC, standard of care

B.3.12 Subgroup analysis

This section is not applicable for this submission.

B.3.13 Benefits not captured in the QALY calculation

The use of pembrolizumab may result in potential substantial HRQoL benefits for patients' caregivers which have not been explicitly captured in the QALY calculation. It has been demonstrated that for patients with cancer, their cancer and its associated treatment can be associated with a significant HRQoL impact on their caregivers and families.[71]

As discussed previously, the KEYNOTE-811 trial results are the first breakthrough in the management of HER2 positive advanced GC since the ToGA trial, and follows a number of negative trials in this cancer (see section B.1.3). The addressing of a profound unmet need is positive news for patients and their families, which may not be reflected in the QALYs estimated by the economic analysis.

B.3.14 Validation

Validation of cost-effectiveness analysis

Efforts have been undertaken to validate the modelling approach and results. This section describes, in turn:

- Expert opinion used to guide the modelling approach
- Quality checks performed on the model
- Comparison with other trial data, including extrapolation of OS, median OS and PFS estimates, and OS at key time points (1 and 2 years).

Clinical expert opinion

As referenced throughout this dossier, clinical input was sought from two expert clinicians who are experienced in the management of HER2 positive 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 in order 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 HER2 positive unresectable locally advanced gastric/GOJ patients
- Use of chemotherapy regimens in combination with trastuzumab
- The role of international guidelines in the treatment pathway
- How patients are treated following progression of their cancer
- The generalisabiltiy of the KEYNOTE-811 population to UK practice, including the trial regional subpopulations
- Discussion of the KEYNOTE-811 efficacy and safety results, including subgroups
- Survival estimates for patients currently treated with the NHS SoC, and how this compares to those reported in clinical trials, including KEYNOTE-811
- Implications for NHS practice of introducing this intervention.

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 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. The checklist includes all checks listed in the published TechVER checklist.[72]

Comparison with other trial data

As discussed previously, there is a paucity of trials conducted in the HER2 positive advanced GC therapy area, and only one previous NICE TA was identified (TA208). This limited the potential for cross-trial comparison of results.

TA208, which was informed by the results of the ToGA trial, reported QALY results for an intervention arm which aligns with the SoC arm in the current economic evaluation. Depending on the chemotherapy used in combination with trastuzumab and the assumptions adopted, the mean QALYs reported by the ERG report ranged from 0.886 to 0.980.[19] The economic analysis informed by KEYNOTE-811 produced a markedly higher mean total QALY estimate for the SoC arm ([redacted]) than those reported in TA208, which is consistent with the higher median OS and survival rates reported in the ToGA trial.[38] Furthermore, the HRQoL values used in the TA208 economic model were sourced from alternative populations (i.e. baseline values for PF patients, and TA179[53] for PD health state) and were consistently lower than those elicited from patients in KEYNOTE-811.

As discussed previously, the intervention in TA208 qualified for a higher WTP threshold due to meeting the NICE end-of-life criteria and would qualify for a 1.2 QALY weighting under the severity modifier approach. The high survival rates observed for CPS≥1 patients in the KEYNOTE-811 SoC arm translate to an implausible outcome where the proportional shortfall estimated using the QALYs of all CPS≥1 patients do not allocate a QALY weighting to this intervention. The base case adjusts for this implausible outcome by applying a 1.2 QALY weight to align with TA208. Using the end-of-life criteria, pembrolizumab with trastuzumab plus chemotherapy would qualify for a WTP threshold of £50,000/QALY.

B.3.15 Interpretation and conclusions of economic evidence

An economic SLR identified no previous economic evaluations of pembrolizumab in combination with trastuzumab and chemotherapy for patients with untreated HER2

positive unresectable locally advanced or metastatic gastric or GOJ adenocarcinoma, expressing a CPS≥1. Therefore, a de novo economic model was developed to support this submission. The economic analysis leveraged certain relevant inputs from the previous appraisal in this population (TA208), where appropriate.

KEYNOTE-811 is a global clinical study and examination of the trial participant characteristics and subgroup results indicated the non-Asia region CPS≥1 population to be more generalisable to clinical practice in the NHS. The economic analysis is informed by this population and the plausibility of the proportional hazards assumption for OS and PFS enabled the application of the OS and PFS HR from the non-Asia region analysis to be applied to survival curves which had been fitted to the CPS≥1 SoC arm data. Uncertainty around this relationship holding at all time points is a limitation of the analysis.

Cost-effectiveness results evaluated deterministically and probabilistically demonstrate the addition of pembrolizumab to the current SoC to be a cost-effective intervention in this population. Patients benefit from significantly improved survival outcomes, as well as longer time spent in health states associated with an improved quality of life. The dosing regimen of pembrolizumab means patients can achieve this improved survival and quality of life without incurring an increased administration frequency, above what is currently used for treatment with trastuzumab. 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 HCRU costs due to patients surviving longer.

The model applied a number of assumptions, such as: clinical equivalence between doublet chemotherapies when combined with trastuzumab, that current treatment caps on chemotherapy regimens will persist with the addition of pembrolizumab to the regimen, and that the patient characteristics of the non-Asia region cohort will lead to similar outcomes in NHS patients. Discussions with clinical experts who treat patients in England with this cancer supported the above assumptions.

Parameter and structural uncertainty were explored through PSA, univariate DSA and scenario analysis. Overall, the sensitivity and scenario analyses explored indicate that, under a range of assumptions, pembrolizumab is associated with an ICER below the NICE willingness-to-pay threshold adjusted for the severity-of-disease decision modifier. Cost-effectiveness results were shown to be most sensitive to the OS HR applied to the SoC arm curve at all time points to generate the survival estimates for the intervention arm, and scenarios where the time horizon is 8 years (as in TA208) and the application of a treatment waning effect between 7 and 9 years after treatment initiation. The shorter time horizon appears inappropriate for the current analysis given the survival projections in the model predict patients to be alive in both treatment arms at this time point, and a longer time horizon is more consistent with the known clinical benefits of an immunotherapy. Furthermore, enhanced and longer clinical experience with immunotherapy drugs demonstrates that the waning of survival benefits, above what is modelled in survival curves, are less plausible than previously accepted. Other scenarios, including changes in subsequent therapies, administration frequency, chemotherapy treatment duration and utility approaches led to modest changes in the cost-effectiveness estimate.

The key strength of the current economic evaluation is that it is informed by the latest available pivotal trial data from KEYNOTE-811 and that evidence versus the relevant comparator is provided by a head-to-head comparison. Furthermore, drug costs and disease management costs were informed by inputs reported directly from UK sources, deemed to be reflective of NHS practice. Utility and AE-related disutility inputs were based on EQ-5D data collected directly from KEYNOTE-811 participants. Subsequent lines of treatment were also appropriately accounted for by incorporating the weighted drug acquisition and administration costs based on the distribution observed in the trial. The evaluation applies methods consistent with the relevant NICE DSU TSD recommendations and is consistent with the NICE reference case and the relevant decision problem. Results of the economic evaluation presented here indicate the addition of pembrolizumab to the current SoC is a cost-effective treatment option for patients with untreated HER2 positive unresectable locally advanced or metastatic

gastric or GOJ adenocarcinoma, expressing a CPS≥1 and that this conclusion is robust and consistent, as shown by a range of sensitivity and scenario analyses.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer [ID3742]

Summary of Information for Patients (SIP)

May 2023

File name	Version	Contains confidential information	Date
MSD submission (ID3742) SIP [ACIC]	V4	No	22 November 2023

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 trastuzumab and 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). 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 your 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) positive 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 October 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.
Genetic Alliance UK	No	Yes	We have met with Genetic Alliance once in 2022 to discuss corporate membership.
Guts UK	No	Yes	Guts UK provided a quote for inclusion in a SMC press release in Q1 2022. We met the CEO of Guts UK in March 2023 to discuss 2023 priorities.
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.

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 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 gastric cancers are locally advanced (stage 3). Of these 52% have a curative treatment plan (resectable) and 48% do not have a curative treatment plan (unresectable). Approximately 45% of gastric cancers 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. There is mounting evidence of the role of HER2 overexpression in patients with gastric cancer, and it leads to poor outcomes and a more aggressive disease.[8] A PD-L1** CPS≥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.[9, 10]

Each year, approximately 300 patients in England with untreated HER2 positive unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, expressing a CPS≥1 are expected to be eligible for treatment with pembrolizumab with trastuzumab plus 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 [11]. For more information on how pembrolizumab with trastuzumab 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.*

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.[12]

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)[13], 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)[14], pending the outcome of the HER2 test. Therefore, no additional diagnostic tests are required for pembrolizumab with trastuzumab and 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 your QoL.

In England and Wales, patients with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction generally receive first-line treatment with trastuzumab plus chemotherapy, in line with NICE's technology appraisal guidance TA208.[13]

Clinical expert opinion indicates that in NHS practice, patients with locally advanced unresectable gastric cancer or gastro-oesophageal junction adenocarcinoma are usually treated like metastatic patients (with trastuzumab and chemotherapy). This is also reflected in European treatment guidelines.[9] Any patients who are ineligible for trastuzumab would therefore also be ineligible for the newly proposed combination of pembrolizumab with trastuzumab plus chemotherapy. Patients who are ineligible for treatment with trastuzumab or pembrolizumab are likely to receive a doublet chemotherapy regimen (two chemotherapies in combination).

Platinum/fluoropyrimidine doublet regimens containing cisplatin or oxaliplatin and 5-FU or capecitabine are recognised worldwide as standard first-line chemotherapy regimens for participants with 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 [15], [9]. 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.

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 [16].

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 [17]. 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[18]:

- 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 [19].
- 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 [20].

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.[21]

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 trastuzumab and the health care professional's choice of doublet chemotherapy. Section 3a describes pembrolizumab and Section 2c describes doublet chemotherapy.

Trastuzumab is a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and attach to a specific structure (called an antigen) that is found on certain cells in the body. Trastuzumab has been designed to attach to HER2, which is overexpressed in about 25% of breast cancers and a 15% of gastric cancers. By attaching to HER2,

trastuzumab activates cells of the immune system, which then kill the tumour cells. Trastuzumab also stops HER2 producing signals that cause the tumour cells to grow.[22]

Unlike pembrolizumab, several brands of trastuzumab are currently available, the first brand name was Herceptin.[23]

The SmPC and the PIL for trastuzumab can be found by following this link:
MHRA Products | Substance

Trastuzumab increases the function of immune cells, which can improve the immune system's response to cancerous tumours. It may also increase tumour expression of PD-L1, which could improve how pembrolizumab works. [24-28] These observations led to the theory that combining a tumour-targeting antibody with a second antibody that boosts the immune system, in combination with standard chemotherapy, will improve the effectiveness of antibodies against cancerous tumours expressing HER2.

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

Safety data from two phase two trials (NCT02954536[29] and NCT02901301[30]) and one phase 3 trial (NCT03615326)[10] have demonstrated an acceptable safety profile for pembrolizumab with trastuzumab 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 [18, 21].

Trastuzumab for gastric cancer is also administered as an infusion into your vein. There is a subcutaneous version available for patients with certain other cancers. Patients who tolerate the first 90-minute infusion of trastuzumab can receive subsequent infusions over 30 minutes. The recommended dose of trastuzumab depends on bodyweight. The recommended initial (loading) dose is 8mg/kg and the recommended subsequent (maintenance) doses, once every 3 weeks thereafter, is 6mg/kg. Treatment will usually take place at an infusion clinic once every 3 weeks.[22, 31]

Trastuzumab administrations and pembrolizumab administrations will often happen at the same visit to the clinic to reduce the number of times the patient needs to visit the hospital. Infusions can be associated with allergic reactions, so patients should be monitored during and after the infusion.

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 and trastuzumab will also 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 XP (capecitabine + cisplatin) is used most often in the UK. Other commonly doublet chemotherapies include CAPOX (capecitabine + oxaliplatin) as oxaliplatin is more suitable than cisplatin for patients with impaired kidney function, cardiac issues and hearing issues) and FP (5-FU + cisplatin) as 5-FU is more suitable for patients with swallowing difficulties as there are no tablets to swallow.

Of these different chemotherapies, only capecitabine is given in a tablet.[32] Cisplatin and oxaliplatin are given as an infusion into your vein (intravenous).[33, 34] 5FU is usually given over 5 days as a continuous infusion through a small portable pump which can be taken home.[35] People with gastric cancer usually have a maximum of 6 cycles of chemotherapy (approximately 18 weeks); most people may continue to receive pembrolizumab or trastuzumab 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 1,663 (search conducted 15th May 2023). Of these, 46 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	Title	Status	Phases
NCT04209686	Paclitaxel, Pembrolizumab and Olaparib in Previously Treated Advanced Gastric Adenocarcinoma	Recruiting	Phase 2
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	Phase 3
NCT04164979	Ph II Study of Cabozantinib With Pembrolizumab in Metastatic Gastric and Gastroesophageal Adenocarcinoma	Recruiting	Phase 2
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	Phase 2
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	Phase 3
NCT02335411	A Study of Pembrolizumab (MK-3475) in Participants With Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (MK-3475-059/KEYNOTE-059)	Completed	Phase 2
NCT03196232	Epacadostat and Pembrolizumab in Treating Patients With Metastatic or Unresectable Gastroesophageal Junction or Gastric Cancer	Completed	Phase 2

NCT04089904	Phase II Trial of Neoadjuvant Pembrolizumab for Patients With Early Stage Gastroesophageal Adenocarcinoma	Recruiting	Phase 2
NCT03488667	Perioperative mFOLFOX Plus Pembrolizumab in Gastroesophageal Junction (GEJ) and Stomach Adenocarcinoma	Recruiting	Phase 2
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	Phase 1
NCT04190745	Toripalimab Combined With Apatinib Mesylate for the Treatment of Gastric Adenocarcinoma in a Prospective Randomized Multicenter Phase II Clinical Study	Recruiting	Phase 2
NCT05311176	A Study of IMU-131 (HER-Vaxx) in Combination With Chemotherapy or Pembrolizumab in Patients With Metastatic HER2/Neu Over-Expressing Gastric Cancer (nextHERIZON)	Recruiting	Phase 2
NCT05041153	Pembrolizumab and Lenvatinib for the Treatment of Advanced, Unresectable, or Metastatic Gastroesophageal Adenocarcinoma	Recruiting	Early Phase 1
NCT02013154	A Study of DKN-01 in Combination With Paclitaxel or Pembrolizumab	Completed	Phase 1
NCT04739202	Personalized Targeted IMMUNOtherapy-based Regimens in Recurrent GASTric Adenocarcinoma (IMMUNOGAST)	Recruiting	Phase 2
NCT04150640	Oxaliplatin and Liposomal Irinotecan (Plus Trastuzumab for HER2-positive Disease) in Advanced Esophageal and Gastric Adenocarcinoma	Recruiting	Phase 2
NCT05269381	Personalized Neoantigen Peptide-Based Vaccine in Combination With Pembrolizumab for the Treatment of Advanced Solid Tumors, The PNeoVCA Study	Recruiting	Phase 1
NCT03918499	IRX-2, Cyclophosphamide, and Pembrolizumab in Treating Participants With Recurrent or Metastatic Gastric or Gastroesophageal Junction Cancer	Completed	Phase 1|Phase 2
NCT05268510	Chemotherapy and Pembrolizumab, Followed by Pembrolizumab and Olaparib as Firstline Therapy in Her-2 Negative Gastric/GEJ Adenocarcinoma	Active, not recruiting	Phase 2
NCT02830594	Pembrolizumab and Palliative Radiation Therapy in Treating Patients With Metastatic Esophagus, Stomach, or Gastroesophageal Junction Cancer	Active, not recruiting	Phase 2
NCT03959293	Clinical Trial Evaluating FOLFIRI + Durvalumab vs FOLFIRI + Durvalumab and Tremelimumab in Second-line Treatment of Patients With Advanced Gastric or Gastro-oesophageal Junction Adenocarcinoma	Active, not recruiting	Phase 2
NCT04430738	Tucatinib Plus Trastuzumab and Oxaliplatin-based Chemotherapy or Pembrolizumab-containing Combinations for HER2+ Gastrointestinal Cancers	Recruiting	Phase 1|Phase 2
NCT05504720	Evaluating Pembrolizumab, Trastuzumab and FLOT as Perioperative Treatment of HER2-positive, Localized Esophagogastric Adenocarcinoma	Recruiting	Phase 2
NCT02599324	Study to Evaluate Ibrutinib Combination Therapy in Patients With Selected Gastrointestinal and Genitourinary Tumors	Completed	Phase 1|Phase 2
NCT04344795	Phase 1a/1b Study of TPST-1495 as a Single Agent and in Combination With Pembrolizumab in Subjects With Solid Tumors	Recruiting	Phase 1
NCT03257163	Pembrolizumab, Capecitabine, and Radiation Therapy in Treating Patients With Mismatch-Repair Deficient and Epstein-Barr Virus Positive Gastric Cancer	Recruiting	Phase 2
NCT03809624	Study of INBRX-105 and INBRX-105 With Pembrolizumab in Patients With Solid Tumors Including Head and Neck Cancer	Recruiting	Phase 2
NCT04007744	Sonidegib and Pembrolizumab in Treating Patients With Advanced Solid Tumors	Recruiting	Phase 1
NCT04682431	A Phase 1a/1b FIH Study of PY159 and in Combination With Pembrolizumab in Subjects With Advanced Solid Tumors	Recruiting	Phase 1
NCT05540145	Neoadjuvant Chemotherapy and Immunotherapy for HER2ï¼ˆ-ï¼‰ŒpMMR Locally Advanced Esophagogastric Junction and Gastric Adenocarcinoma	Recruiting	Phase 2
NCT02918162	Perioperative Chemo and Pembrolizumab in Gastric Cancer	Completed	Phase 2
NCT04032704	A Study of Ladiratuzumab Vedotin in Advanced Solid Tumors	Recruiting	Phase 2
NCT04114136	Anti-PD-1 mAb Plus Metabolic Modulator in Solid Tumor Malignancies	Recruiting	Phase 2
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	Phase 3
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	Phase 3
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	Phase 3

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	Phase 3
NCT03724851	Vactosertib in Combination With Pembrolizumab in Metastatic Colorectal or Gastric Cancer	Active, not recruiting	Phase 1|Phase 2
NCT04069273	Novel SEQUEnced Immunotherapy With Anti-angiogenesis and Chemotherapy in Advanced gastroesophageaL Adenocarcinoma	Recruiting	Phase 2
NCT03505320	A Study to Assess the Antitumor Activity, Safety, Pharmacokinetics and Biomarkers of Zolbetuximab (IMAB362) in Participants With Claudin (CLDN) 18.2 Positive, Metastatic or Advanced Unresectable Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma	Active, not recruiting	Phase 2
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	Phase 1|Phase 2
NCT04632459	Pembrolizumab Plus Ramucirumab in Metastatic Gastric Cancer	Recruiting	Phase 2
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	Phase 1|Phase 2
NCT03395847	Pembrolizumab in Treating Patients With Metastatic or Unresectable Gastroesophageal Adenocarcinoma	Recruiting	Early Phase 1
NCT03921021	Phase 2 Study of Telomelysin (OBP-301) in Combination With Pembrolizumab in Esophagogastric Adenocarcinoma	Active, not recruiting	Phase 2
NCT04997837	Study of Adjuvant Chemotherapy With or Without PD-1 Inhibitors and Chemoradiotherapy in Resected pN3 Gastric (G) or GEJ Adenocarcinoma	Recruiting	Phase 3

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-811 trial provides the data to support this appraisal. KEYNOTE-811 is a phase 3, randomised, placebo-controlled, multi-site, double-blind study in participants diagnosed with previously untreated, locally advanced unresectable or metastatic HER2 positive gastric or gastro-oesophageal junction adenocarcinoma. Approximately 698 participants from 20 countries (including 29 participants from the UK) were randomised in a 1:1 ratio to receive pembrolizumab or placebo each in combination with chemotherapy plus trastuzumab. This appraisal focuses on the results of the PD-L1 CPS≥1 subgroup (594 participants representing 85% of the global cohort), and more specifically also the PD-L1 CPS≥1 subgroup of patients in the non-Asia region (402 participants representing 58% of the global cohort), which are considered to be more generalisable to the population of patients in England and Wales.

To work out how well pembrolizumab with trastuzumab 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 trastuzumab plus chemotherapy decreases the chance of the outcome and a HR exceeding 1 indicates that the pembrolizumab with trastuzumab plus chemotherapy increases the chance of the outcome.

The results are as follows in the CPS≥1 subgroup based on non-Asia geographic region, which are considered to be more generalisable to the population in England and Wales:

- PFS
    - The PFS hazard ratio (HR) was 0.62 (95% confidence interval [CI]: 0.49, 0.78), in favour of pembrolizumab with trastuzumab plus chemotherapy
    - This represents a 38% reduction in the risk of disease progression when treated with pembrolizumab with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone
    - Median PFS was longer in the pembrolizumab with trastuzumab plus chemotherapy group (9.9 months [95% CI: 8.3, 11.3]) compared with the trastuzumab plus chemotherapy group (6.3 months [95% CI: 5.6, 7.3]), in favour of pembrolizumab with trastuzumab plus chemotherapy
- OS
    - The OS HR was 0.67 (95% CI: 0.52, 0.85), in favour of pembrolizumab with trastuzumab plus chemotherapy
    - This represents a 33% reduction in the risk of death when treated with pembrolizumab with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone
    - Median OS was longer in the pembrolizumab with trastuzumab plus chemotherapy group (18.8 months [95% CI: 15.5, 24.3]) compared with the trastuzumab plus chemotherapy group (12.6 months [95% CI: 11.1, 14.9]), in favour of pembrolizumab with trastuzumab plus chemotherapy

The results are as follows in the full CPS≥1 subgroup (regardless of geographic region)

- PFS
    - The PFS HR was 0.70 (95% CI: 0.58, 0.85), in favour of pembrolizumab with trastuzumab plus chemotherapy
    - This represents a 30% reduction in the risk of disease progression when treated with pembrolizumab with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone
    - Median PFS was longer in the pembrolizumab with trastuzumab plus chemotherapy group (10.8 months [95% CI: 8.5, 12.5]) compared with the trastuzumab plus chemotherapy group (7.2 months [95% CI: 6.8, 8.4]), in favour of pembrolizumab with trastuzumab plus chemotherapy
- OS
    - The OS HR was 0.79 (95% CI: 0.64, 0.98), in favour of pembrolizumab with trastuzumab plus chemotherapy
    - This represents a 21% reduction in the risk of death when treated with pembrolizumab with trastuzumab plus chemotherapy compared to trastuzumab plus chemotherapy alone

- Median OS was longer in the pembrolizumab with trastuzumab plus chemotherapy group (20.5 months [95% CI: 18.2, 24.3]) compared with the trastuzumab plus chemotherapy group (15.6 months [95% CI: 13.5, 18.6]), in favour of pembrolizumab with trastuzumab plus chemotherapy

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-811 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 9 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 [36]. 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)[18]. 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.

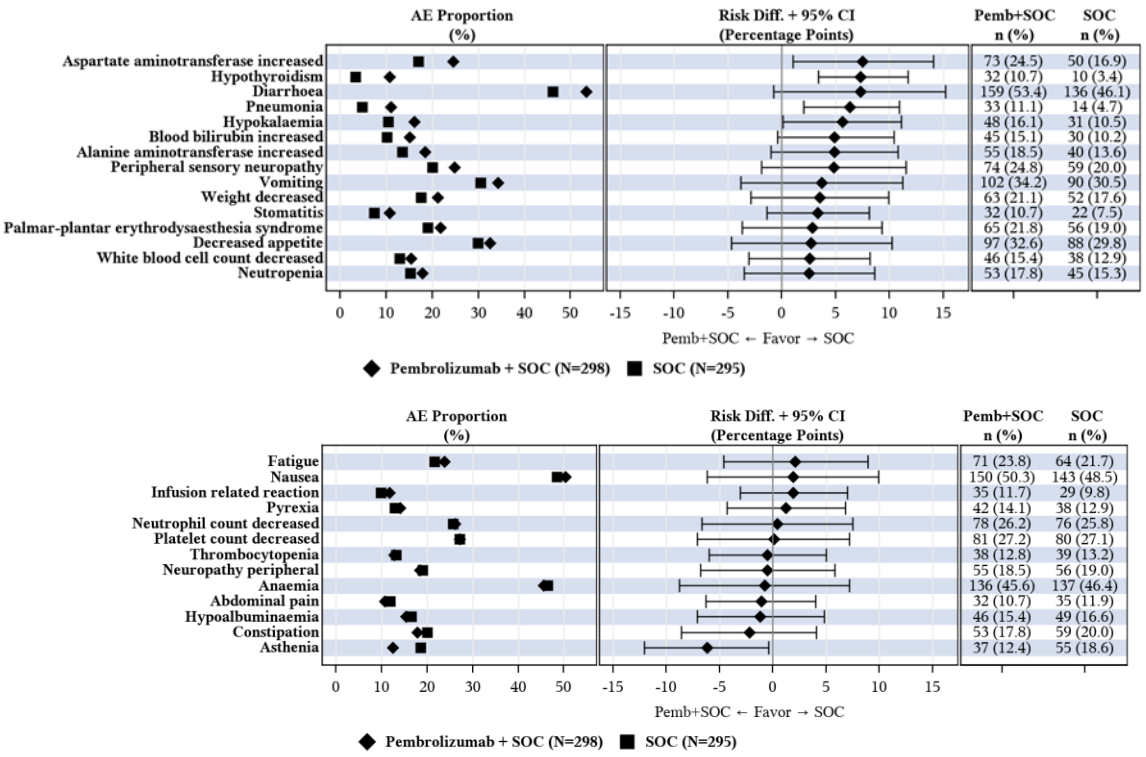
For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should 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-811 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-811. 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 – 811 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-811 data an overall survival HR of 0.67 (based on the non-Asia CPS≥ 1 subgroup) translates into a 33% reduction in the risk of death for patients taking pembrolizumab + trastuzumab + chemotherapy versus trastuzumab + chemotherapy alone.
- The risk of disease progression is also reduced by 38% (based on a HR of 0.62 in the non-Asia CPS≥1 subgroup) when treated with pembrolizumab + trastuzumab + chemotherapy versus trastuzumab + chemotherapy alone.
- 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 with trastuzumab plus chemotherapy in this indication (vs. trastuzumab plus chemotherapy that patients would otherwise receive) 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-811 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 with trastuzumab plus chemotherapy (or the comparator) in this indication.

How long patients stay in each health state depends on the data from the KEYNOTE-811 trial (Kaplan Meier curves for overall and progression-free survival). 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 (what is called "treatment effect waning") and if the duration of treatment should reflect NHS practice or the trial.

A unique characteristic of this appraisal is the different clinical characteristics and results for Asian and Non-Asian region participants. The results from the Asia region are subject to a high level of censoring and lower patient numbers. Furthermore, an examination of the subsequent therapies administered in KEYNOTE-811 reflect noteworthy treatment pathway differences between the regions. A greater proportion of patients in the Asia region received any subsequent therapy and imbalances were observed in the proportions receiving individual therapies, underscoring a trend of a more heavily treated population in the Asia region. The impact of this on trial efficacy outcomes is uncertain but highlights the differences between these trial populations based on geographic region (Asia vs. non-Asia). Based on the inconsistent survival curve shapes and the imbalance in clinical characteristics, the data reported for the non-Asia region participants in KEYNOTE-811 is deemed to be more generalisable to NHS patients in England and Wales; consequently, the economic modelling uses results from the non-Asia region.

Furthermore, the comparator arm in the KEYNOTE-811 trial appears to work better in this trial than it has in previous trials[37, 38] and better than clinical expert predictions, which may underestimate the additional benefit of pembrolizumab. The economic modelling allows for different statistical extrapolation methods to be applied to each treatment arm, which can help to resolve this uncertainty.

Another noteworthy point is that in NHS practice, doublet chemotherapies are given for a maximum of 6 treatment cycles, but in the KEYNOTE-811 trial, some chemotherapies could be given for a maximum 35 treatment cycles. The economic modelling allows different maximums to be applied, which can explore the impact of costing different durations of chemotherapy treatment.

Pembrolizumab with trastuzumab plus chemotherapy works by both helping to prevent patients from progressing and keeping progressed patients alive for longer than if they were receiving chemotherapies.

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 the improved survival – better PFS and OS – the typical pembrolizumab with trastuzumab plus chemotherapy patient will tend to have a better quality of life than a patient receiving trastuzumab plus 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 with trastuzumab plus chemotherapy could be considered cost-effective compared with trastuzumab plus chemotherapy. As mentioned above, a significant amount of scenario analyses that use different methods in different combinations are presented. Some make the results look better and some worse for pembrolizumab with trastuzumab plus chemotherapy. Only a few markedly change the result.

Under NICE's previous methods for evaluating new medicines, pembrolizumab with trastuzumab plus 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.[39] The severity modifier determines a weight which can be assigned to the QALYs accrued by the treatments. Given that survival and QoL outcomes for patients on trastuzumab plus chemotherapy (current NHS treatment) are severe compared with the general population of a similar age, a severity modifier of 1.2 is likely to apply for this condition, which changes the threshold against which NICE considers a medicine to be cost effective. This means that the usual standard for assessing cost-effectiveness is less relevant and higher thresholds apply in this appraisal.

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 TA208 recommends trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, as an option for the treatment of people with HER2-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction.[13] However, for over decade, patients with HER2 positive gastric cancer and gastro-oesophageal junction adenocarcinoma have had no new effective treatment options. This appraisal will address the ongoing unmet need and offer the first immunotherapy treatment option for patients with advanced metastatic HER2 positive gastric cancer and gastro-oesophageal junction adenocarcinoma, 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) [40]. 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:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with trastuzumab and chemotherapy for untreated HER2 positive advanced gastric or gastro-oesophageal junction cancer [ID3742]

MSD response to clarification questions

25th July 2023

File name	Version	Contains confidential information	Date
MSD response to clarification questions [ACIC]	v 3	Yes	25 July 2023

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

Searches

A1. In company submission (CS) appendix D1 Table 1: PICOS criteria excludes any other interventions that are not listed. Can the company explain why the several unlisted drugs (doxetaxel; paclitaxel; s1-tegafur-oxonate; ipilimumab; avelumab; bevacizumab; leucovorin; carboplatin; sorafenib; ramucirumab; pralatrexate; irinotecan; cediranib; golvatinib; epirubicin) are included in the search strategy (e.g. Appendix D1 Tables 2 and Table 3, pages 5 and 26, respectively).

MSD response:

The systematic literature review (SLR) was conducted for a global market including the UK; therefore, the search strategy included a broader list of interventions than were identified in the final scope. The unlisted drugs were excluded at the stage of the UK adaptation and were not included in the feasibility assessment.

KEYNOTE-811

A2. PRIORITY. Provide the clinical study report (CSR) for KEYNOTE-811

MSD response:

The clinical study report has been uploaded to the NICE docs as requested.

A3. Please confirm if the study protocol dated 27th Feb 2019 (provided as a supplementary file for the Chung 2021 paper) is the latest protocol for KEYNOTE-811. If not, please provide a copy of the latest version of the study protocol or indicate where this can be found in the references if it has already been supplied.

MSD response:

The latest study protocol has been uploaded to the NICE docs as requested.

A4. PRIORITY. The draft summary of product characteristics (SmPC) states that in KEYNOTE-811, programmed death-ligand 1 (PD-L1) status was measured using the PD-L1 1HC 22c3 pharmDx™, but the requirement for PD-L1 testing for clinical use given in the SmPC is that tumour expression of PD-L1 should be confirmed by a 'validated test'. The company states that PD-L1 has become established routine NHS care since publication of technology appraisal 587 (TA857), which requires PD-L1 status to be assessed for eligibility to nivolumab for patients with untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. However, in the clinical trial of nivolumab for the indicated considered in TA857 (CheckMate 649 / CA209649), the testing kit used was the PD-L1 IHC 28-8 pharmDx assay (SmPC for nivolumab). Costs of PD-L1 testing using this specific kit were included in the economic analysis for TA857.

- Please clarify which assay kit is used to determine PD-L1 status in current NHS practice and whether clinicians will need access to different assay kits when assessing PD-L1 status for eligibility to nivolumab in HER2-negative patients and eligibility for pembrolizumab in HER2-positive patients.

- Please also clarify whether there are any data on the agreement between different PD-L1 testing assays when used to select patients with a PD-L1 combined positive score (CPS) score ≥1.

- Please also clarify if the same PD-L1 test (PD-L1 1HC 22c3 pharmDx™) was performed in all countries included in the study.

MSD response:

The PD-L1 IHC 28-8 pharmDx assay and PD-L1 1HC 22c3 pharmDx™ assay are both routinely used within NHS clinical practice. Practice differs across centres where some use inhouse testing, and other NHS centres send to a centralised laboratory service. Both tests have become established as routine following the approval of nivolumab in HER2 negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma (TA857) and pembrolizumab in advanced oesophageal and gastro-oesophageal junction cancer (TA737). No new assay will be required for testing of eligibility of patients with HER2-positive gastric/GOJ cancer.

Published data [1] confirms concordance between the PD-L1 IHC 28-8 pharmDx assay and PD-L1 1HC 22c3 pharmDx™ assay across a range of tumour types. Ahn and Kim [2] concluded that '*PD-L1 22C3 and 28-8 pharmDx assays were highly comparable at CPS cut-offs of 1, 10, and 50 in gastric cancer. These results provide evidence for the potential interchangeability of the two PD-L1 assays in gastric cancer*.'

MSD confirms that the same PD-L1 test (PD-L1 1HC 22c3 pharmDx™) was performed in all countries included in the study.

A5. CS, Table 24 states that the submission focuses on the PD-L1 CPS≥1 subgroup because this is in line with the anticipated regulatory indication wording. Has the company conducted any subgroup analysis by CPS score using any cuff-off other than ≥1 and if so please provide subgroup results for progression free survival (PFS) and overall survival (OS) according to these CPS score cut-offs.

MSD response:

Analyses in CPS<1 and CPS≥10 populations have been conducted. The results in CPS<1 population are not relevant for this appraisal as MSD is not seeking regulatory approval and reimbursement in this subgroup of patients.

Results in patients with CPS≥10 population are presented below. Results in patients with CPS≥10 population in non-Asia region will be provided to the EAG during the week commencing July 10th 2023.

Participants Whose Tumours Express PD-L1 CPS ≥10

Participants with CPS ≥10 was not a prespecified subgroup, nor a stratification factor in KEYNOTE-811. The numeric PD-L1 raw score was used to perform the post-hoc analyses requested by the EMA. It should be noted that prior assessments have shown that using raw scores to extrapolate to a defined CPS cut point is not as accurate as when CPS is scored for the entire study at a specifically defined and validated cut point by trained pathologist(s).

These exploratory subgroups were not individually powered to demonstrate treatment effect; therefore, the results of these exploratory analyses should be interpreted with caution. Post-hoc analyses of CPS as a continuous variable were performed within the CPS ≥1 population. The CPS 1-9 population refers to participants with CPS <10 within the CPS ≥1 population.

In participants whose tumours express PD-L1 CPS ≥10 (36.2% in the CPS ≥1 population in both treatment groups), baseline characteristics were generally similar between the pembrolizumab + SOC group and the SOC group (Table 1).

The point estimates for OS and PFS favoured pembrolizumab + SOC. In addition to being post-hoc exploratory analyses, the small sample size limits interpretation of the data.

- The PFS HR was 0.72 (95% CI: 0.52, 1.01) (Table 2), (Figure 1).
- The OS HR was 0.93 (95% CI: 0.66, 1.32) (Table 3), (Figure 2).

Table 1: Participant Characteristics (CPS ≥10 (Raw Score) Participants) (Global Cohort) (CPS ≥1 Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	109		106		215	
Sex						
Male	86	(78.9)	82	(77.4)	168	(78.1)
Female	23	(21.1)	24	(22.6)	47	(21.9)

Age (Years)						
< 65	62	(56.9)	63	(59.4)	125	(58.1)
>= 65	47	(43.1)	43	(40.6)	90	(41.9)
Mean	61.0		61.0		61.0	
SD	11.2		10.7		10.9	
Median	63.0		60.0		62.0	
Range	19 to 84		32 to 85		19 to 85	
Race						
American Indian Or Alaska Native	1	(0.9)	4	(3.8)	5	(2.3)
Asian	38	(34.9)	43	(40.6)	81	(37.7)
Black Or African American	2	(1.8)	2	(1.9)	4	(1.9)
Multiple	2	(1.8)	2	(1.9)	4	(1.9)
White	66	(60.6)	55	(51.9)	121	(56.3)
Ethnicity						
Hispanic Or Latino	12	(11.0)	18	(17.0)	30	(14.0)
Not Hispanic Or Latino	95	(87.2)	88	(83.0)	183	(85.1)
Not Reported	1	(0.9)	0	(0.0)	1	(0.5)
Unknown	1	(0.9)	0	(0.0)	1	(0.5)
Age Group (Years)						
18-39	4	(3.7)	4	(3.8)	8	(3.7)
40-49	14	(12.8)	7	(6.6)	21	(9.8)
50-59	23	(21.1)	39	(36.8)	62	(28.8)
60-69	42	(38.5)	29	(27.4)	71	(33.0)
70-79	24	(22.0)	24	(22.6)	48	(22.3)
>=80	2	(1.8)	3	(2.8)	5	(2.3)
Age Group 2 (Years)						
< 65	62	(56.9)	63	(59.4)	125	(58.1)
65 - 74	38	(34.9)	35	(33.0)	73	(34.0)
75 - 84	9	(8.3)	7	(6.6)	16	(7.4)
85+	0	(0.0)	1	(0.9)	1	(0.5)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	34	(31.2)	27	(25.5)	61	(28.4)
Asia	38	(34.9)	42	(39.6)	80	(37.2)
Rest of the World	37	(33.9)	37	(34.9)	74	(34.4)
ECOG Performance Scale						
0	45	(41.3)	40	(37.7)	85	(39.5)
1	64	(58.7)	66	(62.3)	130	(60.5)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	30	(27.5)	32	(30.2)	62	(28.8)
Adenocarcinoma of the stomach	79	(72.5)	74	(69.8)	153	(71.2)
Current Disease Overall Stage						
IIB	1	(0.9)	0	(0.0)	1	(0.5)
IIIA	1	(0.9)	1	(0.9)	2	(0.9)
IIIB	2	(1.8)	0	(0.0)	2	(0.9)
IIIC	0	(0.0)	2	(1.9)	2	(0.9)
IV	105	(96.3)	103	(97.2)	208	(96.7)
Disease Status						

Locally advanced	4	(3.7)	4	(3.8)	8	(3.7)
Metastatic	105	(96.3)	102	(96.2)	207	(96.3)
Number of Metastatic Sites						
0-2	56	(51.4)	59	(55.7)	115	(53.5)
>=3	53	(48.6)	47	(44.3)	100	(46.5)
Histological Subtype (Lauren classification)						
Diffuse	25	(22.9)	15	(14.2)	40	(18.6)
Intestinal	55	(50.5)	52	(49.1)	107	(49.8)
Indeterminate	29	(26.6)	39	(36.8)	68	(31.6)
Prior Gastrectomy/Esophagectomy						
Yes	12	(11.0)	17	(16.0)	29	(13.5)
No	97	(89.0)	89	(84.0)	186	(86.5)
PD-L1 Status (CPS≥1)						
Positive	109	(100.0)	106	(100.0)	215	(100.0)
Tumour Burden						
< Median	49	(45.0)	52	(49.1)	101	(47.0)
>= Median	55	(50.5)	51	(48.1)	106	(49.3)
Missing	5	(4.6)	3	(2.8)	8	(3.7)
HER2 Status						
IHC 1+	1	(0.9)	0	(0.0)	1	(0.5)
IHC 2+ ISH Negative	0	(0.0)	1	(0.9)	1	(0.5)
IHC 2+ ISH Positive	16	(14.7)	25	(23.6)	41	(19.1)
IHC 3+	92	(84.4)	80	(75.5)	172	(80.0)
MSI Status						
MSI High	4	(3.7)	0	(0.0)	4	(1.9)
non-MSI-High	102	(93.6)	100	(94.3)	202	(94.0)
Unknown	3	(2.8)	6	(5.7)	9	(4.2)
Chemotherapy Regimen						
CAPOX	90	(82.6)	91	(85.8)	181	(84.2)
FP	19	(17.4)	15	(14.2)	34	(15.8)

CAPOX: Backbone chemotherapy oxaliplatin + capecitabine.
a The median of tumour burden was calculated from the global cohort.
Database Cutoff Date: 25 May 2022.

Table 2: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS ≥10 (Raw Score) Participants) (Global Cohort) (CPS ≥1 Population)

	Pembrolizumab + SOC	SOC
	(N=109)	(N=106)
Number of Events (%)	67 (61.5)	75 (70.8)
DEATH	11 (10.1)	11 (10.4)
DOCUMENTED PROGRESSION	56 (51.4)	64 (60.4)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	11.7 (7.2, 15.2)	8.8 (7.0, 11.2)
[Q1, Q3]	[5.4, 33.8]	[5.0, 18.1]
Person-months	1378.8	1069.8
Event Rate / 100 Person-months	4.9	7.0
vs SOC		

Hazard Ratio (95% CI)[b]	0.72 (0.52, 1.01)	
p-value[c]	0.0262	
PFS Rate at month 6 (%) (95% CI)	67.8 (57.8, 75.9)	65.3 (54.9, 73.8)
PFS Rate at month 12 (%) (95% CI)	49.6 (39.5, 58.9)	38.9 (28.8, 48.8)
PFS Rate at month 18 (%) (95% CI)	36.5 (26.8, 46.2)	25.9 (17.1, 35.6)
PFS Rate at month 24 (%) (95% CI)	35.2 (25.5, 44.9)	15.3 (8.2, 24.4)

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.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 25 May 2022

Figure 1: Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS ≥10 (Raw Score) Participants) (Global Cohort) (CPS ≥1 Population)

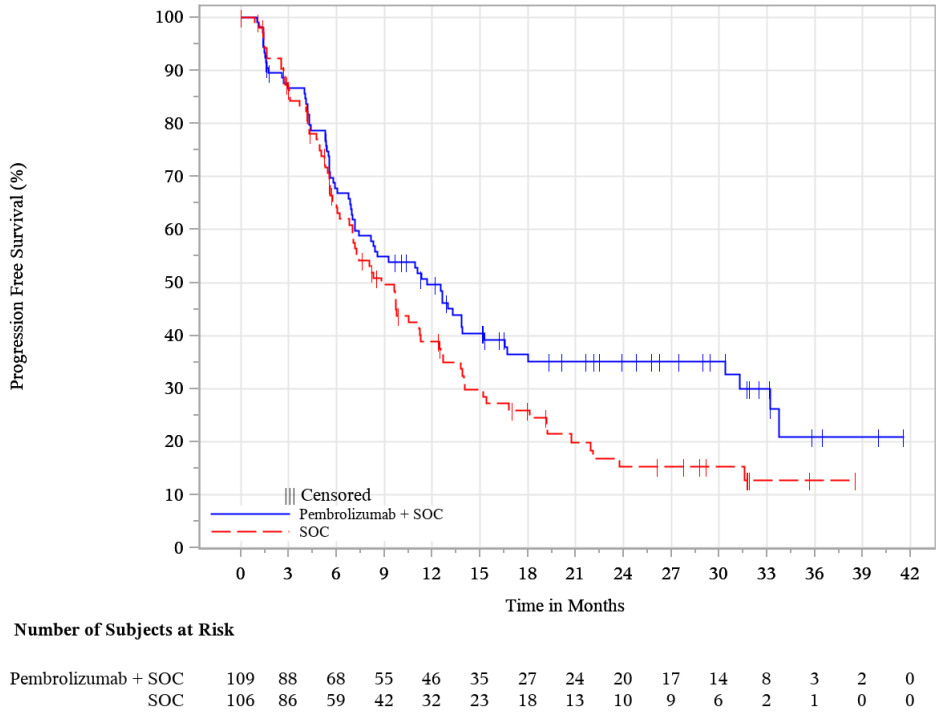


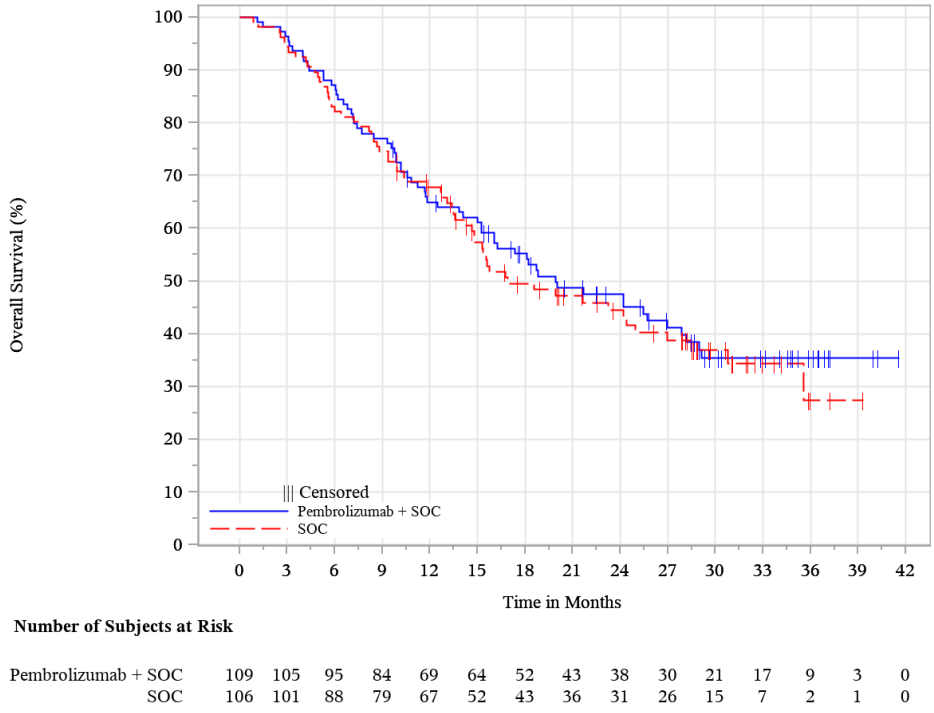
Table 3: Analysis of Overall Survival (CPS ≥10 (Raw Score) Participants) (Global Cohort) (CPS ≥1 Population)

	Pembrolizumab + SOC	SOC
	(N=109)	(N=106)
Number of Events (%)	64 (58.7)	62 (58.5)
DEATH	64 (58.7)	62 (58.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	19.9 (15.2, 27.9)	16.9 (14.6, 27.0)

[Q1, Q3]	[9.8, NR]	[8.8, NR]
Person-months	2039.2	1816.5
Event Rate / 100 Person-months	3.1	3.4
vs SOC		
Hazard Ratio (95% CI)[b]	0.93 (0.66, 1.32)	
p-value[c]	0.3472	
OS Rate at month 6 (%) (95% CI)	87.2 (79.3, 92.2)	83.0 (74.4, 88.9)
OS Rate at month 12 (%) (95% CI)	65.0 (55.2, 73.1)	67.8 (58.0, 75.8)
OS Rate at month 18 (%) (95% CI)	55.2 (45.2, 64.1)	49.5 (39.3, 59.0)
OS Rate at month 24 (%) (95% CI)	47.6 (37.6, 56.9)	44.5 (34.3, 54.2)

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.
NR = Not reached.
Database Cutoff Date: 25 May 2022

Figure 2: Kaplan-Meier Estimates of Overall Survival (CPS ≥10 (Raw Score) Participants) (Global Cohort) (CPS ≥1 Population)



Analysis of PFS and OS in CPS ≥1 Population with CPS as a Continuous Score (After Square Root Transformation) in a Cox Regression Model

The analyses of PFS and OS with CPS as a continuous score do not provide evidence (nominal 2-sided p-value >0.05) of further association between higher CPS scores and PFS or OS in either arm (Table 4), (Table 5).

The p-values provided are nominal only and are provided to assess evidence of any further association with higher levels of CPS within each treatment group when restricting attention to participants with CPS ≥1.

Table 4: Analysis of Association Between PD-L1 CPS and Progression-Free Survival Based on BICR Assessment per RECIST 1.1 (CPS ≥ 1 Participants) (Global Cohort) (CPS ≥1 Population)

Treatment	N	Event n (%)	Hazard Ratio for Square Root of CPS†	
			Hazard Ratio (95% CI)	p-Value‡
Pembrolizumab + SOC	298	199 (66.8)	1.00 (0.91, 1.10)	0.9307
SOC	296	215 (72.6)	0.95 (0.88, 1.04)	0.2840

† From a Cox regression model with Efron's method of tie handling using PD-L1 CPS on the square root scale as a continuous covariate. Each treatment group was analyzed separately. Hazard ratio (HR) represents ratio of the hazard rates for the event as CPS increases by 1 on the square root scale. A HR of 1 indicates that CPS does not affect the hazard rate. A HR of greater than 1 indicates that there is higher hazard as CPS increases. A HR of less than 1 indicates that there is lower hazard as CPS increases.
‡ Two-sided p-value from the Cox regression model.
Database Cutoff Date: 25 May 2022

Table 5: Analysis of Association between PD-L1 CPS and Overall Survival (CPS ≥ 1 Participants) (Global Cohort) (CPS ≥1 Population)

Treatment	N	Event n (%)	Hazard Ratio for Square Root of CPS†	
			Hazard Ratio (95% CI)	p-Value‡
Pembrolizumab + SOC	298	167 (56.0)	1.02 (0.92, 1.12)	0.7091
SOC	296	183 (61.8)	0.94 (0.87, 1.03)	0.2046

† From a Cox regression model with Efron's method of tie handling using PD-L1 CPS on the square root scale as a continuous covariate. Each treatment group was analyzed separately. Hazard ratio (HR) represents ratio of the hazard rates for the event as CPS increases by 1 on the square root scale. A HR of 1 indicates that CPS does not affect the hazard rate. A HR of greater than 1 indicates that there is higher hazard as CPS increases. A HR of less than 1 indicates that there is lower hazard as CPS increases.
‡ Two-sided p-value from the Cox regression model.
Database Cutoff Date: 25 May 2022

These subgroup analyses are post-hoc and not prespecified. Exploratory subgroups were not individually powered to demonstrate treatment effect; therefore, the results of these exploratory analyses should be interpreted with caution and are not considered reliable for determination of efficacy via PD-L1 expression in KEYNOTE-811. Retrospective analyses using raw biomarker scores is not as accurate as when CPS is scored at a specifically defined and validated cutpoint. The most accurate value for tumour PD-L1 expression is via the single specified stratification with a cutoff of CPS ≥1.

The results of the post-hoc exploratory PFS and OS analyses in CPS ≥10 subgroups, based on raw CPS scores, support the predictive value of PD-L1 expression and use of the CPS ≥1 cutoff, to identify patients with a clinically meaningful benefit in PFS and OS.

Based on data from KEYNOTE-811, which utilizes a prespecified cutoff level and stratification factor of CPS ≥1, a clinically meaningful PFS and OS benefit was observed. Hence, in the opinion of MSD, CPS ≥1 is the appropriate cutoff for PD-L1 expression for HER2-positive gastric and GEJ adenocarcinoma.

MSD response submitted on 14th July

Participants from Non-Asian regions Whose Tumours Express PD-L1 CPS ≥10

All comments from the response to question A5 dated 26 June 2023 on participants whose Tumours Express PD-L1 CPS ≥10 apply to the analyses in this response, with lower number of participants (CPS≥10 restricted to non-Asia region participants).

Baseline characteristics were generally similar between the pembrolizumab + SOC group and the SOC group, although some differences can be noted in some characteristics: Age category, Histological subtype, Prior Gastrectomy/Esophagectomy prior (Table 6).

The point estimates for OS and PFS favoured pembrolizumab + SOC. In addition to being post-hoc exploratory analyses, the small sample size limits interpretation of the data.

- The PFS HR was [redacted] (Table 7, Figure 3)
- The OS HR was [redacted] (Table 8, Figure 4).

Table 6: Participant Baseline Characteristics by Treatment Group (CPS≥10 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC		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 (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]		[redacted]		[redacted]	
SE	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[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]
White	[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]
Age Group (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]
Age Group 2 (Years)						
< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
65 - 74	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75 - 84	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of the World	[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 at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma of the stomach	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Disease Overall Stage						
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]
Disease Status						
Locally advanced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of Metastatic Sites						
0-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥3	[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]
Prior Gastrectomy/Esophagectomy						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status (CPS≥1)						
Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HER2 Status						
IHC 1+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IHC 2+ ISH Negative	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IHC 2+ ISH Positive	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IHC 3+	[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]
Chemotherapy Regimen						
CAPOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body Surface Area (m2)						
Participants with data	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
SE	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Weight (kg)						
Participants with data	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
SE	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	
Body Mass Index (kg/m2)						
Participants with data	[redacted]		[redacted]		[redacted]	
Mean	[redacted]		[redacted]		[redacted]	
SD	[redacted]		[redacted]		[redacted]	
SE	[redacted]		[redacted]		[redacted]	
Median	[redacted]		[redacted]		[redacted]	
Range	[redacted]		[redacted]		[redacted]	

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
Participants from Non-Asia region are defined as participants from the geographical location of Western Europe/Israel/North America/Australia and Rest of the World.
Database Cut-off Date: 25MAY2022

Table 7: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS≥10 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

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

a From product-limit (Kaplan-Meier) method for censored data.
b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on log-rank test.
BICR = Blinded Independent Central Review.
Database Cut-off Date: 25MAY2022

Table 8: Analysis of Overall Survival (CPS≥10 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC	SOC
[redacted]	[redacted]	[redacted]
Number of Events (%)	[redacted]	[redacted]
DEATH	[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 SOC		
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]

[a] From product-limit (Kaplan-Meier) method for censored data.
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
[c] One-sided p-value based on log-rank test.
NR = Not reached.
Database Cut-off Date: 25MAY2022

Figure 3: Kaplan-Meier Estimates of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS≥10 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

Figure 4: Kaplan-Meier Estimates of Overall Survival (CPS≥10 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

These subgroup analyses are post-hoc and were not prespecified. Exploratory subgroups were not individually powered to demonstrate treatment effect; therefore, the results of these exploratory analyses should be interpreted with caution and are not considered reliable for determination of efficacy via PD-L1 expression in KEYNOTE-811.

Retrospective analyses using raw biomarker scores is not as accurate as when CPS is scored at a specifically defined and validated cut point. The most accurate value for tumour PD-L1 expression is via the single specified stratification with a cut-off of CPS ≥1.

A6. Please provide the breakdown of the number of patients recruited per treatment group for the countries categorised as Rest of World.

MSD response:

The breakdown of the number of patients recruited per treatment group for the countries categorised as Rest of World is provided below.

Table 9: Randomised Trial Participants by Country and Treatment Group Participants from Rest of the World (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC		Total	
Country Name	(N = 105)		(N = 104)		(N = 209)	
	n	(%)	n	(%)	n	(%)
Brazil	12	(11.4)	9	(8.7)	21	(10.0)
Chile	16	(15.2)	17	(16.3)	33	(15.8)
Germany	1	(1.0)	0	(0.0)	1	(0.5)
Guatemala	8	(7.6)	9	(8.7)	17	(8.1)
Poland	13	(12.4)	8	(7.7)	21	(10.0)
Russian Federation	16	(15.2)	13	(12.5)	29	(13.9)
Turkey	15	(14.3)	28	(26.9)	43	(20.6)
Ukraine	24	(22.9)	20	(19.2)	44	(21.1)
Database Cutoff Date: 25 May 2022						

A7. CS, Table 4 and text on Page 35. In the footnotes of Table 4, it is stated that duration of cisplatin treatment, "may be capped at 6 cycles as per local country guidelines," and, "duration of oxaliplatin may be capped at 6 to 8 cycles as per local country guidelines". However, on page 35 it is stated that cisplatin was administered for "up to 6 cycles". No information is given on any restriction on treatment duration for oxaliplatin on page 35. Please confirm whether a maximum number of cycles was specified in the study protocol for either cisplatin or oxaliplatin, or if duration was purely based on local guidance.

MSD response:

Duration of cisplatin and oxaliplatin was based on local guidance – 6 cycles for cisplatin and 6-8 cycles for oxaliplatin. Clinical advice to MSD suggests that majority of patients in England receive 6 cycles of oxaliplatin.

A8. CS, Table 4, footnotes: It is stated that in KEYNOTE-811 some patients may be eligible for up to 17 additional administrations of pembrolizumab upon experiencing disease progression if (i) they stopped treatment after 35 administrations for reasons other than disease progression or (ii) if they stopped treatment after attaining a complete response. Please clarify the number of patients who restarted pembrolizumab after disease progression, and the proportions who had previously stopped for reasons (i) or (ii). Please provide this information for both the Global CPS ≥1 cohort and the non-Asia CPS ≥1 cohort. Given that these additional

administrations were only allowed in those randomised to pembrolizumab, were additional placebo administrations allowed in the control arm or was blinding to allocation not relevant after progression?

MSD response:

A summary of second course participants in CPS≥1 Global cohort is provided in Table 10. All 3 participants who received second course of pembrolizumab were from non-Asia population.

Table 10: Summary of Second Course Participants (CPS≥1 Participants) (Global Cohort) (All-Participants-as-Treated Population)

	Pembrolizumab + SOC	
	n	(%)
Participants in population	298	
Second Course Status		
Participants who received second course	3	(1.0)
Participants who did not receive second course	295	(99.0)
Exposure Duration of First Course Phase (Weeks)[a]		
Participants with data	298	
Mean	48.4	
SE	2.0	
Median	42.0	
Range	0.1 to 131.7	
Exposure Duration of Second Course Phase (Weeks)[b]		
Participants with data	3	
Mean	8.8	
SE	1.3	
Median	9.1	
Range	6.4 to 10.9	

a: Exposure duration of the first course phase is defined as the time between the date of the first dose until the date of the last dose of Pembrolizumab received during the primary treatment regimen
b: Exposure duration of the second course phase is defined as the time between the date of the first dose until the date of the last dose of Pembrolizumab received during the re-treatment phase
Database Cutoff Date: 25 May 2022

A9. On CS page 71, the company states, "The improvement in PFS for pembrolizumab plus SoC compared with SoC (based on the May 2022 data-cut) was observed across all subgroups and sub-populations analysed (Appendix E.)" Please clarify how this statement is supported by the data in Appendix E given that not all subgroups reported in Table 22 and Figure 7 of Appendix E had a statistically significant treatment effect for PFS.

MSD response:

MSD did not claim the statistically significant treatment effect for PFS across all subgroups and sub-populations analysed. Clinically meaningful PFS improvement was observed in most subgroups and sub-populations analysed.

Analyses of PFS by pre-specified subgroups for the CPS <1 subgroup revealed no clear benefit, as shown by a PFS HR estimate >1 and a wide 95% CI. Also, the majority of participants enrolled in the study had tumours with CPS ≥1 (594 [85.1%]), resulting in comparatively small numbers of participants in the CPS <1 subgroup and thus wide CIs in analyses of this subgroup. The CPS<1 subgroup is not relevant within the context of this appraisal as this population is not covered by the decision problem (consistent with anticipated licence).

A10. For Table 22, Appendix E (PFS subgroups, Global CPS≥1 cohort), please provide tabulated data for age, sex, ECOG, geographic region, as these are included in Figure 7, but not Table 22. Also, has the company conducted subgroup analyses for PFS and OS for any age cut-offs other than above and below 65 years. If so, could these also be provided.

MSD response:

Tabulated data for age, sex, ECOG, geographic region is provided in Table 11 below. MSD has not conducted subgroup analyses for PFS and OS for any age cut-offs other than above and below 65 years for CPS≥1 population.

Table 11: Analysis of Progression-Free Survival (Primary Censoring Rule) for Subgroups Defined in Protocol (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population)

Study: KEYNOTE-811	Pembrolizumab + SOC			SOC			Pembrolizumab + SOC vs. SOC	
Progression-Free Survival (Primary Censoring Rule)	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value for Interaction Test[d]
Age								
< 65 years	174	116 (66.7)	11.07 [8.35; 12.68]	165	123 (74.5)	7.00 [6.01; 8.25]	0.64 [0.50; 0.83]	0.3403
>= 65 years	124	83 (66.9)	9.79 [8.31; 12.85]	131	92 (70.2)	8.31 [6.80; 9.79]	0.78 [0.58; 1.05]	

Sex								
Male	240	165 (68.8)	9.92 [8.35; 12.19]	237	169 (71.3)	7.43 [6.70; 8.61]	0.75 [0.61; 0.93]	0.1186
Female	58	34 (58.6)	12.68 [8.28; 20.93]	59	46 (78.0)	7.03 [5.45; 9.59]	0.52 [0.33; 0.82]	
Race								
Asian	97	59 (60.8)	13.63 [8.35; 17.02]	97	60 (61.9)	12.22 [8.08; 14.06]	0.85 [0.59; 1.22]	0.1494
Non-Asian	200	139 (69.5)	9.92 [8.31; 11.37]	196	153 (78.1)	6.31 [5.59; 7.82]	0.62 [0.50; 0.79]	
Geographic Region of Enrolling Site								
Western Europe/Israel/North America/Australia	97	67 (69.1)	9.00 [6.97; 11.34]	96	74 (77.1)	6.31 [5.45; 7.82]	0.69 [0.50; 0.97]	0.2621
Asia	96	58 (60.4)	13.63 [8.35; 17.02]	96	59 (61.5)	12.52 [8.08; 14.06]	0.85 [0.59; 1.22]	
Rest of the World	105	74 (70.5)	11.11 [8.25; 12.71]	104	82 (78.8)	6.93 [5.55; 8.38]	0.56 [0.41; 0.78]	
MSI								
MSI-H	6	4 (66.7)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.
Non MSI-H	282	185 (65.6)	n.c.	280	204 (72.9)	n.c.	n.c.	
Baseline ECOG								
0	127	78 (61.4)	12.85 [9.92; 16.59]	121	82 (67.8)	8.48 [6.01; 10.35]	0.66 [0.48; 0.90]	0.5342
1	171	121 (70.8)	8.58 [7.39; 10.91]	174	133 (76.4)	7.06 [6.08; 8.21]	0.73 [0.57; 0.94]	
Primary Location								
GEJ	97	69 (71.1)	8.51 [7.33; 11.37]	99	73 (73.7)	7.13 [5.62; 9.66]	0.73 [0.53; 1.02]	0.7814
Stomach	201	130 (64.7)	11.30 [9.10; 13.63]	197	142 (72.1)	7.79 [6.80; 8.74]	0.68 [0.54; 0.87]	
Histological Subtype								
Diffuse	56	38 (67.9)	9.86 [6.80; 15.24]	49	40 (81.6)	5.95 [4.30; 8.21]	0.64 [0.41; 1.01]	0.7626
Intestinal	169	108 (63.9)	11.07 [8.54; 12.85]	158	110 (69.6)	8.12 [6.77; 9.69]	0.70 [0.53; 0.91]	

Indeterminate	73	53 (72.6)	9.82 [6.93; 13.73]	89	65 (73.0)	7.79 [5.59; 9.69]	0.74 [0.51; 1.07]	
Tumour Burden								
< Median	139	86 (61.9)	12.52 [9.23; 15.24]	139	104 (74.8)	8.25 [7.10; 9.79]	0.69 [0.52; 0.92]	0.9430
>= Median	147	105 (71.4)	9.00 [7.33; 11.11]	146	106 (72.6)	6.80 [5.59; 8.31]	0.68 [0.52; 0.90]	
Number of Metastatic Sites								
<=2	149	97 (65.1)	11.66 [9.56; 13.83]	172	121 (70.3)	7.43 [5.95; 9.59]	0.68 [0.52; 0.89]	0.7837
>=3	149	102 (68.5)	8.58 [7.23; 11.30]	124	94 (75.8)	7.13 [6.80; 8.81]	0.70 [0.53; 0.93]	
Prior Gastrectomy/Esophagectomy								
Yes	36	24 (66.7)	11.34 [8.35; 17.97]	48	33 (68.8)	10.35 [7.82; 13.83]	0.70 [0.41; 1.19]	0.8565
No	262	175 (66.8)	9.92 [8.41; 12.52]	248	182 (73.4)	7.03 [6.05; 8.25]	0.69 [0.56; 0.85]	
Chemotherapy Regimen								
CAPOX	251	165 (65.7)	11.07 [8.64; 12.98]	253	182 (71.9)	7.82 [7.00; 8.61]	0.69 [0.56; 0.85]	0.7791
FP	47	34 (72.3)	8.58 [6.54; 11.66]	43	33 (76.7)	6.08 [5.29; 9.66]	0.69 [0.43; 1.12]	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model with treatment as a covariate using Wald confidence interval
d: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
Database Cutoff Date: 25 May 2022
CI: Confidence Interval; n.c.: not calculated (at least 10 participants per subgroup and at least 10 participants with events in one of the subgroups necessary)

A11. PRIORITY. CS, Page 103. A comparison is made between the baseline characteristics of the Asia and non-Asia region participants for some specific characteristics in the text on CS Page 103, with reference made to Table 6 and Table 7 when discussing differences in age. Whilst the baseline characteristics of the non-Asia region have been presented in Table 7, the baseline characteristics for the Asia region are not presented (Table 6 is for the Global cohort). In addition, the text on page 103 specifically comments on the differences in histological subtype which are not presented in Table 7 (some data presented in Table 6 are missing in table 7 and some data, e.g. Age group 2, in Table 7 are repeated). Please present baseline

characteristics for the non-Asia region and each individual region used as a stratification factor (i.e. (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World) in a format similar to data presented in for the Global cohort in Table 6 (all region specific cohorts should be restricted to CPS≥1 as per Table 6). Please also highlight any significant differences between baseline characteristics across the 3 regions used as stratification factors, including any differences between the two regions combined in the 'non-Asia' cohort described in Table 7.

MSD response:

Baseline characteristics for non-Asia region and each individual region used as a stratification factor (i.e. (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World) participants are presented below.

The Asia and non-Asia region participants are noted to differ in terms of the following:

- Diffuse histological subtype (Lauren classification) is twice as prevalent among non-Asia participants (20.9%) compared to among Asia participants (10.9%)
- A primary tumour location in the GOJ is more than twice as prevalent among non-Asia participants (39.8%) compared to among Asia participants (18.8%).

Table 12: Participant Baseline Characteristics by Treatment Group (CPS≥1 Participants) (Global Cohort - Participants from Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC		**SOC**		**Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Participants in population	96		96		192	
Sex						
Male	80	(83.3)	79	(82.3)	159	(82.8)
Female	16	(16.7)	17	(17.7)	33	(17.2)
Age (Years)						
< 65	53	(55.2)	48	(50.0)	101	(52.6)
>= 65	**43**	**(44.8)**	**48**	**(50.0)**	**91**	**(47.4)**
Mean	62.4		63.1		62.8	
SE	1.1		0.9		0.7	
Median	64.0		64.5		64.0	
Range	25 to 84		42 to 85		25 to 85	
Race						
Asian	96	(100.0)	96	(100.0)	192	(100.0)
Ethnicity						

Not Hispanic Or Latino	96	(100.0)	96	(100.0)	192	(100.0)
Age Group (Years)						
18-39	3	(3.1)	0	(0.0)	3	(1.6)
40-49	6	(6.3)	9	(9.4)	15	(7.8)
50-59	21	(21.9)	21	(21.9)	42	(21.9)
60-69	39	(40.6)	39	(40.6)	78	(40.6)
70-79	26	(27.1)	25	(26.0)	51	(26.6)
>=80	1	(1.0)	2	(2.1)	3	(1.6)
Age Group 2 (Years)						
< 65	53	(55.2)	48	(50.0)	101	(52.6)
65 - 74	36	(37.5)	42	(43.8)	78	(40.6)
75 - 84	7	(7.3)	5	(5.2)	12	(6.3)
85+	0	(0.0)	1	(1.0)	1	(0.5)
Geographic Region of Enrolling Site						
Asia	96	(100.0)	96	(100.0)	192	(100.0)
ECOG Performance Scale						
0	36	(37.5)	42	(43.8)	78	(40.6)
1	60	(62.5)	54	(56.3)	114	(59.4)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	**16**	**(16.7)**	**20**	**(20.8)**	**36**	**(18.8)**
Adenocarcinoma of the stomach	80	(83.3)	76	(79.2)	156	(81.3)
Current Disease Overall Stage						
IIIC	0	(0.0)	1	(1.0)	1	(0.5)
IV	96	(100.0)	95	(99.0)	191	(99.5)
Disease Status						
Locally advanced	0	(0.0)	1	(1.0)	1	(0.5)
Metastatic	96	(100.0)	95	(99.0)	191	(99.5)
Number of Metastatic Sites						
0-2	41	(42.7)	58	(60.4)	99	(51.6)
>=3	55	(57.3)	38	(39.6)	93	(48.4)
Histological Subtype (Lauren classification)						
Diffuse	**10**	**(10.4)**	**11**	**(11.5)**	**21**	**(10.9)**
Intestinal	58	(60.4)	50	(52.1)	108	(56.3)
Indeterminate	28	(29.2)	35	(36.5)	63	(32.8)
Prior Gastrectomy/Esophagectomy						
Yes	15	(15.6)	16	(16.7)	31	(16.1)
No	81	(84.4)	80	(83.3)	161	(83.9)
PD-L1 Status (CPS≥1)						
Positive	96	(100.0)	96	(100.0)	192	(100.0)
Tumour Burden						
< Median	52	(54.2)	51	(53.1)	103	(53.6)
>= Median	41	(42.7)	42	(43.8)	83	(43.2)
Missing	3	(3.1)	3	(3.1)	6	(3.1)
HER2 Status						
IHC 2+ ISH Equivocal	0	(0.0)	1	(1.0)	1	(0.5)
IHC 2+ ISH Positive	20	(20.8)	31	(32.3)	51	(26.6)
IHC 3+	76	(79.2)	64	(66.7)	140	(72.9)
MSI Status						
MSI High	1	(1.0)	1	(1.0)	2	(1.0)

non-MSI-High	92	(95.8)	90	(93.8)	182	(94.8)
Unknown	3	(3.1)	5	(5.2)	8	(4.2)
Chemotherapy Regimen						
CAPOX	95	(99.0)	96	(100.0)	191	(99.5)
FP	1	(1.0)	0	(0.0)	1	(0.5)
Body Surface Area (m2)						
Participants with data	96		96		192	
Mean	1.7		1.7		1.7	
SD	0.2		0.2		0.2	
SE	0.0		0.0		0.0	
Median	1.7		1.7		1.7	
Range	1.3 to 2.1		1.2 to 2.0		1.2 to 2.1	
Weight (kg)						
Participants with data	96		96		192	
Mean	60.9		59.9		60.4	
SD	9.5		10.2		9.8	
SE	1.0		1.0		0.7	
Median	60.7		59.5		60.3	
Range	37.0 to 86.9		30.2 to 79.6		30.2 to 86.9	
Body Mass Index (kg/m2)						
Participants with data	96		96		192	
Mean	22.4		21.8		22.1	
SD	3.1		3.1		3.1	
SE	0.3		0.3		0.2	
Median	22.6		22.0		22.2	
Range	15.2 to 31.8		11.9 to 29.8		11.9 to 31.8	
Participants from Asia region are defined as participants from the geographical location of Asia *Database Cutoff Date: 25 May 2022*						

Table 13: Participant Baseline Characteristics by Treatment Group (CPS≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC		**SOC**		**Total**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Participants in population	202		200		402	
Sex						
Male	160	(79.2)	158	(79.0)	318	(79.1)
Female	42	(20.8)	42	(21.0)	84	(20.9)
Age (Years)						
< 65	121	(59.9)	117	(58.5)	238	(59.2)
>= 65	**81**	**(40.1)**	**83**	**(41.5)**	**164**	**(40.8)**
Mean	59.7		60.6		60.2	
SE	0.9		0.8		0.6	
Median	62.0		61.0		61.5	
Range	19 to 85		32 to 82		19 to 85	
Race						

American Indian Or Alaska Native	5	(2.5)	6	(3.0)	11	(2.7)
Asian	1	(0.5)	1	(0.5)	2	(0.5)
Black Or African American	2	(1.0)	2	(1.0)	4	(1.0)
Multiple	5	(2.5)	4	(2.0)	9	(2.2)
White	188	(93.1)	184	(92.0)	372	(92.5)
Missing	1	(0.5)	3	(1.5)	4	(1.0)
Ethnicity						
Hispanic Or Latino	36	(17.8)	41	(20.5)	77	(19.2)
Not Hispanic Or Latino	163	(80.7)	153	(76.5)	316	(78.6)
Not Reported	1	(0.5)	5	(2.5)	6	(1.5)
Unknown	2	(1.0)	1	(0.5)	3	(0.7)
Age Group (Years)						
18-39	13	(6.4)	12	(6.0)	25	(6.2)
40-49	28	(13.9)	18	(9.0)	46	(11.4)
50-59	38	(18.8)	65	(32.5)	103	(25.6)
60-69	79	(39.1)	53	(26.5)	132	(32.8)
70-79	41	(20.3)	48	(24.0)	89	(22.1)
>=80	3	(1.5)	4	(2.0)	7	(1.7)
Age Group 2 (Years)						
< 65	121	(59.9)	117	(58.5)	238	(59.2)
65 - 74	65	(32.2)	62	(31.0)	127	(31.6)
75 - 84	15	(7.4)	21	(10.5)	36	(9.0)
85+	1	(0.5)	0	(0.0)	1	(0.2)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	97	(48.0)	96	(48.0)	193	(48.0)
Rest of the World	105	(52.0)	104	(52.0)	209	(52.0)
ECOG Performance Scale						
0	91	(45.0)	79	(39.5)	170	(42.3)
1	111	(55.0)	120	(60.0)	231	(57.5)
Missing	0	(0.0)	1	(0.5)	1	(0.2)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	**81**	**(40.1)**	**79**	**(39.5)**	**160**	**(39.8)**
Adenocarcinoma of the stomach	121	(59.9)	121	(60.5)	242	(60.2)
Current Disease Overall Stage						
IIB	1	(0.5)	0	(0.0)	1	(0.2)
IIIA	2	(1.0)	1	(0.5)	3	(0.7)
IIIB	5	(2.5)	1	(0.5)	6	(1.5)
IIIC	0	(0.0)	2	(1.0)	2	(0.5)
IV	194	(96.0)	196	(98.0)	390	(97.0)
Disease Status						
Locally advanced	8	(4.0)	5	(2.5)	13	(3.2)
Metastatic	194	(96.0)	195	(97.5)	389	(96.8)
Number of Metastatic Sites						
0-2	108	(53.5)	114	(57.0)	222	(55.2)
>=3	94	(46.5)	86	(43.0)	180	(44.8)

Histological Subtype (Lauren classification)						
Diffuse	**46**	**(22.8)**	**38**	**(19.0)**	**84**	**(20.9)**
Intestinal	111	(55.0)	108	(54.0)	219	(54.5)
Indeterminate	45	(22.3)	54	(27.0)	99	(24.6)
Prior Gastrectomy/Esophagectomy						
Yes	21	(10.4)	32	(16.0)	53	(13.2)
No	181	(89.6)	168	(84.0)	349	(86.8)
PD-L1 Status (CPS≥1)						
Positive	202	(100.0)	200	(100.0)	402	(100.0)
Tumour Burden						
< Median	87	(43.1)	88	(44.0)	175	(43.5)
>= Median	106	(52.5)	104	(52.0)	210	(52.2)
Missing	9	(4.5)	8	(4.0)	17	(4.2)
HER2 Status						
IHC 1+	1	(0.5)	1	(0.5)	2	(0.5)
IHC 2+ ISH Negative	1	(0.5)	1	(0.5)	2	(0.5)
IHC 2+ ISH Positive	31	(15.3)	37	(18.5)	68	(16.9)
IHC 3+	169	(83.7)	161	(80.5)	330	(82.1)
MSI Status						
MSI High	5	(2.5)	1	(0.5)	6	(1.5)
non-MSI-High	190	(94.1)	190	(95.0)	380	(94.5)
Unknown	7	(3.5)	9	(4.5)	16	(4.0)
Chemotherapy Regimen						
CAPOX	156	(77.2)	157	(78.5)	313	(77.9)
FP	46	(22.8)	43	(21.5)	89	(22.1)
Body Surface Area (m2)						
Participants with data	202		199		401	
Mean	1.8		1.8		1.8	
SD	0.2		0.2		0.2	
SE	0.0		0.0		0.0	
Median	1.8		1.8		1.8	
Range	1.3 to 2.8		1.3 to 2.5		1.3 to 2.8	
Weight (kg)						
Participants with data	202		200		402	
Mean	71.9		72.0		72.0	
SD	16.7		16.0		16.3	
SE	1.2		1.1		0.8	
Median	70.2		70.0		70.0	
Range	39.0 to 162.0		39.5 to 125.0		39.0 to 162.0	
Body Mass Index (kg/m2)						
Participants with data	202		199		401	
Mean	24.7		25.1		24.9	
SD	5.1		4.5		4.8	
SE	0.4		0.3		0.2	
Median	23.9		24.8		24.3	
Range	14.9 to 57.4		14.5 to 39.5		14.5 to 57.4	

Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.

Participants from Non-Asia region are defined as participants from the geographical location of Western Europe/Israel/North America/Australia and Rest of the World.

Database Cutoff Date: 25 May 2022

Table 14: Participant Baseline Characteristics by Treatment Group (CPS≥1 Participants) (Global Cohort - Participants from Western Europe/Israel/North America/Australia) (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	97		96		193	
Sex						
Male	79	(81.4)	79	(82.3)	158	(81.9)
Female	18	(18.6)	17	(17.7)	35	(18.1)
Age (Years)						
< 65	63	(64.9)	54	(56.3)	117	(60.6)
>= 65	34	(35.1)	42	(43.8)	76	(39.4)
Mean	58.9		60.2		59.5	
SE	1.3		1.2		0.9	
Median	61.0		61.0		61.0	
Range	19 to 85		33 to 81		19 to 85	
Race						
Asian	0	(0.0)	1	(1.0)	1	(0.5)
Black Or African American	1	(1.0)	0	(0.0)	1	(0.5)
White	95	(97.9)	92	(95.8)	187	(96.9)
Missing	1	(1.0)	3	(3.1)	4	(2.1)
Ethnicity						
Hispanic Or Latino	1	(1.0)	4	(4.2)	5	(2.6)
Not Hispanic Or Latino	93	(95.9)	87	(90.6)	180	(93.3)
Not Reported	1	(1.0)	5	(5.2)	6	(3.1)
Unknown	2	(2.1)	0	(0.0)	2	(1.0)
Age Group (Years)						
18-39	6	(6.2)	6	(6.3)	12	(6.2)
40-49	16	(16.5)	11	(11.5)	27	(14.0)
50-59	18	(18.6)	28	(29.2)	46	(23.8)
60-69	40	(41.2)	26	(27.1)	66	(34.2)
70-79	15	(15.5)	23	(24.0)	38	(19.7)
>=80	2	(2.1)	2	(2.1)	4	(2.1)
Age Group 2 (Years)						
< 65	63	(64.9)	54	(56.3)	117	(60.6)
65 - 74	25	(25.8)	35	(36.5)	60	(31.1)
75 - 84	8	(8.2)	7	(7.3)	15	(7.8)
85+	1	(1.0)	0	(0.0)	1	(0.5)
Geographic Region of Enrolling Site						
Western Europe/Israel/North America/Australia	97	(100.0)	96	(100.0)	193	(100.0)
ECOG Performance Scale						
0	52	(53.6)	43	(44.8)	95	(49.2)
1	45	(46.4)	52	(54.2)	97	(50.3)
Missing	0	(0.0)	1	(1.0)	1	(0.5)
Primary Location at Diagnosis						

Adenocarcinoma of the gastroesophageal junction	57	(58.8)	64	(66.7)	121	(62.7)
Adenocarcinoma of the stomach	40	(41.2)	32	(33.3)	72	(37.3)
Current Disease Overall Stage						
IIIA	1	(1.0)	0	(0.0)	1	(0.5)
IIIB	2	(2.1)	0	(0.0)	2	(1.0)
IIIC	0	(0.0)	1	(1.0)	1	(0.5)
IV	94	(96.9)	95	(99.0)	189	(97.9)
Disease Status						
Locally advanced	3	(3.1)	1	(1.0)	4	(2.1)
Metastatic	94	(96.9)	95	(99.0)	189	(97.9)
Number of Metastatic Sites						
0-2	62	(63.9)	67	(69.8)	129	(66.8)
>=3	35	(36.1)	29	(30.2)	64	(33.2)
Histological Subtype (Lauren classification)						
Diffuse	15	(15.5)	19	(19.8)	34	(17.6)
Intestinal	60	(61.9)	53	(55.2)	113	(58.5)
Indeterminate	22	(22.7)	24	(25.0)	46	(23.8)
Prior Gastrectomy/Esophagectomy						
Yes	12	(12.4)	14	(14.6)	26	(13.5)
No	85	(87.6)	82	(85.4)	167	(86.5)
PD-L1 Status (CPS≥1)						
Positive	97	(100.0)	96	(100.0)	193	(100.0)
Tumour Burden						
< Median	46	(47.4)	50	(52.1)	96	(49.7)
>= Median	47	(48.5)	41	(42.7)	88	(45.6)
Missing	4	(4.1)	5	(5.2)	9	(4.7)
HER2 Status						
IHC 1+	1	(1.0)	1	(1.0)	2	(1.0)
IHC 2+ ISH Negative	1	(1.0)	1	(1.0)	2	(1.0)
IHC 2+ ISH Positive	10	(10.3)	20	(20.8)	30	(15.5)
IHC 3+	85	(87.6)	74	(77.1)	159	(82.4)
MSI Status						
MSI High	2	(2.1)	1	(1.0)	3	(1.6)
non-MSI-High	93	(95.9)	94	(97.9)	187	(96.9)
Unknown	2	(2.1)	1	(1.0)	3	(1.6)
Chemotherapy Regimen						
CAPOX	69	(71.1)	70	(72.9)	139	(72.0)
FP	28	(28.9)	26	(27.1)	54	(28.0)
Body Surface Area (m2)						
Participants with data	97		96		193	
Mean	1.9		1.9		1.9	
SD	0.2		0.2		0.2	
SE	0.0		0.0		0.0	
Median	1.9		1.9		1.9	
Range	1.4 to 2.8		1.4 to 2.5		1.4 to 2.8	
Weight (kg)						
Participants with data	97		96		193	
Mean	74.5		76.4		75.4	
SD	17.8		17.3		17.5	
SE	1.8		1.8		1.3	

Median	73.5		74.3		74.0	
Range	46.5 to 162.0		39.5 to 125.0		39.5 to 162.0	
Body Mass Index (kg/m2)						
Participants with data	97		96		193	
Mean	25.0		25.7		25.4	
SD	5.2		4.8		5.0	
SE	0.5		0.5		0.4	
Median	24.2		25.2		24.7	
Range	16.1 to 57.4		14.5 to 39.5		14.5 to 57.4	
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification. *Database Cutoff Date: 25 May 2022*						

Table 15: Participant Baseline Characteristics by Treatment Group (CPS≥1 Participants) (Global Cohort - Participants from Rest of the World) (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	105		104		209	
Sex						
Male	81	(77.1)	79	(76.0)	160	(76.6)
Female	24	(22.9)	25	(24.0)	49	(23.4)
Age (Years)						
< 65	58	(55.2)	63	(60.6)	121	(57.9)
>= 65	47	(44.8)	41	(39.4)	88	(42.1)
Mean	60.4		61.0		60.7	
SE	1.2		1.1		0.8	
Median	64.0		60.0		62.0	
Range	24 to 80		32 to 82		24 to 82	
Race						
American Indian Or Alaska Native	5	(4.8)	6	(5.8)	11	(5.3)
Asian	1	(1.0)	0	(0.0)	1	(0.5)
Black Or African American	1	(1.0)	2	(1.9)	3	(1.4)
Multiple	5	(4.8)	4	(3.8)	9	(4.3)
White	93	(88.6)	92	(88.5)	185	(88.5)
Ethnicity						
Hispanic Or Latino	35	(33.3)	37	(35.6)	72	(34.4)
Not Hispanic Or Latino	70	(66.7)	66	(63.5)	136	(65.1)
Unknown	0	(0.0)	1	(1.0)	1	(0.5)
Age Group (Years)						
18-39	7	(6.7)	6	(5.8)	13	(6.2)
40-49	12	(11.4)	7	(6.7)	19	(9.1)
50-59	20	(19.0)	37	(35.6)	57	(27.3)

60-69	39	(37.1)	27	(26.0)	66	(31.6)
70-79	26	(24.8)	25	(24.0)	51	(24.4)
>=80	1	(1.0)	2	(1.9)	3	(1.4)
Age Group 2 (Years)						
< 65	58	(55.2)	63	(60.6)	121	(57.9)
65 - 74	40	(38.1)	27	(26.0)	67	(32.1)
75 - 84	7	(6.7)	14	(13.5)	21	(10.0)
Geographic Region of Enrolling Site						
Rest of the World	105	(100.0)	104	(100.0)	209	(100.0)
ECOG Performance Scale						
0	39	(37.1)	36	(34.6)	75	(35.9)
1	66	(62.9)	68	(65.4)	134	(64.1)
Primary Location at Diagnosis						
Adenocarcinoma of the gastroesophageal junction	24	(22.9)	15	(14.4)	39	(18.7)
Adenocarcinoma of the stomach	81	(77.1)	89	(85.6)	170	(81.3)
Current Disease Overall Stage						
IIB	1	(1.0)	0	(0.0)	1	(0.5)
IIIA	1	(1.0)	1	(1.0)	2	(1.0)
IIIB	3	(2.9)	1	(1.0)	4	(1.9)
IIIC	0	(0.0)	1	(1.0)	1	(0.5)
IV	100	(95.2)	101	(97.1)	201	(96.2)
Disease Status						
Locally advanced	5	(4.8)	4	(3.8)	9	(4.3)
Metastatic	100	(95.2)	100	(96.2)	200	(95.7)
Number of Metastatic Sites						
0-2	46	(43.8)	47	(45.2)	93	(44.5)
>=3	59	(56.2)	57	(54.8)	116	(55.5)
Histological Subtype (Lauren classification)						
Diffuse	31	(29.5)	19	(18.3)	50	(23.9)
Intestinal	51	(48.6)	55	(52.9)	106	(50.7)
Indeterminate	23	(21.9)	30	(28.8)	53	(25.4)
Prior Gastrectomy/Esophagectomy						
Yes	9	(8.6)	18	(17.3)	27	(12.9)
No	96	(91.4)	86	(82.7)	182	(87.1)
PD-L1 Status (CPS≥1)						
Positive	105	(100.0)	104	(100.0)	209	(100.0)
Tumour Burden						
< Median	41	(39.0)	38	(36.5)	79	(37.8)
>= Median	59	(56.2)	63	(60.6)	122	(58.4)
Missing	5	(4.8)	3	(2.9)	8	(3.8)
HER2 Status						
IHC 2+ ISH Positive	21	(20.0)	17	(16.3)	38	(18.2)
IHC 3+	84	(80.0)	87	(83.7)	171	(81.8)
MSI Status						
MSI High	3	(2.9)	0	(0.0)	3	(1.4)
non-MSI-High	97	(92.4)	96	(92.3)	193	(92.3)
Unknown	5	(4.8)	8	(7.7)	13	(6.2)
Chemotherapy Regimen						
CAPOX	87	(82.9)	87	(83.7)	174	(83.3)
FP	18	(17.1)	17	(16.3)	35	(16.7)

Body Surface Area (m2)						
Participants with data	105		103		208	
Mean	1.8		1.8		1.8	
SD	0.2		0.2		0.2	
SE	0.0		0.0		0.0	
Median	1.8		1.7		1.8	
Range	1.3 to 2.3		1.3 to 2.3		1.3 to 2.3	
Weight (kg)						
Participants with data	105		104		209	
Mean	69.5		68.0		68.8	
SD	15.2		13.7		14.5	
SE	1.5		1.3		1.0	
Median	69.0		66.5		67.0	
Range	39.0 to 105.0		42.0 to 101.8		39.0 to 105.0	
Body Mass Index (kg/m2)						
Participants with data	105		103		208	
Mean	24.4		24.5		24.4	
SD	4.9		4.1		4.5	
SE	0.5		0.4		0.3	
Median	23.6		24.4		23.9	
Range	14.9 to 36.4		16.4 to 37.2		14.9 to 37.2	
Database Cutoff Date: 25 May 2022						

A12. Please clarify if mismatched repair (MMR) status was assessed in the trial cohort and if so please report this alongside the baseline characteristics requested above.

MSD response:

Mismatch repair (MMR) status was not assessed in the KEYNOTE-811 trial.

A13. When will the data from interim analysis 3 (IA3) become available? If this has recently become available, please update the submission with this information.

MSD response:

Interim analysis 3 database lock occurred on 25 April 2023. The data is currently being analysed. Timelines for the development of an abbreviated statistical report and narrative description of IA3 data are to be confirmed, but these will be provided to NICE at a later stage of the appraisal if they become available at a point in the process when it is acceptable to supplement the submission with additional data.

A14. Appendix D, Tables 18 to 20. Disposition of patients/ participant flow only given for (CPS≥1 Participants) (Global Cohort). Please provide CONSORT Table and Disposition of participants for CPS≥1 participants for 1) Europe/Israel/North America/Australia; 2) Rest of World.

MSD response:

CONSORT tables and disposition of participants for CPS≥1 participants for 1) Europe/Israel/North America/Australia; 2) Rest of World are provided below.

Table 16: Consort Diagram (CPS≥1 Participants) (Global Cohort - Participants from Western Europe/Israel/North America/Australia)

	Pembrolizumab + SOC	SOC	Total
Subjects randomised	97	96	193
Subjects who died	61	64	125
Subjects who did not receive treatment	0	0	0
Subjects who received treatment	61	64	125
Database Cutoff Date: 25 May 2022			

Table 17: Disposition of Participants (CPS≥1 Participants) (Global Cohort - Participants from Western Europe/Israel/North America/Australia) (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	97		96	
Status for Study Medication of Treatment Phase				
Started	97		96	
Completed	3	(3.1)	3	(3.1)
Discontinued	77	(79.4)	85	(88.5)
Adverse Event	10	(10.3)	14	(14.6)
Associated with COVID-19	0	(0.0)	1	(1.0)
Clinical Progression	4	(4.1)	8	(8.3)
Complete Response	1	(1.0)	0	(0.0)
Non-Study Anti-Cancer Therapy	0	(0.0)	1	(1.0)
Physician Decision	1	(1.0)	1	(1.0)
Progressive Disease	59	(60.8)	61	(63.5)
Withdrawal By Subject	2	(2.1)	0	(0.0)
Participants Ongoing	17	(17.5)	8	(8.3)
Status for Trial				
Discontinued	61	(62.9)	65	(67.7)
Death	60	(61.9)	64	(66.7)
Associated with COVID-19	0	(0.0)	1	(1.0)
Withdrawal By Subject	1	(1.0)	1	(1.0)
Not Associated with COVID-19, No Further Information	0	(0.0)	1	(1.0)

Not Associated with COVID-19, Subsequently Died	1	(1.0)	0	(0.0)
Participants Ongoing	36	(37.1)	31	(32.3)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
For the status for study medication of treatment phase, participants treated with study medication is used as the denominator for percentage calculation.
For the status for trial, participants in population is used as the denominator for percentage calculation.
Database Cutoff Date: 25 May 2022

Table 18: Consort Diagram (CPS≥1 Participants) (Global Cohort - Participants from Rest of the World)

	Pembrolizumab + SOC	SOC	Total
Subjects randomised	105	104	209
Subjects who died	59	78	137
Subjects who did not receive treatment	0	1	1
Subjects who received treatment	59	77	136

Database Cutoff Date: 25 May 2022

Table 19: Disposition of Participants (CPS≥1 Participants) (Global Cohort - Participants from Rest of the World) (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC	
	n	(%)	n	(%)
Participants in population	105		104	
Status for Study Medication of Treatment Phase				
Started	105		103	
Completed	11	(10.5)	3	(2.9)
Discontinued	72	(68.6)	88	(85.4)
Adverse Event	15	(14.3)	10	(9.7)
Associated with COVID-19	2	(1.9)	1	(1.0)
Clinical Progression	5	(4.8)	6	(5.8)
Non-Study Anti-Cancer Therapy	0	(0.0)	1	(1.0)
Physician Decision	1	(1.0)	2	(1.9)
Progressive Disease	46	(43.8)	63	(61.2)
Withdrawal By Subject	5	(4.8)	6	(5.8)
Participants Ongoing	22	(21.0)	12	(11.7)
Status for Trial				
Discontinued	59	(56.2)	78	(75.0)
Death	59	(56.2)	76	(73.1)
Associated with COVID-19	2	(1.9)	1	(1.0)
Withdrawal By Subject	0	(0.0)	2	(1.9)
Not Associated with COVID-19, Subsequently Died	0	(0.0)	2	(1.9)
Participants Ongoing	46	(43.8)	26	(25.0)

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
For the status for study medication of treatment phase, participants treated with study medication is used as the denominator for percentage calculation.
For the status for trial, participants in population is used as the denominator for percentage calculation.
Database Cutoff Date: 25 May 2022

A15. CS page 60 and 63 states that "The PFS HR was 0.62 ([95% CI: 0.49; 0.78], p = 0.1449) in favour of pembrolizumab plus SoC". and "The OS HR was 0.67 ([95% CI: 0.52; 0.85], p = 0.0257)". P-value presented seems to match the p-value for interaction on test in Table 14 for PFS and Table 17 for OS. Please provide the correct p-value for HR for PFS and OS.

MSD response:

Correct p-value for HR for PFS and OS are provided below.

Table 20: Analysis of Progression-Free Survival (Primary Analysis) Based on BICR Assessment per RECIST 1.1 (CPS≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC	SOC
	(N=202)	(N=200)
Number of Events (%)	141 (69.8)	156 (78.0)
DEATH	23 (11.4)	27 (13.5)
DOCUMENTED PROGRESSION	118 (58.4)	129 (64.5)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	9.9 (8.3, 11.3)	6.3 (5.6, 7.3)
[Q1, Q3]	[5.5, 18.2]	[4.0, 11.3]
Person-months	2267.0	1561.8
Event Rate / 100 Person-months	6.2	10.0
vs SOC		
Hazard Ratio (95% CI)[b]	0.62 (0.49, 0.78)	
p-value[c]	<0.0001	
PFS Rate at month 6 (%) (95% CI)	71.1 (64.1, 76.9)	52.5 (45.0, 59.5)
PFS Rate at month 12 (%) (95% CI)	41.9 (34.7, 48.8)	24.4 (18.2, 31.0)
PFS Rate at month 18 (%) (95% CI)	26.2 (19.7, 33.0)	15.1 (9.9, 21.2)
PFS Rate at month 24 (%) (95% CI)	23.9 (17.6, 30.7)	9.1 (4.8, 14.9)

a From product-limit (Kaplan-Meier) method for censored data.
b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on log-rank test.
BICR = Blinded Independent Central Review.
Database Cutoff Date: 25 May 2022

Table 21: Analysis of Overall Survival (CPS≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (Intention-to-Treat Population)

	Pembrolizumab + SOC	SOC
	(N=202)	(N=200)
Number of Events (%)	120 (59.4)	142 (71.0)
DEATH	120 (59.4)	142 (71.0)
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	18.8 (15.5, 24.3)	12.6 (11.1, 14.9)
[Q1, Q3]	[9.7, NR]	[7.5, 25.1]
Person-months	3498.9	2792.9
Event Rate / 100 Person-months	3.4	5.1
vs SOC		
Hazard Ratio (95% CI)[b]	0.67 (0.52, 0.85)	
p-value[c]	0.0006	
OS Rate at month 6 (%) (95% CI)	89.1 (83.9, 92.7)	79.0 (72.7, 84.0)
OS Rate at month 12 (%) (95% CI)	66.0 (59.0, 72.1)	52.6 (45.4, 59.3)
OS Rate at month 18 (%) (95% CI)	53.9 (46.6, 60.8)	36.0 (29.1, 42.9)
OS Rate at month 24 (%) (95% CI)	44.4 (36.8, 51.6)	27.7 (21.0, 34.7)

a From product-limit (Kaplan-Meier) method for censored data.
b Based on Cox regression model with Efron's method of tie handling with treatment as a covariate.
c One-sided p-value based on log-rank test.
NR = Not reached.
Database Cutoff Date: 25 May 2022

A16. CS Table 14 provides analysis of PFS for region subgroup (Asia vs. non-Asia) (CPS≥1 participants) (Global cohort). Please update the analysis using stratification factors (i.e., (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World) and update the p-value for interaction test.

MSD response:

Updated PFS analysis using stratification factors (i.e., (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World) and updated the p-value for interaction test are provided below.

Table 22: Analysis of Progression-Free Survival (Primary Censoring Rule) for Subgroups Defined in Protocol (CPS≥1 Participants) (Global Cohort)

Study: KEYNOTE-811	Pembrolizumab + SOC	SOC	Pembrolizumab + SOC vs. SOC	

Progression-Free Survival (Primary Censoring Rule)	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value for Interaction Test[d]
Age								
< 65 years	174	116 (66.7)	11.07 [8.35; 12.68]	165	123 (74.5)	7.00 [6.01; 8.25]	0.64 [0.50; 0.83]	0.3403
>= 65 years	124	83 (66.9)	9.79 [8.31; 12.85]	131	92 (70.2)	8.31 [6.80; 9.79]	0.78 [0.58; 1.05]	
Sex								
Male	240	165 (68.8)	9.92 [8.35; 12.19]	237	169 (71.3)	7.43 [6.70; 8.61]	0.75 [0.61; 0.93]	0.1186
Female	58	34 (58.6)	12.68 [8.28; 20.93]	59	46 (78.0)	7.03 [5.45; 9.59]	0.52 [0.33; 0.82]	
Race								
Asian	97	59 (60.8)	13.63 [8.35; 17.02]	97	60 (61.9)	12.22 [8.08; 14.06]	0.85 [0.59; 1.22]	0.1494
Non-Asian	200	139 (69.5)	9.92 [8.31; 11.37]	196	153 (78.1)	6.31 [5.59; 7.82]	0.62 [0.50; 0.79]	
Geographic Region of Enrolling Site								
Western Europe/Israel/North America/Australia	97	67 (69.1)	9.00 [6.97; 11.34]	96	74 (77.1)	6.31 [5.45; 7.82]	0.69 [0.50; 0.97]	0.2621
Asia	96	58 (60.4)	13.63 [8.35; 17.02]	96	59 (61.5)	12.52 [8.08; 14.06]	0.85 [0.59; 1.22]	
Rest of the World	105	74 (70.5)	11.11 [8.25; 12.71]	104	82 (78.8)	6.93 [5.55; 8.38]	0.56 [0.41; 0.78]	
MSI								
MSI-H	6	4 (66.7)	n.c.	2	2 (100.0)	n.c.	n.c.	n.c.
Non MSI-H	282	185 (65.6)	n.c.	280	204 (72.9)	n.c.	n.c.	
Baseline ECOG								
0	127	78 (61.4)	12.85 [9.92; 16.59]	121	82 (67.8)	8.48 [6.01; 10.35]	0.66 [0.48; 0.90]	0.5342
1	171	121 (70.8)	8.58 [7.39; 10.91]	174	133 (76.4)	7.06 [6.08; 8.21]	0.73 [0.57; 0.94]	
Primary Location								

GEJ	97	69 (71.1)	8.51 [7.33; 11.37]	99	73 (73.7)	7.13 [5.62; 9.66]	0.73 [0.53; 1.02]	0.7814
Stomach	201	130 (64.7)	11.30 [9.10; 13.63]	197	142 (72.1)	7.79 [6.80; 8.74]	0.68 [0.54; 0.87]	
Histological Subtype								
Diffuse	56	38 (67.9)	9.86 [6.80; 15.24]	49	40 (81.6)	5.95 [4.30; 8.21]	0.64 [0.41; 1.01]	0.7626
Intestinal	169	108 (63.9)	11.07 [8.54; 12.85]	158	110 (69.6)	8.12 [6.77; 9.69]	0.70 [0.53; 0.91]	
Indeterminate	73	53 (72.6)	9.82 [6.93; 13.73]	89	65 (73.0)	7.79 [5.59; 9.69]	0.74 [0.51; 1.07]	
Tumour Burden								
< Median	139	86 (61.9)	12.52 [9.23; 15.24]	139	104 (74.8)	8.25 [7.10; 9.79]	0.69 [0.52; 0.92]	0.9430
>= Median	147	105 (71.4)	9.00 [7.33; 11.11]	146	106 (72.6)	6.80 [5.59; 8.31]	0.68 [0.52; 0.90]	
Number of Metastatic Sites								
<=2	149	97 (65.1)	11.66 [9.56; 13.83]	172	121 (70.3)	7.43 [5.95; 9.59]	0.68 [0.52; 0.89]	0.7837
>=3	149	102 (68.5)	8.58 [7.23; 11.30]	124	94 (75.8)	7.13 [6.80; 8.81]	0.70 [0.53; 0.93]	
Prior Gastrectomy/Esophagectomy								
Yes	36	24 (66.7)	11.34 [8.35; 17.97]	48	33 (68.8)	10.35 [7.82; 13.83]	0.70 [0.41; 1.19]	0.8565
No	262	175 (66.8)	9.92 [8.41; 12.52]	248	182 (73.4)	7.03 [6.05; 8.25]	0.69 [0.56; 0.85]	
Chemotherapy Regimen								
CAPOX	251	165 (65.7)	11.07 [8.64; 12.98]	253	182 (71.9)	7.82 [7.00; 8.61]	0.69 [0.56; 0.85]	0.7791
FP	47	34 (72.3)	8.58 [6.54; 11.66]	43	33 (76.7)	6.08 [5.29; 9.66]	0.69 [0.43; 1.12]	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model with treatment as a covariate using Wald confidence interval
d: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
Database Cutoff Date: 25 May 2022
CI: Confidence Interval; n.c.: not calculated (at least 10 participants per subgroup and at least 10 participants with events in one of the subgroups necessary)

A17. CS Table 16 provides analysis of OS for region subgroup (Asia vs. non-Asia) (CPS≥1 participants) (Global cohort). Please update the analysis using stratification factors (i.e., (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World) and update the p-value for interaction test.

MSD response:

Updated OS analysis using stratification factors (i.e., (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World) and updated p-value for interaction test are provided below.

Table 23: Analysis of Overall Survival for Subgroups Defined in Protocol (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population)

Study: KEYNOTE-811	Pembrolizumab + SOC			SOC			Pembrolizumab + SOC vs. SOC	
Overall Survival	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	N[a]	Participants with Event n (%)	Median Time[b] in Months [95 %-CI]	Hazard Ratio [95 %-CI][c]	p-Value for Interaction Test[d]
Age								
< 65 years	174	91 (52.3)	24.21 [18.76; 28.98]	165	111 (67.3)	14.59 [11.83; 17.58]	0.63 [0.48; 0.84]	0.0174
>= 65 years	124	76 (61.3)	17.81 [14.36; 23.98]	131	72 (55.0)	18.56 [14.23; 28.45]	1.06 [0.77; 1.47]	
Sex								
Male	240	138 (57.5)	20.34 [18.14; 24.21]	237	141 (59.5)	15.61 [13.47; 20.07]	0.86 [0.68; 1.09]	0.1061
Female	58	29 (50.0)	25.73 [14.98; -]	59	42 (71.2)	15.01 [10.45; 19.78]	0.56 [0.35; 0.90]	
Race								
Asian	97	48 (49.5)	22.14 [18.20; -]	97	42 (43.3)	35.58 [20.40; -]	1.15 [0.76; 1.74]	0.0300
Non-Asian	200	119 (59.5)	18.83 [15.47; 24.21]	196	138 (70.4)	12.62 [11.14; 15.01]	0.68 [0.53; 0.87]	
Geographic Region of Enrolling Site								
Western Europe/Israel/North America/Australia	97	61 (62.9)	18.76 [14.55; 24.21]	96	64 (66.7)	12.12 [10.35; 15.74]	0.81 [0.57; 1.15]	0.0317

Asia	96	47 (49.0)	23.43 [18.20; -]	96	41 (42.7)	35.58 [20.76; -]	1.15 [0.76; 1.76]	
Rest of the World	105	59 (56.2)	20.34 [14.78; 27.86]	104	78 (75.0)	13.40 [10.42; 15.54]	0.57 [0.40; 0.80]	
MSI								
MSI-H	6	4 (66.7)	n.c.	2	0 (0.0)	n.c.	n.c.	n.c.
Non MSI-H	282	156 (55.3)	n.c.	280	173 (61.8)	n.c.	n.c.	
Baseline ECOG								
0	127	65 (51.2)	24.21 [18.83; 30.13]	121	75 (62.0)	16.76 [12.48; 22.08]	0.68 [0.49; 0.95]	0.2911
1	171	102 (59.6)	18.50 [15.31; 24.21]	174	108 (62.1)	14.59 [12.68; 18.56]	0.88 [0.67; 1.15]	
Primary Location								
GEJ	97	58 (59.8)	18.73 [15.31; 24.28]	99	58 (58.6)	13.08 [10.51; 29.70]	0.94 [0.65; 1.35]	0.2946
Stomach	201	109 (54.2)	21.45 [18.20; 27.73]	197	125 (63.5)	15.74 [13.70; 19.65]	0.73 [0.56; 0.94]	
Histological Subtype								
Diffuse	56	31 (55.4)	18.83 [13.83; -]	49	36 (73.5)	10.35 [7.66; 15.54]	0.53 [0.32; 0.85]	0.0985
Intestinal	169	91 (53.8)	23.43 [19.94; 27.73]	158	90 (57.0)	19.65 [15.34; 24.18]	0.89 [0.67; 1.19]	
Indeterminate	73	45 (61.6)	18.30 [16.03; 24.71]	89	57 (64.0)	14.59 [11.83; 20.76]	0.83 [0.56; 1.22]	
Tumour Burden								
< Median	139	77 (55.4)	21.19 [17.81; 28.62]	139	78 (56.1)	20.07 [14.23; 30.79]	0.93 [0.68; 1.27]	0.1420
>= Median	147	82 (55.8)	20.93 [15.84; 25.73]	146	97 (66.4)	14.26 [11.73; 16.82]	0.67 [0.50; 0.91]	
Number of Metastatic Sites								
<=2	149	85 (57.0)	20.04 [16.23; 26.97]	172	107 (62.2)	15.54 [12.48; 18.63]	0.79 [0.60; 1.05]	0.9538
>=3	149	82 (55.0)	20.93 [18.14; 25.73]	124	76 (61.3)	16.82 [13.14; 24.18]	0.79 [0.58; 1.08]	
Prior Gastrectomy/Oesophagostomy								
Yes	36	17 (47.2)	27.73 [18.20; -]	48	26 (54.2)	19.91 [14.23; -]	0.75 [0.40; 1.38]	0.9373

No	262	150 (57.3)	20.04 [17.45; 24.21]	248	157 (63.3)	14.85 [12.68; 18.04]	0.78 [0.63; 0.98]	
Chemotherapy Regimen								
CAPOX	251	138 (55.0)	21.06 [18.50; 26.97]	253	148 (58.5)	16.92 [14.29; 20.76]	0.82 [0.65; 1.03]	0.4666
FP	47	29 (61.7)	18.23 [10.15; 24.28]	43	35 (81.4)	11.24 [8.25; 15.28]	0.71 [0.43; 1.18]	

a: Number of participants: intention-to-treat population
b: From product-limit (Kaplan-Meier) method for censored data
c: Based on Cox regression model with treatment as a covariate using Wald confidence interval
d: Based on Cox model with treatment and subgroup as covariates, and treatment-by-subgroup interaction (p-value of likelihood ratio test for interaction term)
Database Cutoff Date: 25 May 2022
CI: Confidence Interval; n.c.: not calculated (at least 10 participants per subgroup and at least 10 participants with events in one of the subgroups necessary)

A18. CS page 67 states that "The ORR and median DOR as determined by BICR per RECIST 1.1 were consistent between the CPS ≥1 subgroup and the ITT population (Appendix M)." Appendix M currently does not present the results mentioned. Please provide the relevant results.

MSD response:

The Objective response rate and duration of response for the ITT population are provided below.

Objective response rate Global ITT population

The ORR was higher in the pembrolizumab plus SOC group than in the SOC group: 72.6% (95% CI: 67.6, 77.2) versus 59.8% (95% CI: 54.4, 65.0), representing a difference of 12.8% (95% CI: 5.9, 19.7, nominal p-value = 0.00015). The CR and PR rates were higher in the pembrolizumab plus SOC group compared with the SOC group (14.0% vs 10.9% and 58.6% vs 48.9%, respectively).

Table 24: Analysis of Objective Response with Confirmation Based on BICR Assessment per RECIST 1.1 (Global Cohort) (ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + SOC vs. SOC	
				Estimate (95% CI)[a]	p-Value
Pembrolizumab + SOC	350	254	72.6 (67.6, 77.2)	12.8 (5.9, 19.7)	0.00015

SOC	348	208	59.8 (54.4, 65.0)		

[a] Based on Miettinen & Nurminen method stratified by Geographic region (Western Europe/Israel/North America/Australia, Asia and Rest of the World), PD-L1 status (positive vs. negative), and Chemotherapy regimen (FP or CAPOX) with small strata collapsed as pre-specified in the sSAP. Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in th e 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 Cutoff Date: 25 May 2022.

Table 25: Summary of Objective Response with Confirmation Based on BICR Assessment per RECIST 1.1 (Global Cohort) (ITT Population)

	Pembrolizumab + SOC			SOC		
	n	(%)	(95% CI)	n	(%)	(95% CI)
Number of Subjects in Population	350			348		
Complete Response (CR)	49	14.0	(10.5, 18.1)	38	10.9	(7.8, 14.7)
Partial Response (PR)	205	58.6	(53.2, 63.8)	170	48.9	(43.5, 54.2)
Overall Response (CR+PR)	**254**	**72.6**	**(67.6, 77.2)**	**208**	**59.8**	**(54.4, 65.0)**
Stable Disease (SD)	67	19.1	(15.2, 23.7)	96	27.6	(23.0, 32.6)
Disease Control (CR+PR+SD)	**321**	**91.7**	**(88.3, 94.4)**	**304**	**87.4**	**(83.4, 90.7)**
Progressive Disease (PD)	19	5.4	(3.3, 8.3)	23	6.6	(4.2, 9.8)
Not Evaluable (NE[a])	1	0.3	(0.0, 1.6)	5	1.4	(0.5, 3.3)
No Assessment[b]	9	2.6	(1.2, 4.8)	16	4.6	(2.7, 7.4)

Responses are based on BICR assessment per RECIST 1.1. BICR = Blinded independent central review.
Stable disease includes SD, Non-CR/Non-PD, and NED.
NED: No lesions were identified at baseline assessment and there remained no lesions at post baseline assessment(s).
aNE: post-baseline assessment(s) available however not being evaluable.
bNo Assessment: no post-baseline assessment available for response evaluation. Database Cutoff Date: 25 May 2022.

Duration of response Global ITT population

Pembrolizumab in combination with SOC resulted in a prolonged DOR when compared to SOC as a first-line treatment in participants with previously untreated, locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma.

- The median DOR per RECIST 1.1 based on BICR was longer in the pembrolizumab plus SOC group compared with the SOC group (11.2 vs 9.0 months).

- The median TTR was generally similar in the pembrolizumab plus SOC and SOC groups, respectively (1.4 vs 1.5 months).

- By KM estimation, the extended response duration was higher in the pembrolizumab plus SOC group compared with the SOC group beginning at ≥6 months (74.7% vs 68.9%) and continuing for ≥12 months.

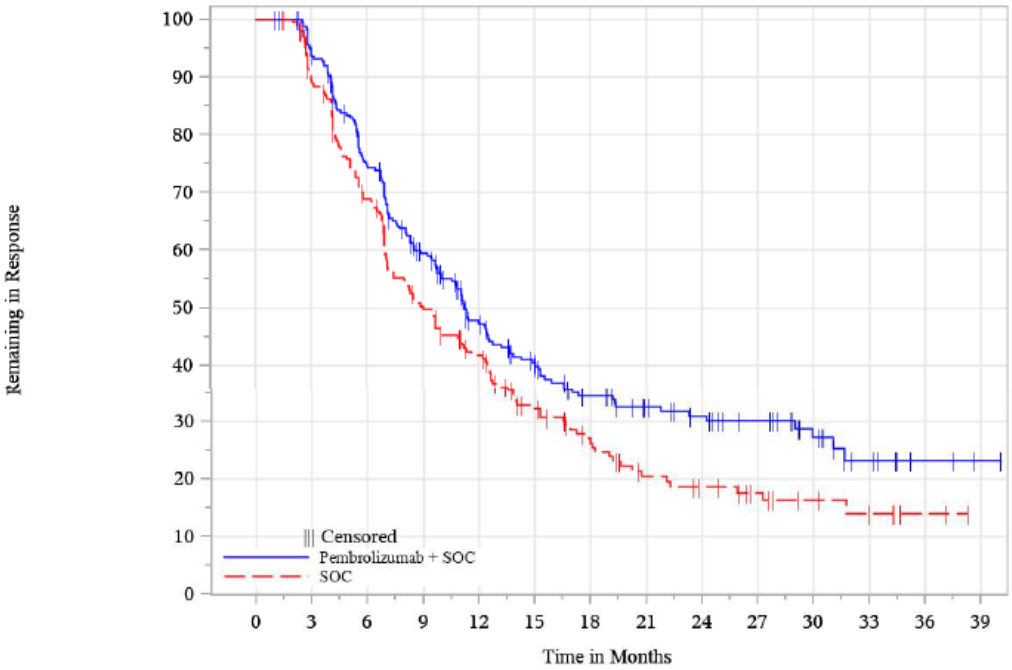
Approximately 38% and 31% of participants in the pembrolizumab plus SOC and SOC groups were censored. Responses were ongoing in 28.3% and 16.3% of participants in the pembrolizumab plus SOC and SOC group.

Table 26: Summary of Time to Response and Duration of Response Based on BICR Assessment per RECIST 1.1 in Participants with Confirmed Response (Global Cohort)

	Pembrolizumab + SOC (N=350)	SOC (N=348)
Number of participants with response[a]	254	208
Time to Response (months)		
Mean (SD)	1.9 (1.3)	2.0 (1.1)
Median (Range)	1.4 (0.9-15.2)	1.5 (0.7-7.0)
Response Duration[b] (months)		
Median (Range)	11.2 (1.1+ - 40.1+)	9.0 (1.4+ - 38.3+)
Number (%b) of Participants with Extended Response Duration:		
≥3 months	234 (94.0)	173 (89.9)
≥6 months	179 (74.7)	129 (68.9)
≥9 months	136 (59.5)	90 (50.3)
≥12 months	94 (47.8)	70 (41.7)

a Includes participants with best objective response as confirmed 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: 25 May 2022

Figure 5: Kaplan-Meier Estimates of Duration of Response Based on BICR Assessment per RECIST 1.1 (Global Cohort) (In Participants with Confirmed Response)



Number of Subjects at Risk

Pembrolizumab + SOC	254	234	179	136	94	73	54	44	36	28	18	8	3	1
SOC	208	173	129	90	70	47	34	23	19	13	9	6	2	0

A19. CS Table 9 states that the statistical methods used for key efficacy analyses was a stratified Cox regression model (i.e. “The HR was estimated using a stratified Cox regression model”). However, the footnote in Table 14 and Table 16 states that the hazard ratio (HR) for PFS and OS was “Based on Cox regression model with treatment as a covariate using Wald confidence interval.” Please explain this apparent discrepancy in the statistical method used for PFS and OS (stratified Cox regression vs. only treatment as a covariate).

MSD response:

CS table 9 stratified Cox regression refers to the pre-specified key statistical analyses for primary objective on the study ITT population (not restricted to CPS≥1). All pre-planned subgroup analyses (including for participants with CPS≥1, as well as for other levels of stratification factors and other pre-planned subgroups were pre-specified to be run with the same (consistent) Cox model with treatment as a covariate using Wald confidence interval.

A20. CS, Table 26: For the fatal adverse events and drug-related fatal adverse events in Table 26, please provide details of the type of adverse event (AE) experienced. Text on CS page 79-80 describes four drug-related AEs resulting in death in the intervention arm and three in the comparator arm, but these numbers do not match the data in Table 26. Please explain the apparent discrepancy.

MSD response:

In the subgroups of participants with CPS≥1, two participants in the intervention arm one participant in the control arm died due to a drug-related adverse events. Text on CS page 79-80 describes deaths due to drug-related adverse events in participants from Global ITT cohort by error.

Fatal adverse events included:

Two AEs resulting in death in the pembrolizumab plus SOC group were considered drug related by the investigator: pneumonitis and hepatitis. One AE resulting in death in the SOC group were considered drug-related by the investigator was myocarditis.

A21. CS. Table 21, EQ-5D-VAS: It is stated in CS section B.3.4. that health-related quality of life data were implausibly high in the Asia cohort, and for this reason the model uses EQ-5D utility data specific to the non-Asia cohort. However, Table 21 only provides EQ-5D-VAS data for the Global CPS≥1 cohort which includes all regions. Please provide data equivalent to Table 21 for the non-Asia CPS ≥1 cohort.

MSD response:

EQ-5D-VAS data for the non-Asia CPS ≥1 cohort provided below.

Table 27: Analysis of Change from Baseline in EQ-5D-5L VAS to Week 24 (CPS≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (PRO FAS Population)

	Baseline		Week 24		Change from Baseline to Week 24	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pairwise Comparison	Difference in LS Means[†] (95% CI)	p-Value[†]
Pembrolizumab + SOC vs. SOC	[redacted]	[redacted]

† 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)).
Western Europe includes Belgium, France, Germany, Spain, Italy, United Kingdom, Ireland, Latvia, Lithuania, which is consistent with the 'Europe' region defined in the protocol for stratification.
For baseline and Week 24, 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 Cutoff Date: 25 May 2022

A22. Please provide summary EQ-5D utility scores (using mapped 3L values as presented in section B.3.4) at baseline and 24 weeks by trial arm in the CPS≥1 cohort for each region used for stratification (i.e., (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World), for the non-Asia cohort and for the Global cohort (i.e. all regions).

MSD response:

Summary of EQ-5D utility scores (using mapped 3L values) at baseline and 24 weeks by trial arm in the CPS≥1 cohort for each region used for stratification (i.e., (i) Western Europe/Israel/North America/Australia, (ii) Asia and (iii) Rest of the World), for the non-Asia cohort and for the Global cohort (i.e. all regions) provided below.

Table 28: Descriptive Summary of EQ-5D Health Utility Scores at Baseline and Week 24 EQ-5D-5L United Kingdom Algorithm Cross-Walk (NICE - DSU) (CPS≥1 Participants) (Global Cohort - Participants from Western Europe/Israel/North America/Australia) (PRO Full Analysis Set Population)

	Study: KEYNOTE-811	
	Pembrolizumab + SOC	SOC
	[redacted]	[redacted]
BASELINE		
N[b]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
WEEK 24		
N[b]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

a: Number of participants: full-analysis-set population (Global Cohort - CPS≥1 Participants from Western Europe/Israel/North America/Australia).
b: Number of observations at each time point.
Database Cutoff Date: 25 May 2022

Table 29: Descriptive Summary of EQ-5D Health Utility Scores at Baseline and Week 24 EQ-5D-5L United Kingdom Algorithm Cross-Walk (NICE - DSU) (CPS≥1 Participants) (Global Cohort - Participants from Asia Region) (PRO Full Analysis Set Population)

	Study: KEYNOTE-811	
	Pembrolizumab + SOC	SOC
	[redacted]	[redacted]
BASELINE		
N[b]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
WEEK 24		
N[b]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

a: Number of participants: full-analysis-set population (Global Cohort - CPS≥1 Participants from Asia Region).
b: Number of observations at each time point.
Database Cutoff Date: 25 May 2022

Table 30: Descriptive Summary of EQ-5D Health Utility Scores at Baseline and Week 24 EQ-5D-5L United Kingdom Algorithm Cross-Walk (NICE - DSU) (CPS≥1 Participants) (Global Cohort - Participants from Rest of the World) (PRO Full Analysis Set Population)

	Study: KEYNOTE-811	
	Pembrolizumab + SOC	SOC
	[redacted]	[redacted]
BASELINE		
N[b]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]
WEEK 24		
N[b]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Q1; Q3)	[redacted]	[redacted]
Min; Max	[redacted]	[redacted]

a: Number of participants: full-analysis-set population (Global Cohort - CPS≥1 Participants from Rest of the World).
b: Number of observations at each time point.
Database Cutoff Date: 25 May 2022

Table 31: Descriptive Summary of EQ-5D Health Utility Scores at Baseline and Week 24 EQ-5D-5L United Kingdom Algorithm Cross-Walk (NICE - DSU) (CPS≥1 Participants) (Global Cohort) (PRO Full Analysis Set Population)

	Study: KEYNOTE-811	
	Pembrolizumab + SOC	SOC
	[redacted]	[redacted]
BASELINE		

N[b]	[redacted]	[redacted]
Mean (SD)		
Median (Q1; Q3)		
Min; Max		
WEEK 24		
N[b]		
Mean (SD)		
Median (Q1; Q3)		
Min; Max		

a: Number of participants: full-analysis-set population (Global Cohort - CPS≥1 Participants).
b: Number of observations at each time point.
Database Cutoff Date: 25 May 2022

Table 32: Descriptive Summary of EQ-5D Health Utility Scores at Baseline and Week 24 EQ-5D-5L United Kingdom Algorithm Cross-Walk (NICE - DSU) (CPS≥1 Participants) (Global Cohort - Participants from Non-Asia Region) (PRO Full Analysis Set Population)

	Study: KEYNOTE-811	
	Pembrolizumab + SOC	SOC
	[redacted]	[redacted]
BASELINE		
N[b]		
Mean (SD)		
Median (Q1; Q3)		
Min; Max		
WEEK 24		
N[b]		
Mean (SD)		
Median (Q1; Q3)		
Min; Max		

a: Number of participants: full-analysis-set population (Global Cohort - CPS≥1 Participants from Non-Asia Region).
b: Number of observations at each time point.
Database Cutoff Date: 25 May 2022

A23. CS states on page 57 that the submission refers only to the Global Cohort that excludes the Japan specific SOX cohort, but the tables describing the studies identified for the indirect comparison (Appendix D, Tables 10 to 15) appear to refer to the whole study including the Japan specific cohort as S1+OX is listed as a comparator. However, the N's per arm seem to match the reporting of results for the Global intention-to-treat (ITT) population without restriction by CPS. Please clarify what population is reported for KEYNOTE-811 in Appendix D, and specifically whether it excludes the Japan cohort and whether it is CPS<=1 or any CPS score.

MSD response:

KEYNOTE 811 results in the Global ITT population (excluding Japan cohort) and CPS≥1 populations are reported in Appendix D. Inclusion of S1+OX intervention is an error, please see the correct tables below.

Table 33: Outcome definitions

Trial ID	NCT Code	Overall survival	Progression-free survival	Objective response rate	Duration of response
KEYNOTE 811	NCT03615326	Time from randomization to death due to any cause	Time from randomization to the first documented disease progression per RECIST 1.1 or death due to any cause; whichever occurs first.	The percentage of participants who have a Complete Response ([CR]; disappearance of all evidence of disease) or Partial Response ([PR]; regression of measurable disease and no new sites) per RECIST 1.1	The time from first response (CR or PR) to subsequent disease progression or death from any cause; whichever occurs first.
ToGA	NCT01041404	Time from randomization until death from any cause	Time from the date of randomization to the date of the first documentation of progressive disease or date of death; whichever occurs first	CR (defined as the disappearance of all TLs) and PR (defined as at least a 30% decrease in the SLD of the TLs; taking as a reference the baseline SLD)	Time from the date on which the CR or PR was first recorded to the date on which PD is first noted

Table 34: Reported overall survival

Trial ID	NCT Code	Intervention	N	Population	Length of follow-up	Overall survival		
						KM (Y/N)	Median (95% CI)	HR (95% CI)
KEYNOTE 811	NCT03615326	5FU+CIS, or CAP+OX, +PEM+TRAS	350	Overall population*	16.1 months	Yes	20.0 months (17.8-23.2)	0.87 (0.72-1.06)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	348		14.8 months	Yes	16.9 months (15-19.8)	REF
		5FU+CIS, or CAP+OX, +PEM+TRAS	298	Subgroup, CPS ≥ 1	17 months	Yes	20.5 months (18.2-24.3)	0.79 (0.64-0.98)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	296		13.9 months	Yes	15.6 months (13.5-18.6)	REF
ToGA	NCT01041404	5-FU+CIS, or CAP+CIS, +TRAS	294	Overall population**	18.6 months	Yes	13.8 months (12-16)	0.74 (0.6-0.91)
		5-FU+CIS, or CAP+CIS	290		17.1 months	Yes	11.1 months (10-13)	REF

Table 35: Reported progression-free survival

Trial ID	NCT Code	Intervention	N	Population	Length of follow-up	Progression free survival		
						KM (Y/N)	Median (95% CI)	HR (95% CI)
KEYNOTE 811	NCT03615326	5FU+CIS, or CAP+OX, +PEM+TRAS	350	Overall population (independent review committee)*	16.1 months	Yes	10 months (8.6-11.7)	0.72 (0.6-0.87)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	348		14.8 months	Yes	8.1 months (7-8.5)	REF
		5FU+CIS, or CAP+OX, +PEM+TRAS	350	Overall population (investigator assessed)	16.1 months	Yes	10.1 months (9.1-12.2)	0.72 (0.61, 0.86)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	348		14.8 months	Yes	7.2 months (6.8-8.3)	REF
		5FU+CIS, or CAP+OX, +PEM+TRAS	298	Subgroup, CPS ≥ 1 (independent review committee)	17 months	Yes	10.8 months (8.5-12.5)	0.7 (0.58-0.85)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	296		13.9 months	Yes	7.2 months (6.8-8.4)	REF
ToGA	NCT01041404	5-FU+CIS, or CAP+CIS, +TRAS	294	Overall population (investigator assessed)	18.6 months	Yes	6.7 months (6-8)	0.71 (0.59-0.85)
		5-FU+CIS, or CAP+CIS	290		17.1 months	Yes	5.5 months (5-6)	REF

Table 36: Reported duration of response

Trial ID	NCT Code	Intervention	N	Population	Length of follow-up	DOR		
						KM	Median (95% CI)	HR (95% CI)
KEYNOTE 811	NCT03615326	5FU+CIS, or CAP+OX, +PEM+TRAS	350	Overall population (independent review committee)	16.1 months	Yes	11.2 months (1.1+, 1.4+)	--
		5FU+CIS, or CAP+OX, +Placebo+TRAS	348		14.8 months	Yes	9 months (1.4+, 38.3+)	--
		5FU+CIS, or CAP+OX, +PEM+TRAS	350	Overall population (investigator assessed)	16.1 months	Yes	11.3 months (1.1+, 38.8+)	--
		5FU+CIS, or CAP+OX, +Placebo+TRAS	348		14.8 months	Yes	9 months (1.4+, 38.3+)	--

		5FU+CIS, or CAP+OX, +PEM+TRAS	298	Subgroup, CPS ≥ 1 (independent review committee)	17 months	Yes	11.3 months (1.1+, 40.1+)	--
		5FU+CIS, or CAP+OX, +Placebo+TRAS	296		13.9 months	Yes	9.5 months (1.4+, 38.3+)	--
ToGA	NCT01041404	5-FU+CIS, or CAP+CIS, +TRAS	294	Overall population (investigator assessed)	18.6 months	No	6.9 months (6-8)	0.54 (0.4-0.73)
		5-FU+CIS, or CAP+CIS	290		17.1 months	No	4.8 months (4-6)	REF

Table 37: Reported objective response rate

Trial ID	NCT Code	Intervention	N	Population	ORR	CR	PR	SD	PD
					N (%)	N (%)	N (%)	N (%)	N (%)
KEYNOTE 811	NCT03615326	5FU+CIS, or CAP+OX, +PEM+TRAS	350	Overall population (independent review committee)	254 (72.6)	49 (14.0)	205 (58.6)	67 (19.1)	19 (5.4)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	348		208 (59.8)	38 (10.9)	170 (48.9)	96 (27.6)	23 (6.6)
		5FU+CIS, or CAP+OX, +PEM+TRAS	350	Overall population (investigator assessed)	257 (73.4)	49 (14.0)	205 (58.6)	67 (19.1)	19 (5.4)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	348		211 (60.6)	38 (10.9)	170 (48.9)	96 (27.6)	23 (6.6)
		5FU+CIS, or CAP+OX, +PEM+TRAS	298	Subgroup, CPS ≥ 1 (independent review committee)	218 (73.2)	42 (14.1)	176 (59.1)	55 (18.5)	16 (5.4)
		5FU+CIS, or CAP+OX, +Placebo+TRAS	296		173 (58.4)	29 (9.8)	144 (48.6)	83 (28.0)	22 (7.4)
ToGA	NCT01041404	5-FU+CIS, or CAP+CIS, +TRAS	294	Overall population	139 (47)	16 (5)	123 (42)	93 (32)	35 (12)

		5-FU+CIS, or CAP+CIS	290	(investigator assessed)	100 (35)	7 (2)	93 (32)	101 (35)	53 (18)

Section B: Clarification on cost-effectiveness data

Survival extrapolation

B1. CS page 105 states that "Both separately fitted and jointly fitted curves were evaluated." The extrapolations presented in the CS Section B.3.3 did not use either approach. Instead, a parametric distribution was fitted to the control arm and applied a constant hazard ratio to this curve to estimate the survival for the intervention arm. Please explain why this approach is preferred over the separately fitting approach and jointly fitting approach.

MSD Response:

The base case approach in the submitted model is as described above. Given the insufficient evidence to reject the proportional hazards assumption, as described in the CS, the appropriate choice of model was between the jointly fitted approach and the application of a constant hazard ratio to the SoC arm curve (i.e. the separately fitted approach was excluded). Following assessment of the generalisability of the global cohort CPS≥1 results for the SoC arm to clinical practice in England and Wales and previous clinical trials, and the anticipated benefit of the intervention treatment based on the KEYNOTE-811 results, the HR approach was deemed to be a better representation of the relative benefits of the two treatment arms under evaluation.

B2. PRIORITY. Please clarify which data were used for the survival analysis for each outcome, i.e. OS, PFS and time to true deterioration (TTD). Specifically, please clarify in each case whether it is the non-Asia subgroup or the Global cohort (all regions) and confirm whether all survival analysis was restricted to patients with CPS≥1. If the Global CPS≥1 cohort was used, please explain why this is more relevant than the non-Asia CPS≥1 cohort. If the company prefers to use the Global CPS≥1 cohort then please provide responses for questions B3 to B6 below for both the Global CPS≥1 cohort and the non-Asia CPS≥1 cohort. Otherwise, providing the data for just the non-Asia CPS≥1 cohort is sufficient.

MSD Response:

Note: MSD have interpreted TTD above as "time to treatment discontinuation".

In the submitted model, OS and PFS extrapolations for the SoC arm were informed by data from the Global CPS≥1 cohort. Analysis of the population submitted for regulatory approval was prioritised with analysis of subgroups completed in succession. At the time of submission, the most complete and quality-assured data set was presented. For the intervention arm, an approach to generate OS and PFS curves based on the application of a constant HR (in accordance with the non-rejection of the proportional hazards assumption) was followed rather than using the trial KM data.

Extrapolations of TTD data for both arms were informed by the non-Asia CPS≥1 cohort. However, the TTD KM data for the non-Asia CPS≥1 cohort were deemed sufficiently complete to use directly in the model without need for extrapolation and the potential associated uncertainty. Maximum treatment durations were also implemented in line with clinical practice (described in the CS).

For responses to questions B.3 to B.6, data has been provided for the non-Asia CPS≥1 cohort only, which MSD consider to be the most relevant to the England and Wales population.

B3. PRIORITY. If the survival analysis has been conducted on the Global CPS≥1 cohort, please repeat the survival analysis for all outcomes using only data from the non-Asia CPS≥1 cohort. Please incorporate these curves in the model.

MSD Response:

MSD have conducted survival analysis using data from the non-Asia CPS≥1 cohort and included in the updated model provided with these responses. The data is used to inform the model when the controls to “Apply constant HR for pembrolizumab with trastuzumab plus chemotherapy” are set to No.

B4. PRIORITY. Please clarify if the assessment of proportional hazards assumption was conducted using data from the Global CPS≥1 cohort. If yes, please repeat the assessment for the non-Asia CPS≥1 cohort.

MSD Response:

The proportional hazards assessment described in the CS was conducted using data from the Global CPS≥1 cohort. Supporting evidence for an assessment for the non-Asia CPS≥1 cohort is described below.

The Schoenfeld residual plot and cumulative hazards plots for OS in this population are presented in the figures below. As with the global cohort, the Schoenfeld residual plot does not vary significantly from zero and the p-value is 1.000. Furthermore, the log cumulative hazards in OS over time for both arms are approximately parallel to the y-axis for most of the trial period, with the tail-end of the KM curves appearing to converge at the end of the curve with heavy censoring. As with the global cohort, there is insufficient information to reject the proportional hazards assumption.

Figure 6: Plot of Kaplan-Meier curve and Schoenfeld residual for graphical diagnosis of proportional hazards in Overall Survival between groups treated with Pembrolizumab + SOC versus SOC (non-Asia CPS≥1)

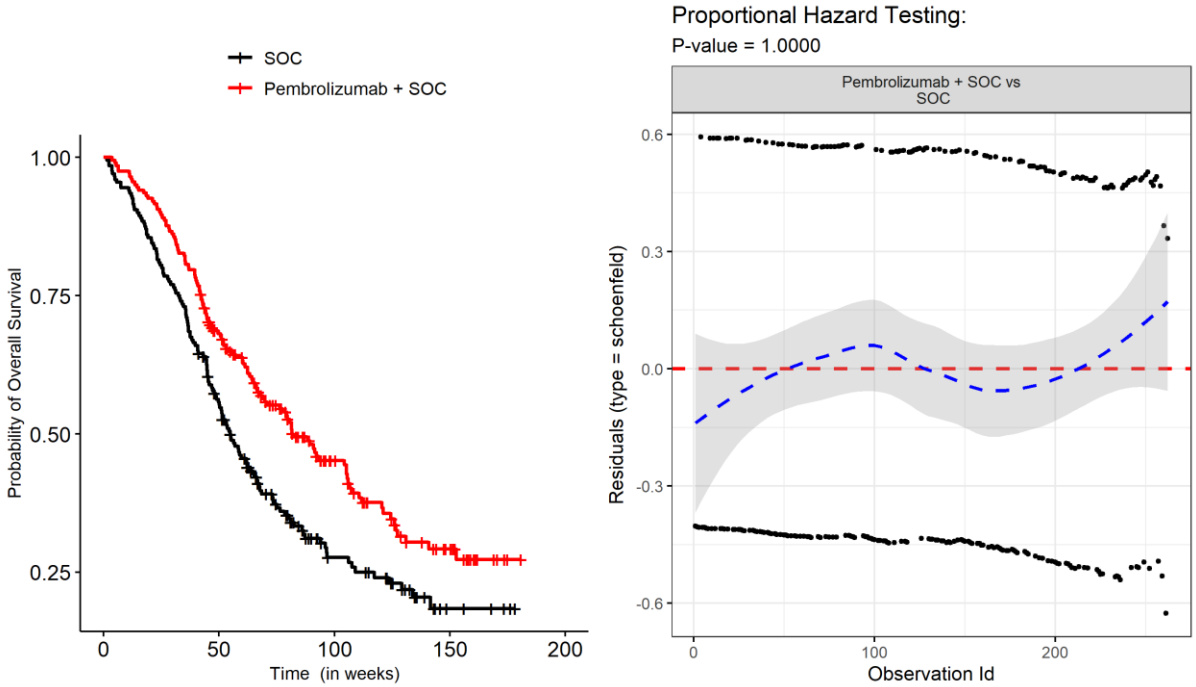
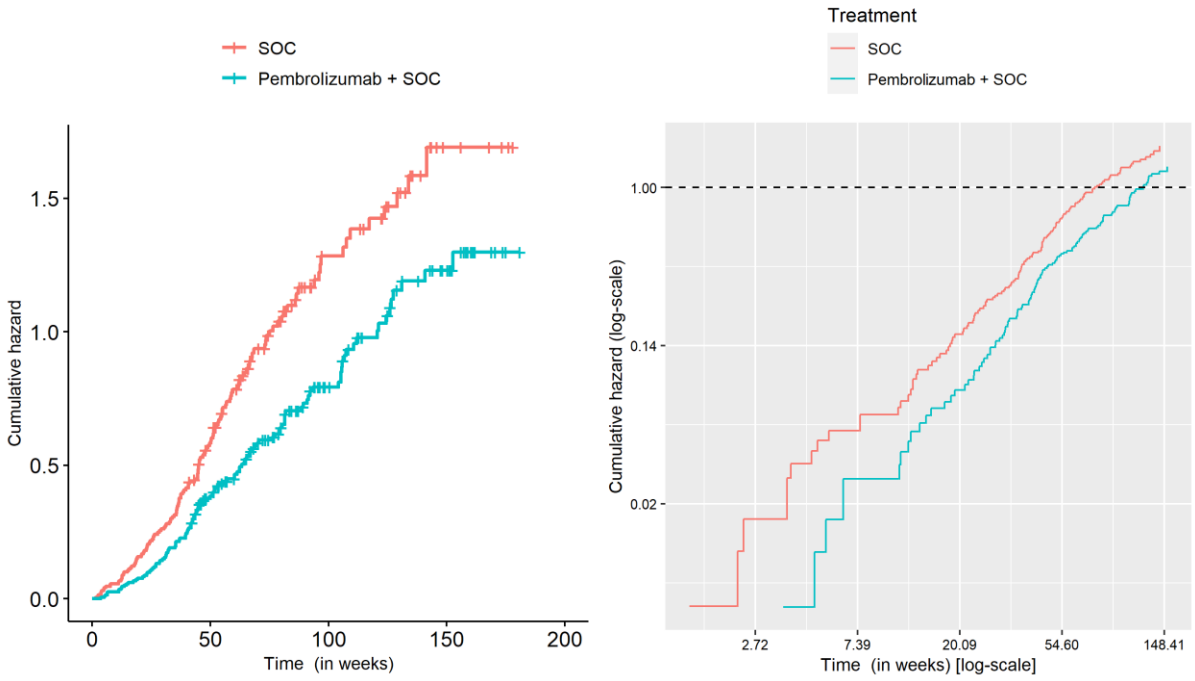


Figure 7: Comparison in cumulative hazard in overall survival over time between groups treated with pembrolizumab + SoC versus SoC



The Schoenfeld residual plot and cumulative hazards plots for PFS in this population are presented in the figures below. As with OS, similar conclusions were made based on this assessment i.e. that there is insufficient evidence to reject the proportional hazards assumption, due to a predominantly linear Schoenfeld residuals plot, and the parallel nature of the cumulative hazards following the initial part of the trial period, where a protocol-driven tumour assessment schedule applied.

The assessments for both OS and PFS endpoints failed to reject the assumption and this outcome informed the approach to generating survival curves for the intervention arm in the economic model.

Figure 8: Plot of Kaplan-Meier curve and Schoenfeld residual for graphical diagnosis of proportional hazards in BIRC-assessed Progression-free Survival between groups treated with Pembrolizumab + SOC versus SOC

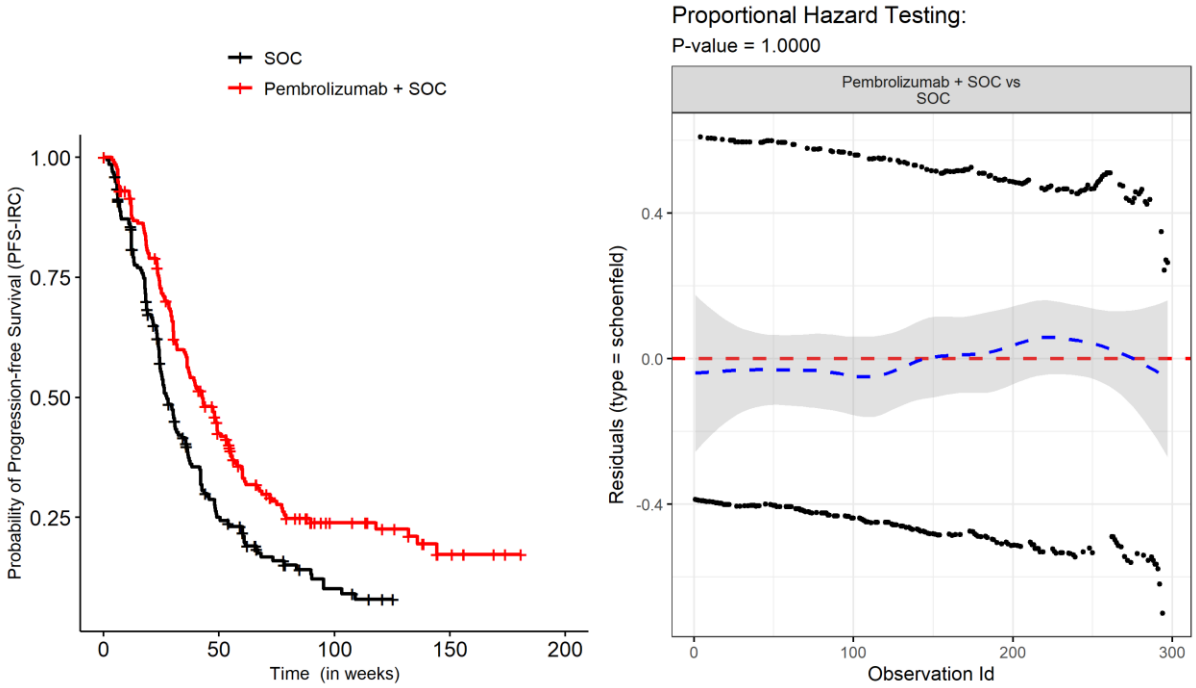
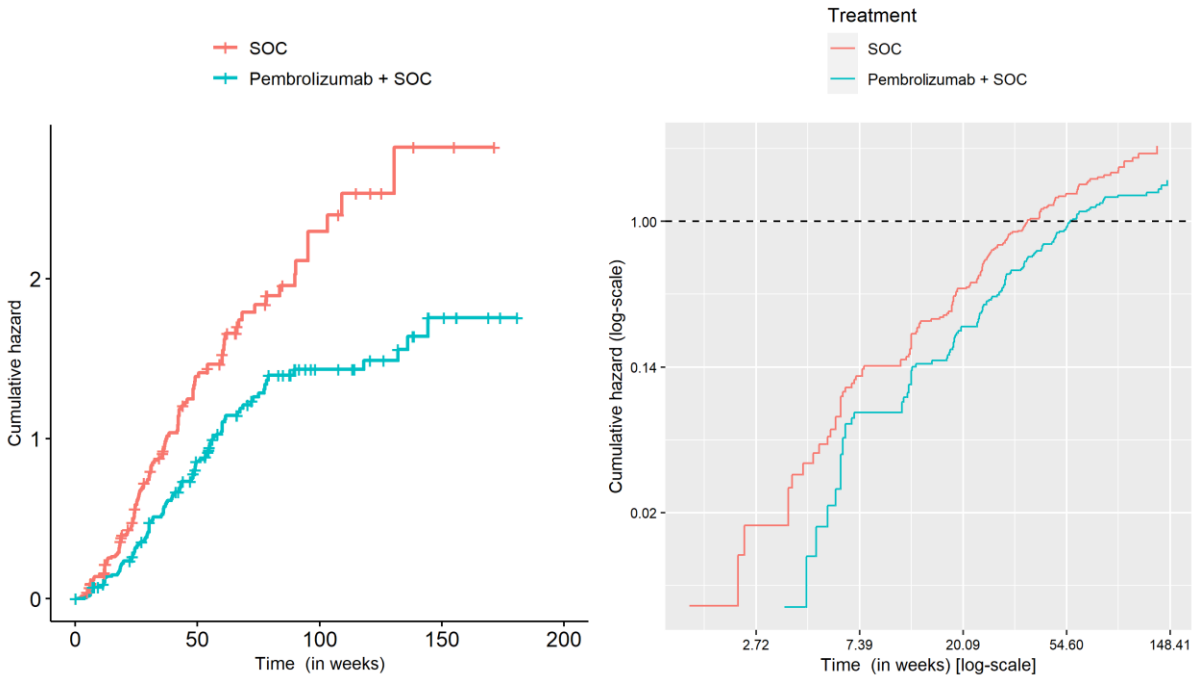


Figure 9: Comparison in cumulative hazard in BIRC-assessed Progression-free Survival over time between groups treated with Pembrolizumab + SOC versus SOC



B5. PRIORITY. Please provide plots showing the empirical hazard functions (unsmoothed and smoothed) of both the intervention and comparator arms for the

data used in the analysis for PFS and OS. Please also plot the modelled hazards of each of the parametric survival models for PFS and OS on top of the empirical hazard. Please also include the code used for plotting the empirical hazard functions. Please do this for both the Global CPS≥1 cohort and the non-Asia CPS≥1 cohort.

MSD Response:

The requested plots are provided below.

A description of the code used is also provided.

OS

Unsmoothed hazard estimates Vs. smoothed hazard plot

We use *bshazard* package to get the smoothed hazard estimate, which is based on B-splines from the perspective of generalized linear mixed models. We took the default number of knots (31) for B-splines; default degree of B-spline, 1. R-package of bshazard (version 1.1) based on Rebora P, Salim A, Reilly M (2014).

References:

- Rebora P, Salim A, Reilly M (2014) bshazard: A Flexible Tool for Nonparametric Smoothing of the Hazard Function.The R Journal Vol. 6/2:114-122.
- Lee Y, Nelder JA, Pawitan Y (2006). Generalized Linear Models with Random Effects: Unified Analysis via H-likelihood, volume 106. Chapman & Hall/CRC.
- Pawitan Y (2001). In All Likelihood: Statistical Modelling and Inference Using Likelihood. Oxford University Press

Figure 10: Pembrolizumab + SoC – OS – Unsmoothed hazards vs. smoothed hazards

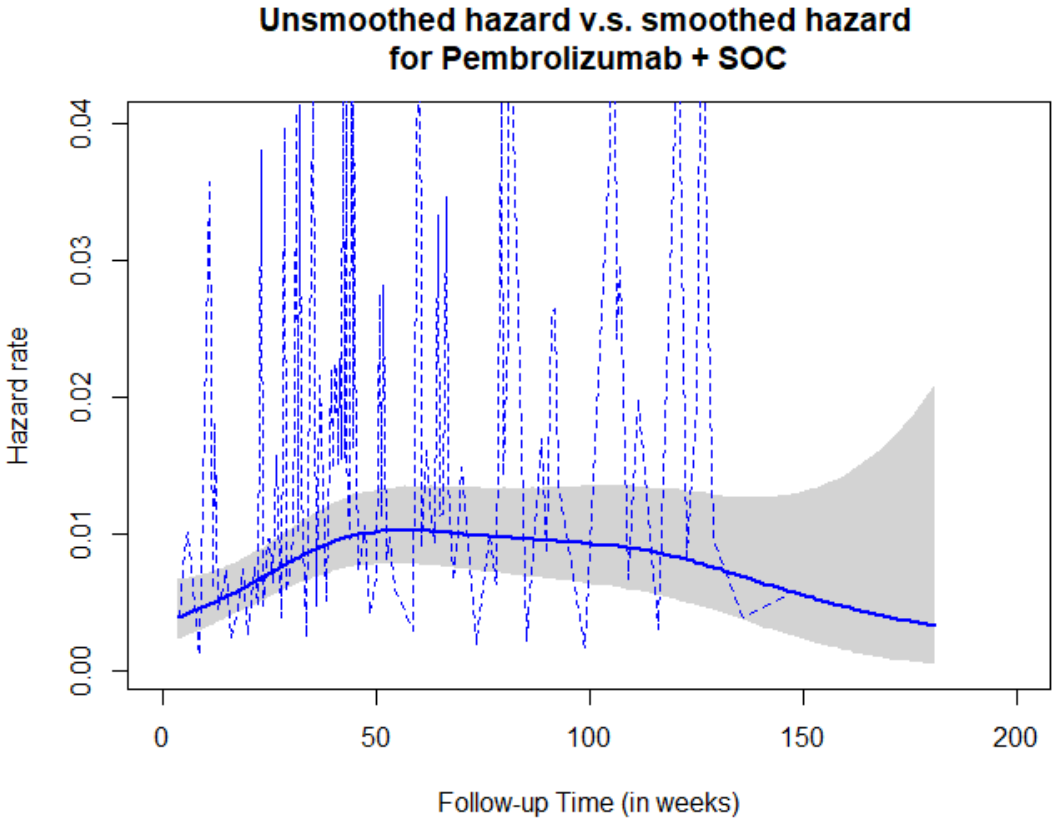
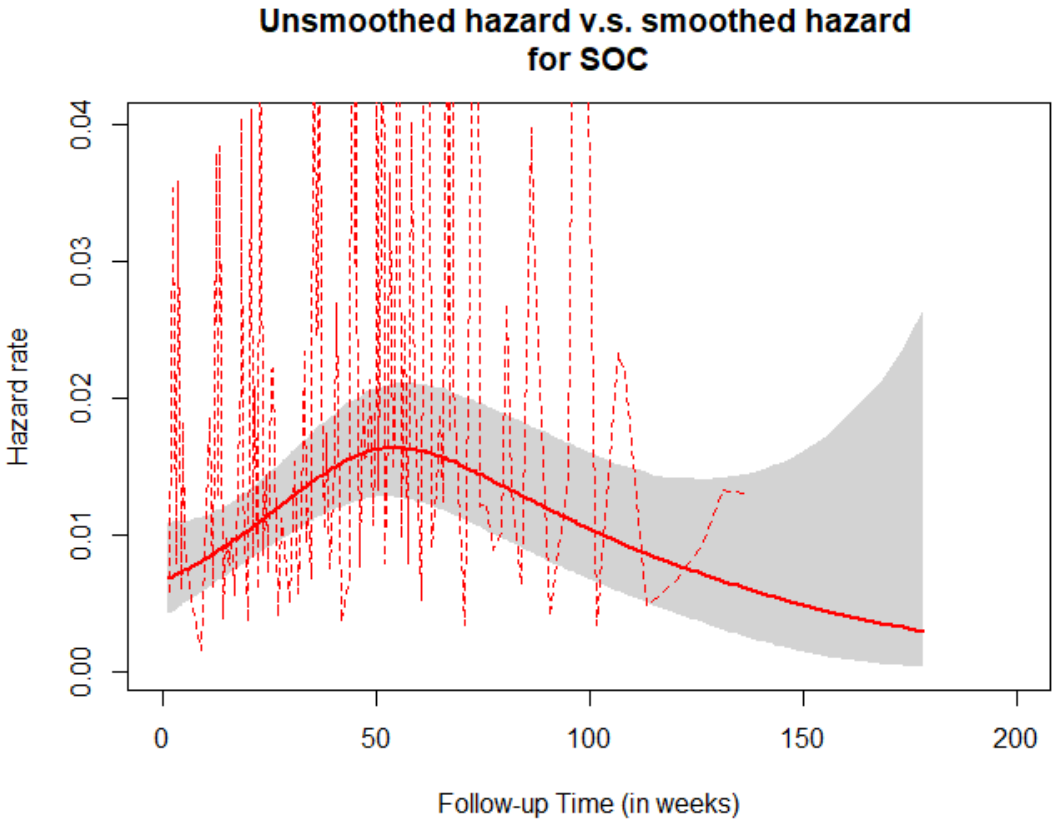


Figure 11: SoC – OS – Unsmoothed hazards vs. smoothed hazards



Smoothed hazard plot for different standard parametric fittings (one piece jointly fit models)

The modelled hazards for jointly (dependent) fit standard parametric curves with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC OS and SoC OS.

Figure 12: Pembrolizumab + SoC – OS - One piece jointly fit - Modelled hazards vs. smoothed hazards

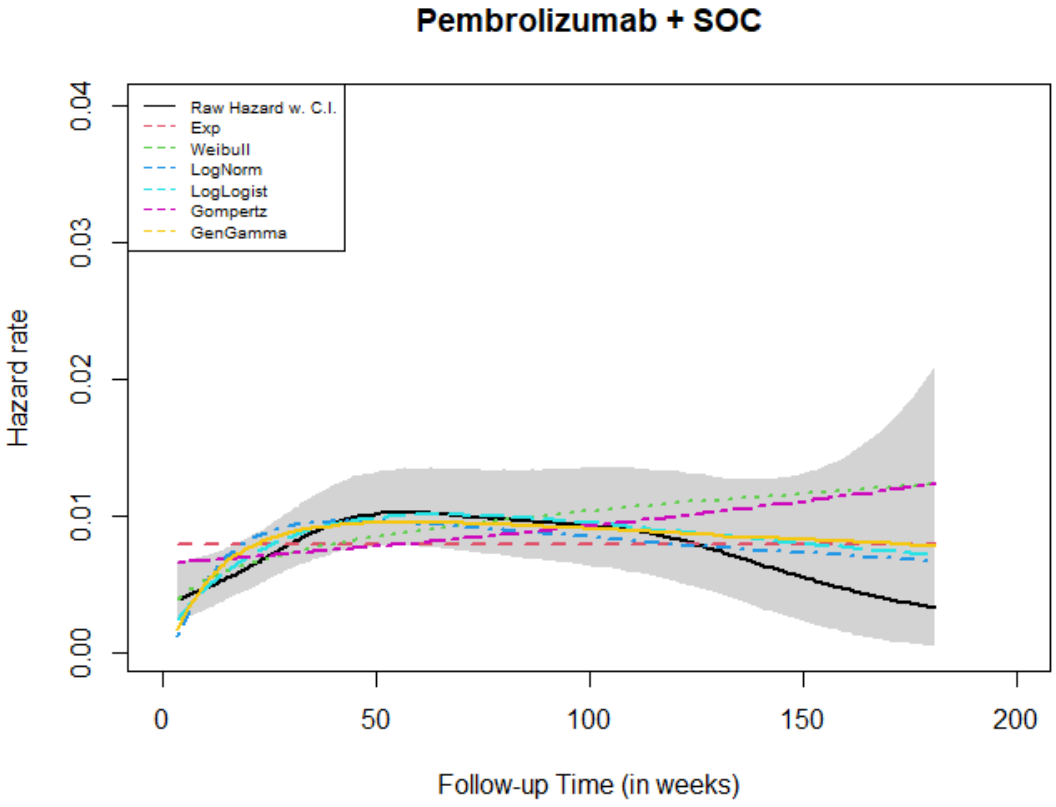
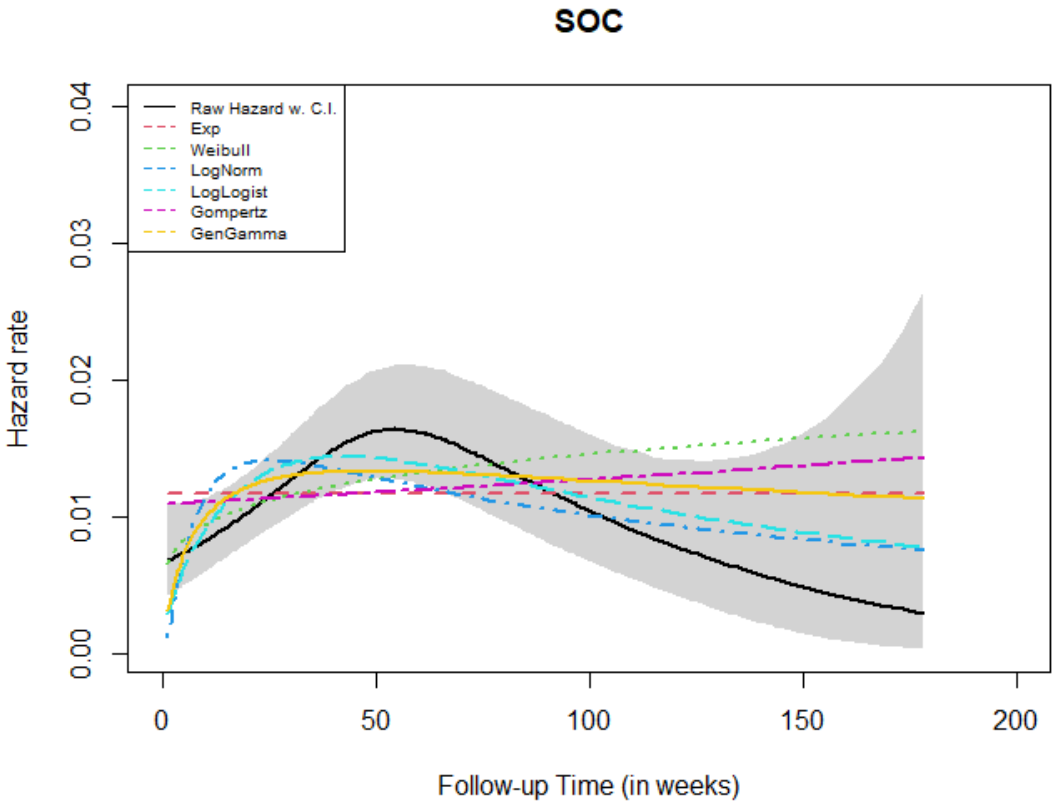


Figure 13: SoC – OS - One piece jointly fit - Modelled hazards vs. smoothed hazards



Smoothed hazard plot for different standard parametric fittings (separately fit models)

The modelled hazards for separately (independent) fit standard parametric curves with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC OS and SoC OS.

Figure 14: Pembrolizumab + SoC – OS - One piece separately fit - Modelled hazards vs. smoothed hazards

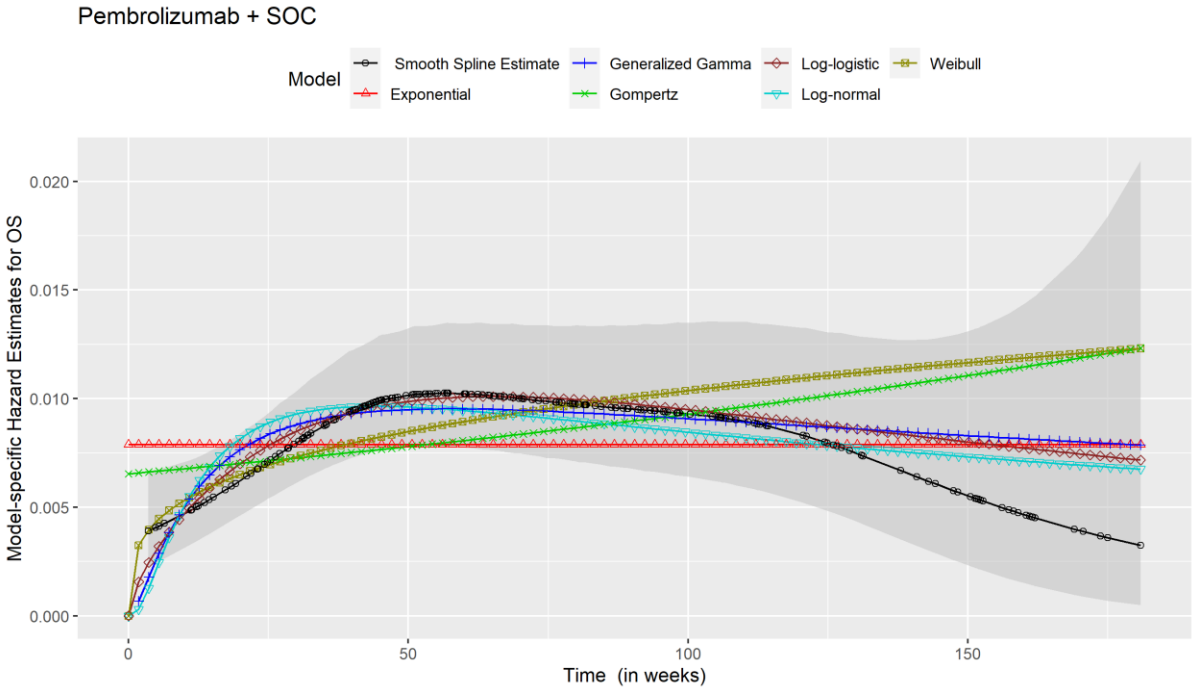
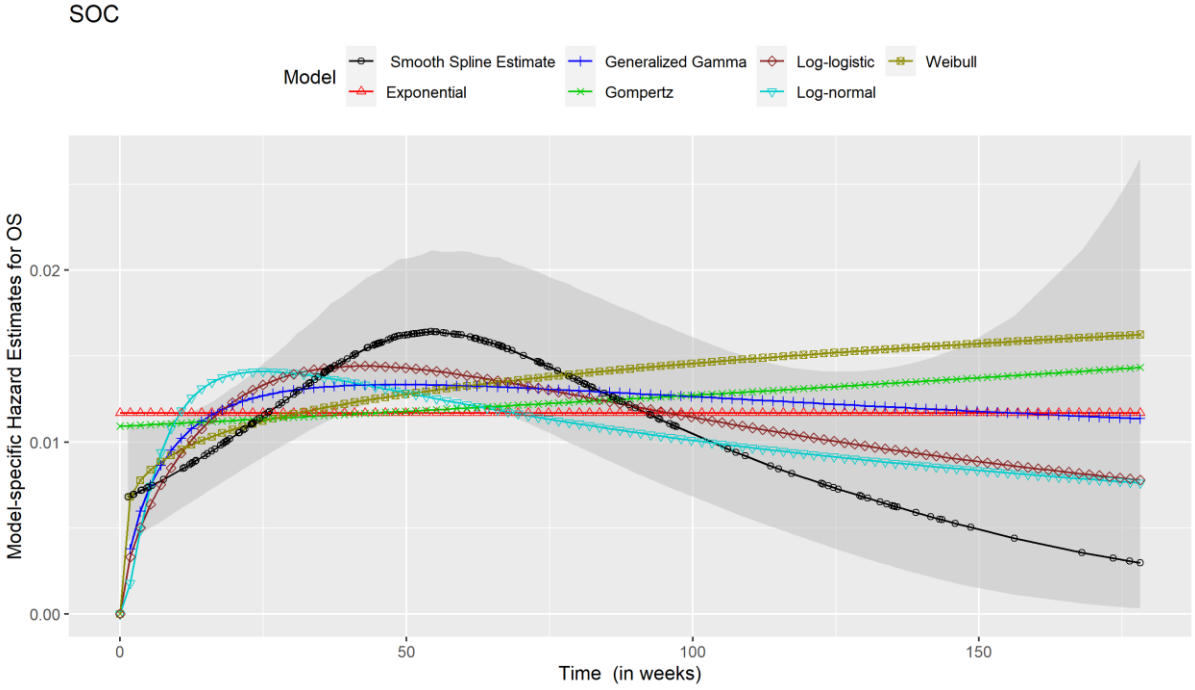


Figure 15: SoC – OS – One piece separately fit – Modelled hazards vs. smoothed hazards



Smoothed hazard plot for separately fit spline models

The modelled hazards for separately (independent) fit spline models with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC OS and SoC OS.

To fit the spline models the “flexsurvspline” function from the “flexsurv” R package was used. This function derives flexible survival regression models using the Royston-Parmar spline model. Spline models were fit on the “hazard”, “odds” and “normal” scale where between 1 and 3 knots for each scale option were explored. The location of the knots were chosen based on the default option in “flexsurv” whereby knots are placed at equally-spaced quantiles of the log uncensored survival times.

For separately fit models, separate spline models were fit to each treatment arm of the trial.

Figure 16: Pembrolizumab + SoC – OS - Separately fit spline models - Modelled hazards vs. smoothed hazards

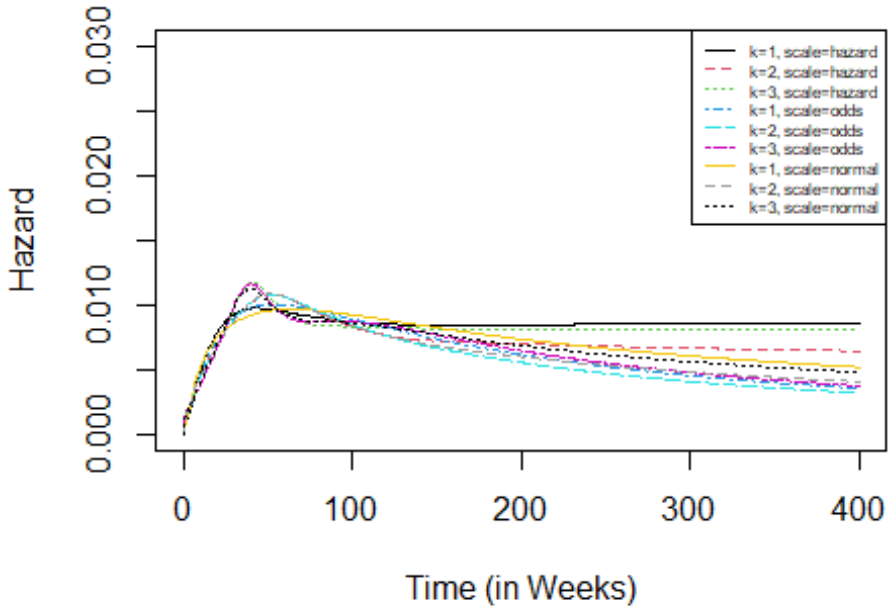
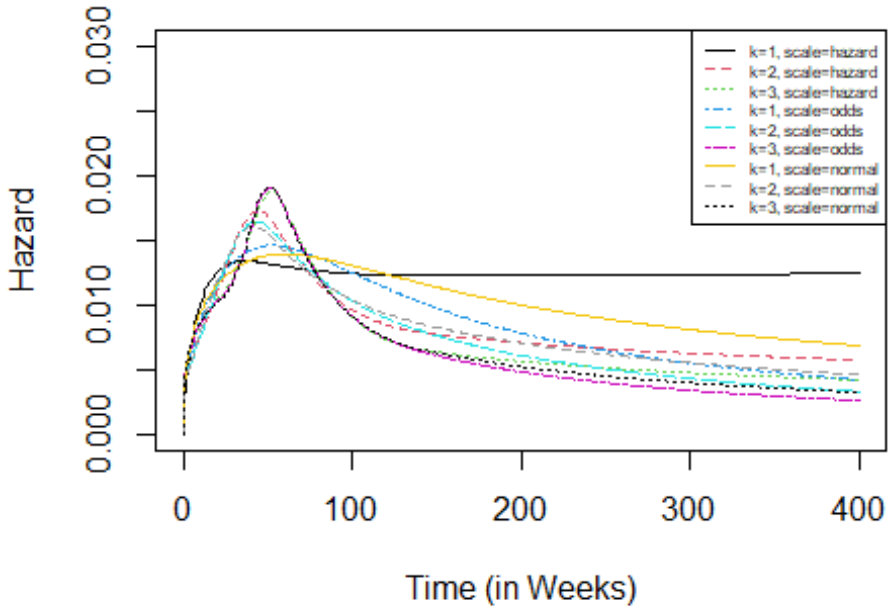


Figure 17: SoC – OS - Separately fit spline models - Modelled hazards vs. smoothed hazards



Smoothed hazard plot for jointly fit spline models

The modelled hazards for jointly (dependent) fit spline models with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC OS and SoC OS.

For jointly fit models, spline models were fit to the pooled trial data and treatment arm included as a predictive covariate.

Figure 18: Pembrolizumab + SoC – OS – Jointly fit spline models - Modelled hazards vs. smoothed hazards

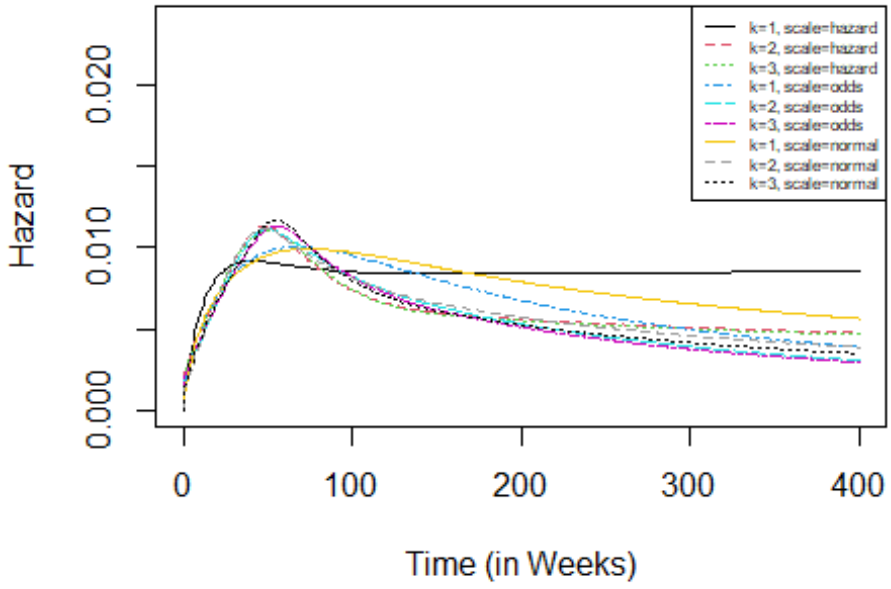
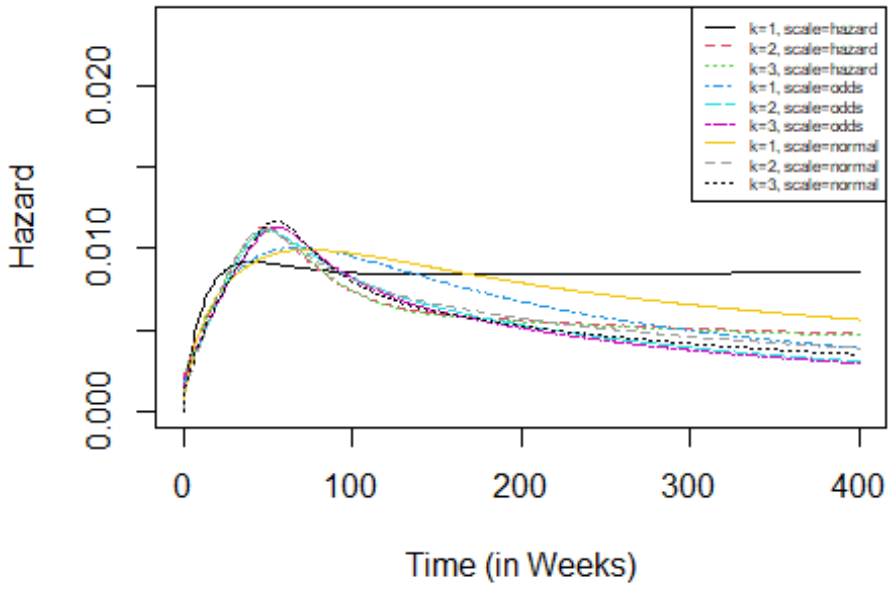


Figure 19: SoC – OS – Jointly fit spline models - Modelled hazards vs. smoothed hazards



PFS

Unsmoothed hazard estimates Vs. smoothed hazard plot

The *bshazard* package was used as described above in the OS section.

Figure 20: Pembrolizumab + SoC – PFS – Unsmoothed hazards vs. smoothed hazards

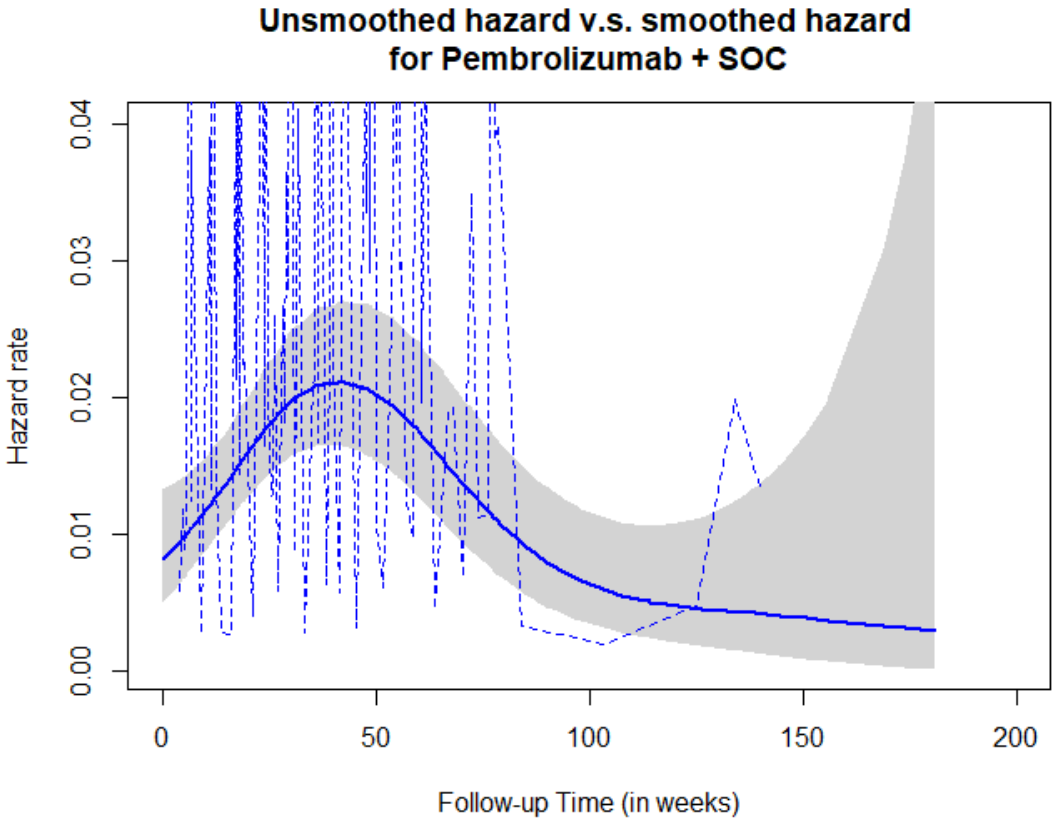
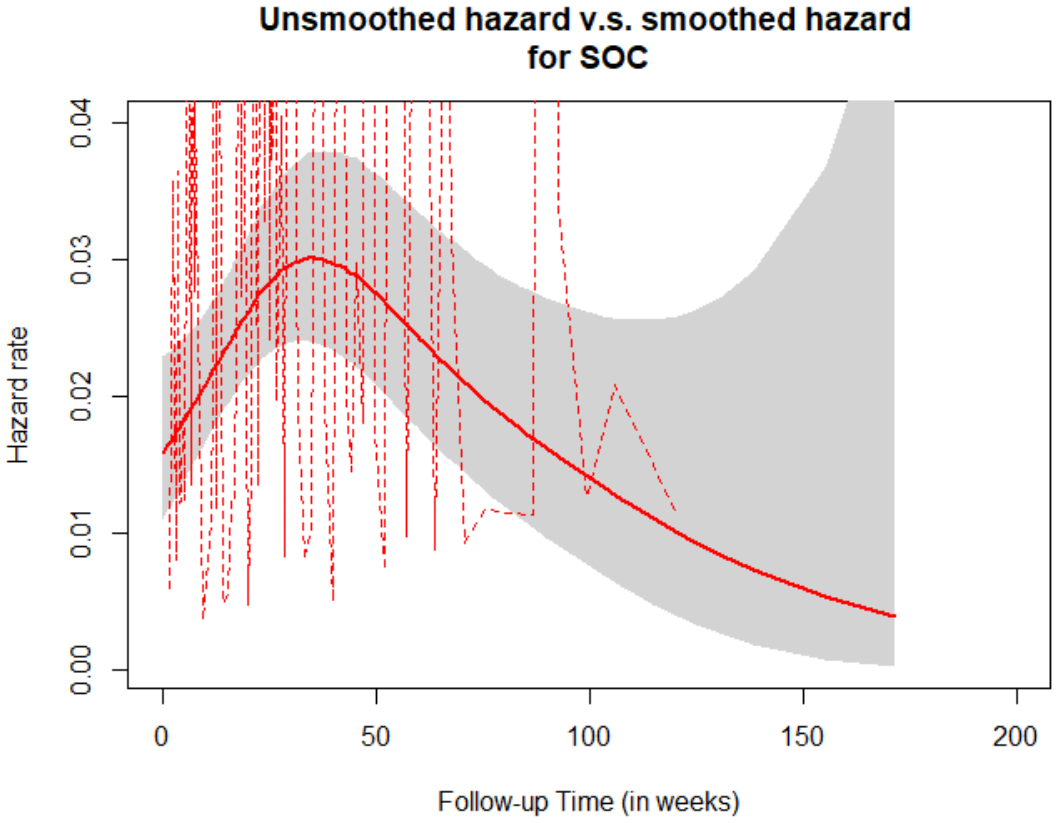


Figure 21: SoC – PFS – Unsmoothed hazards vs. smoothed hazards



Smoothed hazard plot for different standard parametric fittings (one piece jointly fit models)

The modelled hazards for jointly (dependent) fit standard parametric curves with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC PFS and SoC PFS.

Figure 22: Pembrolizumab + SoC – PFS – One piece jointly fit – Modelled hazards vs. smoothed hazards

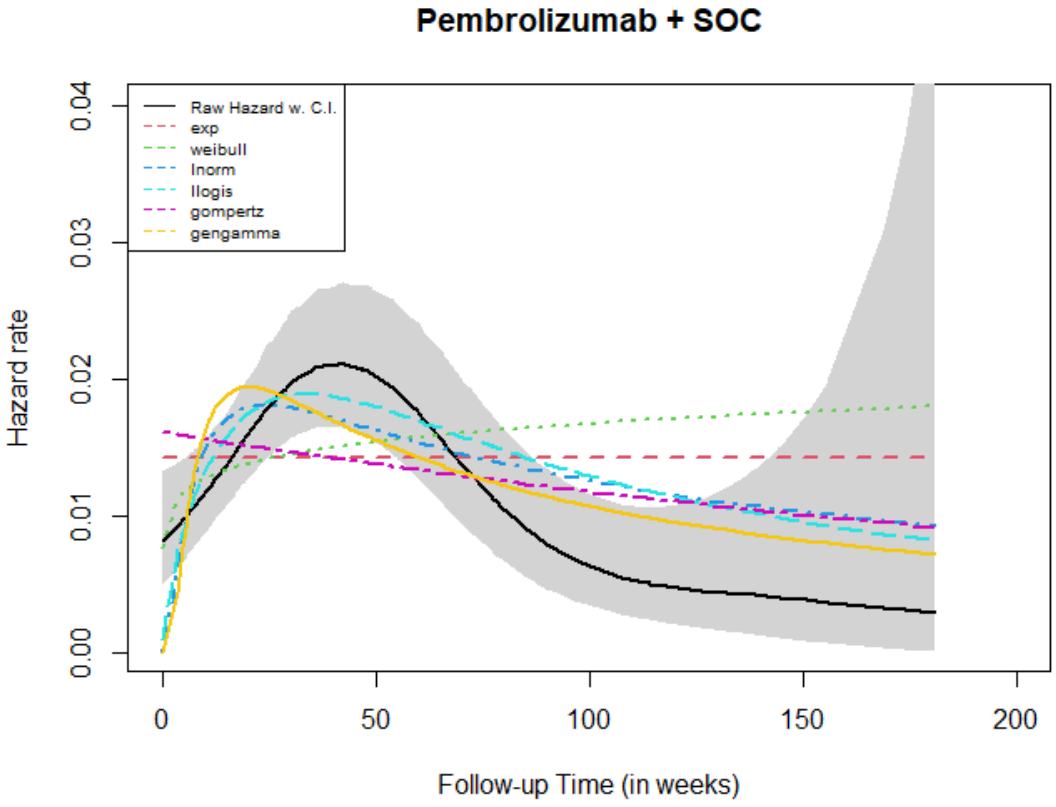
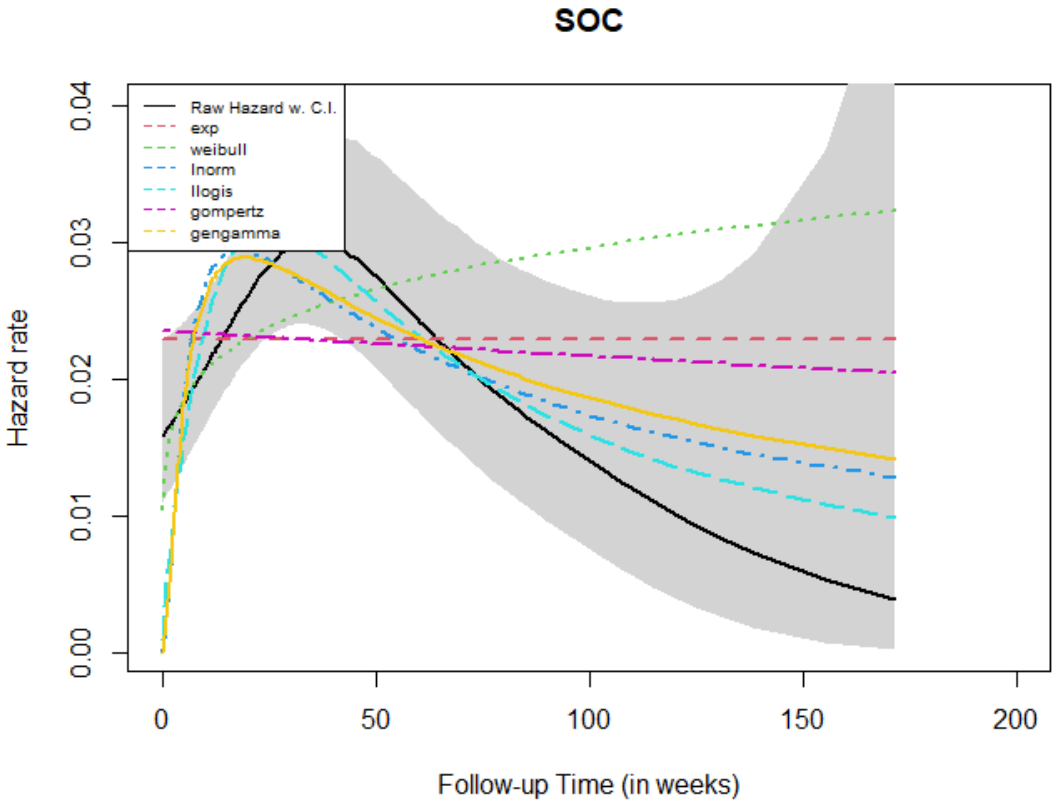


Figure 23: SoC – PFS – One piece jointly fit – Modelled hazards vs. smoothed hazards



Smoothed hazard plot for different standard parametric fittings (one piece separately fit models)

The modelled hazards for separately (independent) fit standard parametric curves with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC PFS and SoC PFS.

Figure 24: Pembrolizumab + SoC – PFS – One piece separately fit – Modelled hazards vs. smoothed hazards

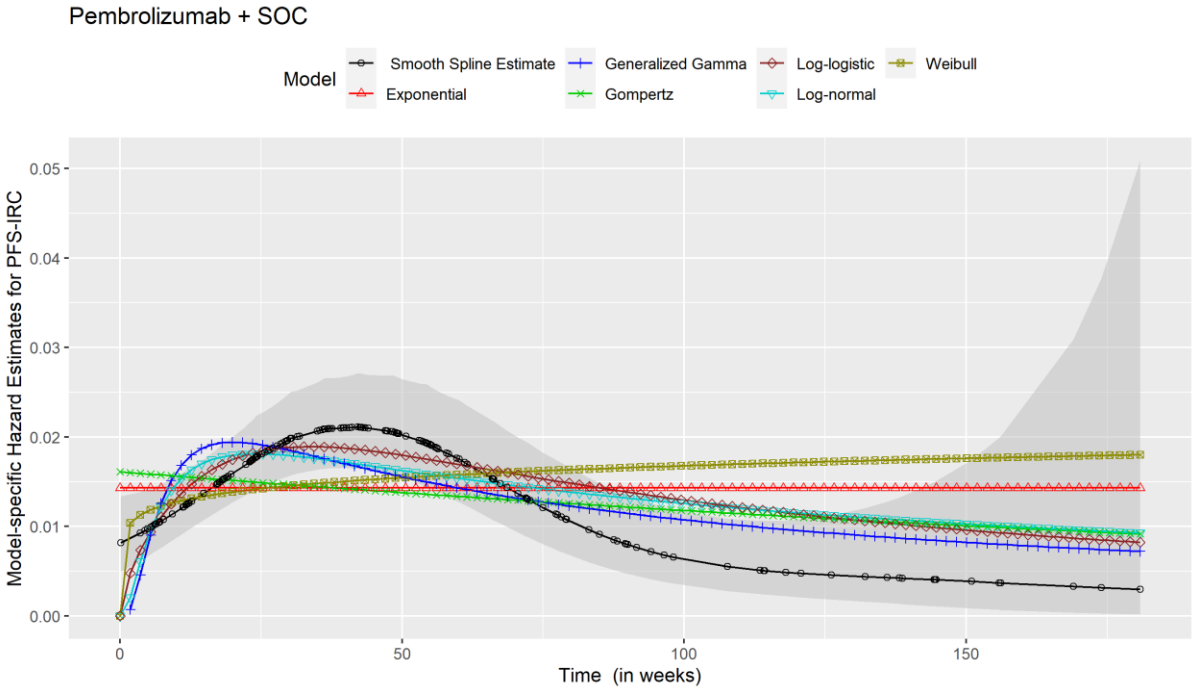
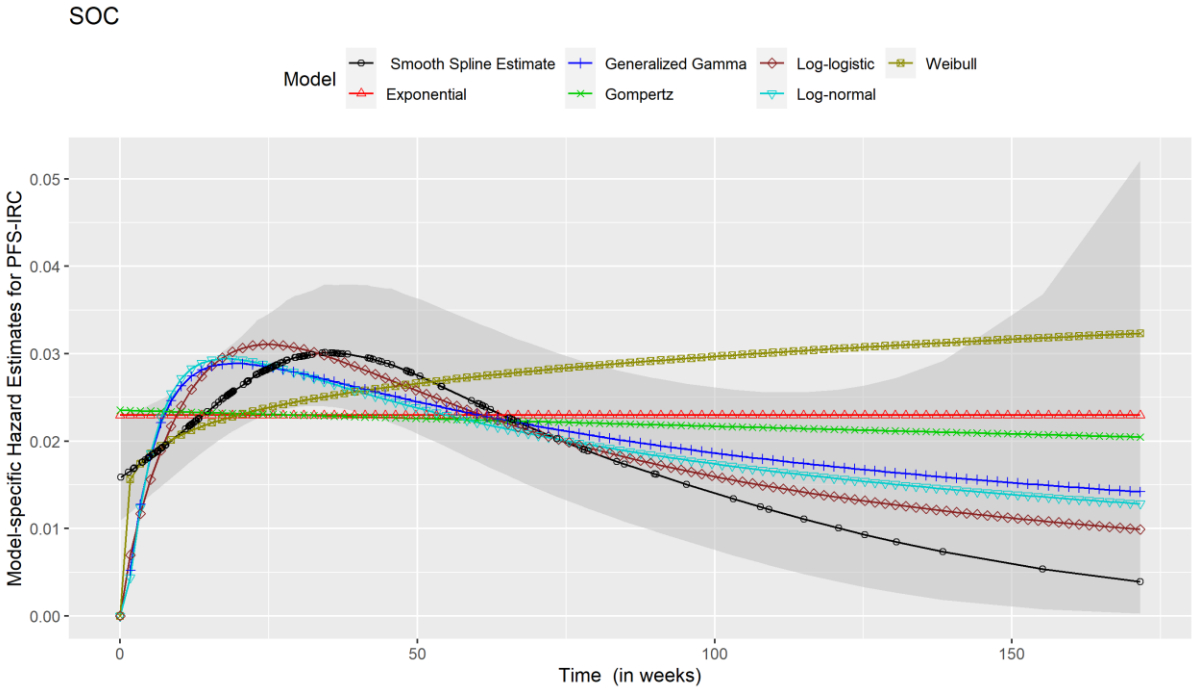


Figure 25: SoC – PFS – One piece separately fit – Modelled hazards vs. smoothed hazards



Smoothed hazard plot for separately fit spline models

The modelled hazards for separately (independent) fit spline models with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC PFS and SoC PFS.

For separately fit models, separate spline models were fit to each treatment arm of the trial.

Figure 26: Pembrolizumab + SoC – PFS - Separately fit spline models - Modelled hazards vs. smoothed hazards

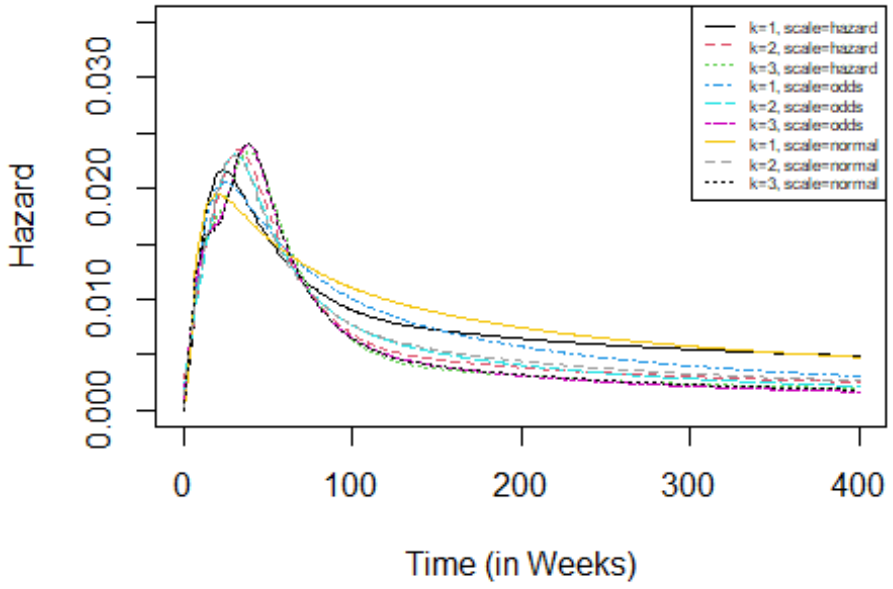
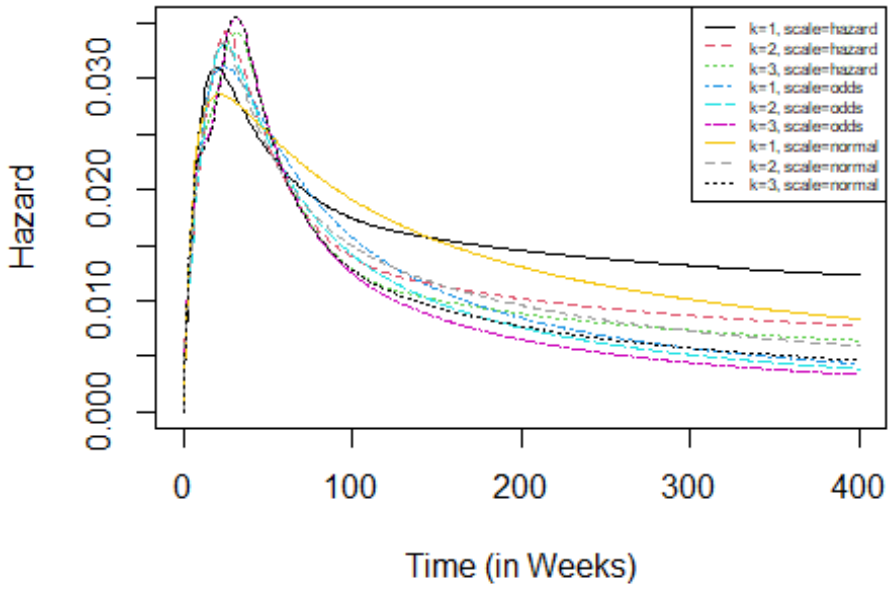


Figure 27: SoC – PFS - Separately fit spline models - Modelled hazards vs. smoothed hazards



Smoothed hazard plot for jointly fit spline models

The modelled hazards for jointly (dependent) fit spline models with the smoothed hazard from the trial are illustrated below for pembrolizumab + SoC PFS and SoC PFS.

For jointly fit models, spline models were fit to the pooled trial data and treatment arm included as a predictive covariate.

Figure 28: Pembrolizumab + SoC – PFS – Jointly fit spline models - Modelled hazards vs. smoothed hazards

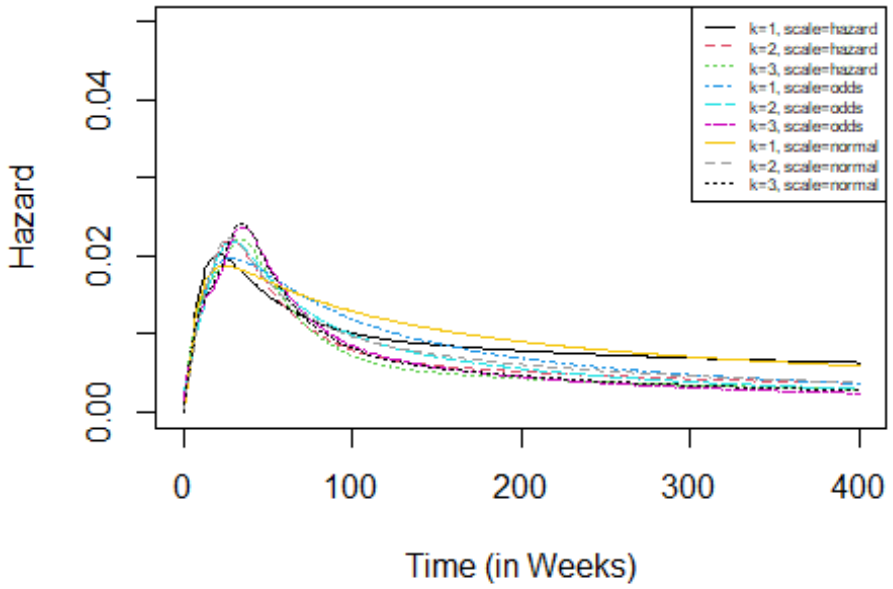
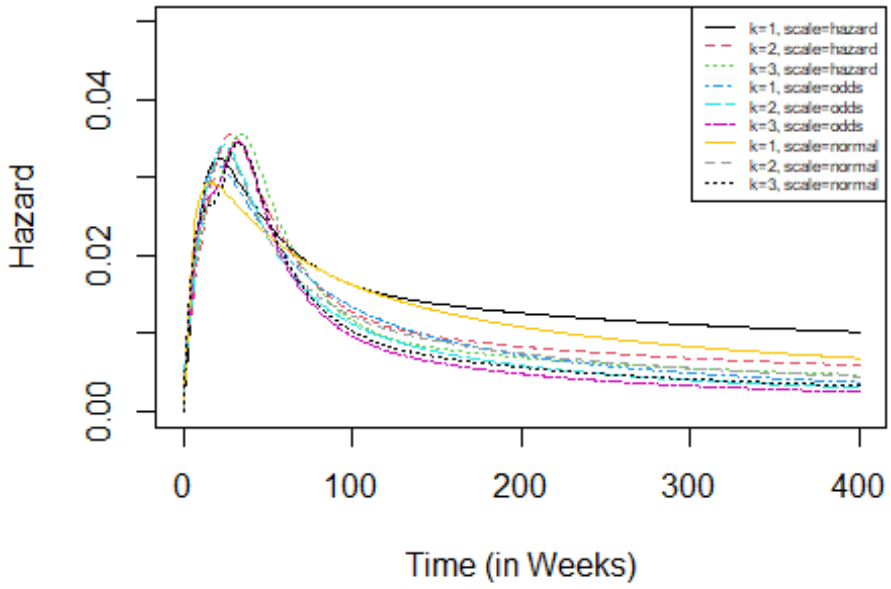


Figure 29: Pembrolizumab + SoC – PFS – Jointly fit spline models - Modelled hazards vs. smoothed hazards



B6. PRIORITY. Please fit the Kaplan-Maier (KM) data for the intervention arm using the standard parametric models and the spline models for PFS and OS. Please present the model results including AIC/BIC, clinical plausibility and the plots that show the fitted curves on top of the KM curve, similar to Figure 19 and Figure 20. Please include these curves in an updated model so these can be implemented. Please do this for both the Global CPS≥1 cohort and the non-Asia CPS≥1 cohort.

MSD Response:

In the updated model provided with these responses, KM data for the intervention arm in the non-Asia CPS≥1 cohort has been fit using the standard parametric models and the spline models for PFS and OS. Due to the non-rejection of the proportional hazards assumption, MSD believe jointly fitted models are appropriate for both endpoints and the results are presented here. Independently fitted results can be found in the updated model.

Overall survival

The goodness-of-fit statistics for the jointly fitted one-piece and spline models are presented in the tables below.

Table 38: Fit statistics of OS extrapolation: intervention arm, jointly fitted one-piece models

Distribution	AIC	BIC
Exponential	2963.8	2971.8
Gamma	2936.7	2948.7
Generalised gamma	2933.1	2949.1
Gompertz	2953.2	2965.2
Log-logistic	2939.2	2951.2
Log-normal	2948.6	2960.6
Weibull	2953.1	2965.1
Exponential	2963.8	2971.8
Gamma	2936.7	2948.7

Table 39: Fit statistics of OS extrapolation: intervention arm, jointly fitted spline models

Model	AIC	BIC
Hazards, 1 knot	2934.799	2950.785
Hazards, 2 knots	**2927.956**	**2947.939**
Hazards, 3 knots	2930.615	2954.594
Odds, 1 knot	2928.941	2944.927
Odds, 2 knots	**2927.164**	**2947.146**
Odds, 3 knots	2929.475	2953.454
Normal, 1 knot	2930.882	2946.868
Normal, 2 knots	2927.172	2947.155
Normal, 3 knots	2929.074	2953.053

The KM data and curves for the different one-piece and spline models are presented in the figures below. Across the candidate options, the 2-knot hazards and 2-knot odds spline models appear to fit the data best, based on a combination of visual inspection and goodness-of-fit statistics presented above. To determine their clinical plausibility, the 5-year survival rate for the SoC arm was consulted for concordance with expectations for patients currently treated in the NHS, as informed by clinical expert opinion, which indicated typical 5-year survival rates of about 5%. The rates predicted

for SoC by the 2-knot hazards and 2-knot odds spline models are 6.8% and 9.6% respectively. The former aligns more closely with practice and hence is deemed to be the most plausible model.

Figure 30: OS for the intervention arm, jointly fitted one-piece models

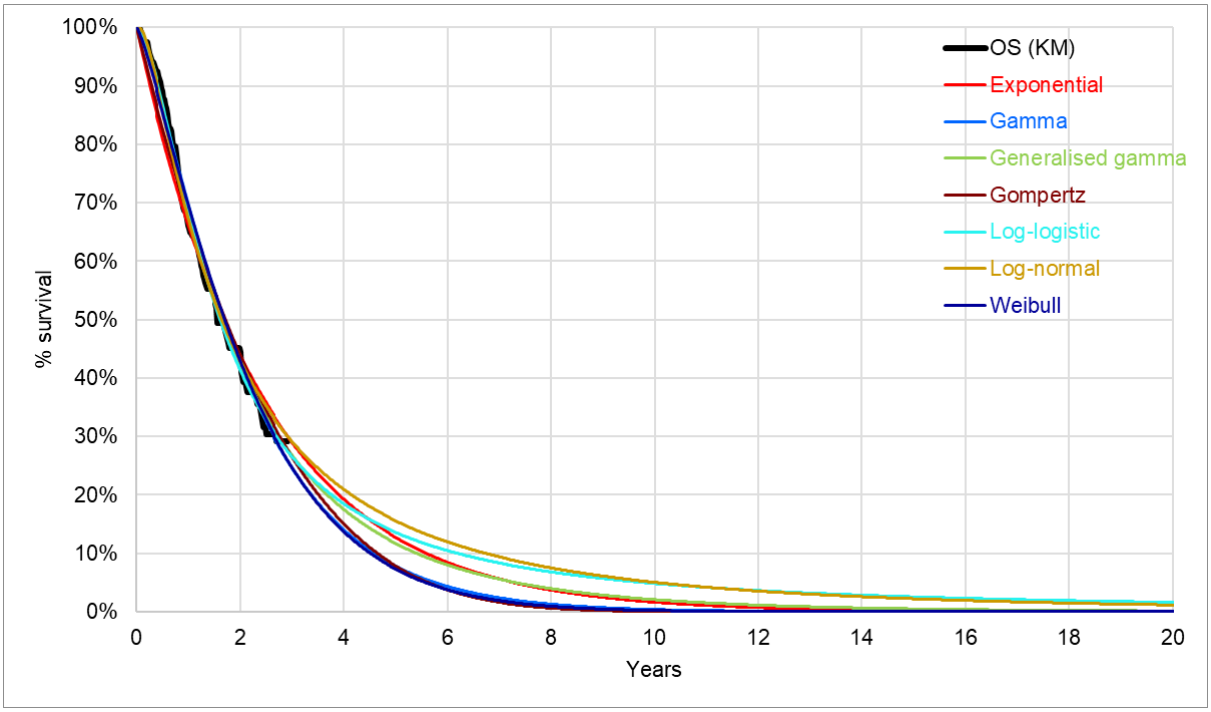
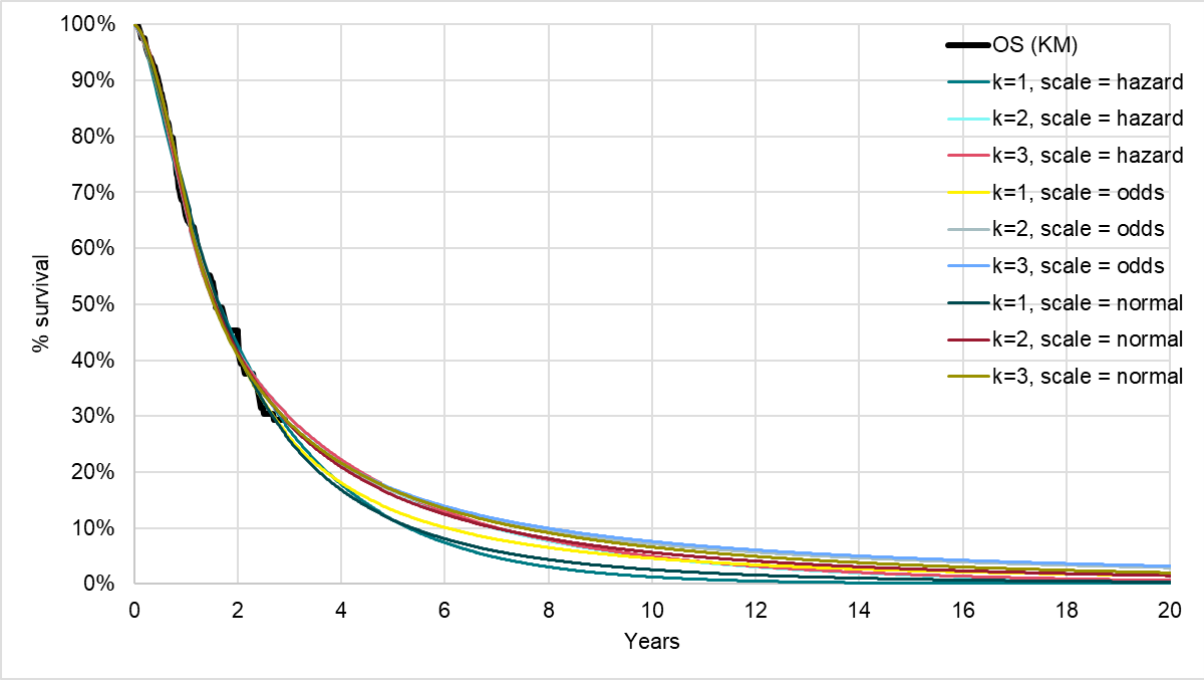


Figure 31: OS for the intervention arm, jointly fitted spline models



The KM curves and extrapolated curves for both arms, informed by the most plausible model, are presented in the figure below.

Figure 32: OS, jointly fitted spline model

Progression-free survival

The goodness-of-fit statistics for the jointly fitted one-piece and spline models are presented in the tables below.

Table 40: Fit statistics of PFS extrapolation: intervention arm, jointly fitted one-piece models

Distribution	AIC	BIC
Exponential	2989.6	2997.6
Gamma	2959.2	2971.2
Generalised gamma	2930	2946
Gompertz	2973.7	2985.7
Log-logistic	**2943.2**	**2955.2**
Log-normal	2945	2957
Weibull	2986.6	2998.6
Exponential	2989.6	2997.6
Gamma	2959.2	2971.2

Table 41: Fit statistics of PFS extrapolation: intervention arm, jointly fitted spline models

Model	AIC	BIC
Hazards, 1 knot	2929.137	2945.123
Hazards, 2 knots	2924.234	2944.216
Hazards, 3 knots	2924.851	2948.83
Odds, 1 knot	2926.924	2942.91
Odds, 2 knots	2926.118	2946.101
Odds, 3 knots	2925.375	2949.354
Normal, 1 knot	2930.156	2946.142
Normal, 2 knots	2924.925	2944.907

Normal, 3 knots	2923.13	2947.109

The KM data and curves for the different one-piece and spline models are presented in the figures below.

Figure 33: PFS for the intervention arm, jointly fitted one-piece models

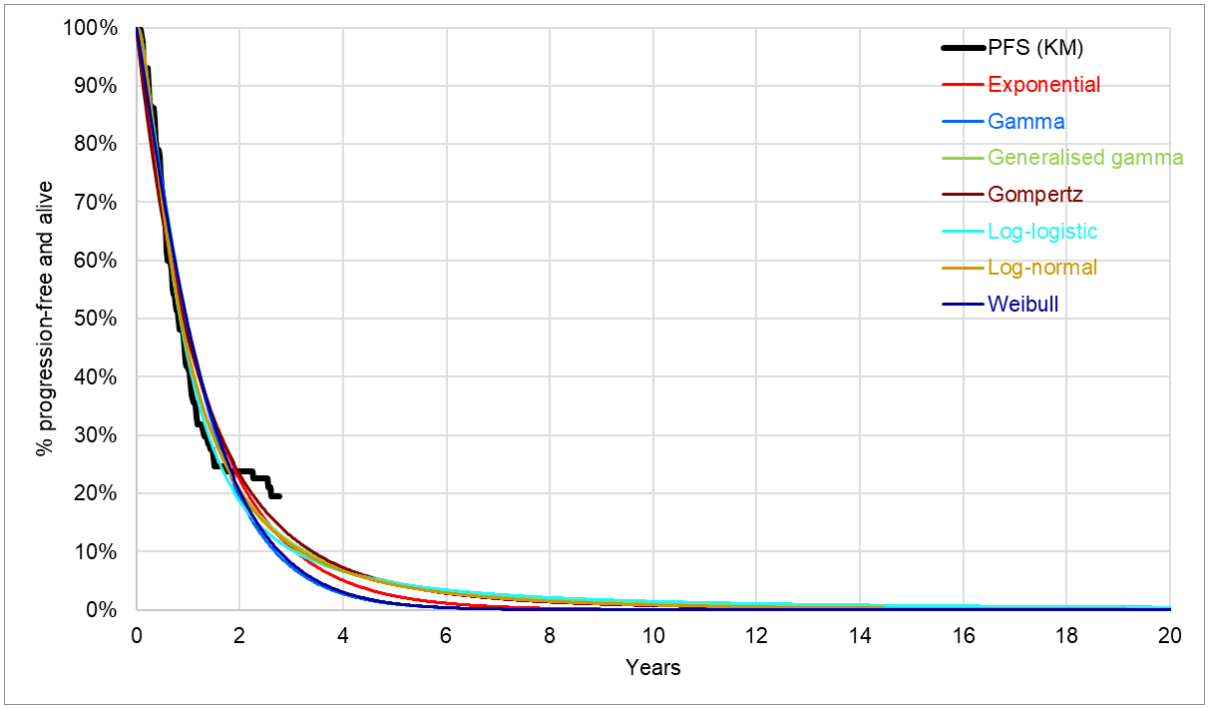
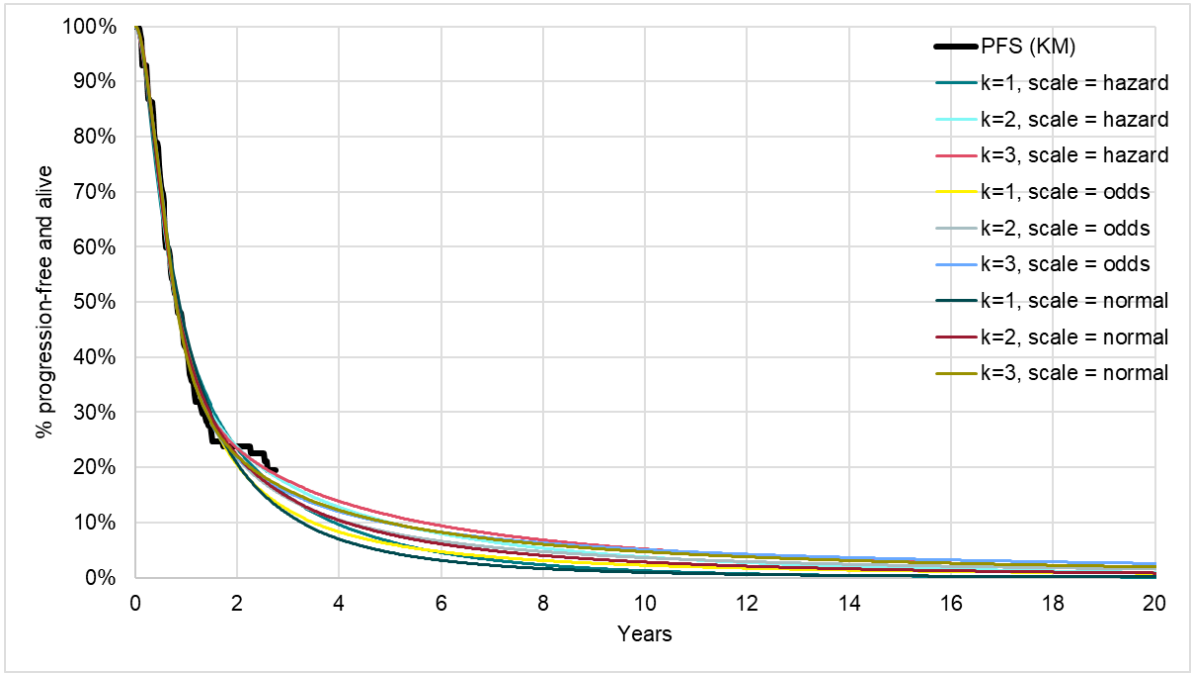


Figure 34: PFS for the intervention arm, jointly fitted spline models



The jointly fitted one-piece log-logistic model appears to be the best candidate for the intervention arm PFS data when informed by the non-Asia CPS≥1 population. MSD acknowledge that the ICER appears to be relatively insensitive to the choice of PFS model. The KM curves and extrapolated curves for both arms, informed by the most plausible model, are presented in the figure below.

Figure 35: PFS, jointly fitted one-piece model

B7. PRIORITY. In the economic model, there appears to be the option to select multiple cohorts for the KM data based on the 'match_population' variable, with the choice of KM data being dependent on "CPS ≥ 1 non-Asia region" being selected on the control sheet. The KM data in the 'KM INT' and 'KM Comp 1' sheets are described in the headers as "CPS ≥ 1 non-Asia region". However, the numbers at risk in the 'KM INT' sheet for OS/PFS/TTD (N=202) appear to correlate with the CPS≥1 non-Asia region whilst the numbers at risk in the 'KM Comp 1' sheet for OS/PFS (N=296) appear to correlate with the CPS≥1 Global cohort and the numbers at risk for TTD (N=199) appear to correlate with the CPS≥1 non-Asia cohort. Please clarify which KM data are included in the model for PFS, OS and TTD for both treatment arms and if different sources are used, please explain why this is the case. Please provide KM data for both the Global CPS≥1 cohort and the non-Asia CPS≥1 cohort for all outcomes in an updated economic model with the option to select either source.

MSD Response:

The KM data contained within the submitted model are summarised in the table below.

Table 42: Summary of KM data presented in submitted economic model

	Intervention arm	**SoC arm**
OS	Non-Asia CPS≥1	Global CPS≥1
PFS	Non-Asia CPS≥1	Global CPS≥1
TTD	Non-Asia CPS≥1	Non-Asia CPS≥1

The KM data populations differ between treatment arms for OS and PFS but the intervention KM data is not used to generate extrapolated curves for the intervention arm, as discussed previously (constant HR applied). In the updated model provided with these responses, KM data for the non-Asia CPS≥1 cohort has been included as requested in previous questions. As described in the CS, MSD believe this population to be more clinically relevant and applicable to the England and Wales setting. TTD data for this population was provided and maximum treatment durations, as per clinical practice, have been applied.

B8. Please add KM data for the intervention arm to Figures 20, 23, 28 and 31.

MSD Response:

Intervention KM data has been added to the four requested figures.

Figure 36: Overall survival, independently fitted one-piece model with non-Asia region HR applied (update of CS Figure 20)

Figure 37: Overall survival, independently fitted spline model with non-Asia region HR applied (update of CS Figure 23)

Figure 38: Progression-free survival, independently fitted one-piece model with non-Asia region HR applied (update of CS Figure 28)

Figure 39: Progression-free survival, independently fitted spline model with non-Asia region HR applied (update of CS Figure 31)

B9. PRIORITY. CS page 105 states that clinical plausibility of the predicted survival was used to select the base case parametric survival curves. Please provide details of this assessment for both PFS and OS.

MSD Response:

The choice of base case OS extrapolations were informed by discussions with UK clinical experts about plausible survival estimates for the SoC arm, based on their clinical experience with the trial control arm. Two experts, based in England, were asked to describe the typical survival rate they would expect over a range of longer-

term timepoints. Due to the poor prognosis of patients with this cancer, the latest timepoint at which they felt most comfortable providing informed rate estimates was at 5 years post-initiation of treatment, hence assessment of the plausibility of the candidate curves was anchored to this timepoint. The estimates provided by the experts are presented in the table below.

Table 43: Expected survival rates in clinical practice, informed by clinical expert opinion

Timepoint	Expected OS rate at 5 years (expert 1)	Expected OS rate at 5 years (expert 2)
1 year	50%	50%
2 years	10%	20%
5 years	5%	2-5%
10 years	2%	0-1%

An assessment of the SoC arm survival curve indicates a higher survival rate using the trial data from the global CPS≥1 cohort than would be expected in clinical practice. Due to differences in treatment practices and pathway, MSD believe the non-Asia region CPS≥1 cohort in KEYNOTE-811 to be more clinically relevant and applicable to practice in England and Wales.

The validation of the PFS model related to reasonable timepoints by which different proportions of the cohort would have experienced disease progression. MSD acknowledge that the ICER appears to be relatively insensitive to the choice of PFS model.

B10. Figures 21 and 29 seem to show the parametric fits from Figures 18 and 26 respectively rather than the hazard functions for the spline models. Please provide correct figures to match the header.

MSD Response:

The correct figures showing the modelled hazards for independently fitted spline models versus the empirical hazards are provided below for trastuzumab plus chemotherapy. Models fitted to the non-Asian population are provided in Figure 40

and Figure 41. Please see the response to Question B5 for corresponding pembrolizumab + SoC spline model figures.

Figure 40: Plot of OS hazard function for trastuzumab plus chemotherapy, independently fitted spline models (non-Asian population)

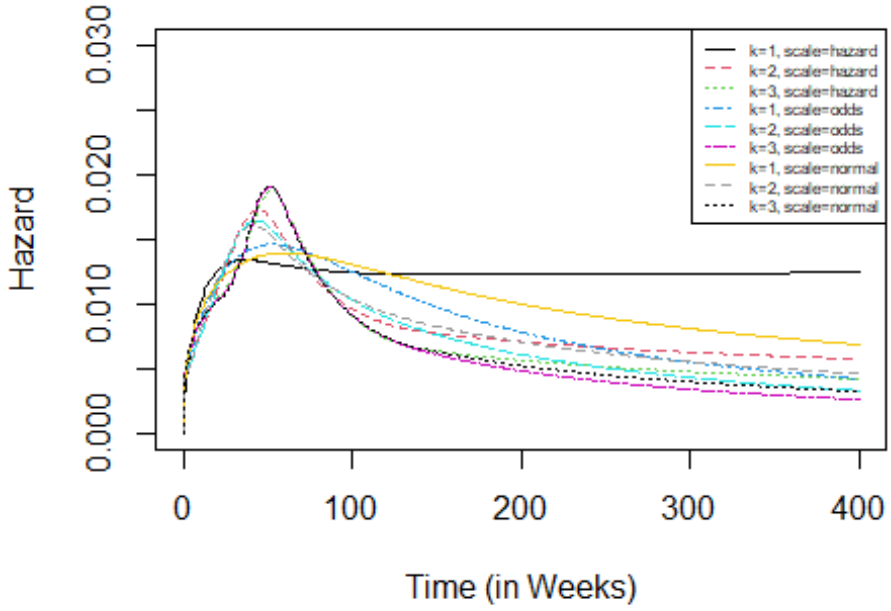
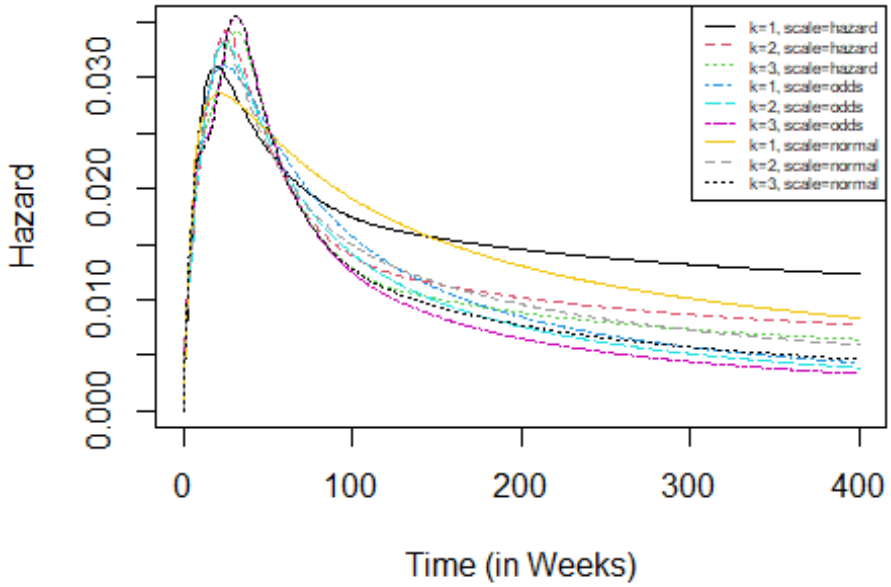


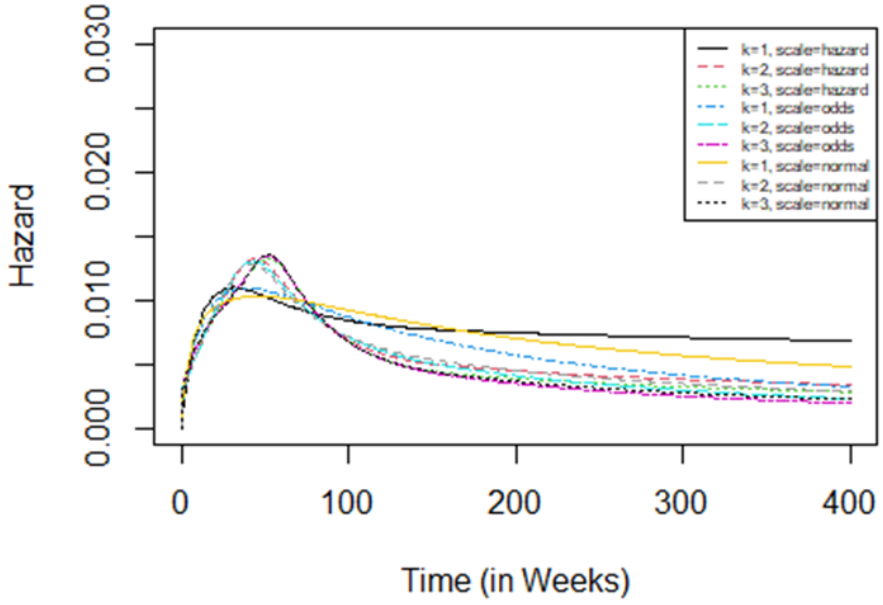
Figure 41: Plot of PFS hazard function for trastuzumab plus chemotherapy, independently fitted spline models (non-Asian population)



The modelled hazards for independently fitted spline models versus the empirical hazards for the global CPS≥ 1 cohort which was presented in the original submission

dossier are provided below. Figure 42 below in this response document corresponds to Figure 21 in the original submission dossier. Figure 43 in this response document corresponds to Figure 29 in the original submission dossier.

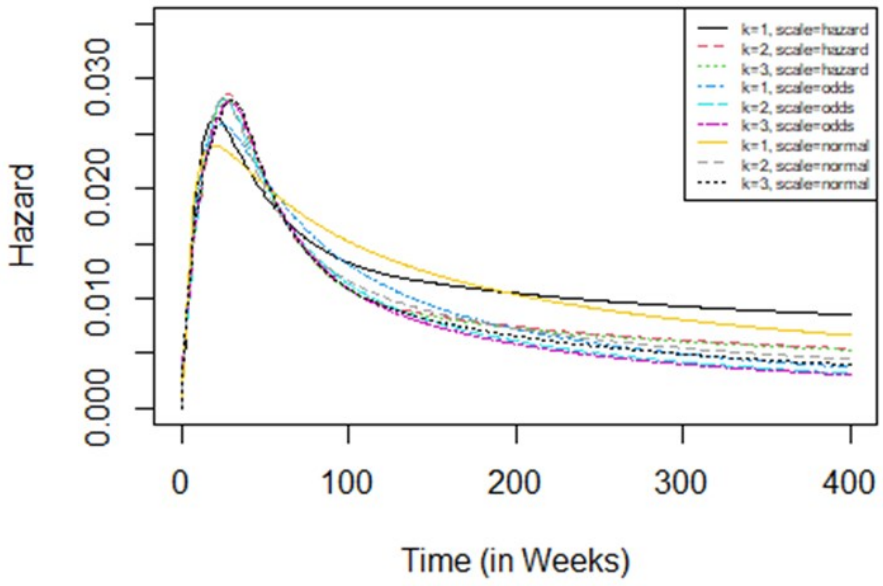
Figure 42: Plot of OS hazard function for trastuzumab plus chemotherapy, independently fitted spline models (global CPS ≥ 1 population)



See separate Powerpoint file for individual curves plotted with the smoothed trial hazards.

*Each spline curve is graphed separately. There are a total of 9 plots (3 functional forms * a total of 3 knots).*

Figure 43: Plot of PFS hazard function for trastuzumab plus chemotherapy, independently fitted spline models (global CPS ≥ 1 population)



See separate Powerpoint file for individual curves plotted with the smoothed trial hazards.

*Each spline curve is graphed separately. There are a total of 9 plots (3 functional forms * a total of 3 knots).*

B11. Please clarify how survival estimates in the model were adjusted to account for general population mortality rates. If the OS was capped by general population mortality risks, please provide the age at which the capping became necessary for each arm.

MSD Response:

Overall survival extrapolations 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. In the scenario where treatment waning is applied, it is the conditional probability of survival after adjustment for treatment waning that is capped.

For progression-free survival 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 model base case, the capping becomes necessary in the intervention arm at 17.79 years (77.99 years old) and in the SoC arm at 19.80 years (80.00 years old).

B12. Please clarify why the treatment waning scenario implements treatment waning from years 7 to 9. In TA737, treatment waning was implemented in years 5 to 7 in a company scenario analysis. Why was treatment waning not assumed from the end of pembrolizumab treatment, where there might be a biological rationale for the treatment effect to reduce or from the end of trial follow-up, after which timepoint there is a lack of evidence to refute a treatment waning effect? Please provide additional scenario analyses exploring these alternative assumptions for treatment waning.

MSD Response:

In a scenario analysis, treatment waning was implemented gradually between the time points of 7 and 9 years in the model lifetime. This is equivalent to 5 to 7 years from the end of pembrolizumab treatment (capped at 2 years). This is a later timepoint than was implemented in TA737, submitted for appraisal in 2021. Waning at these timepoints were also included in the ERG base case in that appraisal. Given the elapse of 2.5 years since that submission, and the absence of evidence of a wane in immunotherapy survival benefit from pembrolizumab trials with longer follow-up duration in the interim, MSD believe it is appropriate to apply the treatment waning assumption at a later timepoint in the model i.e. 2 years later.

Alternative waning timepoints have been investigated in the updated model and the results are presented in the table below.

Table 44: Alternative treatment waning assumptions for scenario analysis

Waning start point in model	**Waning end point in model**	**ICER (£)**
7 years (current)	**9 years**	[redacted]
5 years	7 years	[redacted]
6 years	8 years	[redacted]
8 years	10 years	[redacted]

Utility

B13. CS page 127. The company's base case model uses utilities based on the patients' time-to-death.

- Please justify how the intervals for utilities were determined. Please also comment on the sensitivity of the results on changing the interval specifications.

- Please comment on how the time-to-death approach addresses potential issues relating to informative censoring.

MSD Response:

These time intervals represent a standard set of time intervals used across MSD trials for internal consistency to capture deterioration in quality of life in proximity to death. With alternative interval specifications, the expected trend is still to see lower utility scores nearer to the date of death, consistent with other published data [3]. Alternate categories of time-to-death will not be presented as these categories were not pre-specified and in order to avoid biasing the method selection based on results.

Per the trial design, quality of life was assessed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, and every 2 cycles thereafter up to a year or end of treatment (whichever is first). It was also collected at the 30-day post-treatment visit. Practically, there would be a maximum of two assessments in those with progressed disease: one at the end of treatment assuming treatment was stopped due to progression and one at the 30-day post-treatment 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.

Time to death utility use can overcome the limited information that may be available within the progressed disease state. Because the assessments are routinely collected for the first year, there will be a more balanced distribution of assessments within the time to death categories.

Regarding informative censoring, there are [redacted] and [redacted] utility assessments in the intervention and SOC arms respectively, that are classified as unknown in the time-to-

death approach for the CPS≥1 non-Asia region cohort - for these questionnaires the time from EQ-5D questionnaire completion to death censoring is shorter than 360 days. These are potentially the patients that may live longest (as censored for death at the time of clinical cut-off of IA2). This means there is a potential censoring bias due to the fact that these patients could be patients with higher utilities (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, but that would apply to both arms, and probably more to the pembrolizumab arm as there are more “Unknown“ utility assessments in the intervention arm than in the SOC arm (i.e. longer overall survival leading to more censoring for death in the intervention arm). This could identify the time-to-death approach as a conservative one (i.e. not favouring the intervention arm) in this analysis.

B14. PRIORITY. The model appears to use the utility values in Table 40 as inputs, but these don’t match the values in Table 46. Please explain how the values in Table 46 are calculated and whether they are model outputs based on combining several data sources, or model inputs.

MSD Response:

The correct utility values, based on the non-Asia region, can be found in the economic model (Utilities!I52:55) and Tables 40 and 63 of the CS. The utility values in Table 46 are based on the global cohort, and MSD wish to replace them with the values presented in Tables 40 and 63. The utility value associated with the 360 or more days to death state in Table 46 was capped by the utility of the general population of the same age (60 years) and gender (male 79%).

B15. Please clarify how the disutility associated with Grade 3+ AEs was calculated from the EQ-5D data collected in KEYNOTE-811. In particular, did the collection times of EQ-5D and adverse events coincide with EQ-5D being collected at the time AEs were reported? If not, how were measurements collected at different times related in the analysis? Please clarify why the utility decrement has been calculated as the difference between “During Grade 3+ AE” and “without AE value” instead of the difference between “During Grade 3+ AE” and “without Grade 3+ AE”, when

people not experiencing a Grade 3+ AE may in fact be experiencing a Grade 1-2 AE and the economic model only includes Grade 3+ AEs.

MSD Response:

Per the trial design, quality of life was assessed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, and every 2 cycles thereafter up to a year or end of treatment (whichever is first). Therefore, the assessment was not designed to coincide with when patients reported experiencing an AE.The utility difference between “During Grade 3+ AE” and “without Grade 3+ AE” is estimated to be [redacted]; see table below. Applying this disutility to AEs in place of the value included in the CS has a minor impact on the ICER (see scenario analysis results).

Table 45: EQ-5D Health Utility Scores for Disutility of AEs During Progression-Free State (CPS≥1 Non Asia)

Population	Mean utility	SE
During Grade 3+ AE	[redacted]	[redacted]
Without Grade 3+ AE	[redacted]	[redacted]
During Grade 1-2 AE	[redacted]	[redacted]
Without AE	[redacted]	[redacted]

Abbreviations: AE, adverse event

Adapted from MK3475_prot811_PEM_EQ5D_Report_V3.0 Table 116

B16. PRIORITY. CS page 126 states that all utility analyses were conducted descriptively without adjustment for repeated measurements. Please provide justifications on why no covariates were adjusted (e.g., age and gender). Please also provide a scenario analysis using repeated measure analysis taking into account correlations within each participant and appropriate covariates for both the time-to-death utility approach (CS p127-129) and the progression-based utility approach (CS, p129-130). In these analyses, please also consider having Grade 3+ AEs as a covariate to model disutility of experiencing Grade 3+ AEs.

MSD Response:

MSD can investigate conducting a scenario analysis using a linear mixed-effects regression analysis, which accounts for repeated measures. This analysis may include covariates for age and gender although it should be noted that adjustment of utility

values for age and gender within the cost-effectiveness model was applied using external data published Ara & Brazier (2010). As discussed during the EAG clarification call, MSD will not be in a position to provide this analysis by the response deadline on June 26th. It is expected this analysis will be provided to the EAG during the week commencing July 10th 2023.

MSD response submitted on 14th July

Adjustment of utility values for age and gender within the cost-effectiveness model was applied using external data published by Hernandez Alava et al (2022). This was considered to be a suitable approach given the limited follow-up of the trial and is a common approach followed in previous oncology appraisals.

However, in line with the request in the question above, a utility report with adjustment for repeated measurements is shared alongside this response. Covariates for age, gender and Grade 3+ AEs were included in this analysis. The p values observed for the age and gender variables exceed the 0.05 level selected for the assessment of statistical significance for both the time-to-death utility approach and the progression-based utility approach. They are not significant variables and are excluded from the model. Presence or absence of a Grade3+ AEs are observed to be a statistically significant variable, and this is accounted for in the model through the application of a one-off AE-associated QALY loss in the first cycle (please see CS section B.3.4 for details).

As discussed in the CS section B.3.4, the base case approach is to use utility values from descriptive analyses and 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. If within-individual measurements are positively correlated, this increases the variance due to perceiving there to be ‘less information’ than if all measures were treated as independent. However, whereas traditional repeated measures adjustment approaches are appropriate for many applications involving health data, they 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.

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 following (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

Furthermore, in the context of health economic modelling of the trial population, patients with multiple measurements spending longer time in a health state should receive proportionately greater weight for their health utilities than those with a single measurement, as they account for relatively more of the time and QALYs spent in that state within the model and are more representative of that health state experience. Thus, in the context of oncology trials, providing relatively greater weight to the observations of individuals with a single trial measurement for a health state through repeated measures adjustment can serve to downward bias estimated mean values for the health state.

Descriptive analyses, without adjustment, weight utility measurements in proportion to the number of measurements observed in each health state for each patient such that patients with longer time in a health state, and more measurements, receive greater weight than an individual in the health state for a short time and with only a single measurement.

While this does not directly address the issue of appropriate estimation of the variance when repeated measures are present, there are a few mitigating factors which suggest this to be a lesser or non-issue. First, improvements in the estimation of the mean and the variance with repeated measures approaches are likely to be more pronounced

with smaller sample sizes, and when within-patient variability in values for a health state is low compared to inter-patient variability. As previously described, within-patient health state values are expected to decline as patients approach a point of transition to a worse health state and not to remain fixed. In terms of sample size, if for example only eight subjects have data for a health state, with six reporting one measurement, one reporting two measurements and one reporting eight measurements, a repeated measures approach can ensure the last patient does not dominate the results when estimating a mean and variance. However, as is more typical for oncology trial health states, if there are larger sample sizes of 50 to 500 patients, each with for example 1 to 4 measurements for a health state, the impact of within-patient correlation on the estimation of the overall mean value and estimate variability around that mean, relative to if each measurement were to have come from a different patient, is likely to be very low. Lastly, for the purposes of one-way and probabilistic sensitivity analyses, the trial-based estimate of variability for the mean utility value of a given health state based on sampling variation is likely to under-estimate the true potential variability within the target population of interest. Sources of additional variability beyond sampling variation in the trial may include the trial population reflecting a broader or different set of patient geographies, a more limited follow-up time, differing patient characteristics due to trial inclusion/exclusion criteria etc. As larger trial sample sizes can lead to implausibly tight confidence intervals for utility values for health states, it is instead recommended to conduct one-way and probabilistic sensitivity analyses using a more plausible range for variation.

Nevertheless, a linear regression, which accounts for repeated measures, was conducted (see attached report) and a scenario analysis was conducted in the cost-effectiveness model using the resulting utility values for patients who did not experience an AE. Disutility associated with AEs was accounted for through the application of a one-off QALY loss in the first cycle, as described in the CS. The scenario analysis values per health state for both approaches are presented in the tables below.

Table 46: Health state utility values based on linear regression (time-to-death) CPS≥1 non-Asia

Time-to-death (days)	Without AE	SE
<30	[redacted]	[redacted]

30 to 180	[redacted]	[redacted]
180 to 360	[redacted]	[redacted]
≥ 360	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]
Abbreviations: AE, adverse event; SE, standard error *Source: Utility-Analysis_KN811_ia02_UK_NICE-DSU_v1.0*		

Table 47: Health state utility values based on linear regression (progression-based) CPS≥1 non-Asia

Health state	Without AE	SE
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]
Abbreviations: AE, adverse event; NA, not applicable; SE, standard error *Source: Utility-Analysis_KN811_ia02_UK_NICE-DSU_v1.0*		

The cost-effectiveness results (deterministic) of the scenario analysis using the values presented above are presented below.

Table 48: Scenario analysis discounted results (deterministic) using linear regression-derived utility values (time-to-death)

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	4.94	[redacted]	-	-	-	
Trastuzumab plus chemotherapy	[redacted]	3.03	[redacted]	[redacted]	1.91	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years **Inclusive of x1.2 weighting*							

Table 49: Scenario analysis discounted results (deterministic) using linear regression-derived utility values (progression-based)

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)

Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	4.94	[redacted]	-	-	-	
Trastuzumab plus chemotherapy	[redacted]	3.03	[redacted]	[redacted]	1.91	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Inclusive of x1.2 weighting*							

Resource use

B17. CS Table 57. Please show the source data used to derive the proportions in Table 57 and confirm which Table in the HTA report on Drug Utilization they have been extracted from as the EAG has been unable to find corresponding data in the report. We would expect the data in the model to match Table 4.1-28 if the Global CPS≥1 cohort has been used or Table 4.1-30 if the non-Asia CPS≥1 cohort has been used but we cannot corroborate the figures in the model (E53 to F63 of 'Subsequent Tx Costs' sheet) with either table. Please also show how the figures in Table 57 have been calculated from the original data including how 'other subsequent therapies' including paclitaxel with ramucirumab were redistributed across the seven treatments included in Table 57.

MSD Response:

The number of patients receiving each subsequent therapy regimen has been summed across all lines. The numbers presented in E53 to F63 of 'Subsequent Tx Costs' sheet include the sum of all patients receiving the regimen across the lines. MSD acknowledge that it is possible for patients who receive the regimen in more than one line to be re-counted, rather than the value representing a number of unique patients; however for the purposes of deriving acquisition costs, it is deemed appropriate. In the updated model, in accordance with the response to question B.40, MSD are replacing the data presented in Table 57 with data reported for the non-Asia CPS≥1 cohort and an extract from the source document is provided alongside this response.

The values in Table 57 reflect those in cells E25:F31 of the same model sheet. They are a redistribution of values in cells I25:J32 (which includes a proportion of patients receiving ramucirumab). When ramucirumab is excluded (as in the base case), the values for each other treatment are expressed as a proportion of the total without ramucirumab (i.e. the ramucirumab proportion is redistributed amongst the other treatments. The values before redistribution are calculated in cells K54:L62 of the model sheet. These include a redistribution of "other treatments" administered in smaller proportions in the trial amongst the most frequently administered treatments proportionate to the treatment's share of the most frequent category.

B18. Please provide tables of subsequent therapies for the CPS≥1 cohort (equivalent to Table 57) restricted to the non-Asia CPS≥1 cohort and restricted to European CPS≥1 participants and include an option within the economic model to select these different data sources instead of the data shown in Table 57. The HTA Drug Utilization report appears to present data according to European vs non-European instead of using the regions defined as stratification factors. Please state why a European cohort is defined in the context of drug utilization when this grouping of countries was not a stratification factor. Please also list the countries included in the European cohort.

MSD Response:

Please see the subsequent therapies administered to the non-Asia CPS≥1 cohort in KEYNOTE-811 in the table below. The method for calculating these proportions followed that described in the response to question B.17 above.

Table 50: Proportions of patients receiving subsequent treatments per treatment arm (non-Asia CPS≥1 cohort)

Subsequent Treatment (across all arms)	Proportions per arm	
	Pembrolizumab with trastuzumab plus chemotherapy	Trastuzumab plus chemotherapy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

A European cohort was defined for the subsequent therapies input in order to align with the pre-specified regions in the trial protocol. However, MSD do not believe this to be a relevant subgroup for this evaluation and deem the non-Asia region to be more clinically relevant and applicable to the England and Wales setting. Regional variation in treatment practices and outcomes has been discussed in the context of the difference between Asia and the rest of the world [4] and this inconsistency of treatment approach (e.g. screening programmes, approaches to treating early stage cancers) is reflected by inconsistent results between these populations in the KEYNOTE-811 trial. Furthermore, generalising the non-Asia region results enables a larger sample size to inform the results (compared to the European subpopulation) and produces a more robust evidence base, maximising the use of data that is relevant to the eligible population in England and Wales. The non-Asia results presented in the table above have been included in the model as requested and MSD believe these to be more appropriate than a European cohort analysis for consistency with the trial efficacy inputs. To address any concerns about the applicability of the trial treatment distribution to the UK setting, a scenario analysis using a distribution informed by UK clinical experts was included in the submission (CS Table 68), which demonstrated a minor impact on the base case ICER.

B19. CS Table 63. Please clarify where the data on duration of subsequent treatment (shown in Table 63 but not described elsewhere) have been sourced from. If they represent data from the Global CPS≥1 cohort, please provide equivalent figures for the non-Asia CPS≥1 cohort and include these in the model with the option to select either source. Please clarify why a duration is provided for Capecitabine + Oxaliplatin in Table 63 but this subsequent treatment option is omitted from Table 57.

MSD Response:

This treatment duration is only applied in the scenario analysis modelling a UK distribution of subsequent treatments (informed by clinical expert opinion). CS Table 63 presents base case inputs so this value should have been omitted from the table.

MSD have updated subsequent treatment data (including duration of treatment) for the non-Asia CPS≥1 cohort in the updated model, in accordance with the response to question B.40.

B20. Please explain why the proportion receiving subsequent treatments (cells G64:H64 of 'Subsequent Tx Costs' sheet) is higher than the proportion who progressed (cells E46:F46). Were patients allowed to receive subsequent treatments if they stopped their study drug for reasons other than progression?

MSD Response:

Patients could receive multiple lines of subsequent treatment in KEYNOTE-811. All available lines of subsequent treatment from the trial were included in the subsequent treatments calculation (i.e. summed) so as not to bias against patients who received more than one line of treatment. Hence the total number of patients who received more than one line of treatment is higher than the proportion who progressed, because certain patients were counted more than once.

Patients were allowed to receive subsequent treatments if they stopped their study drug for reasons other than progression (e.g. due to experiencing an AE).

B21. Please clarify why are acquisition costs included in PSA for subsequent treatments?

MSD Response:

Acquisition costs for subsequent treatment are not varied in PSA as these costs are assumed to be fixed in the NHS; see Parameters!G137:166 and the third column in CS Table 63.

The following text in the Run_PSA macro also shows how the "Use in PSA" and "Control" dropdowns in the Parameters sheet will retain deterministic acquisition costs for subsequent treatments as the "Use in PSA" is set to "No".

```
'Change parameters to probabilistic
For Params_looper = 1 To Params_rows 'Loop through each parameter and switch to probabilisitic if 'use in PSA' = Yes
    If [misc_param_PSA].Offset(Params_looper, 0).Value = "Yes" Then
        [misc_param_control].Offset(Params_looper, 0).Value = 4
    End If
```

B22. CS, Page 135 discusses the calculation of RDI but the text appears to give two different definitions. One relates to the proportion in mg of the planned dose. which appears to be a measure of whether the full dose was given at any given administration, whereas the other definition relates to the actual number of doses versus the expected number of doses, which seems to relate to whether each administration was given not whether the full planned dose was given. Please clarify by further explaining the method. Please also clarify how “expected number of doses” was defined when it was possible for some treatments to be extended beyond the 35 cycles and others to be capped at 6 to 8 cycles. Please also discuss how this relates to the definition of dose intensity provided on page 8 of the HTA report on Drug Utilization.

MSD Response:

The RDI implemented within the cost-effectiveness analysis uses the percentage of actual number of doses administered divided by the expected number of doses administered, consistent with the description in section 2.1.1.2 of the Drug Utilization report.

The actual number of dose administrations is defined as the number of documented distinct cycles of the study treatment component the participants received.

For pembrolizumab, placebo, trastuzumab, cisplatin and oxaliplatin, one infusion is considered as one administration, and subsequently as one cycle. However, for capecitabine, a cycle is counted when at least one record of capecitabine intake was documented for this cycle, regardless of how many capecitabine tablets were actually taken during this cycle (28 tablets were planned for one cycle). The same approach is applied for 5-fluorouracil, which is administered on consecutive days (1 to 5) of each cycle (5 injections within 5 consecutive days were planned for one cycle).

The expected number of doses is defined as the number of cycles of the study treatment component planned per protocol while the patient is on treatment up to the database lock. The maximum number of expected cycles for pembrolizumab is 35

cycles. Second course pembrolizumab is not part of this calculation, and this pertains to only three patients.

The maximum duration of 6 to 8 cycles was not specified directly in the trial protocol. Instead, the clinical trial protocol specified that the treatment cap for chemotherapy could be applied per local guidelines. Therefore, in some countries, chemotherapy may have been capped at 6 to 8 cycles and in other countries chemotherapy may be administered until progression.

B23. Please clarify why the time on treatment curves shown in Figures 34 to Figure 37 show pembrolizumab treatment beyond 35 cycles (2 years), cisplatin treatment beyond 6 cycles (18 weeks) and oxaliplatin treatment beyond 8 cycles (24 weeks), given the maximum treatment durations described on page 35 and in the footnotes of CS, Table 4. Did some patients receive more than the specified number of cycles of treatment or was treatment extended beyond the expected time frame due to unplanned delays between cycles?

MSD Response:

There is a small proportion of KEYNOTE-811 patients continuing to receive treatment beyond the maximum treatment durations outlined in the footnotes of CS Table 4. This can be both attributable to certain patients exceeding the duration and to unplanned delays between cycles (e.g. due to patients taking treatment breaks due to tolerability). In the case of pembrolizumab, 3 patients exceeded the maximum number of 35 cycles (as was permitted in the trial protocol; described as second-course phase of pembrolizumab); see response to question A8. In other case, the exceeding of the maximum pembrolizumab duration is attributable to the dose delays described above. As mentioned in the response to question B.22, the protocol permitted the duration of chemotherapy treatment to be capped as per local guidelines. KEYNOTE-811 is a multinational trial and not every country which enrolled subjects imposes a treatment cap for chemotherapy so local investigators may have offered additional cycles to the subjects. As outlined in the CS, clinical practice in the UK does recommend maximum treatment durations. These maximums were applied in the model base case. The impact of administering chemotherapies in line with the mean number of cycles from the trial was investigated in a scenario analysis, and the impact on the base case ICER was minor (see scenario analysis results).

B24. CS, Table 52. Why do patients receive a first attendance outpatient appointment every cycle as well as a follow-up appointment every other cycle in the progression-free state (in addition to any administration costs associated with receiving study drugs)?

MSD Response:

This resource use frequency was informed by TA208. The CS for TA208 states, "Consultations with an oncologist were assumed to take place approximately every 3 weeks during treatment with chemotherapy and every 6 weeks after including during whiles on maintenance trastuzumab therapy (Expert Opinion)". MSD was unclear how best to interpret the latter part of this sentence. As such, a conservative approach was taken and both types of outpatient appointments were included. If the follow-up appointments included in every other cycle are removed, the ICER reduces by about £1000.

MSD also assumed that the Q3W appointments during treatment with chemotherapy would be more resource-intensive than the additional appointments implemented every other cycle; hence the different currency codes (first attendance and follow-up). A first attendance appointment is assumed to be more resource-intensive for the health service.

B25. PRIORITY. CS, Table 53. Please clarify why costs per month are lower for patients with progressed disease when they are likely to be experiencing worse symptoms and requiring more supportive care? In particular were palliative care services provided either in secondary care or community settings included in the study by Golmez-Ulloa et al. Please clarify how the estimates from Golmez-Ulloa et al. differ from the costs used in TA208 of £542 per month for progressed disease.

MSD Response:

Palliative care services were not included in the study by Gomez-Ulloa, which states "the use of healthcare resources associated with palliative care was not specifically captured in this study."

PD costs in TA208 were informed by the following types of resource use estimates in the clinical guideline for breast cancer (CG81):

- Community nurses
- Clinical nurse specialists
- GPs
- Therapists.

MSD considers these resources use estimates to be irrelevant to the current decision problem as they have been reported for patients diagnosed with a different cancer. Furthermore, they are based on NHS practice in 2009, which NHS deem to be outdated. As shown in CS Table 53, Gomez-Ulloa considered a wider range of resources than TA208 e.g., inpatient stays and imaging tests.

MSD acknowledges it is inconsistent to update the PD source and not the PFS source, and utilise a source based on guidelines for PFS and a source based on real-world evidence for PD. To explore the impact of these inconsistencies on the ICER, a scenario employing the monthly PD costs from TA208 (£542 inflated to £679 in 2021/22 prices) was undertaken and the ICER increased by about £3000.

Given that no other relevant studies reporting cost and resource use data in first-line patients were identified in the SLR, MSD maintains that TA208 and Gomez Ulloa are the best available sources to inform PFS costs and PD costs, respectively.

B26. PRIORITY. Please provide a scenario analysis including the cost for PD-L1 testing which should take into account the specific assay required to assess eligibility for pembrolizumab, the number needed to test to identify one patient eligible for treatment and the proportion of those patients already being tested to ascertain eligibility for current NHS therapies with overlapping indications. Please include these parameters explicitly in the model so the EAG can explore alternative assumptions.

MSD Response:

As noted in the CS, gastric or GOJ adenocarcinoma patients are already tested for HER2 status and PD-L1 status when they are deemed incurable (locally advanced unresectable or metastatic) in order to determine eligibility for trastuzumab (if HER2 positive) and nivolumab (if HER2-negative with CPS≥5) as per TA208 and TA857

respectively. Approximately 15% of these patients will be HER2 positive [5] and 85% of those who are HER2 positive will express CPS≥1 (KEYNOTE-811).

MSD estimates there to be approximately 2,400 patients with incurable gastric or GOJ adenocarcinoma tested for HER2 status and PD-L1 status in 2023 [6], [7], [8]. Of these, approximately 300 will be HER2 positive and express CPS≥1 (12.5%). The recent NHS England BIT submission for this appraisal also estimated approximately 250 patients to be eligible for pembrolizumab with trastuzumab plus chemotherapy. Based on these estimates, approximately 8 patients will need to be tested to identify one eligible patient.

A PD-L1 testing cost of £40 was employed in a previous pembrolizumab submission (TA522/674). If this is inflated from 2015/16 prices to 2021/22 prices (£53), the cost to identify one eligible patient would be £424. This cost should be applied to both treatment arms as PD-L1 testing is done at the same point in the pathway as HER2 testing, hence MSD believe it appropriate to exclude the cost from the model. The recent NHS England BIT submission for this appraisal also affirmed that PD-L1 testing is established in gastrointestinal cancers and excluded PD-L1 testing costs from the budget impact analysis. Thus, if PD-L1 testing costs are applied in line with NHS practice there will be no incremental difference in costs.

Although MSD's position is that PD-L1 testing costs are irrelevant to this appraisal as they are applicable to both treatment arms, functionality has been added to the model to include PD-L1 testing costs in the total costs for both intervention and comparator, see HCRU Costs!C69.

B27. PRIORITY. Please clarify why it is appropriate to assume the same resource use when giving either one, two or three intravenous treatments (e.g. trastuzumab alone, pembrolizumab with trastuzumab, or pembrolizumab with trastuzumab and platinum). Presumably there will be a real-world opportunity cost from adding pembrolizumab to the existing standard of care in terms of chemotherapy suite chair time available for other patients?

MSD Response:

UK clinical experts advised MSD that each drug within a combination would be administered at the same hospital appointment. The drugs within a combination would

usually be administered in sequence (except doublet chemotherapies, which are usually bundled together) so the duration of the appointment is likely to increase with the number of drugs within a combination. However, a separate administration cost for each drug within a combination would not be needed as this would overestimate the "paperwork" costs required for one patient. MSD acknowledge an opportunity cost of reduced chair time for other patients is feasible but the National Schedule of NHS Costs is not produced in a format which can estimate this.

MSD's approach is also consistent with previous NICE appraisals that have costed one appointment when administering combinations. In TA208, the combinations HCX (trastuzumab in combination with cisplatin and capecitabine) and HCF (trastuzumab in combination with cisplatin and 5-FU) were associated with one administration cost code (£268 from NHS reference costs 2008/9: SB14Z, deliver complex chemotherapy, including prolonged infusion treatment at first attendance). Nivolumab in combination with ipilimumab (two intravenous drugs) has also been associated with one administration cost code (SB13Z or SB14Z) (TA400, TA818, TA716 and TA418).

Furthermore, the recent NHS England BIT submission for this appraisal states, "The current Heregulin for trastuzumab + cisplatin + 5-fluourouracil is SB14Z (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance). Pembrolizumab will be added to day 1 and will not affect the Heregulin (i.e. will remain as SB14Z)."

For these reasons, MSD maintains that it is appropriate to only include one cost code is when administering a combination.

In estimating the type of cost code, infusion times should be considered:

- Pembrolizumab, 30 minutes
- Trastuzumab, 30 or 90 minutes
- Oxaliplatin, 60 or 120 minutes
- Cisplatin, 60 or 120 minutes
- 5-FU, 5 days.

Even though pembrolizumab and trastuzumab have the shortest infusion times, SB13Z was chosen over SB12Z as pembrolizumab and trastuzumab are considered "complex" treatments.

However, given that trastuzumab monotherapy and nivolumab monotherapy have been associated with lower administration costs than their combination in some of the aforementioned appraisals, a scenario using SB12Z for trastuzumab monotherapy was explored; the impact on the ICER was negligible (minor increase). The cost for pembrolizumab monotherapy was not adjusted in this scenario given that few patients receive pembrolizumab monotherapy.

In line with the recent NHS England BIT submission for this appraisal, MSD maintains that SB14Z is the most appropriate code for pembrolizumab with trastuzumab plus FP and trastuzumab plus FP as no other combinations in this appraisal require a prolonged infusion, and SB13Z is the most appropriate code for pembrolizumab with trastuzumab plus CAPOX or XP and trastuzumab plus CAPOX or XP.

B28. Please clarify whether additional blood tests are required for patients receiving pembrolizumab with trastuzumab versus those receiving trastuzumab alone. Please incorporate additional costs for these in a scenario analysis.

MSD Response:

On the day of pembrolizumab or trastuzumab treatment, a nurse may take a blood sample from the patient to check they are well enough to receive treatment. No additional blood tests are required by adding pembrolizumab to trastuzumab as only one blood sample would be required.

Adverse events

B29. Please clarify how the AEs frequencies in Table 55 have been calculated and please provide a source Table for these data in the CSR or the Appendices so these can be verified by the EAG. In particular, what population have they been estimated in? If they have been estimated in the Global CPS≥1 cohort, then please provide an equivalent set of data for the non-Asia CPS≥1 cohort. Please also include an option to select these data as a scenario within the updated economic model.

MSD Response:

The AE frequencies presented in CS Table 55 are those reported for the Global CPS≥1 cohort. The updated model includes safety data for the non-Asia CPS≥1 cohort, in accordance with the response to question B.40.

The method of calculating the proportions in Table 55 accounts for the fact that patients could have experienced more than one event. The proportion of the cohort who experienced each type of AE was adjusted by multiplying the proportion who experienced *any* incidence of that event by the mean number of events per subject for that AE per treatment arm. The frequencies in the table should be interpreted as "the frequency of each AE if one event was experienced per patient who experienced that AE". This frequency is then multiplied by the unit cost of resolving that AE to derive the AE management cost.

B30. Our clinical expert thinks that rare but severe immune-related AEs could have relatively a high impact on resource use and patients' quality of life compared to other types of AEs. Please provide a scenario where these grade 3 to 5 AEs are considered in calculating costs and quality-adjusted life years (QALYs) even if they are rare (<3%).

MSD Response:

This question was discussed on the EAG clarification call, and clarity was sought on which events this advice related to. The EAG indicated that the category of "immune related disorders" could be a suitable data set on which to base a scenario analysis. MSD consulted this category and were uncertain about which events to classify as having a relatively high impact on resource use and patients' quality of life compared to other types of AEs and felt assumptions around this expect advice could be subjective. In order to address the request for a scenario analysis, investigating if the intervention arm's cost were underestimated by the base case approach, the one-off cost of resolving AEs in this arm was increased by 10% (i.e. the value in Adverse Event Data! E77). This resulted in a minor increase to the ICER. MSD view the base case approach to AEs to be robust.

Scenario analyses

B31. Scenario 6 in Table 68 is described as “Progression-based utility approach with PFS value = baseline and PD value = 0.706”. Is this implemented by setting drop_util_baseline_yesno=”Yes” and drop_util_base=”Health states”

MSD Response:

Yes, that is the correct method for implementing this scenario.

B32. Scenario 11 in Table 68 is described as “% subsequent treatments adjusted by % patients who progressed”. Please describe how this scenario was implemented within the model. Does it uplift the subsequent treatment costs so they are estimated per progressed patient rather than per randomised patient, and if so, are costs of subsequent treatments then applied only to progressed patients? Are they applied to the whole cohort regardless of progression status in the base case?

MSD Response:

This scenario takes the ‘% who receive subsequent treatment (all lines of subsequent treatment) out of those participants who completed or discontinued from study treatment’ and divides it by the proportion of patients who progressed upon leaving the PF health state. This inflation of the subsequent treatments is intended to account for those who may receive subsequent treatment where the trial follow-up may not be sufficiently long enough to capture the entire duration of subsequent treatment.

B33. Scenario 13 in Table 68 is described as “UK subsequent treatments costs distribution – informed by clinical experts”. This appears to be implemented by setting drop_subtrt_platinum_yesno= “Yes” which results in subsequent treatments of docetaxel for 25% and CAPOX for 25%. Please clarify if this scenario is the one referred to on page 147 as “50% of patients receive a subsequent treatment, which is typically split in equal proportions between those treated with docetaxel and platinum re-challenge,” based on clinical expert opinion.

MSD Response:

Yes, Scenario 13 in CS Table 68 is implemented as described above and refers to the scenario: “50% of patients receive a subsequent treatment, which is typically split in equal proportions between those treated with docetaxel and platinum re-challenge”.

B34. Scenario 15 in Table 68 is described as “UK chemotherapy regimen distribution - informed by clinical experts”. Please describe how this scenario was implemented within the model and tabulate the distribution of primary chemotherapy treatments assumed. Please clarify if this is the scenario referred to in Table 28 where it is stated, “A scenario where XP is also administered, based on TA208 and clinical expert opinion, is presented.”

MSD Response:

The model base case uses the proportions of patients receiving the chemotherapies administered in KEYNOTE-811 (CAPOX, FP). Scenario 15 in CS Table 68 refers to a scenario where UK practice is reflected. This includes the administration of XP (which is recommended for co-administration with trastuzumab in TA208) and the distribution is based on input from clinical experts. The proportions are presented in the table below.

Table 51: Chemotherapy proportions administered in UK clinical practice scenario analysis

Chemotherapy regimen	Proportion of patients in Scenario 13
XP	80%
FP	10%
CAPOX	10%

In the scenario analysis, the intervention and comparator arms are modelled to include the chemotherapy proportions in the above proportions, rather than the trial-based base case analysis.

B35. Scenario 16 in Table 68 is described as, “Chemotherapy mean number of cycles as observed in trial”. Please describe how this scenario was implemented within the model and provide the mean number of cycles per individual drug for each

trial arm. CS, page 153 says that the impact of treatment duration caps has been investigated in scenario analysis. Please clarify if this is referring to Scenario 16.

MSD Scenario:

The mean number of cycles per chemotherapy for each trial arm has been presented in the CS Table 32 (page 101). These values refer to the CPS≥1 population in KEYNOTE-811. The corresponding mean values for the non-Asia CPS≥1 cohort are presented in the tables below (values are very similar). In the scenario analysis (Scenario 16), the chemotherapy regimens are administered for this number of cycles and costed accordingly, rather than using the UK maximum number of cycles, as in the base case. Adjustments to efficacy were not made.

Table 52: Mean number of chemotherapy cycles administered per treatment arm in KEYNOTE-811 (non-Asia CPS≥1 cohort)

	Pembrolizumab with trastuzumab plus chemotherapy; mean (SD)	Trastuzumab plus chemotherapy; mean (SD)
Capecitabine (in CAPOX)	13.3 (10.7)	9.6 (8.3)
Oxaliplatin (in CAPOX)	7.3 (4.6)	6.8 (4.6)
Cisplatin (in FP)	5.3 (1.8)	5.6 (1.9)
5-FU (in FP)	9.5 (6.7)	11.2 (9.5)
Abbreviations: SD, standard deviation		

B36. Please provide a scenario analysis using the KM data for time on treatment to estimate treatment duration for each drug without restriction on the maximum number of cycles if this has not been done in any of the scenarios already presented.

MSD Response:

The maximum treatment duration applied to each drug was removed (by setting the maximum treatment cycles value to 100 for each drug on Controls!D188) and the KM data was followed to its conclusion. This has the impact of increasing the ICER in the updated model from [redacted] to [redacted].

Scenario analyses

B37. Please clarify why the utility set selected for estimating general population QALY gains in the Schnider et al. tool was the “HSE 2017-18 EQ-5D-5L mapped to EQ-5D-3L using the Hernandez Alava et al. algorithm” rather than the option

described on the web tool as the ‘reference case’ which is the “MVH value set +HSE 2014 ALDVMM model (Hernandez Alavez et al.)” which generates expected QALYs of 12.62 when selecting a starting age of 60 and a proportion female of 21%.

MSD Response:

The CS incorrectly states both that the Schneider et al. tool was used to generate QALY shortfall estimates and that HSE 2017-18 utility values were used. Instead QALY shortfall estimates were calculated within the economic model itself and aligned to the “reference case” described in the Schneider et al. tool as they apply the HSE 2014 ALDVMM model to generate utility values for the general population.

However, while results between the Schneider tool and model are comparable, it is reasonable that the Schneider et al. tool and reference case settings of “MVH value set +HSE 2014 ALDVMM model (Hernandez Alavez et al.) be used to ensure consistency of methodology and source data between appraisals.

B38. Given that trial populations are generally younger than those treated in clinical practice, please explore whether the QALY weighting for severity is sensitive to the average age of the cohort being treated in clinical practice.

MSD Response:

It was agreed on the EAG clarification call that the method for implementing this scenario is to update the model cohort mean starting age (Controls!G45). In the scenario, this value was set to 68.00 years, based on a discussion with UK clinical experts who estimated this to be the mean age of the patients they treat with this cancer. This scenario demonstrated the QALY weighting to be insensitive to the update, with the same category estimated by the model as when the KEYNOTE-811 mean age is used. As stated in the CS, MSD believe the appropriate QALY weighting for this population is 1.2.

B39. PRIORITY. Please define the exact scenario used to estimate the 0.980 QALYs quoted in Table 60 with reference to the specific table this value has been extracted from within the committee papers for TA208. Please also clarify why the QALY gain for the comparator group from TA208 is considered more representative

of the expected QALYs in clinical practice than those predicted by the model including a summary of the comparability of the trial populations and any key changes in clinical management that have occurred since TA208 was published.

MSD Response:

The QALYs per patient (0.980) were taken from Tables 23, 25, 26 and 28 of the TA208 ERG report (pages 90-96 of 121) and include the ERG's revisions to the company base case.

MSD believe the results for the trastuzumab + chemotherapy arm in TA208 are a more appropriate representation of the severity of this disease than those reported for the SoC arm in KEYNOTE-811. As noted in the CS, the survival rates observed for patients treated with trastuzumab plus chemotherapy in the ToGA trial and the JACOB trial, which used a similar control arm to KEYNOTE-811, indicate the SoC results for all CPS≥1 patients in KEYNOTE-811 to be an outlier (e.g., 2-year OS rate reported to be 38% in KEYNOTE-811 vs. approximately 25% and 30% in ToGA and JACOB respectively, based on visual inspection of KM curves). Even though the non-Asia region OS curve in KEYNOTE-811 presents survival rates which are closer to those previously reported for the SoC arm, MSD considers it important to utilise the data accepted in previous related appraisals to promote consistent decision making.

Since the TA208 guidance publication, patients with HER2 positive GC and GOJ adenocarcinoma have lacked new effective treatment options. Numerous HER2-targeting drugs such as the tyrosine kinase inhibitor lapatinib, the antibody-drug conjugate trastuzumab-emtansine and addition of pertuzumab to trastuzumab failed to demonstrate an improvement in OS in phase III studies in metastatic HER2 positive GC [9], [10], [11], [12], [13]. Thus, if a 1.2 QALY weighting could be retrospectively achieved using the data from TA208, it would be illogical to assume a lower QALY weighting for this appraisal, in the absence of a significant clinical advancement in the management of these patients since the publication of TA208.

A summary of the comparability of trial populations, using selected factors, is presented in the table below:

Table 53: Comparability of KEYNOTE-811 and ToGA trial populations

Factor	KEYNOTE-811 (non-Asia CPS≥1 cohort)	ToGA (Bang et al. 2010)
Proportion male	79%	75 – 77%
Mean age, years	60.2	58.5 – 59.2
Primary Tumour Location		
Gastroesophageal junction	39.8%	17 – 20%
Stomach	60.2%	80 – 83%
ECOG PS		
0-1	99.8%	90 - 91%
2	NA	9 – 10%
Previous gastrectomy	13.2%	21 – 24%

B40. PRIORITY. Page 151 suggests that the estimate of QALYs from the standard of care arm of the model is not representative of the UK population because it is based on KM data for all CPS≥1 patients (i.e. all regions), and patients in the non-Asia region had lower OS than those in the Asia region. The EAG has requested clarification on whether the Global CPS≥1 cohort or the non-Asia CPS≥1 cohort has been used to populate the model for various parameter inputs in previous questions. If the model has used data from the Global CPS≥1 for some inputs and the company acknowledges that the Asia cohort is not representative of expected outcomes in the UK, why has data from the non-Asia CPS≥1 cohort not been used in the company's base case for all model parameters?

MSD Response:

In the updated model provided with this response, MSD have updated a number of model inputs to those reported for the non-Asia region CPS≥1 cohort in KEYNOTE-811, for consistency with the efficacy results previously included. These inputs comprise:

- Relative dose intensity values
- Adverse event frequency, duration

- Subsequent treatments distribution
- Mean number of chemotherapy cycles administered (scenario analysis)

B41. Please provide all company cost-effectiveness results tabulated in the CS both with and without the QALY weighting applied.

MSD Response:

The cost-effectiveness results presented in the CS have a x1.2 QALY weighting applied. The results have been presented in the tables below with the weighting removed.

Table 54: Base-case discounted results (deterministic) without QALY weight applied

Technologies	Total costs (£)	Total LYG	Total QALYs*	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	4.94	[redacted]	-	-	-	-
Trastuzumab plus chemotherapy	[redacted]	3.03	[redacted]	[redacted]	1.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 55: Incremental cost-effectiveness results based on PSA vs. SoC without QALY weight applied

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	[redacted]	-	-	-
Trastuzumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Table 56: Scenario analyses results (deterministic) vs. SoC without QALY weight applied

Rank	Scenario Name	Incremental Costs	Incremental QALYs	ICER	Difference vs. base case
1	Time horizon = 8 years	[redacted]	[redacted]	[redacted]	[redacted]
2	0% discounting	[redacted]	[redacted]	[redacted]	[redacted]

3	OS – gradual treatment waning between 7 & 9 years	[redacted]	[redacted]	[redacted]	[redacted]
4	1.5% discounting	[redacted]	[redacted]	[redacted]	[redacted]
5	Time horizon = 20 years	[redacted]	[redacted]	[redacted]	[redacted]
6	Progression-based utility approach with PFS value = baseline and PD value = 0.732	[redacted]	[redacted]	[redacted]	[redacted]
7	Progression-based utilities	[redacted]	[redacted]	[redacted]	[redacted]
8	Exclude age-related gen pop utility multiplier	[redacted]	[redacted]	[redacted]	[redacted]
9	Exclude RDI for 1L drugs	[redacted]	[redacted]	[redacted]	[redacted]
10	Pembrolizumab administration: 100% of patients on Q6W pembro	[redacted]	[redacted]	[redacted]	[redacted]
11	% subsequent treatments adjusted by % patients who progressed	[redacted]	[redacted]	[redacted]	[redacted]
12	Exclude drug wastage (i.e. assume vial sharing)	[redacted]	[redacted]	[redacted]	[redacted]
13	UK subsequent treatments costs distribution – informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
14	Exclude terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]
15	UK chemotherapy regimen distribution - informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
16	Chemotherapy mean number of cycles as observed in trial	[redacted]	[redacted]	[redacted]	[redacted]
17	Include half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]

B42. If an updated model has been provided, please repeat all base case and scenario analyses presented in the CS for the updated model. In doing so, please report results both with and without the QALY weighting applied.

MSD Response:

An updated model has been provided and the base case and scenario analyses results (with and without the QALY weighting applied) have been presented in the tables below (which are replicas of Table 65, Table 67 and Table 68 in the CS).

Table 57: Base-case discounted results (deterministic) with QALY weight applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	4.94	[redacted]	-	-	-	-
Trastuzumab plus chemotherapy	[redacted]	3.03	[redacted]	54,888	1.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 58: Base-case discounted results (deterministic) without QALY weight applied

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	4.94	[redacted]	-			
Trastuzumab plus chemotherapy	[redacted]	3.03	[redacted]	54,888	1.91	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 59: Incremental cost-effectiveness results based on PSA vs. SoC with QALY weight applied

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	[redacted]	-	-	-
Trastuzumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Table 60: Incremental cost-effectiveness results based on PSA vs. SoC without QALY weight applied

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	[redacted]	-	-	-
Trastuzumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Table 61: Scenario analyses results (deterministic) vs. SoC with QALY weight applied

Rank	Scenario Name	Incremental Costs	Incremental QALYs	ICER	Difference vs. base case
1	Time horizon = 8 years	[redacted]	[redacted]	[redacted]	[redacted]
2	0% discounting	[redacted]	[redacted]	[redacted]	[redacted]
3	OS – gradual treatment waning between 7 & 9 years	[redacted]	[redacted]	[redacted]	[redacted]
4	1.5% discounting	[redacted]	[redacted]	[redacted]	[redacted]
5	Time horizon = 20 years	[redacted]	[redacted]	[redacted]	[redacted]
6	Progression-based utility approach with PFS value = baseline and PD value = 0.732	[redacted]	[redacted]	[redacted]	[redacted]
7	Progression-based utilities	[redacted]	[redacted]	[redacted]	[redacted]
8	Exclude age-related gen pop utility multiplier	[redacted]	[redacted]	[redacted]	[redacted]
9	Exclude RDI for 1L drugs	[redacted]	[redacted]	[redacted]	[redacted]
10	% subsequent treatments adjusted by % patients who progressed	[redacted]	[redacted]	[redacted]	[redacted]
11	UK subsequent treatments costs distribution – informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
12	Pembrolizumab administration: 100% of patients on Q6W pembro	[redacted]	[redacted]	[redacted]	[redacted]
13	Exclude drug wastage (i.e. assume vial sharing)	[redacted]	[redacted]	[redacted]	[redacted]
14	Exclude terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]
15	Exclude AE disutility	[redacted]	[redacted]	[redacted]	[redacted]

16	UK chemotherapy regimen distribution - informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
17	Chemotherapy mean number of cycles as observed in trial	[redacted]	[redacted]	[redacted]	[redacted]
18	AE disutility of -0.053	[redacted]	[redacted]	[redacted]	[redacted]
19	Include half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]
20	Include PD-L1 diagnostic testing costs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; SoC, standard of care

Table 62: Scenario analyses results (deterministic) vs. SoC without QALY weight applied

Rank	Scenario Name	Incremental Costs	Incremental QALYs	ICER	Difference vs. base case
1	Time horizon = 8 years	[redacted]	[redacted]	[redacted]	[redacted]
2	0% discounting	[redacted]	[redacted]	[redacted]	[redacted]
3	OS – gradual treatment waning between 7 & 9 years	[redacted]	[redacted]	[redacted]	[redacted]
4	1.5% discounting	[redacted]	[redacted]	[redacted]	[redacted]
5	Time horizon = 20 years	[redacted]	[redacted]	[redacted]	[redacted]
6	Progression-based utility approach with PFS value = baseline and PD value = 0.732	[redacted]	[redacted]	[redacted]	[redacted]
7	Progression-based utilities	[redacted]	[redacted]	[redacted]	[redacted]
8	Exclude age-related gen pop utility multiplier	[redacted]	[redacted]	[redacted]	[redacted]
9	Exclude RDI for 1L drugs	[redacted]	[redacted]	[redacted]	[redacted]
10	% subsequent treatments adjusted by % patients who progressed	[redacted]	[redacted]	[redacted]	[redacted]
11	UK subsequent treatments costs distribution – informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
12	Pembrolizumab administration: 100% of patients on Q6W pembro	[redacted]	[redacted]	[redacted]	[redacted]
13	Exclude drug wastage (i.e. assume vial sharing)	[redacted]	[redacted]	[redacted]	[redacted]
14	Exclude terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]
15	Exclude AE disutility	[redacted]	[redacted]	[redacted]	[redacted]

16	UK chemotherapy regimen distribution - informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
17	Chemotherapy mean number of cycles as observed in trial	[redacted]	[redacted]	[redacted]	[redacted]
18	AE disutility of -0.053	[redacted]	[redacted]	[redacted]	[redacted]
19	Include half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]
20	Include PD-L1 diagnostic testing costs	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; SoC, standard of care

Section C: Textual clarification and additional points

C1. CS page 29 states that "Approximately 692 participants were randomised in the Global cohort in a 1:1 ratio to receive pembrolizumab or placebo each in combination with chemotherapy plus trastuzumab," but this appears to be the recruitment target and not the number randomised. Please clarify the exact number of patients randomised in the Global cohort.

MSD response:

Details of study population for Global cohort are provided in a table below. 698 participants were randomised in the Global cohort.

Table 63: Study Population (Global Cohort)

	Pembrolizumab + SOC	SOC	Total
Number of Participants Screened[a]			1367
Number of Participants Randomised (Planned Treatment) (ITT)	350	348	698
Number of Participants Received Treatment (Actual Treatment) (ApaT)	350	346	696
Number of Participants Randomised and Did not Receive Treatment	0	2	2
Number of Participants Discontinued Study Medication (Actual Treatment)	257	286	543
[a]Participants screened include participants from Global and Japan cohorts. Database Cutoff Date: 25 May 2022.			

C2. Tables 6, 7, 14, and 15 say "Database Cut-off Date: 25 May 2023" which seems unlikely given that the CS is dated May 23rd 2023. Should this read '25 May 2022'?

MSD response:

MSD confirm that Database Cut-off Date was 25 May 2022.

C3. Should the ICER in table 65 be [redacted] instead of [redacted]?

The correct ICER is [redacted].

C4. Please clearly state which cohort is represented in each Figure in the CS where KM data or hazard functions are presented (Figures 16 to 37) so that the EAG can ensure these are properly labelled if they are reproduced in the EAG report.

Please see the cohort information for each figure in the table below.

Table 64: Summary of cohort information for CS Figures 16 to 37

Figure number in CS	Population cohort
16	Global CPS≥1
17	Global CPS≥1
18	Global CPS≥1
19	Global CPS≥1
20	Global CPS≥1 SoC arm
21	Global CPS≥1
22	Global CPS≥1
23	Global CPS≥1 SoC arm
24	Global CPS≥1
25	Global CPS≥1
26	Global CPS≥1
27	Global CPS≥1
28	Global CPS≥1 SoC arm
29	Global CPS≥1
30	Global CPS≥1
31	Global CPS≥1 SoC arm
32	Global CPS≥1
33	Global CPS≥1
34	Global CPS≥1
35	Global CPS≥1
36	Global CPS≥1

C5. The “drop_util_PF_resp” control does not appear to have any impact on the results. Please clarify if this control parameter is redundant

This control is redundant.

[i]**References**

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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.

About you

1.Your name	[redacted]
2. Name of organisation	Guts UK Charity
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Guts UK are a charity that fundraises for research and provides information to help people manage diseases and conditions affecting the digestive tract, liver and pancreas. The charities mission is to • Provide expert information: Information is power! When armed with information, patients can take control of their health and make informed decisions. We do this by information leaflets sent to patients and sold to hospitals, our website and social media accounts. Guts UK also produce a biannual magazine. • Raise public awareness: Guts UK research shows that 58% of people are embarrassed to talk about their digestive condition or symptoms. 51% of people delay seeking advice for their symptoms for over 6 months. When the Guts UK roadshow comes to town, we empower people to seek help. We also fund science of digestion events to increase knowledge. Fund life-changing & life-saving research: Guts UK is the only UK charity funding research into the digestive system from top to tail. It's time the UK got to grips with guts!
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	To be fully transparent with this process Guts UK are founder members of the Less Survivable Cancers Taskforce (LSCT) and whilst Guts UK have not received any direct funding from the manufacturers in the last 12 months LSCT may have. As LSCT is a separate concern no details of funding amounts can be provided as this is commercially sensitive information.

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO
5. How did you gather information about the experiences of patients and carers to include in your submission?	We asked within support groups for people living with oesophageal cancer and cancer between the stomach and gullet (gastro-oesophageal junction) to get in touch to share their story of living with or caring for someone diagnosed with these cancers. Understandably, it is difficult for people to input time into submissions with advanced cancer, so we also searched for qualitative studies for quality of life and life experience of people diagnosed with these cancers to understand their experience. We also interviewed support group leaders who help people living with oesophageal cancers and have lived experience themselves. We have a Expert by Experience (EBE) Panel which have two members on it that have gone through oesophageal cancer.

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?	Oesophageal cancer are two of the six less survivable cancers, for which there are no screening tools to identify them that are widely used, and as early symptoms are vague, people are frequently diagnosed late, when treatment options are limited. The chance of surviving beyond five years with oesophageal cancer is approximately 15 out of 100 people diagnosed. Often patients and their families have limited time together, as many as 7 in 10 (Humphreys E et al 2020) people are diagnosed at a stage (III or IV) when it has spread to the lymph nodes and has spread to nearby organs and distant body sites. Larsen et al (2020) reported "patients with oesophageal cancer are putting their ordinary lives on hold and experiencing the meal as a battleground during treatment. Patients strive to maintain autonomy, gain control, and take ownership and their suffering was associated with symptoms and side effects of treatment, which affect their and their relatives' social world and relationships." For people with oesophageal cancer swallowing problems can be severe even at times people are unable to swallow their own saliva and this is associated with pain, reflux and indigestion. These symptoms severely affect quality of life, lead to weight loss and fatigue. Not only does eating provoke symptoms but the diet can significantly change not only in texture but food choices are affected by the side effects of treatment. People with cancer also may have a feeding tube and if the cancer is not curable a stent to open the oesophagus and help with swallowing. Fatigue is a major symptom that people with these cancers experience. When I was told, 'You'll feel a bit of fatigue,' you automatically think, 'Ah yeah, so I'll feel a bit tired.' But fatigue is totally different—you have to explain that it's a total knackered—all over. And you haven't done anything, but suddenly you're knackered and you don't know why. And it plays on your mind, where you're saying, 'What's gone wrong now that I'm suddenly like this?' (Bennett et al 2020.) Symptoms have wider impact on quality of life and will affect social activities such as eating with family, enjoyment of food and attending social events. Sharing food and meal provision is an important aspect of family care provision and loss of weight and inability to enjoy meals is often distressing to both the person with cancer and their families and carers. Often people can manage only small portions of food or fluids, if any, and this impacts on eating out as some facilities will that people living with these cancers enjoy time with their family and controlling tumour progression can help people to participate.

	Non curative treatments are difficult to tolerate alongside physically debilitating symptoms make it impossible to continue working or take part in social events for some people. Awareness of a poor prognosis and the demanding treatment pathways triggered psychological distress, as patients gave expressions of their feelings of vulnerability. (Larson 2020) not cater for those requirements – some people do not want to make a fuss, so don't go out. With limited lifespan it is extremely important Bennett AE, O'Neill L, Connolly D, et al. Perspectives of Esophageal Cancer Survivors on Diagnosis, Treatment, and Recovery. *Cancers (Basel)*. 2020;13(1):100. Published 2020 Dec 31. doi:10.3390/cancers13010100 Larsen MK, Schultz H, Mortensen MB, Birkelund R. Patients' Experiences With Illness, Treatment, and Decision-Making for Esophageal Cancer: A Qualitative Study in a Danish Hospital Setting. *Glob Qual Nurs Res*. 2020;7:2333393620935098. Published 2020 Jun 29. doi:10.1177/2333393620935098

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments are challenging to experience, and they are not always effective. People with cancer feel that the treatment schedule constantly interrupts their normal everyday life and this is particularly true of chemotherapy (Larsen et al 2020). Decision making regarding treatment can be a burden for some people with respect to complexity of the treatment and side effects, people often have not heard the medical terminology and people will often defer decisions about treatment to their healthcare practitioners (Larsen et al 2020)
8. Is there an unmet need for patients with this condition?	There are few effective treatments for these cancers that are available so yes there is an unmet need. There are relatively few options in advanced disease and is usually chemotherapy, radiotherapy or a combination of both. Patients are wanting more options as the disease is complex, its not a one treatment fits all.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients are wanting as many options as possible, they are very aware of survival ratio's and know that one type of treatment doesn't fit all. It is very important to them that there are alternatives or additional treatments. The additional treatment does not impact on current chemotherapy treatment time as it is given consecutively with chemotherapy.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients don't believe that there is any disadvantages, they are aware of potential side effects The additional treatment does not change treatment time as it is given consecutively with current treatment.

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.	All groups of people will benefit from this treatment. Some however due to age, fitness and other underlining comorbidities might suffer from different side effects.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	It might be challenging for hard-to-reach community groups to access information due to language barriers. Inequalities may be particularly true of squamous cell carcinoma as there is an increased risk of this cancer with traditional use in some cultures of areca nut. Culture may also play a part as some cultures may be reluctant to visit their GP or be registered. Also, inequalities in health in respect to cancer mean that people from the most deprived areas are more likely to be diagnosed later as people have reduced ability and opportunity to access healthcare. This is particularly true of oesophageal cancer.

Other issues

13. Are there any other issues that you would like the committee to consider?	Yes, these cancers are difficult for GPs to identify or suspect symptoms of cancer at an early stage so often diagnosis is not made until the cancer has progressed. Quality of life vs treatment all depends on the patient's functional fitness and nutritional status, ability to eat or if they are using a feeding tube. Family/carers want answers and treatments which puts pressure on the patient to try additional treatments.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• These cancers are less survivable cancers, for which there are no screening tools to identify them which, so they are frequently diagnosed late, when the treatment options are limited. • People with lived experience of these cancers strive to maintain fitness and gain control of their situation and their suffering is associated with symptoms and treatment side effects, which massively affects their quality of life, social experience and relationships with family and carers. • With a life limited condition, it is extremely important that people living with these cancers enjoy time with their family and this treatment could help people participate and provide them with valuable time. • This treatment works by a different mechanism and offers another option for treatment where there are currently few options available. • Patient's family/carers will always look for hope in new treatments, or trials for themselves and others.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer. A Single Technology Appraisal

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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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

Sarah Davis and Andrew Metry critiqued the health economic analysis submitted by the company. Emma Simpson summarised and critiqued the clinical effectiveness data reported within the company's submission. Shijie Ren and Sarah Ren critiqued the statistical aspects of the submission. Ruth Wong critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report.

CONTENTS

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ABBREVIATIONS

5-FU	Fluorouracil
AEs	Adverse events
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formulary
BSA	Body Surface Area
CAPOX	Capecitabine and oxaliplatin doublet chemotherapy
CEAC	Cost-Effectiveness Acceptability Curve
cLDA	Constrained longitudinal data analysis
CMU	Commercial medicines unit
CPS	Combined positive score
CR	Complete response
CS	Company Submission
CSR	Clinical study report
CT	Computerised tomography
DOR	Duration of response
DSU	Decision Support Unit
eMIT	electronic Market Information Tool
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
EQ-5D-3L	EuroQol 5 dimensions 3 level
EQ-5D-5L	EuroQol 5 dimensions 5 level
EQ-VAS	EuroQol 5 dimensions Visual Analogue Scale
EAG	External Assessment Group
ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
FISH	Fluorescent in-situ hybridization
FOLFOX	Fluorouracil and oxaliplatin doublet chemotherapy
FOLFIRI	Irinotecan with 5-FU and folinic acid
FP	Fluorouracil and cisplatin doublet chemotherapy

GOJ	Gastro-Oesophageal Junction Cancer
HCHS	Hospital & community health services
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
HRG	Health resource group
HRQoL	Health-Related Quality of Life
HTA	Health Technology Appraisal
IA	Interim analysis
ICER	Incremental Cost Effectiveness Ratio
IHC	Immunohistochemistry
ITT	Intention to treat
IV	Intravenously
KM	Kaplan-Meier
LSMean	Least square mean
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MUGA	Multigated acquisition scan
NICE	National Institute for Health and Care Excellence
NG83	NICE's guideline 83 on assessment and management in adults with oesophago-gastric cancer
NHS	National Health Service
NHSCII	NHS Cost Inflation Index
NR	Not Reported
ORR	Overall Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD-L1	Programmed death-ligand-1
PET	Positron emission tomography
PFS	Progression-Free Survival
PR	Partial response
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
Q3W	Every three weeks
QALY	Quality-Adjusted Life Year

RECIST	Response Evaluation Criteria In Solid Tumours
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
SAE	Serious adverse events
SLR	Systematic Literature Review
SoC	Standard of care
SOX	S-1 and oxaliplatin doublet chemotherapy
STA	Single Technology Appraisal
TA	Technology Appraisal
TA208	Technology Appraisal of trastuzumab for the treatment of HER2-positive metastatic gastric cancer
TA378	Technology Appraisal of ramucirumab for treating advanced gastric cancer or GOJ adenocarcinoma previously treated with chemotherapy
TA737	Technology Appraisal of pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated advanced oesophageal and gastro-oesophageal junction cancer
TA852	Technology Appraisal of Trifluridine–tipiracil for treating metastatic gastric cancer or GOJ adenocarcinoma after 2 or more treatments
TSD	Technical Support Document
TTD	Time To Treatment Discontinuation
TWiST	Time without symptoms or toxicity
UK	United Kingdom
WHO	World Health Organisation
XP	Capecitabine and cisplatin doublet chemotherapy

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making in its review of the company submission (CS) for the appraisal of pembrolizumab in combination with trastuzumab and chemotherapy for the treatment of adult patients with previously untreated locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) positive gastric or gastro-oesophageal junction (GOJ) adenocarcinoma whose tumours express programmed death-ligand-1 (PD-L1) with a combined positive score (CPS) ≥ 1. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) for the comparison of pembrolizumab in combination with trastuzumab and chemotherapy against the current standard of care (SoC) which is trastuzumab and chemotherapy.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail and Section 1.7 provides a summary of the EAG's preferred assumptions and its base case ICER. Background information on the condition, technology, evidence used and information on non-key issues are in the main EAG report.

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 Summary of the key issues identified in the EAG critique

ID3742	Summary of issue	Report sections
1	The use of a *post hoc* analysis of the non-Asia cohort which excluded data from the Asia region, but combined data from two other regions	3.2.3 and 4.3.3.1
2	Method used to extrapolate overall survival (OS) and progression-free survival (PFS) in the economic model by applying a hazard ratio (HR) from the non-Asia (CPS ≥1) cohort to parametric curves fitted to the comparator (SoC) arm of the global (CPS ≥1) cohort	4.3.3.2, 4.4.2.2 & 4.4.2.3
3	Utilities based on time-to-death rather than using utilities based on progression status (i.e., progressed disease versus progression-free)	4.3.3.4
4	Severity modifier is not based on the expected quality-adjusted life-years (QALYs) predicted by the company's cost-effectiveness analysis because this incorporates data from the Asia cohort which the company considers not generalisable to England	5

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the EAG's approach to modelling OS and PFS using curves fitted separately to the intervention (pembrolizumab plus SoC) and comparator (SoC) arms of Kaplan-Meier data (KM) from the non-Asia (CPS≥1) cohort. In comparison, the company used parametric curves fitted to data to the comparator arm of the global (CPS≥1) cohort to model OS and PFS for SoC and then applied a HR from the non-Asia (CPS≥1) cohort to estimate OS and PFS for pembrolizumab plus SoC.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (OS) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing survival which also increases the time spent in health states with higher quality of life as quality of life is related to time-to-death in the model
- Marginally reducing quality of life at the beginning of treatment due to adverse events (AEs).

Overall, the technology is modelled to affect costs by:

- Increasing the costs required for drug acquisition and administration
- Increasing disease management costs, mainly by extending the period of PFS
- Marginally increasing costs required to manage AEs and provide subsequent treatment
- Marginally reducing end-of-life costs.

The modelling assumptions that have the greatest effect on the ICER are:

- Whether the data from the non-Asia region or the global cohort are used to model OS for SoC
- Whether OS for pembrolizumab plus SoC is modelled by fitting parametric curves to the data from the intervention arm of the KEYNOTE-811 study or by applying a HR to the curve fitted to the global cohort SoC arm
- The choice of parametric curves used to extrapolate OS and PFS
- The assumption that time-to-death rather than progression status best predicts quality of life.

1.3 The decision problem: summary of the EAG's key issues

The EAG did not have any key issues related to the decision problem, however, it wishes to briefly highlight several discrepancies between the decision problem addressed in the CS and that specified in the NICE scope which are further described in Section 2.

Firstly, in the pivotal KEYNOTE-811 study, which forms the primary evidence supporting the license, only a minority of patients in the SoC arm received a platinum–fluoropyrimidine doublet chemotherapy regimen that is compatible with the NICE recommendation for trastuzumab with chemotherapy (TA208) in this patient population. The company considers that all doublet chemotherapies which combine a platinum-containing agent with a fluoropyrimidine are clinically equivalent. The EAG's clinical experts considered this assumption to be broadly acceptable and for this reason the EAG does not consider this discrepancy to be a key issue.

Secondly, in TA208, trastuzumab is recommended in combination with chemotherapy for patients with HER2-postitive metastatic gastric or GOJ adenocarcinoma, as the marketing authorisation for trastuzumab did not include patients with locally advanced disease. However, the CS assumes that patients with unresectable locally advanced disease are treated like patients with metastatic disease and a comparison against trastuzumab without chemotherapy has not been presented for patients with locally advanced disease. The EAG's clinical advisors stated that the distinction between unresectable locally advanced disease and metastatic disease cannot always be made without invasive investigations to identify peritoneal metastases, and they would therefore want to offer trastuzumab to any HER2-positive patients who are not suitable for perioperative chemotherapy and surgery. In addition, any patient who is contraindicated for trastuzumab would also be contraindicated for pembrolizumab in combination with trastuzumab and chemotherapy. For these reasons, the lack of a comparison against doublet chemotherapy without trastuzumab is not considered a key issue.

Thirdly, the CS does not provide a comparison against triplet chemotherapy (i.e., a platinum–fluoropyrimidine chemotherapy with the addition of epirubicin). The EAG did not consider this to be a key issue because the EAG's clinical advisors stated that triplet chemotherapy is not usually used as a first-line palliative treatment in this patient population, as it is not thought to improve survival compared with offering doublet chemotherapy, but it does increase toxicity.

Finally, the CS focuses on data from the population with PD-L1 CPS $\geq$ 1 as this is in line with the anticipated marketing authorisation. The EAG considers this to be broadly acceptable as the CPS $\geq$ 1 group was a pre-specified subgroup and CPS status (i.e. 0 or $\geq$ 1) was a stratification factor for randomisation. The CS assumes that tests to determine PD-L1 status are already part of routine care in the NHS in England for this population because PD-L1 CPS score is used to determine eligibility for other treatments already recommended by NICE in the HER2-ngative subgroup and PD-L1 testing is undertaken concurrently with HER2 testing to avoid delays.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 The use of a *post hoc* analysis to define the non-Asia cohort

Report section	3.2.4 and 4.3.3.1
Description of issue and why the EAG has identified it as important	The company claims that data from the Asia region are not generalisable to England as screening programmes for gastric cancer are common in many Asia region countries, but screening is not routinely performed in England. The company's cost-effectiveness analysis is informed by a HR from the non-Asia (CPS≥1) cohort which was generated in a *post hoc* analysis by combining data from the other two regions (Western Europe/Israel/North America/Australia cohort and Rest of the World cohort) for patients with CPS≥1. The EAG questions the validity of such a subgroup analysis (Asia vs. non-Asia) due to the *post hoc* nature.
What alternative approach has the EAG suggested?	The EAG agrees with excluding the Asia (CPS≥1) cohort but considers that the Western Europe/Israel/North America/Australia (CPS≥1) cohort may be more applicable to clinical practice in England and was a pre-specified subgroup and stratification factor.
What is the expected effect on the cost-effectiveness estimates?	Including data from the Rest of World (CPS≥1) cohort provides more favourable estimates for both OS and PFS. An increase in the ICER is expected using data from only the Western Europe/Israel/North America/Australia (CPS≥1) cohort.
What additional evidence or analyses might help to resolve this key issue?	Using data from the Western Europe/Israel/North America/Australia (in CPS ≥ 1) cohort only as a scenario analysis in cost-effectiveness modelling.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

Only those issues identified in the EAG's critique of the economic modelling which have an important impact on ICER, or are otherwise expected to materially impact on the conclusions regarding the cost-effectiveness of pembrolizumab plus SoC compared to SoC, are discussed in Section 1.5. A full discussion of the main issues identified in the EAG's critique of the company's economic analysis can be found in Section 4.3, including those factors which were found to have a more modest impact on the ICER in the EAG's exploratory analyses described in Section 4.4. Any ICERs discussed in this Section are those generated without applying any QALY weighting for severity.

Issue 2 Method used to extrapolate OS and PFS

Report section	4.2.6.1, 4.3.3.2, 4.4.2.2 & 4.4.2.3
Description of issue and why the EAG has identified it as important	The company used a proportional hazards modelling approach to extrapolate OS and PFS. A parametric survival model was fitted to the KM data for the comparator arm of the global (CPS≥1) cohort, and a HR estimate obtained from the non-Asia (CPS≥1) cohort was then applied to the extrapolated control arm to estimate the survival in the intervention arm. The use of OS and PFS data from the global (CPS≥1) cohort to extrapolate OS and PFS for the control arm contradicts the company's position that the non-Asia (CPS≥1) cohort is considered the most generalisable to the eligible population in England. The company's extrapolated curve for the intervention arm for both OS and PFS does not fit the intervention arm data from the non-Asia (CPS≥1) cohort.
What alternative approach has the EAG suggested?	Modelling OS and PFS using models fitted independently to the intervention and comparator arms of KM from the non-Asia (CPS≥1) cohort.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analysis which uses OS curves fitted independently to both arms of the non-Asia (CPS≥1) cohort substantially increased the ICER from £[redacted] to £[redacted] per QALY. The analysis using the EAG's preferred approach for PFS had a smaller impact and decreased the ICER to £[redacted] per QALY. However, these analyses combined both the EAG's preference for using the non-Asia (CPS≥1) cohort to model the OS and PFS in the comparator arm and the EAG's preference to model the intervention arm separately instead of using a HR approach. The choice of data used to model OS in the comparator arm is expected to be the main driver of change in the ICER.
What additional evidence or analyses might help to resolve this key issue?	The EAG suggests that the company should also explore the use of OS and PFS data based on the Western Europe/Israel/North America/Australia (CPS ≥ 1) cohort as per Issue 1.

Issue 3 Utility analysis

Report section	4.2.6.2 & 4.3.3.4
Description of issue and why the EAG has identified it as important	Utility data used in the company's base case were based on the non-Asia (CPS≥1) cohort. Utility values were estimated based on a time-to-death approach with four categorical groups (<30 days; 30 to 179 days; 180 to 359 days, and ≥360 days) using descriptive statistics. The EAG considers that there is considerable 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, and the company's estimated utility values lack face validity as the values for patients with a time-to-death >360 days are very similar to the age-adjusted utility values expected for the general population.
What alternative approach has the EAG suggested?	Analysing utility data using a linear mixed effect regression model for both time-to-death and progression-based approaches.
What is the expected effect on the cost-effectiveness estimates?	Using the time-to-death utility estimates from the linear mixed effect regression increased the ICER from £[redacted] to £[redacted] per QALY when applying these to the company's base case analysis. The ICER for the EAG's preferred base case scenario increased from £[redacted] to £[redacted] per QALY when switching from the time-to-death utilities to the progression-based utilities but still using the linear mixed effect regression approach.
What additional evidence or analyses might help to resolve this key issue?	The EAG suggests that the company should also explore using utility data from the Western Europe/Israel/North America/Australia (CPS ≥ 1) cohort as per Issue 1.

1.6 Other key issues: summary of the EAG's view

Issue 4 Severity modifier

Report section	Section 5
Description of issue and why the EAG has identified it as important	The company has applied a QALY weighting of 1.2 in its base case. The estimate of expected lifetime QALYs from the company's model for patients receiving current SoC provides estimates of absolute and proportional QALY shortfall, compared to age and sex matched members of the general population without gastric or GOJ cancer, which would support a QALY weighting of 1.0. However, the company argues that the estimate of expected lifetime QALYs in the SoC arm of the model is unrealistic because it is based on OS data that includes patients from the Asia region who have higher survival and which the company considers is not generalisable to clinical practice in England due to the widespread use of gastric cancer screening in Asia region countries. The company therefore prefers to use an estimate of the expected lifetime QALYs under current SoC from the appraisal of trastuzumab in combination with chemotherapy (TA208) which would support a QALY weighting of 1.2. The EAG argues that if the OS and PFS data from the Asia (CPS≥1) region are not considered generalisable to England, then the company should use data from the non-Asia (CPS≥1) region to estimate OS and PFS under SoC, but for consistency, these data should also be used to inform the QALYs used to estimate the ICERs in the cost-effectiveness analysis (see Issue 2).
What alternative approach has the EAG suggested?	The estimate of expected lifetime QALYs for the SoC arm from the EAG's preferred base case scenario is lower than predicted by the company's base case because the EAG has used data from the non-Asia (CPS≥1) cohort to estimate OS and PFS in the SoC arm. The estimate from the EAG's preferred base case would support a QALY multiplier of 1.2.
What is the expected effect on the cost-effectiveness estimates?	The committee's judgement regarding the cost-effectiveness of pembrolizumab plus SoC compared to SoC alone is dependent on both the ICER and the choice of QALY weight. These are both dependent on whether data from the non-Asia (CPS≥1) cohort are considered more generalisable to clinical practice in England than the data from the global (CPS≥1) cohort which include patients recruited in the Asia region.
What additional evidence or analyses might help to resolve this key issue?	The EAG suggests that the company should also explore what QALY weight would be supported by analyses using data from Western Europe/Israel/North America/Australia (CPS ≥ 1) cohort.

1.7 Summary of EAG's preferred assumptions and resulting ICER

A summary of the EAG's exploratory analyses is provided in Table 2. Each of the individual changes included in the EAG's preferred base case is presented as a single change applied to the company's base case model. The EAG's preferred base case, which combines all of these changes, is then presented. This is followed by scenario analyses which use the EAG's preferred base case as their starting point. All of the results presented have been generated using the deterministic model, with the exception of the EAG's preferred base case for which both deterministic and probabilistic results are provided. Full details on the methods used in EAG of the analyses conducted by the EAG is provided in Section 4.4.2. These results include the company's patient access scheme (PAS) price for pembrolizumab but do not include any confidential PAS prices or confidential prices from the commercial medicines unit (CMU) for any other drugs. These can be found in the confidential appendix. All ICERs discussed in the text below are those generated without a QALY weighting for severity. For reference, ICERs are provided in Table 2 both without a QALY weighting and when using a QALY weighting of 1.2.

The EAG's preferred estimate of the ICER is £[redacted] per QALY (£[redacted] when the probabilistic analysis). This is substantially higher than the company's base case estimate of £[redacted] per QALY (£[redacted] when using the probabilistic analysis). The main reason for this difference is that the EAG's preferred approach to modelling OS used parametric survival curves fitted to each arm of the KM data from the non-Asia (CPS≥1) cohort, whereas the company used data from the global (CPS≥1) cohort to estimate OS in the SoC arm, including data from the Asia region where OS survival was higher. The company then estimated OS in the pembrolizumab plus SoC arm by applying a HR from the non-Asia (CPS≥1) cohort to the parametric curve fitted to the SoC arm of the global (CPS≥1) cohort. The EAG's scenario analysis provide an ICER that ranges from £[redacted] to £[redacted] per QALY. The lower range is provided by a scenario applying alternative parametric survival curves (log-logistic for both PFS and OS) still fitted independently to each arm of the non-Asia (CPS≥1) cohort. The upper range is provided by the scenario using progression-based rather than time-to-death based utilities.

Table 2 Summary of the results of the EAG's exploratory analyses

Option	LYs	QALYs	Costs	Incremental		ICER (QALY weight x1)	ICER (QALY weight x1.2)
				QALYs	Costs		
Company base case – post-clarification							
SoC*	3.03	[redacted]	[redacted]	-	-		
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: correcting programming and implementation errors in the company's economic model							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Using the EAG's preferred survival extrapolation for OS							
SoC*	1.59	[redacted]	[redacted]	-	-	-	-
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Using the EAG's preferred survival extrapolation for PFS							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Removing the cap for TTD of trastuzumab							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Applying lower administration costs for trastuzumab when administered without pembrolizumab							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: Assuming subsequent therapy to include only taxanes and applying that to only a proportion of PFS events who get progressed (25% get paclitaxel and 25% get docetaxel)							
SoC*	3.03	[redacted]	[redacted]	-	-		
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 7: Limiting outpatient visits to 6 weekly after chemotherapy and adding CT scans 4 times per annum for patients on PFS							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 8: Increasing outpatient visits and CT scans to 4 times per annum for patients with progressed disease							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 9: Time-to-death utilities estimated using a linear mixed effects model							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Option	LYs	QALYs	Costs	Incremental		ICER (QALY weight x1)	ICER (QALY weight x1.2)
				QALYs	Costs		
EAG preferred base case scenario							
EAG base case applying analyses 1-9 (Deterministic)							
SoC*	1.59	[redacted]	[redacted]	-	-	-	-
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-9 (Probabilistic)							
SoC*	1.61	[redacted]	[redacted]	-	-	-	-
Intervention**	2.21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario analyses applying individual changes to the EAG base case							
EAG scenario 1 (Assuming a log-logistic curve for OS and PFS extrapolations)							
SoC*	1.84	[redacted]	[redacted]	-	-		
Intervention**	2.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (Using restricted mean duration to estimate costs for first-line chemotherapy)							
SoC*	1.59	[redacted]	[redacted]	-	-	-	-
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (Reducing the cap applied to TTD of first-line chemotherapy to 4 cycles)							
SoC*	1.59	[redacted]	[redacted]	-	-		
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (Using utility values based on progression status)							
SoC*	1.59	[redacted]	[redacted]	-	-		
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Assuming 100% of doublet chemotherapy is with XP)							
SoC*	1.59	[redacted]	[redacted]	-	-		
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CT – computerised tomography; EAG – external assessment group, ICER – incremental cost-effectiveness ratio; LYs - life-years; OS – overall survival, PFS – progression-free survival, QALYs - quality-adjusted life-years; TTD – time to treatment discontinuation; XP - cisplatin with capecitabine

** SoC: Trastuzumab plus chemotherapy*

*** Intervention: Pembrolizumab with SoC*

2 BACKGROUND

This section presents a brief summary and critique of the company's description of locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma which is classed as human epidermal growth factor receptor 2 (HER2) positive and the current treatment pathway in England for this disease. This is followed by a critique of the decision problem addressed in the company submission (CS).[1]

2.1 Critique of company's description of underlying health problem

The External Assessment Group (EAG) is broadly satisfied with the company's description of the underlying health problem. The CS (Section B.1.3)[1] describes gastric cancer as the fifth most common cancer worldwide, accounting for 2% of all new cancers in the United Kingdom (UK).[2, 3] Approximately half of all cases of gastric cancers are diagnosed in people aged 75 and over.[3] Gastric cancers are generally classified into those occurring where the oesophagus meets the stomach, referred to in the CS as cancers of the gastro-oesophageal junction (GOJ), and those arising elsewhere in the stomach, which the CS refers to as gastric cancer.[1] Adenocarcinomas, which are the type of gastric and GOJ cancer addressed in the CS, are the most common histological subgroup of gastric, GOJ and oesophageal cancer.[4] In addition to adenocarcinomas, there are other types of cancer which can occur in the stomach (for example gastrointestinal stromal tumours, neuroendocrine tumours, lymphomas), but these fall outside of the scope of this appraisal. The CS uses the Laurén classification, which is commonly used in clinical trials, and which categorises adenocarcinomas into four types: intestinal type, diffuse type, indeterminate type and unclassified type.[1, 5]

The CS describes the staging of cancer as dependent on whether the cancer is localised to the stomach (stage 1) or has spread beyond the stomach.[1] Locally advanced disease (stage 2 or 3) is when the cancer has spread to the surrounding tissues. The treatment for locally advanced disease is usually surgery to remove the affected area, which is described as surgical resection. However, in some cases this is not possible and then the disease is classified as unresectable locally advanced disease. If the cancer has spread beyond the stomach and surrounding tissues to the abdominal lining (peritoneum), bones or other organs, this is described as metastatic disease (stage 4). The proportion of patients diagnosed with metastatic disease was 44.9% in 2020/21.[6] The focus of the CS is on patients with unresectable locally advanced disease or metastatic disease, who have a poorer prognosis than those who can be treated by surgical resection.[1, 7] The EAG's clinical advisors stated that in practice the distinction between unresectable locally advanced and metastatic disease is not always easy to make as those classified as having unresectable locally advanced disease may also have undetected peritoneal metastases. Invasive investigations to distinguish metastatic from locally advanced disease, such as laparoscopy to identify peritoneal metastases, are only recommended if they will help guide ongoing management[8], and are

therefore not undertaken if the patient has already been deemed not suitable for perioperative chemotherapy and surgery and the decision has been made to offer first-line palliative chemotherapy.

The CS states that gastric and GOJ cancers are often diagnosed when the disease is as at an advanced stage, with 60% of people not eligible for curative treatment due to late presentation or comorbidities.[9] This is partly because the common symptoms - indigestion, poor appetite, weight loss, abdominal pain, and difficulty swallowing - can be vague, absent or not recognised as being potentially indicative of a serious health condition such as cancer.[1]

2.2 Critique of company's overview of current service provision

The CS describes the current treatment pathway for patients with locally advanced unresectable or metastatic gastric or GOJ HER2-positive adenocarcinoma, which is the population specified in the NICE scope. The treatment pathway for gastric cancer and the company's proposed positioning of pembrolizumab within the pathway is summarised in Figure 1. The CS states that there is currently no national screening programme for gastric cancer.[1] It describes palliative chemotherapy as being the first-line treatment for people with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and no significant comorbidities. CS, Figure 2 (reproduced here as Figure 1)[1] highlights TA208 which recommends trastuzumab in combination with cisplatin and capecitabine or 5-fluorouracil as a treatment option for people with HER2-positive metastatic adenocarcinoma of the stomach or GOJ.[10] It also highlights TA191 which recommends capecitabine in combination with a platinum-based regimens for the first-line treatment of inoperable gastric cancer.[11]

The CS mentions NICE's guideline 83 on assessment and management in adults with oesophago-gastric cancer (NG83),[8] which recommends doublet chemotherapy as an option for first-line palliative combination chemotherapy.[1] However, rather than describing all the possible platinum–fluoropyrimidine doublet chemotherapy combinations that are possible under NG83, the company's description of the current treatment pathway (CS, pages 20-21) focuses on those doublet chemotherapy options that are recommended in combination with trastuzumab within TA208.[1] Those are cisplatin plus capecitabine (referred to as XP in the CS, where X is capecitabine and P is cisplatin) and cisplatin plus fluorouracil (referred to as FP in the CS, where F refers to the fluorouracil component - sometimes abbreviated to 5-FU). However, these are only two of the four possible platinum–fluoropyrimidine doublet chemotherapy options available. For clarity, the EAG has provided Table 3, which summarises the possible platinum–fluoropyrimidine doublet chemotherapy options available under NG83.[8] These also include capecitabine plus oxaliplatin (referred to as CAPOX in the submission) or oxaliplatin plus 5-FU, which is usually accompanied by folinic acid (referred to as FOLFOX in the submission). The CS states that, "*ESMO [European Society for Medical Oncology] guidelines and clinical opinion suggest that doublet chemotherapies (cisplatin and oxaliplatin; 5FU and capecitabine) are clinically*

equivalent[12, 13].”[1] The EAG’s clinical advisors agreed that there was no strong evidence to suggest that one particular doublet chemotherapy combination was more clinically effective than another. However, they stated that capecitabine, which is an oral treatment, was generally preferred to 5-FU which needs to be given intravenously over an extended period. The exception was when patients were unable to swallow oral medication, in which case 5-FU was a useful alternative. In addition, oxaliplatin was generally considered to have a better side-effect profile than cisplatin but clinicians in England were restricted by TA208 to using cisplatin when giving chemotherapy alongside trastuzumab.

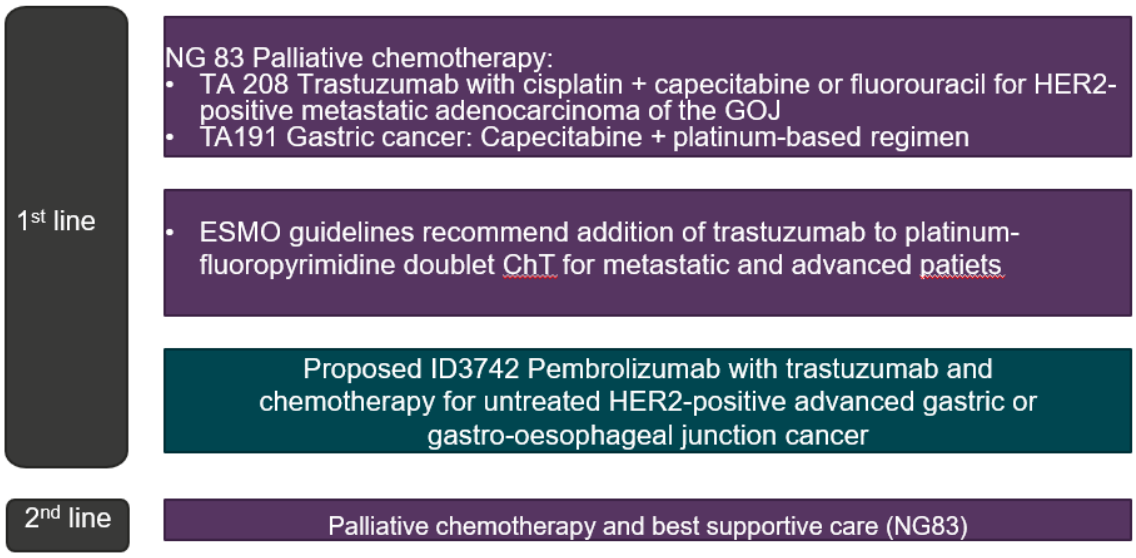
The CS also states that the ESMO guidelines recommend platinum–fluoropyrimidine doublet chemotherapy with trastuzumab as a standard of care in patients with advanced metastatic HER2-positive gastric cancer or GOJ adenocarcinoma.[1, 7] The company’s description of current practice in CS, Section B.1 does not highlight the fact that the wording in TA208 specifically states that trastuzumab with chemotherapy is recommended for metastatic cancer.[1,10] Instead, the CS highlights that treatment of locally advanced patients with unresectable disease is similar in clinical practice to those with metastatic disease (CS, pages 73 & 75).[1] The EAG’s clinical advisors agreed that they would want to use trastuzumab in HER2-positive patients regardless of whether the patient’s disease was classified as metastatic disease or unresectable locally advanced disease, given that the distinction between the two may not be clear when there may be undetected peritoneal metastases and they would expect a similar treatment response. The EAG’s clinical advisors also stated that there is a small group of patients HER2-positive disease, in whom trastuzumab may be contraindicated, usually due to cardiac comorbidities. Doublet chemotherapy without trastuzumab would be an option in some of these patients, provided they are not also contraindicated for chemotherapy. However, the EAG notes that any patient who is ineligible for trastuzumab would also not be eligible for pembrolizumab given in combination with trastuzumab and chemotherapy.

The EAG notes that NG83 recommends both doublet and triplet chemotherapy regimens as options for first-line palliative combination chemotherapy in people with advanced oesophago-gastric cancer.[8] Triplet chemotherapy as defined within NG83 comprises of epirubicin in combination with doublet chemotherapy (see Table 3).[8] However, the CS states that triplet chemotherapy regimens, “*do not have a role in treating HER2 positive metastatic or locally advanced GC [gastric cancer] or GOJ adenocarcinoma due to increased toxicity and lack of added clinical effect*.” The EAG’s clinical advisors stated that in current practice in England, triplet chemotherapy was not usually used as a first-line palliative treatment in patients with metastatic or locally unresectable advanced disease, despite being an option under NG83. This is because it is not thought to improve survival compared with offering doublet chemotherapy, but it does increase toxicity. The clinical advisors said that it is sometimes used in a small minority of patients with locally advanced disease with the aim of reducing tumour size to allow surgical resection, but that this is different from using it palliatively for those with

unresectable disease. However, the triplet chemotherapy combination recommended by ESMO in this downstaging neoadjuvant indication is a taxane containing regimen rather than the epirubicin containing triplet regimen recommended in NG83.[7, 8]

CS, Section B.1 does not specify doses or duration of treatment for any of the chemotherapy regimens that form part of the current standard treatment pathway.[1] The relevance of the treatment regimens received in the comparator arm of the pivotal KEYNOTE-811 study and the comparator treatments assumed in economic analysis to current clinical practice in discussed further in Sections 3 and 4 respectively.

Figure 1 Gastric cancer treatment pathway and proposed pembrolizumab positioning (reproduced from CS, Figure 2)[1]



Abbreviations: ChT, chemotherapy; ESMO, European Society of Medical Oncology; HER2, human epidermal growth factor receptor 2; GOJ, gastro-oesophageal junction

The CS states that HER2 testing and programmed death-ligand-1(PD-L1) testing have become part of routine care for patients with gastric and GOJ cancer,[1] because HER2 testing is necessary in order to determine whether patients are eligible for trastuzumab under TA208,[10] and PD-L1 testing is necessary to determine eligibility for nivolumab in patients with HER2-negative disease under TA857.[14] The EAG noted that PD-L1 testing would also be required in patients with HER2-negative GOJ cancer under TA737.[15] The EAG's clinical advisors agreed that testing for both HER2 and PD-L1 was standard clinical practice and both tests would be requested at the same time to expedite treatment, rather than PD-L1 testing being requested only in those who are HER2-negative. The current summary of produce characteristics (SmPC) for pembrolizumab states, "*when assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false*

positive determinations."[16] The EAG noted that the PD-L1 testing assay used in KEYNOTE-811 (PD-L1 1HC 22c3 pharmDx™),[17] was different from the assay used in CheckMate 649 (PD-L1 IHC 28-8 pharmDx™),[18] the main clinical trial considered in TA857. In the company's response to clarification question A4,[19] the company stated that both of these testing assays were used routinely in National Health Service (NHS) clinical practice and that published studies concluded that "*PD-L1 22C3 and 28-8 pharmDx assays were highly comparable at CPS cut-offs of 1, 10, and 50 in gastric cancer. These results provide evidence for the potential interchangeability of the two PD-L1 assays in gastric cancer".*[20] Based on this response, the EAG was satisfied that either assay could be used in clinical practice to assess suitability for pembrolizumab or nivolumab. The EAG also noted advice from clinical experts that some centres have access to only one assay, whereas other centres have access to multiple assays and clinicians may request both assays for patients with GOJ cancer.

Table 3 Summary of different treatment combinations for first-line treatment

Combination abbreviation	PD-L1 targeted therapy	HER2 targeted therapy	Doublet chemotherapy		Addition for triplet chemotherapy	NICE recommended	Included KEYNOTE -811	Included in model
			Platinum	Fluoro-pyrimidine				
Pembrolizumab & trastuzumab & XP	Pembrolizumab	Trastuzumab	Cisplatin	Capecitabine	NA	Subject of current appraisal [4]	No	Yes, as scenario
Pembrolizumab & trastuzumab & FP	Pembrolizumab	Trastuzumab	Cisplatin	5-FU	NA		Yes	Yes
Pembrolizumab & trastuzumab & CAPOX	Pembrolizumab	Trastuzumab	Oxaliplatin	Capecitabine	NA		Yes	Yes
Pembrolizumab trastuzumab & FOLFOX	Pembrolizumab	Trastuzumab	Oxaliplatin	5-FU	NA		No	No
Trastuzumab & XP	None	Trastuzumab	Cisplatin	Capecitabine	NA	TA208: Untreated HER2-positive metastatic cancer of stomach or GOJ[10]	No	Yes, as scenario
Trastuzumab & FP	None	Trastuzumab	Cisplatin	5-FU	NA		Yes	Yes
Trastuzumab & CAPOX	None	Trastuzumab	Oxaliplatin	Capecitabine	NA	No	Yes	Yes
Trastuzumab & FOLFOX	None	Trastuzumab	Oxaliplatin	5-FU	NA	No	No	No
XP	None	None	Cisplatin	Capecitabine	NA	NG83: Doublet chemotherapy as first-line palliative treatment of locally advanced or metastatic oesophago-gastric cancer[8]	No	No
FP	None	None	Cisplatin	5-FU	NA		No	No
CAPOX	None	None	Oxaliplatin	Capecitabine	NA		No	No
FOLFOX	None	None	Oxaliplatin	5-FU	NA		No	No
ECX	None	None	Cisplatin	Capecitabine	Epirubicin	NG83: Triplet chemotherapy as first-line palliative treatment of locally advanced or metastatic oesophago-gastric cancer[8]	No	No
ECF	None	None	Cisplatin	5-FU	Epirubicin		No	No
EOX	None	None	Oxaliplatin	Capecitabin	Epirubicin		No	No
EOF	None	None	Oxaliplatin	5-FU	Epirubicin		No	No

Abbreviations: 5-FU, fluorouracil; GOJ, Gastro-Oesophageal Junction Cancer; HER2, Human Epidermal Growth Factor Receptor; PD-L1, Programmed death-ligand-1

2.3 Critique of company's definition of the decision problem

2.3.1 Population

The population addressed in the CS is patients with previously untreated locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS)≥ 1 (CS, Table 1).[1] This is described by the company as being in-line with the proposed marketing authorisation.[17] The proposed indication is for first-line treatment, and the KEYNOTE-811 study, which forms the primary evidence supporting the license, was restricted to patients who have not had previous treatment for metastatic or locally advanced unresectable disease, but included those who had received prior neoadjuvant or adjuvant therapy completed at least 6 months prior to randomization provided there was no evidence of progression within that timeframe[21]. This specification of the population does not exclude patients who received adjuvant or neoadjuvant treatment for localised disease earlier in their treatment pathway. The proposed marketing authorisation in the draft SmPC is also restricted to adults as per the population specified in the NICE scope.[4, 17]

The NICE scope specified that subgroups should be considered according to whether the patient has metastatic disease or locally advanced disease.[4] The CS states that the subgroup with locally advanced unresectable disease was not a pre-specified subgroup in the KEYNOTE-811 study, and it makes up only 3% of the trial population (CS, Table 1).[1] For these reasons, the CS does not present results for the locally advanced subgroup, however, results are provided for a limited set of outcomes (PFS and OS) for the metastatic subgroup (CS, Appendix E).[1] The EAG's clinical advisors considered that this approach was reasonable given the small numbers of patients with unresectable locally advanced disease in the KEYNOTE-811 trial and the fact that they would expect them to respond similarly to the treatment. In addition, the EAG's clinical advisors stated that in practice the distinction between locally advanced unresectable and metastatic disease is not always easy to make as those classified as having locally advanced unresectable disease may also have undetected peritoneal metastases. The NICE scope did not specify that subgroup analyses should be considered for gastric versus GOJ cancer.[4] The EAG's clinical advisors noted that the distinction between gastric and GOJ cancer may not always be clear cut given that gastric cancer can spread to the GOJ. In addition, the distinction between gastric and GOJ cancer is more relevant when considering surgical treatment options and less relevant when considering first-line palliative chemotherapy options as the palliative management of gastric and GOJ cancer would be similar for patients with HER2-positive disease.

The NICE scope also specified that subgroup analyses should be provided by PD-L1 status, without specifying what level of PD-L1 expression should be used to categorise patients The CS focuses on presenting results for the subgroup with PD-L1 CPS ≥ 1 as this restriction is included in the anticipated marketing authorisation.[1, 4] The EAG considers that it is reasonable for the CS to present results for the CPS ≥ 1 subgroup as PD-L1 status (CPS 0 versus CPS ≥ 1) was used as a stratification factor for

randomisation.[21] The EAG notes that other CPS scores have been used to defined PD-L1 status in other indications for pembrolizumab. For example, in the pembrolizumab indication for HER2-negative GOJ cancer, treatment with pembrolizumab is restricted using a PD-L1 CPS cut-off score of 10.[16] This was because a more pronounced treatment benefit was demonstrated for CPS ≥ 10 than CPS <10, in the KEYNOTE-590 study, although it should be noted that PD-L1 status was not a stratification factor in that study.[22] The EAG noted that the study protocol for KEYNOTE-811 stated in its study rationale section that based on previous studies in advanced gastric cancer, pembrolizumab demonstrated a high level of tumour response regardless of PD-L1 status (KEYNOTE-811 protocol, page 37).[21] This may explain why patients with a PD-L1 CPS score of zero were included when pembrolizumab is known to specifically target PD-L1 receptors. Overall, the EAG is satisfied that the CS has focused on data from the CPS ≥ 1 subgroup, given that this is consistent with the anticipated marketing authorisation.

In the CS the company argues that data from patients recruited in the Asia region, where screening programmes for upper gastrointestinal cancer are more widespread, may not be as appliable to countries such as England which do not have a screening programme.[1] Therefore, the CS focusses on presenting data from the 'non-Asia' region. However, it should be noted that this relates to the country in which the patients were recruited and not to the race/ethnicity of the individual. A separate subgroup analysis for race is presented for Asian and non-Asian patients, but this subgroup is not a focus of the submission, and this subgroup analysis should not be confused with the subgroup analysis for the non-Asia region.

2.3.2 Intervention

The intervention given in the NICE scope is pembrolizumab in combination with trastuzumab and chemotherapy.[4] The draft SmPC is slightly more specific and states that pembrolizumab is indicated for use in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy.[17] The exact combinations of chemotherapy agents that pembrolizumab can be given with are discussed further under Section 2.3.3 where comparator treatments are described.

The dose of pembrolizumab specified in the draft SmPC is 200 mg by intravenous infusion on day 1 of a 3-week cycle or 400 mg by intravenous infusion given on day 1 of a 6-week cycle.[17] The draft SmPC states that pembrolizumab should be continued until [redacted]

The EAG notes that CS, Table 2 states that that the method of administration is 200 mg every 3 weeks up to a maximum duration of 35 cycles,[1] but [redacted].[17] Treatment duration in the KEYNOTE-811 trial was until disease progression or unacceptable toxicities, up to a maximum of 35 doses.[21] There was also the option for a second course of pembrolizumab (up to 17 cycles) in

KEYNOTE-811, but only in patients who met specific criteria and this was a rare occurrence (see Section 3.2.1.2).

2.3.3 Comparators

The comparator intervention addressed in the CS is described as trastuzumab with cisplatin plus capecitabine or fluorouracil (CS, Table 1).[1] The EAG notes that in TA208, trastuzumab is only recommended in combination with either XP or FP (see Table 3).[10] Therefore, the company's stated comparator contains the two doublet chemotherapy regimens that are most applicable to clinical practice in England. However, the comparator in the KEYNOTE-811 trial, which is they key source of evidence for the CS, only included CAPOX and FP, with a minority of patients receiving FP.[21] Also, the draft SmPC for pembrolizumab does not specify an exact combination of fluoropyrimidine and platinum-containing chemotherapy,[17] and therefore it could be interpreted as being indicated in combination with trastuzumab and any of the four possible doublet chemotherapy regimens, as shown in Table 3. The EAG also notes that various biosimilar versions of trastuzumab are now available and the EAG uses the term trastuzumab to refer to any medicine licensed as being biosimilar to the reference medicine for trastuzumab, which was Herceptin.

Doublet chemotherapy and triplet chemotherapy without trastuzumab are also included as comparators in the NICE scope,[4] but these are not addressed as comparators in the CS.[1] The company's rationale for excluding doublet chemotherapy without trastuzumab is that ESMO guidelines and clinical opinion suggest that locally advanced unresectable and metastatic gastric or GOJ adenocarcinoma are treated like metastatic disease.[1] The EAG considered that this was reasonable based on the advice from its clinical advisors (see Section 2.1 and 2.2) that it is not always possible to distinguish between metastatic and unresectable locally advanced disease due to the potential presence of undetected peritoneal metastases, and that they would want to offer trastuzumab to any HER2-positive patients. Although doublet chemotherapy treatment without trastuzumab may be offered when trastuzumab is contraindicated, any patient contraindicated for trastuzumab will also be contraindicated for pembrolizumab as this is given in combination with trastuzumab. Therefore, the group eligible for doublet chemotherapy is unlikely to be eligible for pembrolizumab under its proposed marketing authorisation and the EAG accept that it is reasonable for the company not to have provided a comparison against doublet chemotherapy. The EAG also accepts the company's rationale for excluding triplet chemotherapy (see Table 3 for examples of triplet chemotherapy) based on advice from its clinical advisors (see Section 2.2) that triplet chemotherapy is likely to increase toxicity without improving survival.

2.3.4 Outcomes

The CS states that it has addressed all outcomes specified in the NICE Scope (see Table 4).[1] The EAG agrees that the CS addresses both overall survival (OS) and progression-free survival (PFS). For the primary outcome in KEYNOTE-811, the progression component of PFS was reported by blinded independent central review (BICR) using Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 criteria.[1] PFS using investigator assessment of progression using a modified version of RECIST 1.1 for immune therapies (iRECIST) was an exploratory objective.[1] Response was reported using overall response rate (ORR) with ORR defined as the proportion having either complete or partial response. Adverse events (AEs) and health-related quality of life (HRQoL) were both addressed in the CS, however, the EAG noted that the reporting of HRQoL in Doc B, Section 2, was limited to EuroQoL Visual Analogue Scale (EQ-VAS) outcomes and other patient reported outcomes measures (European Organisation for Research and Treatment of Cancer [EORTC] Quality-of-Life Questionnaire Core 30 [QLQ-C30] and EORTC QLQ-STO22) were not reported.[1] Utility outcomes based on EuroQol 5 dimensions 5 level (EQ-5D-5L) by trial arm were not summarised in the original CS,[1] however, these were provided in response to the clarification letter (question A22).[19]

2.3.5 Other relevant factors

The company does not report any equality considerations in CS, Section B.1.4.[1] The company has provided an assessment of the severity modifier and has applied a quality-adjusted life-year (QALY) weighting of 1.2 based on its assessment of the absolute and proportional QALY shortfall (CS, Section B.3.6).[1] The company also notes in CS Section B1.3, that recent previous appraisals of treatments for this indication met the now superseded End-of-Life criteria.[1] The EAG's critique of the company's assessment of the appropriate severity modifier is provided in Section 5.

Table 4 The decision problem (adapted from CS, Table 1[1] with minor amendments and comments from the EAG)

	Final scope issued by NICE[4]	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
Population	Adults with untreated locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma	Patients with untreated locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma whose tumours express PD-L1 with a CPS≥ 1. Population is based on the proposed marketing authorisation wording.	The CS focuses on presenting trial outcomes for the PD-L1 positive subgroup of the KEYNOTE-811 trial, defined as those with a CPS ≥ 1, who made up 85% of the global cohort.[1] The company claims that PD-L1 status is already being routinely assessed in current practice.
Intervention	Pembrolizumab with trastuzumab and chemotherapy	In line with final scope	The EAG notes that the draft SmPC specifies that pembrolizumab is indicated in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy[17]
Comparators	• Chemotherapy only, which includes: o doublet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin o triplet treatment with fluorouracil or capecitabine in combination with cisplatin or oxaliplatin plus epirubicin Trastuzumab with cisplatin plus capecitabine or fluorouracil	Trastuzumab with cisplatin plus capecitabine or fluorouracil KEYNOTE-811 trial results provide direct evidence between: • pembrolizumab with trastuzumab and CAPOX or FP vs. • trastuzumab plus CAPOX or FP for locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma. Based on previous appraisals in this setting, ESMO guidelines and clinical opinion received, doublet chemotherapy regimens are considered to be clinically equivalent.	The EAG considers that the company's assumption that all doublet chemotherapy regimens are clinically equivalent is broadly acceptable. However, it notes that in TA208, trastuzumab is only recommended in combination with cisplatin and either capecitabine or 5-FU (i.e., XP or FP).[10] Adherence to this guidance in clinical practice restricts the choice of doublet chemotherapy given in combination with trastuzumab for patients with metastatic disease. In addition, whilst TA208 is strictly speaking restricted to patients with HER2-postivie metastatic disease, in clinical practice trastuzumab with doublet chemotherapy is usually offered to those with HER2-positive

	Final scope issued by NICE[4]	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
		ESMO guidelines and clinical opinion suggest that locally advanced unresectable and metastatic gastric or GOJ adenocarcinoma are treated like metastatic disease; therefore, a comparison versus chemotherapy without trastuzumab has not been conducted and is not presented in this submission.	locally advanced unresectable disease. This is because in practice the distinction between locally advanced unresectable and metastatic disease is not always easy to define as those classified as having locally advanced unresectable disease may have undetected peritoneal metastases. The EAG's clinical experts agreed that triplet chemotherapy is not usually used as a first-line palliative treatment in this patient group because it is likely to increase toxicity without improving survival compared with offering doublet chemotherapy.
Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	In line with final scope	The EAG notes that for HRQoL outcomes, the clinical efficacy section of the CS (CS, Document B, Section B.2) only summarises trial outcomes for the EQ-VAS but data were also collected for both EORTC QLQ-C30 and EORTC QLQ-STO22.[1] Utilities by trial arm based on EQ-5D were provided in response to the clarification request.
Subgroups to be considered	• PD-L1 status • Locally advanced unresectable • Metastatic	• PD-L1 status KEYNOTE-811 included less than 3% of locally advanced unresectable population which was not pre-specified subgroup of patients, therefore	PD-L1 status (CPS 0 versus CPS ≥ 1) was used as a stratification factor for randomisation, making it reasonable to assess effectiveness in the CPS ≥ 1 subgroup.[1] However, given that patients with a higher CPS score have been shown to have a higher response in other indications for

	Final scope issued by NICE[4]	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
		analysis in this subgroup of patients was not performed and not included in this submission. Clinical efficacy results in the metastatic population are available and have been provided in Appendix E.	pembrolizumab,[22] the EAG requested that the company provide any analyses already conducted that were stratified by CPS score. In response the company provided results for the CPS score ≥ 10 subgroup, but no results were provided for CPS <10 or CPS 1 to 9. An economic analysis was not conducted for the CPS score ≥ 10 subgroup. The EAG's clinical advisors considered that it was reasonable not to provide results for the subgroup of patients with locally advanced unresectable disease as this group is a small proportion of the population covered by the licensed indication. In addition, they stated that it was sometimes difficult to distinguish these patients from those with metastatic disease and they would be expected to respond similarly to patients with metastatic disease. The company has focused its presentation of efficacy outcomes in the submission on data from two of the three geographical regions used as stratification factors, which it has combined into a single 'non-Asia region' subgroup. The EAG notes that this trial subgroup relates to geographical region for the recruitment site rather than the ethnicity of the patient. The company's rationale for this subgroup relates to the widespread use of screening programmes in Asian countries which would be expected to lead to earlier

	Final scope issued by NICE[4]	Decision problem addressed in the CS and rationale if different from NICE scope	EAG comments
			diagnosis and would make the results from Asian countries less applicable to countries such as England where there is no screening programme.
Special considerations including issues related to equity or equality	None identified in the scope	The company does not report any equality considerations in CS, Section B.1.4.[1] The company has applied a QALY weighting of 1.2 based on its assessment of disease severity using absolute and proportional QALY shortfall	The EAG's agrees that there is evidence to support a QALY weighting of 1.2 but its assessment is based on a different approach to the company's (see Section 5).

Abbreviations: EAG - external assessment group; HER2 - Human epidermal growth factor receptor 2; HorR - hormone receptor; NHS - National Health Service; NICE - National Institute for Health and Care Excellence; PSS - personal social services; TPC - treatment of physician's choice;

3 CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical effectiveness evidence contained within the CS for pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or GOJ cancer. Section 3.1 describes the company's systematic review of clinical and safety evidence. Section 3.2 provides a summary of the clinical effectiveness and safety results.

3.1 Methods of review of clinical evidence

The systematic review methods for the clinical evidence are detailed in Section B.2.2 of the CS and CS Appendix D.[1] The company undertook a systematic literature review (SLR) to identify randomised controlled trials (RCTs) relating to the efficacy and safety of pembrolizumab in combination with trastuzumab and chemotherapy in patients with locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma.

3.1.1 Searches

The company performed one clinical effectiveness search to identify all clinical effectiveness and safety studies of pembrolizumab or comparator treatments of adult patients with HER2-positive advanced gastric and GOJ adenocarcinoma in previously untreated settings.

The company searched several electronic bibliographic databases in January 2023 (Appendix D.1 Identification and selection of relevant studies): MEDLINE [via Ovid], EMBASE [via Ovid], Cochrane Central Register of Controlled Trials [via Ovid].

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram (Appendix D.1 Figure 1, page 66), the company reported records identified from other sources (N=3,625): from Conference Proceedings (n=388), ClinicalTrials.gov Registry (n=2,773), citation searches from published SLRs and conference abstracts (n=462) and expert recommendations (n=2). The company did not report the search strategies for the searches from the conference proceedings sources. The EAG would expect the following sources to be searched in recent years: American Society of Clinical Oncology (ASCO), ESMO. The company only searched the clinical trials registry. A cross-sectional study by Banno, Tsujimoto & Kataoka (2020) compared the coverage of the two trial registry records, ClinicalTrials.gov, World Health Organisation (WHO) International Clinical Trials Registry Platform and CENTRAL and concluded that all three sources should also be searched to identify unpublished trials.[23]

The company searched for the interventions that were listed in Appendix D1.1.1 Table 1. Interventions that are not listed were excluded. However, the EAG sought clarification (question A1) for the following interventions that were included in the search strategy (for example, Appendix D1 Tables 2 and Table

3, pages 5 and 26) but not listed in the inclusion criteria: doxetaxel; paclitaxel; s1-tegafur-oxonate; ipilimumab; avelumab; bevacizumab; leucovorin; carboplatin; sorafenib; ramucirumab; pralatrexate; irinotecan; cediranib; golvatinib; and epirubicin. The company acknowledged in the response that a broader list of interventions was included in the search strategy because it was designed for the global market, but the interventions were excluded at the stage of UK submission and thus not included in the feasibility assessment (not in scope).[19] Therefore, the records retrieved from database searches (identification stage) are not a representation of the number of records that are specifically for the UK context, as found in Appendix D Figure 1 PRISMA Flow Diagram. While the company acknowledges that the search was developed for the global market, the search strategy is restricted to English language publication only. Consequently, there may be studies that are missed in countries where a particular intervention is more common than in other countries, resulting in language bias.[24]

The EAG having reviewed the search strategies considers them to be comprehensive.

3.1.2 Inclusion criteria

The inclusion criteria for the company's SLR are described in CS Appendix D1.1.1. The inclusion criteria in the company's SLR for population were adult patients (≥18 years old) with previously untreated, locally advanced unresectable or metastatic gastric or GOJ adenocarcinoma who received no prior systemic therapy for treatment of advanced or metastatic disease. This was in line with the NICE final scope.[4] The intervention included in the company's SLR was pembrolizumab + trastuzumab + fluoropyrimidine (5-FU or capecitabine) ± leucovorin + platinum agent (oxaliplatin or cisplatin). This was consistent with the NICE final scope. The inclusion criteria in the company's SLR for comparators (trastuzumab + fluoropyrimidine [5-FU or capecitabine] ± leucovorin + platinum agent [oxaliplatin or cisplatin]; or fluoropyrimidine [5-FU or capecitabine] ± leucovorin + platinum agent [oxaliplatin or cisplatin]). Although epirubicin was included in the search strategy, epirubicin-containing triplet therapy was not listed as an eligible comparator for the SLR (CS Appendix D Table 1). Placebo-controlled or best supportive care controlled studies were eligible as trial comparators. All the outcomes in the NICE final scope[4] were included in the outcomes inclusion criteria in the company's SLR.

Eligibility was restricted to English language publications, which introduces the risk that relevant data not published in the English language may have been missed, however the EAG does not anticipate that key RCTs would have been missed. The included study design was limited to RCTs (Section B.2.1 of CS). This is standard practice to restrict to high quality study designs where they are available. It was not clear from Appendix D of the CS if study selection was conducted by one or more reviewers.[1]

While the inclusion criteria for the company's SLR were generally consistent with the NICE final scope,[4] except for epirubicin-containing triplet therapy not being included as a comparator, the inclusion criteria in the company's decision problem differed in terms of population and comparators, based on

the company's KEYNOTE-811 trial. The population was restricted to patients whose tumours express PD-L1 with a CPS≥ 1. The company's explanation for this was that this was in line with the anticipated marketing authorisation.[17]

PD-L1 status CPS<1 vs CPS≥1 was a randomisation stratification factor, and as such, it should be expected that participants be balanced between treatment groups, and it was also one of the pre-planned subgroup analyses. Given this and the anticipated marketing authorisation, the EAG considered it reasonable to present results for the subgroup of CPS≥1 patients. Comparators were restricted to trastuzumab with cisplatin plus capecitabine or fluorouracil. The draft SmPC[17] recommends for this population, pembrolizumab "*in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy*". Clinical advisors to the EAG stated that in clinical practice, trastuzumab would be used in HER2-positive patients, unless contraindicated (such as in patients with cardiac conditions), as such the EAG considered it reasonable to restrict to therapy including trastuzumab. Clinical advisors to the EAG stated that in clinical practice doublet (fluorouracil or capecitabine in combination with cisplatin or oxaliplatin), rather than triplet, chemotherapy would be given, as triplet therapy increased toxicity without much improvement in effectiveness, and many patients would be too frail for triplet chemotherapy.[25, 26] There may be preference for capecitabine over fluorouracil, as the mode of administration is oral, including via feeding tubes. This avoids the need for a central line, which is required for 5-FU and is associated with risks such as line infections. Dose interruptions to manage AEs are also simpler when using an oral treatment. The company's decision problem is discussed in EAG report Section 2.3.

Two trials were included in the CS SLR: KEYNOTE-811; and ToGA (Table 5). KEYNOTE-811 is described in Section 3.2. The company assessed the feasibility of using the KEYNOTE-811 and ToGA studies to provide an indirect comparison of pembrolizumab with trastuzumab and CAPOX/FP against trastuzumab and XP (CS, Section B2.9.1). It concluded that this comparison could only be made by assuming equivalence between doublet chemotherapy regimens, and the results would mirror the KEYNOTE-811 trial results. ToGA was not used further in the CS, and is therefore not described in detail in the EAG report, but some details on study design, risk of bias, and results are provided for reference in EAG report Appendix 1.

Table 5 KEYNOTE-811 and ToGA overview of study characteristics

Trial names and references	Trial design	Population	Intervention	Comparator	Primary outcomes
KEYNOTE-811 NCT03615326 EudraCT 2018-000224-34 MK-3475-811 Janjigian *et al.* 2021 [27] 2021[28] CSR[29] KEYNOTE-811 clinical trials registry [30]	Phase III Randomised Placebo-Controlled Trial, Double-Blind	Adults with HER2 positive participants with previously untreated, locally advanced unresectable or metastatic advanced gastric or GOJ adenocarcinoma	Trastuzumab and pembrolizumab plus either cisplatin plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX)	Trastuzumab and placebo plus FP or CAPOX	PFS per RECIST 1.1 assessed by BICR - Time to Event OS - Time to Event
ToGA NCT01041404 BO18255 Bang *et al.* 2010[31] ToGA clinical trials registry [32]	Phase III RCT, open-label	Adults with HER2- positive locally advanced, recurrent, and/or metastatic cancer gastric or GOJ adenocarcinoma	Trastuzumab plus capecitabine plus cisplatin (XP) or fluorouracil plus cisplatin (FP)	Capecitabine plus cisplatin or fluorouracil plus cisplatin	OS - Percentage of participants With an Event OS - Time to Event

Abbreviations: FP= cisplatin plus 5-FU; CAPOX= oxaliplatin plus capecitabine; OS=overall survival; PFS=progression-free survival; HER2= human epidermal growth factor receptor 2; GOJ=gastro-oesophageal junction; BICR=blinded independent central review.

Neither the EAG nor clinical advisors to the EAG are aware of any additional studies of pembrolizumab within the scope of this appraisal.

3.1.3 Data extraction

No detail was reported in the CS Appendix D about the process of data extraction, and thus it is not clear by how many reviewers this was done, if it was checked, how any disagreements were resolved, or which fields were extracted.

Data extracted in the CS for the KEYNOTE-811 trial were checked by the EAG against the trial registry. The main publication for the KEYNOTE-811 trial[27] provided data from an earlier interim analysis than that in the CS, so was not relevant for checking. Following clarification questions, the clinical study report (CSR) [29] was provided and so data were checked by the EAG against the CSR.

3.1.4 Risk of bias assessment

Risk of bias was assessed based on the Cochrane Risk of Bias tool 2.0,[33] which is widely regarded as a robust tool for the assessment of bias in RCTs. It was not clear from Appendix D of the CS if risk of bias assessment was conducted by one or more reviewers.[1]

Risk of bias assessment of the included study, KEYNOTE-811, as undertaken by the company and the EAG, is presented in Section 3.2.3.

3.2 Trial of the technology of interest

3.2.1 Included pembrolizumab trial

The CS (CS Section B.2.2) included one study that examined the effectiveness of pembrolizumab in combination with trastuzumab and chemotherapy, KEYNOTE-811.

KEYNOTE-811 is a phase III double-blind RCT, ongoing at the time of writing. It is a multicentre RCT, with the global cohort recruiting from 192 centres in 20 countries[30]: Australia, Brazil, Chile, China, France, Germany, Guatemala, Ireland, Israel, Italy, Japan, New Zealand, Poland, Russia, South Korea, Spain, Turkey, UK, Ukraine, USA (CS Section B.2.3). There were 29 subjects from 10 UK centres. It consisted of two cohorts, global and Japan-specific SOX (S-1 + oxaliplatin) treated cohort, of which only the global cohort is considered in the CS.[1] SOX was not a comparator included in the NICE final scope,[4] the trial only planned to recruit 40 patients for this cohort,[28] [redacted][29] so the EAG considered it was appropriate to exclude the Japan-specific SOX cohort from the CS.

KEYNOTE-811 study characteristics are shown in

Table 6. Patients in the global cohort were randomised to pembrolizumab in combination with trastuzumab and chemotherapy, or placebo in combination with trastuzumab and chemotherapy. Randomisation was stratified by geographic region (1 Europe [note this refers to Western Europe, CS Clarification response A6] /Israel/North America/Australia, 2 Asia, 3 Rest of the World including South America [note this includes Eastern Europe, CS Clarification response A6]); and PD-L1 status CPS<1 versus CPS≥1; and chemotherapy treatment (FP or CAPOX), which was chosen by the investigating physician prior to randomisation.[19]

Table 6 KEYNOTE-811 (NCT03615326) study characteristics

Population	Intervention	Comparator	Primary outcomes
Adults with HER2 positive participants with previously untreated, locally advanced unresectable or metastatic advanced gastric or GOJ adenocarcinoma	Pembrolizumab 200mg i.v. and trastuzumab 8 mg/kg loading dose, then 6 mg/kg plus either cisplatin 80 mg/m^2 plus 5-FU (FP) or oxaliplatin plus capecitabine (CAPOX)	Placebo (normal saline, i.v.) and trastuzumab plus FP or CAPOX (doses as for intervention)	PFS per RECIST 1.1 assessed by BICR OS

Abbreviations: FP= cisplatin plus 5-FU; CAPOX= oxaliplatin plus capecitabine; OS=overall survival; PFS=progression-free survival; HER2= human epidermal growth factor receptor 2; GOJ=gastro-oesophageal junction; BICR=blinded independent central review; i.v.=intravenous.

PD-L1 status was assessed by PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, CA, USA) at a central laboratory facility.[28] CS clarification response A4 references Ahn and Kim 2021 [20] which reported that the PD-L1 22C3 and PD-L1 1HC 22c3 pharmDx assays produced comparable results in gastric cancer at CPS cut-offs of 1, 10, and 50. CS clarification response A4 states that both these assays are "*routinely used within NHS clinical practice*".[19] According to clinical advice to the EAG, many units may have access to one or the other of these, however there are multiple assays available depending on the pathology laboratory used, and other assays may give different results. There may also be inherent tumour heterogeneity, meaning even in the same tumour there are regions of positive and negative PD-L1.

KEYNOTE-811 was ongoing at the time of writing. Data in the CS were from interim analysis 2 (IA2) which had a data cut-off date of May 2022.[1] CS Clarification response A13 explained that the database lock for interim analysis (IA3) had occurred but analyses were ongoing, and so were unavailable at the time of writing.[19]

IA2 had been scheduled to be performed after approximately 542 PFS events, and approximately nine months after the last participant had been randomised, with allowance made for conducting the analysis with up to 3 months of additional follow-up, if events accrued slower than expected (CS Section B.2.4). In practice, IA2 occurred after 484 PFS events (of which 414 in CPS>=1 participants) (CS Section B.2.6).

Power is reported for the global cohort, that is, not the subgroup of CPS>=1 participants, or restricted to subgroups by region of the world. CS Section B2.4 gives power for ORR at IA1, for which the planned sample size had been reached[27] and so had approximately *"90% power for detecting a 25%*

difference in ORR (73% vs 48%) at an initially assigned 0.002 (1-sided) significance level" (CS Section B2.4). CS section B.2.4 gives power for PFS at IA3, and OS at the final analysis (CS Section B2.4) but does not report power for PFS or OS at IA2. [redacted]

There were pre-specified subgroup analyses for: PD-L1 Positive versus Negative; Region 1 Europe/Israel/North America/Australia versus 2 Asia versus 3 Rest of World (including South America); age <65 versus ≥65 years; sex female versus male; race Asian versus non-Asian; Microsatellite instability (MSI) status; primary location stomach versus GOJ; histological subtype diffuse versus intestinal versus indeterminate; tumour burden ≥median versus <median; number of metastatic sites ≤2 versus ≥3; prior gastrectomy yes versus no (CS Appendix E) (KEYNOTE-811 protocol amendment 2022).[21]

3.2.1.1 Patients

Eligibility criteria for the KEYNOTE-811 study were presented in CS Section B.2.3 (pages 30-33). The population met the specification of the NICE final scope,[4] in being adults (aged 18 or older) with untreated locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma.[28] Diagnosis was histologically or cytologically confirmed,[30] measurable disease as defined by RECIST v1.1 (Response Evaluation Criteria in Solid Tumors version 1.1).[34] HER2-positive status was defined as either immunohistochemistry (IHC) 3+ or IHC 2+ in combination with in-situ hybridization positive (ISH+), or fluorescent in-situ hybridization (FISH), as assessed by central review on primary or metastatic tumour.[30]

The trial population was narrower than the NICE final scope,[4] in being restricted to Eastern Cooperative Oncology Group (ECOG) Performance Scale 0 or 1, with a life expectancy >6 months, and adequate organ function, and excluding a range of co-morbidities (CS Section B.2.3 pages 30-33). Clinical advice to the EAG suggested that patients with ECOG >1 are often excluded from RCTs. In practice, most participant have ECOG 1 or 2. ECOG 2 patients may be considered too frail for immunotherapy, however with nutrition and chemotherapy they may recover to ECOG 1.

3.2.1.2 Intervention

The intervention group were to receive pembrolizumab in combination with trastuzumab and chemotherapy.

Doses were:[28]

pembrolizumab 200mg i.v. Q3W (day 1 of each cycle);

trastuzumab 8 mg/kg loading dose, then 6 mg/kg maintenance dose i.v. Q3W (day 1 of each cycle);
FP – cisplatin 80 mg/m^2 i.v. Q3W (day 1 of each cycle), plus 5-fluorouracil 800 mg/m^2/day i.v. Q3W (day 1-5 of each cycle);
CAPOX – oxaliplatin 130 mg/m^2 i.v. Q3W (day 1 of each cycle), plus capecitabine 1000 mg/m^2 oral BID (day 1-14 of each cycle).

Treatment was continued for up to 35 cycles, or until disease progression, unacceptable toxicity, or noncompliance, or if the investigator or patient decided to withdraw a participant from the study.[28] Patients with complete response could discontinue treatment after eight or more doses of study treatment.[28] Investigating physicians could choose to continue treating those with disease progression if they were clinically stable.[28] [redacted] Patients with stable disease or better may be eligible for a second course of pembrolizumab (17 doses) if their disease progresses while they are off study treatment.[28] According to local guidelines, some regions discontinued cisplatin at six cycles.[28] CS clarification response A7 states there were up to six cycles for cisplatin, and 6-8 cycles of oxaliplatin.[19]

3.2.1.2.1. Comparator

The comparator group were to receive placebo in combination with trastuzumab and chemotherapy. Doses of trastuzumab and chemotherapy were as for the intervention group.[28]

Clinical advisors to the EAG stated that in clinical practice, trastuzumab would be used in HER2-positive patients, unless contraindicated (such as in patients with cardiac conditions). In cases where trastuzumab is contraindicated, it is unusual for patients to be fit for chemotherapy. The advisors also stated that in clinical practice, doublet, rather than triplet, chemotherapy would be given for 4-8 cycles, in general.[25]

Concomitant treatments (across both treatment groups) were allowed at the physician's discretion, with the exception of the following excluded treatments: antineoplastic systemic chemotherapy; biologic therapy; immunotherapy or chemotherapy not specified in the protocol; other investigational agents; radiotherapy; live vaccines within 30 days prior to (and throughout) trial treatment; systemic glucocorticoids (unless to treat AE or for cisplatin or 5-FU supportive care); inhibitors of the enzyme dihydropyrimidine dehydrogenase for participant given 5-FU therapy (CS Section B2.3).

3.2.1.2.2. Outcomes

The primary outcomes of KEYNOTE-811 were PFS and OS.[30] [28]

PFS was defined as the time from randomisation to the first documented disease progression per RECIST 1.1 as assessed by blinded independent central review (BICR) or death due to any cause, whichever occurred first.[28,30] As in RECIST 1.1, progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study.[30] In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.[30] The appearance of one or more new lesions was also considered progression.[30] Assessment of tumour status was performed every six weeks,[28] until progressive disease, death, start of new anticancer treatment, or withdrawal of consent. The use of established response evaluation criteria (i.e. RECIST) is recommended practice by the European Medicines Agency (EMA) for chemotherapy trials, although not established for immunotherapy.[35,36] iRECIST is available for immunotherapy.[37] According to clinical advice to the EAG, immunotherapy may lead to "pseudo-progression" whereby there is an increase in size of the target lesion within a few weeks/months of starting immunotherapy. Scanning that is more frequent than in UK practice (that is, three months following treatment initiation) may result in a patient erroneously being regarded as having progressed disease.

OS was defined as the time from randomisation to death due to any cause.[28,30] For patients no longer being monitored every six weeks, follow-up for survival was conducted every twelve weeks. EMA research recommendations [38] advise that OS should be considered a secondary outcome in Phase III trials where PFS is the primary outcome, and should demonstrate or show a trend towards superiority.

Secondary outcomes were: Objective Response Rate (ORR); Duration of Response (DOR); AEs [28,30] and treatment discontinuation due to AEs.[30] ORR was defined as the percentage of participants who have a complete response (CR) that is disappearance of all evidence of disease, or partial response (PR) that is regression of measurable disease and no new sites), per RECIST 1.1 as assessed by BICR.[30] DOR was defined as the time from first response (CR or PR) to subsequent disease progression or death from any cause, whichever occurs first, per RECIST 1.1 as assessed by BICR.[30] Adverse events were defined in the protocol,[28] in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[39] Serious adverse events (SAE) were defined as: fatal; life-threatening; requiring hospitalisation or prolonged existing hospitalisation; resulting in persistent or significant disability/incapacity; congenital anomaly/birth defect; other important medical event according to medical or scientific judgement (KEYNOTE-811 protocol amendment 2022).[21]

Exploratory outcomes were HRQoL, utilities, molecular biomarkers, and PFS and ORR per immune-related RECIST as assessed by investigating physicians.[28]

Effectiveness outcomes were analysed in the intent to treat (ITT) population, that is all randomly assigned patients in the group they were assigned to.[28] The safety population included all randomly assigned patients who received ≥1 dose of study treatment, analysed by treatment received.[28]

Three interim analyses and final analyses were planned according to project milestones (CS Section B.2.4 Table 12).[1] At time of writing, the results of IA2 were provided in the CS but had not been published, and the results of IA1 had been published (Janjigan *et al.* 2021).[27]

3.2.1.2.3. Ongoing studies

KEYNOTE-811 was ongoing at time of writing. CS Section B.2.11 states that there are no other ongoing trials of pembrolizumab in patients with previously untreated locally advanced unresectable or metastatic HER2-positive gastric or GOJ adenocarcinoma. Neither the EAG nor clinical advisors to the EAG are aware of any additional studies of pembrolizumab within the scope of this appraisal.

3.2.2 Details of relevant RCTs not included in the submission

Neither the EAG nor clinical advisors to the EAG were aware of any additional RCTs within the scope of this appraisal. According to clinical advice there are ongoing trials of novel HER2 inhibitors in this condition, however these would not meet the final NICE scope criteria.

3.2.3 Risk of bias assessment KEYNOTE-811

The company provided a risk of bias was assessed based on the Cochrane Risk of Bias tool 2.0. A summary of the risk of bias in the KEYNOTE-811 study undertaken by the company alongside the EAG's independent quality assessment (from the publications of Janjigan *et al,.*[27] and Chung *et al.*,[28] clinical trials registry[30] and the CSR[29]) is presented in Table 7. The company's critical appraisal and the EAG's critical appraisal of the KEYNOTE-811study were similar.

Randomisation allocation concealment was adequate.[28] Baseline characteristics at IA2 appear balanced between treatment groups in [redacted] CS Section B2.3.2). Participants and clinicians were blind to treatment, and PFS was assessed by BICR (clinicaltrials.gov). Outcome measurement was the same for both treatment groups.[28] ITT analyses were planned for effectiveness measures and all participants were included in the ITT analyses for the global cohort (CS Appendix M) (CSR)[29].

Subgroup analyses were pre-specified for the randomisation stratification factors of: geographic region (1 Europe/Israel/North America/Australia, 2 Asia, 3 Rest of the World including South America); PD-L1 status CPS<1 vs CPS≥1. However, CS presents data for *post hoc* analyses of the subgroup of CPS≥1, and within that CPS≥1 subgroup, the non-Asian participants; that is the combination of the two

subgroups Europe/Israel/North America/Australia, and Rest of the World including South America. Both CPS and region were stratification factors, and so treatment groups should be balanced. However, the exclusion of the Asia region subgroup was a *post hoc* analysis. Presenting results for the subgroup of CPS≥1 was in line with the anticipated marketing authorisation,[17] and so were relevant for this submission. Clinical practice in the Asia region is dissimilar to clinical practice in England, and so data from the Asia region may not be generalisable to the population likely to be treated England. However, it is unclear if the Western Europe population would be more generalisable to England than the Rest of the World region (which had more favourable results to pembrolizumab then the Europe population). The Rest of the World region included South American and Eastern Europe, and according to clinical advice there may be less access to care in these settings than in England.

The results of IA2 of KEYNOTE-811 had not yet been published at the time of writing; as such, it cannot be assessed if the authors measured more outcomes than they reported. However, data for outcomes of relevance to this review were provided by the company in the CS and clarification response.[19]

Overall, the KEYNOTE-811 was well-designed to give a low risk of bias. Data from IA2 had lower numbers of PFS events than was anticipated, and there is some uncertainty about statistical power of the PFS analysis, and the trial was not powered for subgroups. There is some concern about the *post hoc* analysis of CPS≥1 excluding the Asia region, as it is uncertain whether the Western Europe subgroup alone would be more generalisable to England, than the grouping together with Rest of World subgroup.

Table 7 Risk of bias assessment KEYNOTE-811

Type of bias	KEYNOTE 811			
	Review authors' judgement	**Support for judgement**	**EAG judgement**	**Support for judgement**
Bias arising from the randomization process	Low risk	Double-blind study; participants were randomly assigned 1:1 to pembrolizumab or placebo via an integrated interactive voice- and web-response system and assignment was masked to both participants and investigators.	Low risk	Allocation sequence – stratified randomisation via interactive voice/web response system implies computer-generated random numbers [28] Allocation concealment - Randomisation performed centrally using an interactive voice/web response system [28] Baseline characteristics – balanced across treatment groups for CPS≥1 participants, and for whole global cohort at IA1 [redacted]
Bias due to deviations from intended interventions	Low risk	Double blind study; no deviations from the intended interventions arose because of trial context and appropriate analysis methods were employed to estimate treatment effects.	ITT population - low risk. CPS≥1 and non-Asian participants – some concerns	Participant awareness of assigned intervention – blinded, placebo controlled (unclear if side effects alerted some participants to intervention) Clinician/carer awareness of assigned intervention – blinded, placebo controlled (unclear if side effects alerted some clinicians to participants' interventions) Trial context – no strong reason to believe that the trial context led to failure to implement the protocol interventions Appropriate analyses - ITT analyses planned for effectiveness measures.[28] However, CS presents *post hoc* data for CPS≥1 and non-Asia region participants, which excludes eligible trial participants.

Type of bias	KEYNOTE 811			
	Review authors' judgement	**Support for judgement**	**EAG judgement**	**Support for judgement**
				Impact of excluding eligible participants from analyses – potential for impact of CPS≥1 mitigated by randomisation stratification. Regional subgroups were stratified, however subgroups had different treatment effects, and the excluded Asia region had a less favourable effect for pembrolizumab.
Bias due to missing outcome data	Low risk	Data for outcomes available represented all or nearly all randomized participants.	Low risk	Available outcome data – OS and PFS ITT analyses; also subgroup CPS≥1 ITT
Bias in measurement of the outcome	Low risk	Appropriate method used to measure outcomes.	Low risk	Method of measuring outcomes – appropriate Outcome measurement for treatment groups – same measurements and same time points (every 6 weeks for PFS; every 12 weeks following progression or treatment change for OS) [28]
Bias in selection of the reported result	Low risk	Analysis was in accordance with a pre-specified analysis plan that was finalized before the outcome data were available for analysis.	ITT population - low risk. CPS≥1 and non-Asian participants – some concerns	Analyses pre-specified – subgroup analyses prespecified for stratification factors, however *post hoc* to combine Europe and Rest of World (excluding Asia) Multiple outcome measurements – effectiveness outcomes were pre-defined with one clear measurement for the outcome domain
Overall bias	Low risk	Low risk of bias across all domains.	ITT population - low risk. CPS≥1 and non-Asian participants – some concerns	

3.2.4 KEYNOTE-811 results

Data are from KEYNOTE-811 IA2. Data from IA3 were not available at time of writing (CS clarification response A13).[19] Data are from the global cohort of KEYNOTE-811 (the Japan specific SOX cohort was excluded throughout the CS). Median follow-up at IA2 was 16.1 months for the pembrolizumab group, and 14.8 months for the comparator group (CS Clarification response A23)(CSR).[19,29]

The CS concentrated on data from the subgroup of patients with PD-L1 with a CPS≥ 1. This was in line with the anticipated marketing authorisation. This was a randomisation stratification factor, and as such, it should be expected that participants be balanced between treatment groups. Within the CPS≥1 subgroup, the CS concentrated on the non-Asian participants, that is the combination of the two subgroups: Europe/Israel/North America/Australia; and Rest of the World including South America. Region was a randomisation stratification factor. The combinations of the two subgroups were *post hoc* analyses.

The global cohort of KEYNOTE-811 randomised 698 patients. Of these, 594 had CPS ≥1, and 104 had CPS<1. There were 224 patients recruited in Europe/Israel/North America/Australia; 237 recruited in Asia; and 237 in Rest of the World including South America (CS Appendix M). Within the CPS ≥1 subgroup, there were 193 patients recruited in Europe/Israel/North America/Australia; 192 recruited in Asia; and 209 in Rest of the World including South America (CS Appendix E).

CS Appendix D.1.2 reports participant flow for CPS ≥1 participants. All but one patient (randomised to comparator) started study treatment. At the time of database cut-off for IA2, 71.8% of the pembrolizumab group, and 83.1% of the comparator group, had discontinued study treatment. In the majority of cases, discontinuation of study treatment was due to progressive disease or death, 50.7% of the pembrolizumab group, and 63.1% of the comparator group. Adverse events led to discontinuation for 10.4% of the pembrolizumab group, and 8.8% of the comparator group (CS Appendix Table 19). Discontinuation rates were similar for the Western Europe/Israel/North America/Australia and Rest of World regions. For Western Europe/Israel/North America/Australia at time of database cut-off for IA2, there was discontinuation of treatment for 79.4% of the pembrolizumab group (10.3% due to AE), and 88.5% of the comparator group (14.6% due to AE) (CS Clarification response A14).[19] For the Rest of World region, there was discontinuation of treatment for 68.6% of the pembrolizumab group (14.3% due to AE), and 85.4% of the comparator group (9.7% due to AE) (CS Clarification response A14).[19]

Baseline characteristics of the CPS ≥1 participants are reported in CS Table 6. Characteristics appear balanced between the treatment groups.

According to clinical advice, trial participants were younger than would be seen in clinical practice in England (by about ten years). It is common for trial participants to be younger or fitter than would be seen in practice.[40] The difference in the average age between patients in the RCT and in England may result in a different treatment effect. There is some uncertainty as KEYNOTE-811 was not powered for subgroups, however patients under 65 years appeared to have more favourable treatment effects for pembrolizumab for PFS and OS, than older patients (CS Appendix E). Most English patients are 70 years or older according to clinical advice.[41]

In terms of primary location at diagnosis, and the mix of locally advanced versus metastatic disease, clinical advisors thought this was representative of the eligible population in England.[41] The eligible population in England would be likely to comprise a higher proportion of black patients, however clinical advice suggested this was unlikely to alter the treatment effect. The company's preferred population (CPS≥1 and non-Asia region) contains only 2 Asian participants. The eligible population in England would be likely to comprise a higher proportion of Asian patients, however clinical advice suggested this was unlikely to alter the treatment effect. Note that ethnicity and region are separate subgroups (EAG report Section 2.3.1).

At IA2, for CPS ≥1 participants, the median duration of follow up for the pembrolizumab group was 17.0 months (range: 0.6 to 41.6 months), and in the comparator group 13.9 months (range: 0.3 to 41.2 months) (CS Appendix D1.2)

Drug exposure for CPS ≥1 participants (in treated participants: pembrolizumab n=298; comparator n=295) was reported in CS Tables 23 and 24. Exposure to study drug was longer in the pembrolizumab group (median 10.2 months, range 0.3 to 36.6) compared with the comparator group (median 7.1 months, range 0.0 to 36.1) (CS Section B2.10)(Keytruda (MK-3475) HTA report 2022).[42] Only three patients received a second course of pembrolizumab (CS Clarification response A8).[19]

Of the CPS ≥1 participants, 504 were prescribed CAPOX (n=251 pembrolizumab group, n=253 comparator group), and 90 were prescribed FP (n=47 pembrolizumab group, n=43 comparator group) (CS Section B2.3). Mean number of chemotherapy cycles for CPS ≥1 non-Asia region participants were reported in CS Clarification response B35 (

Table 8).[19]

Table 8 Mean number of chemotherapy cycles administered per treatment arm in KEYNOTE-811 (non-Asia CPS≥1 cohort) (reproduced from clarification response, Table 45[19]; supersedes CS, Table 32[1])

	Pembrolizumab with trastuzumab plus chemotherapy; mean (SD)	Trastuzumab plus chemotherapy; mean (SD)
Capecitabine (in CAPOX)	13.3 (10.7)	9.6 (8.3)
Oxaliplatin (in CAPOX)	7.3 (4.6)	6.8 (4.6)
Cisplatin (in FP)	5.3 (1.8)	5.6 (1.9)
5-FU (in FP)	9.5 (6.7)	11.2 (9.5)

Abbreviations: SD, standard deviation

3.2.4.1 PFS

IA2 was conducted after the occurrence of 484 PFS events in the global cohort (CS Section B2.6.1).

At IA2, of the 594 participants with CPS≥1, 414 had PFS events (CS Section B2.6.1). Median follow-up at IA2 was 17 months for the pembrolizumab group, and 13.9 months for the comparator group (CS Appendix D1.2, CS Clarification response A23).[19] In the pembrolizumab group, 199/298 (66.8%) patients had a PFS event (n=29 death, n=170 progression), and median PFS was 10.8 months (95% confidence interval [CI] 8.5, 12.5). In the comparator group, 215/296 (72.6%) patients had a PFS event (n=30 death, n=185 progression), and median PFS was 7.2 months (95%CI 6.8, 8.4). For CPS≥1 patients, the hazard ratio (HR) for PFS significantly favoured the pembrolizumab group, HR 0.70 (95% CI 0.58, 0.85, p = 0.0001) (CS Section B2.6.1 Table 15).

Within CPS≥1, subgroup data were reported (CS Appendix E). [redacted]

Within the stratified CPS≥1, subgroup data for the RCT's other stratification factors (region and chemotherapy type) were reported (CS Appendix E). Hazard ratios for pembrolizumab with reference comparator group were similar for CAPOX (HR 0.69 [95%CI 0.56; 0.85] and FP (HR 0.69 [95%CI 0.43; 1.12]), with a wider confidence interval for FP which had a smaller sample size (n=90) (CS Appendix E Table 22 and Figure 7). Data by region varied considerably. Western Europe/Israel/North America/Australia had a HR of 0.69 [95%CI 0.50; 0.97]; Asia had a HR of 0.85 [95%CI 0.59; 1.22]; Rest of the World had a HR of 0.56 [95%CI 0.41; 0.78] (CS Clarification response A10).[19] This implied a more favourable effect for pembrolizumab on PFS for the Rest of the world region than for the other regions; and also a less favourable effect for pembrolizumab on PFS for the Asia region. However, the interaction across the three regions did not reach statistical significance (CS Clarification response A10).[19]

Other pre-planned subgroup data, for non-stratified subgroups, were reported in CS Appendix E Table 22 and Figure 7). There appeared to be a more favourable effect for pembrolizumab on PFS for age<65years than for older patients, however the interaction did not reach statistical significance (for this, or any of the other pre-planned subgroups within the CPS≥1 subgroup) (CS Clarification response A10).[19]

A *post hoc* analysis of the combined subgroup of non-Asia regions, within CPS≥1 patients, (the company's preference of population). Median PFS for the pembrolizumab group was 9.9 months (95%CI 8.3, 11.3), and for the comparator group 6.3 months (95%CI 5.6, 7.3) (CS Clarification response A15). The HR for PFS favoured the pembrolizumab group, HR 0.62 ([95% CI: 0.49; 0.78] <0.0001) (CS Section B2.6.1 Table 14, and CS Clarification response A15).[19]

In the global cohort, using a different cut-off for CPS, a *post hoc* analysis of the subgroup CPS≥10 did not find a significant treatment group difference for PFS, HR 0.72 (95% CI: 0.52, 1.01) (CS Clarification response A5).[19] When restricted to non-Asia region participants, CPS≥10, PFS HR was [redacted] (CS Clarification response A5).[43]

3.2.4.2 OS

At IA2, of the 594 participants with CPS≥1, 350 had OS events (CS Section B2.6.1). In the pembrolizumab group, 167/298 patients had an OS event, and median time to death was 20.5 months (95%CI 18.2, 24.3). In the comparator group, 183/296 patients had an OS event, and median time to death was 15.6 months (95%CI 13.5, 18.6). For CPS≥1 patients, the HR for OS favoured the pembrolizumab group, HR 0.79 (95% CI 0.64, 0.98, p = 0.0143) (CS Section B2.6.1 Table 17).

Within the CPS≥1 subgroup, the HR for pembrolizumab with reference comparator group for CAPOX was HR 0.82 (95%CI 0.65, 1.03), and for FP was HR 0.71 (95%CI 0.43, 1.18), neither being statistically significant, FP appearing more favourable for pembrolizumab but with wide confidence interval (CS Appendix E Table 23 and Figure 8).

Within the CPS≥1 subgroup, data by region varied significantly (interaction effect p=0.0317) (CS Clarification response A17).[19] Direction of effect favoured pembrolizumab for the regions: Western Europe/Israel/North America/Australia had a HR of 0.81 (95%CI 0.57, 1.15); and Rest of the World had a HR of 0.57 (95%CI 0.40, 0.80) (CS Clarification response A17). Median OS for CPS≥1 participants, Western Europe/Israel/North America/Australia, the pembrolizumab group (n=97) was 18.8 months (95%CI 14.6, 24.2), and for the comparator group (n=96) median OS was 12.2 months (95%CI 10.4, 15.7). Median OS for CPS≥1 participants, Rest of the World, the pembrolizumab group

(n=105) was 20.3 months (95%CI 14.8, 27.9), and for the comparator group (n=104) median OS was 13.4 months (95%CI 10.4, 15.5).

For the Asia region, direction of effect favoured the comparator group, HR for pembrolizumab (reference comparator group) HR 1.15 (95%CI 0.76, 1.76) (CS Clarification response A17).[19]

PFS is generally, but not always, a suitable surrogate for OS, and EMA recommends trials with PFS as a primary endpoint include OS as an outcome.[35, 38] PFS may not be a suitable surrogate for OS due to treatment subsequent to study-treatment, or may be more pronounced where detection of progressed disease is improved, thus leading to a longer duration of post-progression survival.[44] For frailer patients with upper gastro-intestinal cancers, there are few subsequent treatment options available, and so PFS may be more reflective of OS. However, according to clinical advice, there is also the issue of pseudo-progression in immunotherapy, whereby there is an increase in size of the target lesion within a few weeks/months of starting immunotherapy, and so may overestimate progression rates at early measurements.

One meta-analysis found that treatment effects for PFS and OS were only moderately correlated in gastric cancer, although this included Asia region and non-Asia region trials, was not restricted by HER2 status (thus differing from the population in the company's model), and included trials with second-line treatments (which may act to dilute the effect of first-line treatment.[45]

Within the CPS≥1 subgroup, for patients aged <65 years there was a more favourable effect for pembrolizumab for OS (HR 0.63 [95%CI 0.48; 0.84]), than for patients aged 65 years or older (HR 1.06 [0.77; 1.47]), with a significant interaction effect p=0.0174 (CS Appendix E Table 23).

In a *post hoc* analysis of the combined subgroup of non-Asia regions, within CPS≥1 patients, (the company's preference of population) median time to death for the pembrolizumab group was 18.8 months (95%CI 15.5, 24.3), and for the comparator group 12.6 months (95%CI 11.1, 14.9) (CS clarification response A15).[19] The HR for OS favoured the pembrolizumab group, HR 0.67 ([95% CI: 0.52; 0.85], p=0.0006) (CS Section B2.6.1 Table 16 and CS Clarification response A15).[19]

Looking at a different cut-off for CPS, a *post hoc* analysis of the subgroup CPS≥10 did not find a significant treatment group difference for OS, HR 0.93 (95% CI: 0.66, 1.32) (CS Clarification response A5).[19] When restricted to non-Asia region participants, CPS≥10, OS HR for pembrolizumab (n=71) with reference comparator (n=64) was [redacted] (CS Clarification response A5).[43]

3.2.4.3 Response rate

At IA2, of the participants with CPS≥1, the pembrolizumab group had an ORR of 218/298 (73.2% [95%CI 67.7, 78.1]) (CS Section B2.6.1 Table 18). This comprised of 42 patients with CR, and 176 with PR (CS Section B2.6.1 Table 19). The comparator group had an ORR of 173/296 (58.4% (95%CI 52.6, 64.1)). This comprised of 29 patients with CR, and 144 with PR (CS Section B2.6.1 Table 19). The difference in ORR favoured the pembrolizumab group, estimate 14.7% (95%CI 7.1%, 22.2%) p=0.00008 (CS Section B2.6.1 Table 18). ORR for the ITT population were reported in CS Clarification response A18.[19]

The median DOR, of the participants with CPS≥1, was 11.3 months in the pembrolizumab group, and 9.5 months in the comparator group (CS Section B2.6.1 Table 20) and CS clarification response A23).[19]

3.2.4.4 Adverse events

The safety population included all randomly assigned patients who received ≥1 dose of study treatment, analysed by treatment received.[28]

In the global cohort there were four physician-assessed, drug-related, AEs resulting in death in the pembrolizumab group (pneumonitis, hepatitis, sepsis, and cerebral infarction) and three in the comparator group (myocarditis, pulmonary embolism, and cholangitis) (CS Section B2.10).

The safety population, for participants with CPS≥1, included 298 patients in the pembrolizumab group, and 295 in the comparator group (CS Section B2.10). For participants with CPS≥1, there were two physician-assessed. drug-related AEs resulting in death in the pembrolizumab group (pneumonitis, hepatitis) and one in the comparator group (myocarditis) (CS clarification response A20).[19]

At IA2, of the participants with CPS≥1, AEs led to discontinuation for 10.4% of the pembrolizumab group, and 8.8% of the comparator group (CS Appendix D1.2 Table 19). AEs of special interest led to discontinuation for 7.0% of the pembrolizumab group, and 4.1% of the comparator group (CS B2.10 Table 26).

For participants with CPS≥1, 97.0% of pembrolizumab treated patients experienced one or more AEs, and 96.3% of comparator treated patients (CS Section B2.10). Grade ≥3 AEs were experienced by 73.2% of the pembrolizumab treated patients, and 65.1% of the comparator treated patients (CS Appendix F). The most common grade 3-5 AEs were anaemia, diarrhoea, neutropenia, vomiting, nausea, fatigue, thrombocytopenia, neutrophil count decreased, platelet count decreased and peripheral sensory neuropathy (CS Section B3 Table 55 and CS Clarification response).[1,19]

An overview of AEs of special interest in the subgroup of participants with CPS≥1 is provided in CS Section B2.10 Table 26 and CS Appendix F. For participants with CPS≥1, 37.6% of pembrolizumab treated patients experienced one or more AEs of special interest, and 23.1% of comparator treated patients (CS Section B2.10). Grade ≥3 AEs of special interest were experienced by 10.4% of the pembrolizumab treated patients, and 3.4% of the comparator treated patients (CS Section B2.10).

3.2.4.5 Health-related quality of life (HRQoL)

HRQoL was analysed in participants with at least one dose of study treatment and at least one patient-reported outcome (PRO) assessment (CS Section B2.10). Change from baseline was based on a constrained longitudinal data analysis cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction and trial stratification factors. At IA2 in the CPS≥1 global cohort, change from baseline to week 24 in EQ-5D-5L was least square mean (LSMean) 1.20 (95%CI -0.81, 3.21) in the pembrolizumab group (n=292), and LSMean 1.36 (95%CI -0.81, 3.53) in the comparator group (n=290), with no significant change for either group, and no significant difference between groups (CS Section B2.6 Table 21; LSMean reported as analysis adjusted for covariates and stratification factors).

In the CPS≥1 non-Asia region participants, change from baseline to week 24 in EQ-5D-5L was LSMean [redacted] in the pembrolizumab group (n=[redacted]), and LSMean [redacted] in the comparator group (n=[redacted]) [redacted] (CS clarification response A21).[19]

3.3 Conclusions of the clinical effectiveness section

The EAG believes that no RCTs of pembrolizumab meeting the inclusion criteria of the NICE final scope have been missed. The company's search for clinical evidence reflected the decision problem in the NICE final scope, although the company's decision problem was limited by population (limited to the subgroup with PD-L1 CPS ≥ 1 in line with the anticipated marketing authorisation) and comparators (limited to trastuzumab and doublet chemotherapy). These restrictions were thought to be acceptable by the EAG.

One RCTs of pembrolizumab in previously untreated HER2- positive locally advanced, recurrent, and/or metastatic cancer gastric or GOJ cancer was included in the CS SLR: KEYNOTE-811. The key clinical evidence for pembrolizumab was based on the KEYNOTE-811 RCT. KEYNOTE-811 is a phase III, multi-centre, double-blind RCT, ongoing at the time of writing. Data were provided for interim analysis 2 (IA2). The study randomised 698 patients to either pembrolizumab in combination

with trastuzumab and chemotherapy, or placebo in combination with trastuzumab and chemotherapy. Chemotherapy was CAPOX or FP, with CAPOX given to the majority of patients in both treatment groups.

The CS concentrated on the subgroup of PD-L1 CPS ≥ 1 patients, and within that a subgroup by region that combined the two regions of Western Europe/Israel/North America/Australia, and Rest of World (including South America); that is excluding the Asia region. Both of these subgroup variables had been randomisation stratification factors. Patients with PD-L1 CPS ≥ 1 was a pre-planned subgroup analysis, the exclusion of the Asia region was a *post hoc* analysis. Although combining Western Europe/Israel/North America/Australia and Rest of the world does not break the randomisation as randomisation was preserved within each region, the EAG questions the validity of such subgroup analysis (Asia vs. non-Asia) due to the *post hoc* nature.

The KEYNOTE-811 RCT was well-designed to give a low risk of bias, however there is some uncertainty about statistical power of the PFS analysis. The trial was not powered for subgroups. There is some concern about the *post hoc* analysis of CPS≥1 excluding the Asia region, as it is uncertain whether the Western Europe subgroup alone would be more generalisable to England, than the grouping together with Rest of World subgroup.

According to clinical advice, patients in KEYNOTE-811 RCT were younger, with a higher proportion of white patients than would be seen in clinical practice in England, but were generally representative in terms of primary location of disease at diagnosis, and the mix of locally advanced versus metastatic disease. Age may influence effectiveness, as patients under 65 years appeared to have more favourable treatment effect toward pembrolizumab for PFS and OS than older patients, however there is uncertainty in this as KEYNOTE-811 was not powered for subgroups.

The primary outcomes were OS and PFS. At IA2, for CPS≥1 participants excluding the Asia region, the HR for OS favoured the pembrolizumab group, HR 0.67 ([95% CI: 0.52; 0.85], p=0.0006). Median OS for the pembrolizumab group was 18.8 months (95%CI 15.5, 24.3), and for the comparator group 12.6 months (95%CI 11.1, 14.9). At IA2, for CPS≥1 participants excluding the Asia region, the HR for PFS favoured the pembrolizumab group, HR 0.62 ([95% CI: 0.49; 0.78] <0.0001). Median PFS for the pembrolizumab group was 9.9 months (95%CI 8.3, 11.3), and for the comparator group 6.3 months (95%CI 5.6, 7.3).

For CPS≥1 participants, Grade ≥3 AEs were experienced by 73.2% of the pembrolizumab treated patients, and 65.1% of the comparator treated patients. For CPS≥1 participants, there was no significant

change for either group in HRQoL as measured by EQ-5D-5L, and no significant treatment group difference.

4 COST EFFECTIVENESS

4.1 EAG's comment on company's review of cost-effectiveness evidence

4.1.1 Objective of cost effectiveness review

The objective of the company's review of published cost-effectiveness studies is not entirely clear from the submission. CS, Appendix G, Section G.1 describes the review question as being to understand the economic burden of patients with untreated locally advanced unresectable gastric or GOJ adenocarcinoma, in addition to identifying studies reporting economic evaluations and health care resource use in this population. This objective is much broader than reviewing cost-effectiveness studies that match the decision problem in the NICE scope. However, the reporting of the review in CS, Section B.3.1 is more focused on the decision problem specified in the NICE scope, but this more focused objective is not clearly stated in the CS.

4.1.2 Searches

The company performed systematic literature searches in April 2023 for published cost-effectiveness studies, economic burden, and healthcare resource use (including cost data) of patients with untreated locally advanced unresectable gastric or GOJ adenocarcinoma (CS Appendix G). These searches were also used to identify studies that reported data on utilities associated with gastric cancer (section G.5.7., page 201) although supplementary HRQoL searches are also found in CS Appendix H.

In the cost-effectiveness studies, economic burden, cost, and resource use study search strategies were combined into one search strategy and the following sources were searched: MEDLINE [via Embase.com]; MEDLINE In-Process [PubMed]; Embase [via Embase.com]; NHS Economic Evaluation Database [via CRD databases]; and Tufts Cost-effectiveness Analysis Registry. The company has also undertaken searches of the bibliographies of the included studies and reviews.

The company searched several conference abstract websites in the last five years (2018-2023): ASCO; ASCO-Society for Immunotherapy of Cancer; ASCO-Gastrointestinal; American Society for Radiation Oncology; European Society for Medical Oncology; European Society for Medical Oncology; European Society for Medical Oncology-Gastrointestinal; European Society for Medical Oncology-Immuno-Oncology Congress; Asia-pacific Gastroesophageal Cancer Congress; American Association for Cancer Research; Japanese Society of Medical Oncology; Society for Immunotherapy of Cancer; European Cancer Congress; International Society for Pharmacoeconomics and Outcomes Research (Europe and International); Annual Meeting of Academy of Managed Care Pharmacy; and NEXUS.

Additionally, the company searched several country-specific and international Health Technology Appraisal websites: NICE; Scottish Medicines Consortium; Institute for Quality and Efficiency in Health Care; Haute Autorité de Santé; Canadian Agency for Drugs and Technologies in Health; Pharmaceutical Benefits Advisory Committee; International Network of Agencies for Health Technology Assessment; International Society for the promotion of health technology assessment (htai.org); and European Network for Health Technology Assessment. The EAG considers that the search is comprehensive.

The company conducted supplementary HRQoL and outcome searches for patients with locally advanced unresectable gastric or GOJ adenocarcinoma and their carers (CS Appendix H). The searches were undertaken in April 2023 in the following sources: MEDLINE [via Embase.com]; MEDLINE In-Process [PubMed]; Embase [via Embase.com]; the Central Register of Controlled Trials; and the Cochrane database of systematic reviews [via Wiley]. The company also searched several conference proceedings sources in the last five years, as listed in Appendix G of the CS (pages 149-150). There were no consequential errors in the search, and the EAG considers that the search is comprehensive.

While the searches in Appendix G.2 encompass the searches for cost and healthcare resource use (Appendix I), in addition to data from NICE HTAs, the company carried out additional searches of the excluded studies list to find disease management costs to reflect the current practice (Appendix I, pages 291-292). The strategies for the additional searches were not reported in the submission.

4.1.3 The inclusion and exclusion criteria used in the study selection

The target population for the review is described in Appendix G as "*adult (≥18 years) patients with previously untreated, locally advanced, unresectable gastric or GOJ adenocarcinoma*" (CS, Appendix G, Section G.3), with the table of inclusion/exclusion criteria defining this further as "*stage II-III-IVa*". The review search criteria suggest that the company also intended to identify studies in patients with stage 4b and 4c disease, and the review does appear to have included studies in patients with metastatic disease, despite not using this terminology when describing the target population. Based on this, the EAG's interpretation is that the review intended to cover both metastatic and unresectable locally advanced disease as per the population specified in the NICE scope.

The review is described as not limited to the treatment combinations listed in the NICE scope or whether treatment is being given as first-line treatment despite describing the target population as "*previously untreated*" (Document B, Appendix G). The review was not restricted to any country or geographical region. The review was not restricted to cost-effectiveness studies and also includes cost minimisation studies, budget impact studies, cost of illness studies and resource use studies. Therefore, the

inclusion/exclusion criteria for the review described in Appendix G appears to be much broader than the decision problem specified in the NICE scope.

4.1.4 Findings of the cost effectiveness review

Section B.3.1 of the CS states that no studies were identified which evaluated pembrolizumab in combination with trastuzumab in the specified population. The CS then goes on to describe details of the model that informed the NICE appraisal of trastuzumab (TA208). This is the only study described in Section B.3.1 despite 62 published studies being included in the broader review described in Appendix G.

4.1.5 Conclusions of the cost effectiveness review

The conclusion of the review in CS, Section B.3.1, appears to be that no cost-effectiveness studies evaluating pembrolizumab in combination with trastuzumab in the specified population were identified.

4.1.6 EAG critique of the company's review of cost effectiveness

The company's reporting of the results of the review implies that the objective of the review was to identify cost-effectiveness studies of either pembrolizumab in combination with trastuzumab or of the comparator strategies described in the scope, one of which is the treatment combination assessed in TA208.[10] It is unclear to the EAG why the company has conducted a review with such a broad remit in Appendix G, and has then restricted its reporting of the results of the review to a subset of these studies without providing a specific objective for the review which would justify this restriction. However, the EAG considered that it is unlikely that the company's review has failed to identify any cost-effectiveness analyses that are directly relevant to the decision problem specified in the NICE scope.

4.2 **Summary of the company's submitted economic evaluation**

4.2.1 Population

The population for the economic evaluation is described in CS, Table 28 as, "*adult patients with untreated locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction adenocarcinoma whose tumours express PD-L1 with a CPS≥1 (based on non-Asia region cohort).*"[1] The company's rationale is that this is aligned with the anticipated marketing authorisation and is informed by a trial population that is representative of NHS patients. As previously discussed, this is narrower than the population specified in the NICE scope which was not restricted by PD-L1 status. In addition, the company has chosen to use data from the non-Asia region, to populate the model, including the baseline characteristics summarised in Table 9.

Table 9 Baseline patient characteristics of base case model cohort (non-Asia CPS≥1 patients) (reproduced from CS, Table 29[1])

Characteristics	CPS≥1 (non-Asia region)
Age (years), mean	60.2
Male (%)	79.1
Body weight (kg), mean	72.0
Body weight (kg), standard deviation	16.3
BSA (m^2), mean	1.8
BSA (m^2), standard deviation	0.2

Abbreviations: BSA, body surface area; CPS, combined positive score.
Source: KEYNOTE-811 (database cut-off date: May 25, 2022).

4.2.2 Interventions and comparators

The intervention arm in the model is pembrolizumab plus trastuzumab plus chemotherapy. In the base case pembrolizumab is assumed to be given once every 3 weeks at a dose of 200mg by intravenous infusion. A scenario analysis explores the impact of 6-weekly dosing at a dose of 400mg. Pembrolizumab is assumed to be given until progression or unacceptable toxicity, up to a maximum of 35 cycles. As previously discussed in Section 2.3.2, [redacted] but otherwise the usage of pembrolizumab is consistent with the draft SmPC.

The chemotherapy given alongside pembrolizumab and trastuzumab in the intervention arm is assumed to be either CAPOX or FP as these were the two chemotherapy regimens used in KEYNOTE-811. The proportions receiving CAPOX and FP in the pembrolizumab are assumed to be 77.2% and 22.8% respectively based on data from the pembrolizumab arm of the KEYNOTE-811 study.

The comparator in the company's economic analysis is trastuzumab plus chemotherapy, again assumed in the company's base case to be CAPOX or FP, with the proportions receiving each treatment based on usage in the KEYNOTE-811 study (78.5% and 21.5% respectively). The company also provided a scenario analysis in which XP was also an option in the comparator arm. The company's response to clarification question B34 stated that this presumed that 80% of patients received XP, with the remaining proportion being distributed equally between CAPOX and FP.[19] This distribution was based on clinical expert advice.

The doses for trastuzumab, CAPOX, FP and XP are summarised in Table 10. All treatments are given using a 3-week cycle, with capecitabine taken orally on days 1 to 14, 5-FU given by continuous infusion

on days 1-5 and the other treatments given on day 1 of the cycle intravenously. Trastuzumab is the only treatment to include a higher loading dose in the first cycle. The maximum number of cycles was assumed to be 35 for trastuzumab and 6 for the double chemotherapy agents, however, the number of cycles actually received is determined by the time on treatment data from KEYNOTE-811, which is then capped at the maximum value stated in Table 10. The EAG notes that the caps on the duration of treatment for each drug shown in Table 10 were not strictly applied in KEYNOTE-811 and this discrepancy is discussed further in Section 4.3.3.2. Scenario analyses were provided by the company in which the treatment durations were not capped.

Table 10 Dosing schedules assumed in the model (reproduced from CS, Table 48[1])

Regimen	Drug	Frequency	Dosage	Maximum treatment cycles	Source for dosage
	Pembrolizumab	Q3W	200mg IV	35 [29]	SmPC[16]
Loading dose	Trastuzumab	NA	8 mg/kg IV on Day 1	35 [29]	NICE TA208[10]
Maintenance dose		Q3W	6 mg/kg IV on Day 1		
CAPOX	Capecitabine	Q3W	1000 mg/m2 orally BID on Days 1–14	6	KEYNOTE-811[27]
	Oxaliplatin		130 mg/m2 IV on Day 1	6	
FP	5-FU	Q3W	800 mg/m2 IV on Days 1–5	6	
	Cisplatin		80 mg/m2 IV on Day 1	6	
XP (Scenario analysis only)	Capecitabine	Q3W	1000 mg/m2 orally BID on Days 1–14	6	NICE Guideline NG83[8]
	Cisplatin		80 mg/m2 IV on Day 1	6	

Abbreviations: 5-FU, fluorouracil; BID, twice daily; IV, intravenous; NA, not applicable; NICE, National Institute for Health and Care Excellence; Q2W, ever 2 weeks; Q3W, every 3 weeks; SmPC, summary of product characteristics.
Note: all chemotherapy regimens are capped at a maximum of 6 cycles based on UK clinical expert opinion

4.2.3 Perspective, time horizon and discounting

The company's economic analysis is described in the CS as taking an NHS and Personal Social Services (PSS) perspective (CS, Table 28).[1] The source used to estimate health care costs for progressed disease did not specifically capture palliative care and did not assess costs falling on community, hospice or social care services. However, the end-of-life costs included did cover community nursing and hospice costs for patient dying outside of a hospital setting. This is further discussed in Section 4.3.3.9.

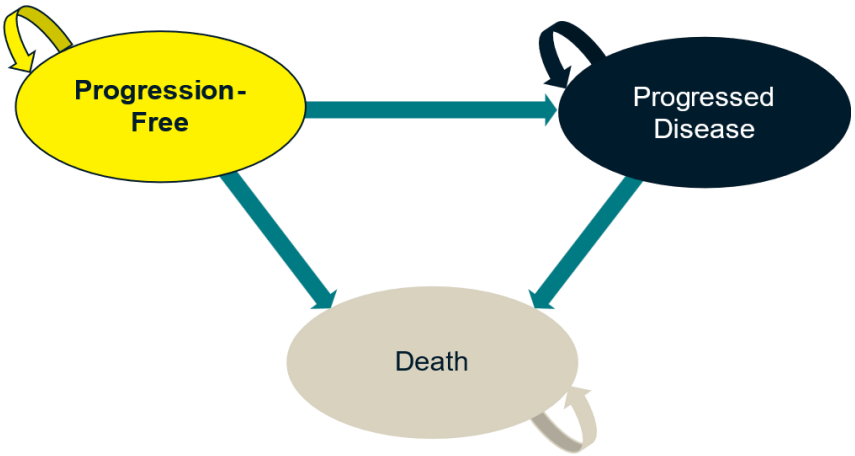
The company's base case uses a time horizon of 40 years with shorter time horizons of 8 and 20 years explored in scenario analyses. The company's model discounts future costs and benefits at 3.5% per annum.

4.2.4 Model structure

The general structure of the company's economic model is described on pages 95-97 of the CS[1] as a partitioned survival model based on three health states: (1) progression-free and alive; (2) post- disease progression and alive, and (3) dead (see Figure 2).

The EAG notes that occupancy of these health states influences only costs in the company's base-case analysis as HRQoL outcomes are modelled using a time-to-death approach rather than being based on the patient's progression status. However, the structure of the model allows the use of utilities by progression status which is explored by the company in a scenario analysis.

Figure 2: Company's model structure (reproduced from CS, Figure 12)[1]



In the company's base case analysis, patients enter the model in the progression-free state and receive first-line treatment with either pembrolizumab plus trastuzumab and doublet chemotherapy or trastuzumab and doublet chemotherapy; trastuzumab and doublet chemotherapy has been denoted standard of care (SoC) when describing the economic modelling.

The allocation of patients amongst the health states are determined by two chosen distributions, one for OS, and one for PFS. At any time, the probability of being alive and progression-free is given by the cumulative PFS survival curve. The probability of being alive following disease progression at any time is calculated as the cumulative probability of survival minus the cumulative probability of PFS. The probability of being dead at any time is the complement of the cumulative probability of survival. A partition survival approach does not explicitly model transitions between health states. Time on first-

line treatment is estimated directly from the treatment-specific time to treatment discontinuation (TTD) Kaplan-Meier (KM) data from KEYNOTE-811 study as explained in Section 4.2.6.1.3.

For the SoC arm, the cumulative probabilities of OS and PFS in each time interval are modelled using parametric distributions fitted to time-to-event data from the global (CPS≥ 1) cohort from KEYNOTE-811.[27] The OS and PFS curves for pembrolizumab plus trastuzumab and doublet chemotherapy (pembrolizumab plus SoC) are then modelled by applying constant HRs for OS and PFS from KEYNOTE-811 to the respective survival probabilities chosen for SoC. In contrast to the time-to-event data used for modelling OS and PFS for SoC, the HRs applied for OS and PFS were the ones reported for the non-Asia subpopulation.

The survivor functions and the evidence sources used to derive these functions are summarised in Table 11, with further detail provided in Section 4.2.6.1. Within each treatment group, the model applies two structural constraints: (i) that PFS must be less than or equal to OS, and (ii) that the OS risk for the modelled population must be at least as high as the mortality risk of the age- and sex-matched general population of the UK.

The EAG notes that the company in its clarification response stated that the global cohort data were used for modelling the survival curves for SoC as it was *"the most complete and quality-assured data set"* at the time of submission. However, it acknowledges that the company consider the non-Asia CPS ≥ 1 cohort, *"to be the most relevant to the England and Wales population"* (clarification response to question B2).[19]

HRQoL is assumed to be independent of treatment received and determined by the patient's time to death, based on four categorical groups (<30 days; ≥30 to 180 days; ≥180 to 360 days, and ≥360 days) with utility declining as patients approach death. Health utilities used in the model are based on the EQ-5D-5L data collected from the CPS ≥ 1 non-Asia region in KEYNOTE-811. Health utilities are adjusted to reflect reducing utilities with age across the life-time horizon.[46] In addition, the model explicitly includes QALY loss associated with Grade ≥3 AEs for pembrolizumab plus SoC and SoC alone. HRQoL inputs are further discussed in Section 4.2.6.2.

The model includes costs associated with: (i) drug acquisition; (ii) drug administration; (iii) subsequent treatment received; (iv) disease management; (v) management of AEs and (vi) end-of-life (terminal care) costs. Costs related to PD-L1 testing were not included as these *"tests are administered to all patients in both treatment arms of the model"*. Cost details are discussed in Section 4.2.6.4

The incremental health gains, costs and cost-effectiveness of pembrolizumab plus SoC versus SoC are modelled over a time horizon of 40 years using 1-week cycles. Half-cycle correction is applied only as a scenario analysis.

4.2.5 Key assumptions employed in the company's model

The company's model employs the following key assumptions for its base case:

- OS and PFS estimates from the trastuzumab and chemotherapy (CAPOX or FP) arm of the KEYNOTE-811 global cohort with PD-L1 CPS ≥1 are representative of expected OS and PFS under current standard care in England;
- The HRs for OS and PFS from the company's reported results for the non-Asia subgroup of patients with PD-L1 CPS ≥1 from KEYNOTE-811 are representative of the treatment effect expected from adding pembrolizumab to SoC in England;
- The HRs estimated during the trial period of KEYNOTE-811 (see Section 3.2.4) are expected to be constant over time both during and after treatment with pembrolizumab whereas waning of treatment effect was explored in scenario analyses;
- The model includes a general population mortality constraint to ensure that the risk of death for the modelled population is never lower than for the age-sex matched general population;
- The occupancy of the progression-free health state is constrained to ensure that there can never be more people in the progression-free health state than are alive;
- The rates of treatment discontinuation observed in the non-Asia subgroup of patients with PD-L1 CPS ≥1 from the respective treatment arms in KEYNOTE-811, for each separate component of treatment, are representative of the expected rates of discontinuation when these treatments are used for this patient group in England;
- Total number of treatment cycles given is constrained by a maximum number of treatment cycles that is specific to each component of the treatment combination (see Section 4.2.2), but is not constrained by progression status, meaning that the model allows patients to still get first-line treatment after progression;
- HRQoL is modelled according to the patients' time to death with utility declining as a patient approaches death and is therefore independent of treatment or progression status;
- A single administration cost is applied each cycle and this is based on the administration cost for the treatment component with the highest cost;
- Drug costing assumes no vial sharing for any intravenous drugs
- The proportions of patients receiving subsequent lines of treatment in each arm and are based on treatment arm specific data from KEYNOTE-811 but the durations of subsequent treatments are assumed to be the same across arms;

- The frequency of clinical follow-up visits and cardiac monitoring are assumed independent of treatment, but dependent on progression status with lower costs applied post-progression;
- A cost associated with terminal care was assumed in the model which was the same for all treatments evaluated;
- Only grade ≥3 AEs that occurred in ≥3% of all non-Asia CPS≥1 patients in either treatment group of KEYNOTE-811 are included in the company's model and these are assumed to occur at the start of treatment;
- All grade ≥3 AEs included in the model are assumed to have the same impact on HRQoL, but the utility decrement is applied for different durations for each AE
- All grade ≥3 AEs are assumed to require a hospital admission

The EAG notes in particular that the company has stated that they assume that the data from the non-Asia cohort are more clinically relevant and applicable to patients receiving treatment in England and therefore the majority of the model inputs were updated to use data from the non-Asia (CPS≥1) cohort (clarification response, B40).[19] The key exception was the OS and PFS data applied in the SoC arm which was based on the global (CPS≥1) cohort. These estimates also informed the OS and PFS in the pembrolizumab with SoC arm as these were estimated by applying a HR to the data for the SoC arm, although the HR was estimated from the non-Asia (CPS≥1) cohort.

4.2.6 Evidence used to inform the company's model parameters

Table 11 summarises the evidence sources used to inform the model's parameters in the company's updated base case analyses following the clarification process.[19] These are discussed in detail in the subsequent sections.

Table 11: Summary of evidence used to inform the company's base case analyses

Parameter group	Source
Patient characteristics (age, BSA, weight, proportion of females)	Based on characteristics of trial participants with PD-L1 CPS≥1 from the non-Asia region enrolled in KEYNOTE-811[27]
OS – SoC	A 2-knot odds spline model separately fitted to observed comparator* group OS data from KEYNOTE-811 (global cohort population with CPS ≥1).
OS – pembrolizumab plus SoC	The HR for OS for intervention** versus control group* estimated from KEYNOTE-811 (non-Asia subgroup with CPS ≥1) is applied to the OS survival function for SoC.
PFS – SoC	A 2-knot hazard spline model separately fitted to observed comparator* group PFS data from KEYNOTE-811 (global cohort population with CPS ≥1).
OS – pembrolizumab plus SoC	The HR for PFS for the intervention** versus control group* estimated from KEYNOTE-811 (non-Asia subgroup with CPS ≥1) is applied to the PFS survival function for SoC.

Parameter group	Source
TTD – pembrolizumab	Observed intervention group** TTD KM data from KEYNOTE-811 (non-Asia cohort with CPS ≥1) (truncated at 35 cycles).
TTD – trastuzumab and each component of either doublet chemotherapy (capecitabine, oxaliplatin, cisplatin, 5-FU)	Observed intervention group** and comparator group* TTD KM data from KEYNOTE-811 (non-Asia cohort with CPS ≥1). Separate KM data applied for each component of treatment in each arm. Trastuzumab capped at 35 cycles, chemotherapy capped at 6 cycles.
HRQoL	EQ-5D-5L data collected in KEYNOTE-811 (non-Asia subgroup with CPS ≥1) and mapped onto the 3L value set. Data analysed according to time to death (<30 days; ≥30 to 180 days; ≥180 to 360 days, and ≥360 days).
Frequency of AEs	AE frequencies for either treatment arm based on Grade ≥3 AEs with incidence of ≥3% from KEYNOTE-811 (non-Asia CPS≥1 analysis). Event frequencies were treatment arm specific and were adjusted to account for multiple AE episodes per patient.
QALY loss resulting from AEs	Estimated disutility was calculated based on analyses of EQ-5D-5L data from the KEYNOTE-811 as the difference between the "During Grade ≥3 AE" value and the "*without AE value*". This was the same irrespective of treatment arm. The duration for each AE was sourced from KEYNOTE-811 (non-Asia CPS≥1) and was assumed the same between treatment arms. QALY losses therefore only differ between arms due to differing frequencies of specific AEs
Probability of receiving subsequent therapy	Arm-specific proportions receiving each agent of subsequent treatments in KEYNOTE-811 (non-Asia cohort with CPS ≥1).
Mean duration of subsequent therapy	Agent-specific mean duration in KEYNOTE-811 (non-Asia cohort with CPS ≥1).
Drug acquisition costs	Electronic Market Information Tool (eMIT) and British National Formulary (BNF).[47, 48]
Drug administration costs	National Schedule of NHS Costs 2021/22[49]
RDI	Based on KEYNOTE-811 study (non-Asia cohort with CPS≥1) for first-line treatments but assumed to be 100% for subsequent therapies.
Disease management costs	Based on NICE TA208,[10] National Schedule of NHS Costs 2021/22,[49] and Gomez-Ulloa *et al*.[50]
Costs associated with AEs	Unit costs based on previous NICE TAs,[10, 14, 51] National Schedule of NHS Costs 2021/22.[49]
End of life care costs	Based on a previous NICE appraisal (TA522),[52] inflated to 2021/22 costs using the HCHS pay & prices and the NHSCII indices.[53]

5-FU - 5-fluorouracil; AE - adverse event; BSA - body surface area; CSP - combined positive score; EQ-5D-5L - EuroQol EQ-5D 5-level; HCHS - hospital & community health services; HR - hazard ratio; HRQoL - health-related quality of life; KM - Kaplan-Meier; NHSCII - NHS Cost Inflation Index; OS - overall survival; PFS - progression-free survival; QALY - quality-adjusted life year; RDI - relative dose intensity; TA - technology appraisal, TTD - time to treatment discontinuation
**Control group corresponds to the placebo plus trastuzumab and CAPOX/FP arm in KEYNOTE-811 study*
***Intervention group corresponds to the pembrolizumab plus trastuzumab and CAPOX/FP arm in KEYNOTE-811 study.*

4.2.6.1 Time-to-event parameters

The company's approach used for each individual endpoint and each arm is described in further detail in the subsequent sections. Time-to-event outcomes for the SoC and pembrolizumab plus SoC groups are based on data from the comparator and intervention arms of KEYNOTE-811.[27]

The EAG notes that based on the company's response to clarification questions, the non-Asia CPS ≥1 subgroup from the trial should be considered the most relevant to the population of England.[19] However, the company's base case still uses the KM data for PFS and OS from the global cohort CPS ≥1 of the KEYNOTE-811 to model the survival outcomes for the SoC arm.

4.2.6.1.1 Overall survival (OS)

The company used a proportional hazards modelling approach to extrapolate OS "*in accordance with the non-rejection of the proportional hazards assumption*". The proportional hazards modelling approach consists of two steps. The first step is to fit both standard parametric and Royston-Parmer spline models to the individual patient-level data (IPD) from the SoC arm of the global cohort with CPS≥1 KEYNOTE-811 (trastuzumab with CAPOX or FP [N= 296]). The second step is to apply the HR (0.67) calculated from a Cox regression model using the non-Asia CPS≥1 subgroup to the selected comparator model to derive the survival for the intervention arm.

In response to clarification question B2, the company clarified the reason for using the global (CPS≥1) cohort for the control arm as follows "*In the submitted model, OS and PFS extrapolations for the SoC arm were informed by data from the Global CPS≥1 cohort. Analysis of the population submitted for regulatory approval was prioritised with analysis of subgroups completed in succession. At the time of submission, the most complete and quality-assured data set was presented*."[19]

The company considered six standard parametric survival models: exponential, Weibull, Gompertz, log-logistic, log-normal and generalized gamma. In addition, various spline models with different assumptions (modelling the log cumulative hazard [hazard], the log cumulative odds [odds], or the inverse normal distribution of the survival function [normal] as a spline function) and different numbers of knots were also investigated.

The CS states that the candidate models were assessed for inclusion in the base case analysis through consideration of relative goodness-of-fit statistics (the Akaike Information Criterion [AIC] and the Bayesian Information Criterion [BIC]); visual inspection of the fitted distributions to the observed data; examination of the Schoenfeld residual and the cumulative hazard functions to judge the proportional hazard assumption; and expert opinion.

Among the standard parametric models, the company selected the log-logistic model based on AIC/BIC for the SoC arm which also had a reasonable visual fit to the hazard plot and to the KM curve. Similarly, the 2-knot odds model was selected as the best fit among the spline models. The latter was preferred over the log-logistic model based on *"visual comparison"*. Figure 3 presents the KM survival functions and modelled OS survival functions for both arms. In its base case the company assumed no treatment waning effect, therefore the survival benefit associated with adding pembrolizumab to SoC is sustained for the entire modelled time horizon. The company also presented a scenario analysis implementing a treatment waning from 7 years to 9 years.

Figure 3: OS survival functions included in company's base case analysis (adapted from CS, Figure 23)

In response to clarification question B6, the company performed alternative extrapolation approaches (jointly modelling approach with treatment as a covariate and independent modelling approach) using the non-Asia (CPS≥1) subgroup.[19] However, the results from these survival analyses have not been applied in the updated economic model. This is discussed in detail in in Section 4.3.3.2 of the EAG's critique, with the EAG's preferred approach to modelling OS described in Section 4.4.2.2.

4.2.6.1.2 Progression-free survival (PFS)

As with the OS analysis, the analysis of PFS was based on a proportional hazards modelling approach "*in accordance with the non-rejection of the proportional hazards assumption*". The first step is to fit a survival model to the SoC arm from the global cohort with CPS≥1 in KEYNOTE-811 (trastuzumab and CAPOX or FP [N=296]). The company fitted the same range of standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma) and spline models.

The second step is to apply the HR (0.62) calculated from a Cox regression model using the non-Asia CPS≥1 subgroup to the selected comparator model to derive the survival for the intervention arm.

Among the standard parametric models, the log-logistic model was selected as the best fit for the SoC arm based on the AIC/BIC and having a reasonable visual fit to the hazard plot and to the KM curve. Similarly, the 2-knot hazard model was selected as the best fit among the spline models. The latter was preferred over the log-logistic model based on *"visual comparison"*. Treatment waning was not considered by the company due to the maturity of the trial data. A constraint is applied to the model to ensure that PFS must be less than or equal to OS at any given time. Figure 4 presents the KM survival functions and modelled PFS survival functions for both arms.

Figure 4: PFS survival functions included in company's base case analysis (adapted from CS, Figure 31)

In response to clarification question B6, the company performed alternative extrapolation approaches (jointly modelling approach with treatment as a covariate and independent modelling approach) using the non-Asia (CPS≥1) subgroup.[19] However, the results from these survival analyses have not been applied in the updated economic model. This is discussed in detail in in Section 4.3.3.2 of the EAG's critique, with the EAG's preferred approach described in Section 4.4.2.3.

4.2.6.1.3 Time to treatment discontinuation (TTD)

In KEYNOTE-811, TTD data for all CPS ≥1 global cohort patients were relatively mature, and the KM data were used directly to inform the company's base case model without the need for parametric extrapolation which the company deemed to *"introduce additional uncertainty to a dataset which is deemed reasonably informative"*. Arm-specific TTD data were used to inform treatment acquisition

and administration costs and were available for each single agent involved (i.e., pembrolizumab, trastuzumab, capecitabine, oxaliplatin, 5-FU, and cisplatin) as depicted in the CS, Figures 32 to 37.[1]

In addition, all treatments had maximum durations after which all patients discontinue this treatment. These were 35 cycles for pembrolizumab and trastuzumab in line with the trial protocol, and 6 cycles for all chemotherapy agents, in line with NHS clinical practice, as confirmed by the company's clinical experts. The EAG has commented on the appropriateness of capping the number of cycles for each treatment in the combination in Section 4.3.3.3.

The EAG notes, however, that a constraint to ensure that TTD does not exceed PFS is not included in the base case analyses. This leads to the assumption that patients can receive first-line treatment after disease progression. However, after examining the TTD and PFS curves the EAG did not think this was likely to be a significant issue.

4.2.6.2 Health-related quality of life (HRQoL)

HRQoL data used in the company's model are based on EQ-5D-5L data collected in KEYNOTE-811 from the non-Asia subgroup with CPS≥1. Within the study, the questionnaire was administered at baseline, every 3 weeks for the first 5 treatment cycles (weeks 1, 4, 7, 10 and 13), then every 6 weeks until week 52 or end of treatment, whichever was earlier; in the case of treatment discontinuation, the questionnaire was also applied at the treatment discontinuation and 30-day post-treatment safety follow-up visits. The utility values were then mapped to the 3L value set using the mapping function developed by the Decision Support Unit (DSU).[54]

Utility values in the base case analysis were estimated for the pooled treatment arms by proximity to death, based on four categorical groups (<30 days; 30 to 179 days; 180 to 359 days, and ≥360 days). The utilities for each time-to-death category are assumed to be independent of initial treatment.

Within the model, the proportion of patients in the time-to-death categories at each time *t* were calculated as follows:

- < 30 days from death: calculated as the probability of dying during the interval *t*+0 cycles and *t*+4 cycles;
- 30 days to 179 days from death: calculated as the probability of dying during the interval *t*+5 cycles and *t*+25 cycles;
- 180 days to 359 days from death: calculated as the probability of dying during the interval *t*+26 cycles and *t*+50 cycles;

- ≥360 days from death: calculated as the 1 minus of the sum of the probabilities of being in the other three states.

The EAG notes that the description of the time-to-death categories do not align with the implementation in the model. In the model, the four categories are: <4 weeks (28 days); ≥4 to 24 weeks (28 to 175 days); ≥25 to 51 weeks (175 to 357 days), and ≥51 weeks (357 days). The EAG notes, however, that this is unlikely to noticeably affect the ICER and fitted in with the weekly time cycle in the model.
The use of a time-to-death approach for modelling HRQoL is justified by the company on the basis that it would overcome the problem of limited questionnaire availability to inform the post-progression health state utility estimates, which is a consequence of the EQ-5D questionnaire collection not being collected after treatment discontinuation or beyond 30-days after disease progression. Therefore, the estimates of utility data for post-progression health state may not be representative of the patient's quality of life in the whole post progression state. The estimates for utility data applied in the company's model are summarised in Table 12. Additionally, the company provided a scenario analysis where the EQ-5D data were analysed by the progression status using data pooled across both trial arms, and this resulted in mean utility values of [redacted] and [redacted] for the progression-free and progressed-disease health states respectively. A second scenario was also conducted which used the baseline utility value from the trial for the PFS state ([redacted]), and then utility for the progressed disease state was estimated using the difference in utilities between progression-free and progressed disease patients in the trial, giving a utility of 0.706 ([redacted]).

Table 12: Mean EQ-5D utilities used in the company's base case analyses (reproduced from CS Table 40)

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

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

Health utilities are adjusted for aging by using utility multipliers for each age. This was achieved by estimating general population utility values at the baseline starting age of the model and subsequent ages using the DSU database.[54] The multiplier was then calculated by dividing the utility value at any specific age by the baseline utility value, this value was then multiplied by the QALYs calculated for each of the time-to-death categories per cycle.

Table **13** shows a selection of multipliers used at certain ages. The removal of the health utilities age-adjustment was explored in the company's scenario analyses.

Table 13: Utility multipliers used in the company's base case to adjust for utility decline by age*

Age	General population utility	Utility multiplier
60.2 (starting age)	0.845	1.00
65	0.828	0.98
70	0.810	0.96
75	0.789	0.93
80	0.768	0.91
85	0.744	0.88
90	0.718	0.85
95	0.689	0.82
100	0.656	0.78

** annual declines implemented but only 5-year values presented here*

4.2.6.3 Adverse events

The company's model included all Grade 3+ AEs and those that occurred in at least 3% of all patients in either arm of the KEYNOTE-811 trial. These data were initially based on the global cohort, as presented in CS, Table 55.[1] However, in response to clarification question B40, these data were updated in the model to reflect the non-Asia subgroup for the non-Asia (CPS≥1) cohort.[19] The updated data, extracted from the model by the EAG, are presented in Table 14 were further adjusted by the company to account for the mean number of each AE per patient.

Table 14: AE frequency per treatment arm used in the company's base case model (non-Asia subgroup CPS ≥1 in KEYNOTE-811; supersedes global cohort data in CS, Table 55[1])

Adverse event	% of patients experiencing the event		Mean number of events per patient		Adjusted % of patients experiencing the event*	
	Pembrolizumab + SoC†	SoC†	Pembrolizumab + SoC†	SoC†	Pembrolizumab + SoC†	SoC†
Anaemia						
Neutropenia						
Thrombocytopenia						
Diarrhoea						
Nausea						
Vomiting						
Asthenia						
Fatigue						
Neutrophil count decreased						
Platelet count decreased						
Decreased appetite						
Hypokalaemia						
Peripheral sensory neuropathy						

**defined as the total number of AE episodes (considering that some patients experienced multiple AE episodes) divided by the total patient number*

† SoC = trastuzumab and chemotherapy

The disutility for modelled AEs ([redacted]), which was assumed to be the same for all modelled AEs, was estimated based on analyses of EQ-5D data from the KEYNOTE-811 trial, as the difference between the "*During Grade 3+ AE*" utility value and the "*without AE*" utility value. In response to clarification question B15, that company stated that the difference between the "*During Grade 3+ AE*" value and the "*without Grade 3+ AE*" value was similar ([redacted]) and using this alternative estimate had only a minor impact on the ICER.[19]

Mean duration of AE per affected patient in KEYNOTE-811 were reported in Table 44 of the CS.[1] The company stated in response to clarification B40, that the AE duration had been updated to use data from the non-Asia region,[19] but the EAG noted that the data appeared to be identical to those provided prior to clarification.

QALY loss due to AEs was incorporated in the model for the modelled cohort by multiplying the disutility by AE-specific mean duration and by AE incidence (specific to both the treatment arm and the individual AE) and applying this as a one-off QALY loss in the first cycle of the model. This accounted to QALY losses of [redacted] and [redacted] for the pembrolizumab and the SoC arms respectively.

4.2.6.4 Resource use

4.2.6.4.1 Drug acquisition and administration costs

Drug acquisition costs have been calculated based on the dosing schedules provided in Table 10. There is a patient access scheme (PAS) in place for pembrolizumab. The cost per cycle provided in Table 15 incorporates this PAS. None of the other treatments included in the first-line treatment regimens covered in Table 15 have a confidential PAS. The company obtained used an NHS indicative price for trastuzumab and eMIT prices for all other first-line therapies. NICE has provided the EAG with confidential prices for trastuzumab and capecitabine from the commercial medicines unit (CMU) and the impact of including these is explored in a confidential appendix. The prices cited by the company have been used in the EAG analyses reported in Section 4.4.

The company has applied a simple relative dose intensity (RDI) approach to account for missed or delayed doses between the first and last dose received in KEYNOTE-811 (see clarification response B22).[19] This is calculated as the actual number of cycles administered divided by the expected number of cycles administered based on the time between the first and last dose (multiplied by 100 to convert the proportion into a %). For drugs received once per cycle, this correlates to the proportion of doses received, whereas for drugs where more than one dose is administered per cycle, a cycle is counted as having been administered provided a single dose has been received. Therefore, this approach does not account for missed doses for patients self-administering oral capecitabine. It also does not account for any administrations where the dose was reduced but still administered even though dose modifications

were permitted in KEYNOTE-811.[29] As the company considers the RDI to be confidential, the EAG has summarised the drug costs when assuming 100% RDI in Table 15. The actual RDI values applied in the model can be found in CS, Table 49.[1]

For pembrolizumab the dose is not dependent on weight or body surface area (BSA) and the 200mg dose can be achieved using a whole number of vials. For all other intravenous drugs, the company's base case analysis includes drug wastage, assuming in its calculations that no vial sharing across patients occurs and any partially used vials are discarded. The company uses a method of moments approach to estimate the average number of vials required based on assuming a lognormal distribution for patient weight. The company assumes no wastage when estimating the costs for treatments administered orally. The company also provides a scenario analysis in which vial sharing is assumed to occur in 100% of intravenous administrations resulting in zero drug wastage.

The CS assumes that all combinations of intravenous treatments can be given within a single session covered by a single reference cost. Treatment combinations including 5-FU are assumed to be covered by SB14Z (Deliver complex chemotherapy, including prolonged infusion treatment, at first attendance) at a cost of £474.94, due to the requirement for prolonged infusion over 5 days. All other treatment combinations are assumed to be covered by SB13Z (Deliver more complex parenteral chemotherapy at first attendance) at a cost of £353.64. The company states that both trastuzumab and pembrolizumab are considered to be complex treatments with short infusion times. It argues that it is appropriate to include only a single reference cost for complex chemotherapy (SB13Z) when these drugs are given after chemotherapy is completed (i.e after CAPOX or XP) whether trastuzumab is given alone or in combination with pembrolizumab. However, the company did provide a scenario in which a lower cost was applied when trastuzumab is given alone, in response to clarification question B27, and the further critique is provided on this issue in Section 4.3.3.6. Administration of oral capecitabine is assumed to incur no additional cost when given alongside an intravenous treatment.

Table 15 Drug acquisition and administration costs per cycle (when assuming 100% RDI, base case assumes wastage)

Treatment	Dose per administration	Administrations per cycle	Drug dose in mg (no wastage)	Drug dose in mg (with wastage)	Drug cost per cycle, £ (no wastage)	Drug cost per cycle, £ (with wastage)	Admin cost per cycle, £
Pembrolizumab	200 mg	1	200	200	[redacted]	[redacted]	0
Trastuzumab	6 mg/kg*	1	576	665	1,056	1,267	/ 354**
Capecitabine (CAPOX)	1000 mg/m^2	28	1800	1800	31	31	354
Oxaliplatin (CAPOX)	130 mg/ m^2	1	234	384	25	41	
5FU (FP)	800 mg/ m^2	5	1440	2500	12	20	475
Cisplatin (FP)	80 mg/ m^2	1	144	200	16	22	
Capecitabine (XP)	1000 mg/m^2	28	1800	1800	31	31	354
Cisplatin (XP)	80 mg/ m^2	1	144	200	16	22	

* 8 mg/kg loading dose has a drug cost of £1,408 without wastage and £1,625 with wastage;

** £354 when given after chemotherapy, either together or alone – zero additional cost when given with chemotherapy

4.2.6.4.2 Subsequent treatments

The company has estimated subsequent treatment by combining treatments received in any treatment line after completing or discontinuing the study drug. The company has restricted its analysis to the top eight subsequent treatments received but has increased the usage of these to incorporate the usage of other less frequently received treatments. It has also redistributed the proportion receiving paclitaxel with ramucirumab as this treatment combination is not available in clinical practice in England despite being one of the eight most common subsequent treatments in KEYNOTE-811. This redistribution is assumed to affect only the cost of the subsequent therapies with clinical outcomes being assumed to be unchanged by the distribution of subsequent therapies. The resultant proportions are summarised in Table 16, alongside the durations of subsequent treatment which have been estimated across both study arms. When calculating the drug acquisition and administration costs for subsequent treatments, the company has used as similar approach to that taken for first-line therapies but has assumed an RDI of 100%. Combining the information on the distribution of subsequent therapies, their duration and their costs provides a total cost for subsequent therapies of £5,556 and £3,683 for the intervention and comparator arms (these supersede the figures given in CS, Table 58 of £8,283 and £8,549 respectively[1]). The EAG notes that the company's analysis does not include the confidential PAS price for trastuzumab deruxtecan as this information was not available to the company. The EAG has provided a confidential appendix which includes the impact of incorporating the confidential PAS for trastuzumab deruxtecan. The price for trastuzumab deruxtecan cited by the company has been used by the EAG in the analyses reported in Section 4.4.

The average cost of subsequent treatment per patient completing or discontinuing their study drug has been applied to patients leaving the progression-free health state. This means it is applied to patients at the time of either progression or death, rather than at the time of completing or discontinuing study drug. The company has also provided a scenario analysis in which the costs of subsequent treatment are increased to account for the fact that only a proportion of the cohort have progressed at the time of the study follow-up. The proportions for this scenario are also presented in Table 16. In this scenario the subsequent treatment costs are £9,739 and £5,892 for intervention and comparator arms respectively. Based on clinical advice, a scenario analysis has also been provided assuming that only 50% of patients receive subsequent therapies and these are evenly split between docetaxel and platinum rechallenge with CAPOX, with the intention of reflecting treatments received in current clinical practice in England rather than those received in KEYNOTE-811. The subsequent treatment costs in this scenario are £902 for both arms. Further critique of the company's estimation of subsequent therapies is provided in Section 4.3.3.7.

Table 16 Proportions of patients receiving subsequent treatments per treatment arm (non-Asia CPS≥1 cohort)[*]

Subsequent treatments[†]	Company's base case		Scenario where % is uplifted to account for proportion who have not progressed		Mean duration of subsequent treatment across both arms (weeks)	Drug acquisition cost per week, £	Drug administration costs per week, £
	Pembrolizumab with SoC[‡], %	SoC[‡], %	Pembrolizumab with SoC[‡], %	SoC[‡], %			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	8.04	88.41
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2,234.88	95.57
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.26	143.36
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.19	237.47
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4.41	95.57
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85	237.47
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	351.98	95.57
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA	NA	NA

[*] adapted from clarification response Table 43,[19] which supersedes CS Table 57; mean duration has been extracted from the model as data from CS Table 63 have been superseded by data for the non-Asia CPS≥1 cohort but these were not presented in the clarification response[19]

[†]Most common treatment combinations or monotherapies excluding paclitaxel with ramucirumab - accounted for 6.7% and 12.8% across intervention and control arms – % receiving this combination and % receiving any other treatments were redistributed to give correct total % receiving subsequent therapies

[‡]SoC = trastuzumab with chemotherapy

4.2.6.4.3 Disease management by health state

Resource use for the progression-free health state (excluding administration of first-line treatment) is based on information from the appraisal of trastuzumab in TA208. The company assumes an overall cost of £176 per week, (see CS Table 52 for details) which covers oncology outpatient attendances and cardiac monitoring. The CS applies two difference reference costs for follow-up oncology appointments, with one applied once per three weeks and the other applied once every six weeks, giving a total of 26 follow-up visits per annum during PFS. The CS assumes cardiac monitoring 4 times a year with one third of this monitoring being by multigated acquisition scan (MUGA) scan and the other two thirds by echocardiogram. The monitoring costs are being applied for the whole of the PFS duration rather than for the duration of trastuzumab, although the EAG notes that the intention would be to continue trastuzumab until disease progression, with treatment being only stopped before then only due to unacceptable toxicity. Therefore, the duration of trastuzumab treatment is likely to be similar to the progression free duration in the majority of patients.

Resource use for the progressed disease health state were based on a retrospective chart review of patients receiving second line treatment for confirmed metastatic or unresectable gastric or GOJ adenocarcinoma in one of 5 countries, including the UK. Each patient's charts were reviewed for 12 months after starting second line treatment or until death, which ever occurred first. The majority of patients UK (92%) patients had received HER2 status testing and 20% were HER2-postive. The majority had received triplet chemotherapy at 1st line (73%). The paper reports the percentage of patients receiving different types of health care resources including hospital admission, emergency room visits and outpatient visits. The mean observation period was 6.6 months and the CS states that each patient reported as having used a particular type of resource is assumed to have used it once in that period. The overall cost is £2,132 per annum (£42 per week, see CS, Table 53 for details).[1] The EAG has provided further commentary on the appropriateness of the resource use estimates based on this study in Section 4.3.3.8.

4.2.6.4.4 Adverse event management

The company model includes resource use for hospital admission for a non-elective short stay for each of the grade 3+ AEs included in the model, and these are reproduced in Table 17. These are applied as a one-off cost assuming that AEs occur mainly during the first cycle of treatment. The proportion of patients experiencing one or more AE of each type is increased to account for the mean number of AEs per patient (see Table 14). Overall, this results in a cost of £565 for the pembrolizumab arm and £394 for the comparator arm (these supersede values in Table 56 of the CS[1], which was based on the frequency of AEs in the global CPS >=1 cohort rather than the non-Asia CPS>=1 cohort). The EAG's clinical advisors stated that sepsis and diarrhoea were the main AEs that result in admission in this

patient population. They agreed that AEs related to chemotherapy would be likely to occur early in the model, however, they noted that rare but severe AEs can occur with ongoing pembrolizumab treatment. In response to clarification question B30, which asked the company to explore the potential impact of rare but severe immune-related AEs for patients receiving pembrolizumab, the company conducted an analysis which increased the cost due to AEs by 10% for the intervention arm only.[19] Based on this analysis which showed limited impact on the ICER, the company concluded that its base case approach to modelling AEs was robust.

Table 17 Adverse event unit costs (reproduced from CS, Table 54[1])

Adverse event	Unit cost (£)	Notes
Anaemia	770	Weighted average of SA01G-K non-elective short stay: based on ERG criticism in TA737
Neutropenia	2,257	Weighted average of SA35A-E; note that TA208 currency codes for febrile neutropenia have been discontinued
Thrombocytopenia	993	Weighted average of SA12G-K: consistent with TA857
Diarrhoea	522	FD10M non-elective short stay; consistent with TA857, TA208 codes have been discontinued
Nausea	522	Assumed equal to diarrhoea
Vomiting	522	Assumed equal to diarrhoea
Asthenia	780	Assumed equal to fatigue
Fatigue	780	SA01G - Aplasia or Other Aplastic Anaemia, with CC Score 8+. Non-elective short stay (consistent with TA737). NR in TA208
Neutrophil count decreased	445	Non-elective short stay. WJ11Z Other disorders of immunity (consistent with TA737). NR in TA208
Platelet count decreased	993	Assumed equivalent to thrombocytopenia
Decreased appetite	561	Weighted average of Non-elective short stay FD04B-E; NR in TA208
Hypokalaemia	2,257	Assumed equivalent to neutropenia
Peripheral sensory neuropathy	607	Weighted average of AA26C-H, Acute setting

Abbreviations: ERG, Evidence Review Group; NR, not reported; TA, technology appraisal

4.2.6.4.5 End of life costs

The company's estimate of end-of-life costs was taken from the appraisal of pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer (TA522).[52] This CS reported this cost as £7,253 (2015/2016 value) for hospital care in the last three months of life.[1] This was increased by the company to £8,169 to reflect current prices.[1, 55]

4.2.6.4.6 PD-L1 testing costs

The company has assumed in its base case that no additional testing will be required to determine eligibility for pembrolizumab in this cohort based on PD-L1 status because patients are already routinely tested for HER2 and PD-L1 status concurrently in order to determine eligibility for nivolumab which is already recommended by NICE in the HER2-negative cohort (TA857).[1, 14] In its response to clarification question B26, the company provided information on the potential PD-L1 testing costs that would apply if testing was not already being carried out.[19] They estimate a cost of £424 per patient eligible to receive pembrolizumab based on a cost of £53 per test and an estimate that eight patients would need to be testing to identify a single eligible patient. However, when these data are incorporated in the model inputs, this cost is applied to both treatment arms and therefore it has no impact on the ICER.

4.2.7 Model validation and face validity check

The company describes its model validation process as including quality checks, clinical expert opinion and comparison with external data sources. The quality checks on the model (verification) were conducted by an independent health economist using the TechVER checklist.[56] The company sought expert opinion from two clinical experts who are experienced in the management of HER2-positive advanced gastric or GOJ cancer patients in England. It said that these discussions were used to ensure that the base case reflects current UK practice and to assess the face validity of the outcomes predicted by the model. The CS states that the comparison with other trial data was limited by the paucity of trials available and its comparison of model outcomes was limited to the model used to inform the appraisal of trastuzumab in TA208.

4.2.8 Cost effectiveness results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process. The results presented in this section include the company's agreed PAS for pembrolizumab whilst excluding price discounts available for any other drugs used in subsequent treatments. The results incorporating the confidential PAS discount for trastuzumab deruxtecan and the CMU prices for trastuzumab and capecitabine are provided in a confidential appendix to this EAG report. The company has presented evidence to support a QALY weight of 1.2, based on its assessment of the severity modifier. The company's evidence to support this severity modifier is further discussed in Section 5. The EAG has presented company results both with, and without, this QALY weight.

Central estimates of cost-effectiveness

The company's base case cost-effectiveness results are presented in Table 18, which shows the probabilistic estimates of the company's base case estimated using the average costs and QALYs across 1,000 probabilistic sensitivity analysis (PSA) samples when the model was rerun by the EAG. Total costs, QALYs and ICERs were judged to have converged after running the PSA 1,000 iterations.

The probabilistic version of the model suggests that the pembrolizumab arm is expected to generate an additional [redacted] QALYs at an additional cost of £[redacted] per patient compared to the SoC arm resulting in an ICER of £[redacted] per QALY gained (£[redacted] when the QALY weight is 1.2). The deterministic version of the model produces a slightly lower ICER (£[redacted] per QALY gained without QALY weight). QALY gains predominantly relate to differences in survival as utility is related to time-to-death rather than progression status (1.94 additional life years gained on the pembrolizumab arm in the probabilistic model).

Table 18 The company's base case results

Technology	LYs	QALYs accrued	Total costs incurred	Incremental			ICER	ICER with 1.2x QALY weight
				LYs	QALYs	Costs		
Probabilistic model (1000 runs by the EAG)								
SoC*	3.12	[redacted]	[redacted]	-	-	-		
Intervention**	5.06	[redacted]	[redacted]	1.94	[redacted]	[redacted]	[redacted]	[redacted]
Deterministic model								
SoC*	3.03	[redacted]	[redacted]	-	-	-		
Intervention**	4.94	[redacted]	[redacted]	1.91	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years
** SoC: Trastuzumab plus chemotherapy*
*** Intervention: Pembrolizumab with SoC*

The company's model presents disaggregated outcomes for the deterministic model in terms of costs accrued by different elements and QALYs accrued in different time-to-death categories. These results are presented in Table 19. The differences in costs are primarily associated with the acquisition cost of pembrolizumab whilst the additional QALY gain is mainly a consequence of additional time spent on the pembrolizumab arm in the over-360-day time to death category compared to the SoC arm, and the higher utility value associated with such category.

Table 19 Base case disaggregated outcomes for company's base case (deterministic model)

Description	Intervention**	SoC*	Incremental
Disaggregated costs (discounted)			
Drug acquisition costs	[redacted]	[redacted]	[redacted]
Drug administration costs	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
AE related costs	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
End of life costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]
Disaggregated QALYs (discounted)			
Time to death <30 days	[redacted]	[redacted]	[redacted]
Time to death 30-179 days	[redacted]	[redacted]	[redacted]
Time to death 180-359 days	[redacted]	[redacted]	[redacted]
Time to death ≥360 days	[redacted]	[redacted]	[redacted]
QALYs gained with AEs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; QALY, quality-adjusted life-years.
** SoC: Trastuzumab plus chemotherapy*
*** Intervention: Pembrolizumab with SoC*

Figure 5 presents the cost-effectiveness plane for the company's base case PSA, and Figure 6 shows the corresponding cost-effectiveness acceptability curve (CEAC) (both based on the EAG's re-run of 1,000 PSA samples). The EAG's re-run of the company's PSA suggests that the probability that the pembrolizumab arm generates more net monetary benefit than the SoC arm at a WTP threshold of £20,000 and £30,000 per QALY gained is approximately [redacted] and [redacted] respectively. The same probabilities are [redacted] and [redacted] respectively when a QALY has 1.2x weight.

Figure 5: Company's base case PSA scatterplot with the QALY weight of 1x (run by the EAG)

Figure 6: Company's base case CEAC with the QALY weight of 1x (run by the EAG)

4.2.9 Company's deterministic sensitivity analyses

The company's deterministic sensitivity analyses were rerun by the EAG post-clarification and are presented using a tornado plot (Figure 7 and Figure 8 for a QALY weight of 1 and 1.2 respectively). The analyses are performed by using the lower and upper bounds of 95% confidence intervals assuming that the standard error was set as 20% of the mean if not reported.

The company's results show that the parameters which had the biggest impact on the ICER were: the HR value used to extrapolate the OS survival curve for the pembrolizumab arm (ICER difference of ~£ between when using the lower bound and upper bound values); relative dose intensity associated with pembrolizumab (ICER difference of ~£); the HR value used to extrapolate the PFS survival curve for the pembrolizumab arm (ICER difference of less than £); relative dose intensity associated with trastuzumab (ICER differences of), and the unit cost and frequency of clinician's visits while still progression-free (ICER differences of less than £). None of the other parameter ranges explored produced an ICER difference above £ per QALY gained.

Figure 7: One-way scenario analysis results for the company's post-clarification base case at a QALY weight of 1

Figure 8: One-way scenario analysis results for the company's post-clarification base case at a QALY weight of 1.2

4.2.10 Sensitivity analyses

Updated results for scenario analyses for the pembrolizumab arm versus the SoC arm are provided in the clarification response to question B42 with, and without, using the QALY weight (CS, Tables 54 and Table 55 respectively). The EAG requested additional scenarios which were provided in the clarification response to questions B12 and B36. All the ICERs reported within the text of this section are without the QALY weight. The scenarios with the largest impact that increased the ICER were limiting the model's time horizon to 8 years (which increases the ICER from £[redacted] to £[redacted]), the treatment effect on OS waning gradually between 7 and 9 years from the model start (i.e. applying a gradual increase to the OS HR till it approaches 1) (increases the ICER to ~£[redacted]), limiting the model's time horizon to 20 years (ICER increases to ~£[redacted]), and using a utility value set based on the progression status (which increases the ICER to between £[redacted] when progression-based utilities are used from KEYNOTE-811 and ~£[redacted] when using baseline utilities from KEYNOTE-811 for PFS and maintaining the proportionate difference between PFS and progressed-disease from KEYNOTE-811). The only scenarios that had a large impact but decreased the ICER were those assuming no discounting or 1.5% discounting (ICERs between ~£[redacted] with no discounting and ~£[redacted] with 1.5% discounting).

The following scenarios had less impact on the ICER (less than £[redacted]) compared with the above mentioned scenarios: assuming an RDI of unity for pembrolizumab, trastuzumab, and all first-line chemotherapy; not applying age-related disutilities; different assumptions regarding subsequent therapy in the UK and the proportions receiving it; pembrolizumab administered at a dose of 400 mg every 6 weeks instead of a 200 mg 3-week cycle; assuming vial sharing; excluding end-of-life costs; excluding disutility attributed to AEs; first-line chemotherapy distribution informed by clinical experts instead of using trial data; using the mean number of cycles as observed in the trial to decide treatment duration; and removing the treatment duration cap.

4.3 Critique of company's submitted economic evaluation by the EAG

4.3.1 Model verification

The EAG believes the company's updated version of the model to be generally well programmed with two exceptions. The way the model is coded means it is not possible to select the choice of cohort (global versus non-Asia) used to inform the OS and PFS in the comparator arm separately from the choice between using a HR approach or using separately fitted curves to model the intervention arm. The EAG also identified a minor error related to the administration costs for paclitaxel when used as a subsequent therapy, which is described in Section 4.3.3.6. The impact of correcting this error is explored in Section 4.4.2.1. The EAG also experienced issues when working with the company's model which sometimes froze or closed unexpectedly without saving a recovery backup version.

4.3.2 Adherence of the company's model to the NICE reference case

The EAG has summarised the adherence of the company's model to the NICE reference case in Table 20. The main issues identified related to the choice of relevant comparators, in particular the choice of doublet chemotherapy given in combination with trastuzumab. However, these issues have been previously covered in detail in Section 2.3.3 and 4.2.2.

Table 20 Adherence of the company's economic analysis to the NICE reference case

Element	Reference case	EAG comments
Population	The scope developed by NICE	The population in the company's economic model is narrower than the population in the NICE scope because it is restricted to patients with PD-L1 CPS ≥ 1. The EAG accepts that this is appropriate because it is aligned with the anticipated marketing authorisation. The company has also assumed that the non-Asia region cohort from KEYNOTE-811 are most representative of the patients likely to be offered treatment in clinical practice in England and has therefore used this cohort to define the starting characteristics in the model and to source the majority of the model parameters.
Intervention	As listed in the scope developed by NICE	The intervention is pembrolizumab in combination with trastuzumab and chemotherapy (pembrolizumab plus SoC). The chemotherapy offered in the intervention arm is assumed to be the same as offered in the comparator arm and is therefore discussed below.
Comparator(s)	As listed in the scope developed by NICE	The comparator is trastuzumab with chemotherapy (SoC), with chemotherapy assumed to be either CAPOX or FP in the company's base case analysis. The proportions receiving either doublet chemotherapy is informed by the treatment regimens offered in KEYNOTE-811. The EAG notes that only FP or XP are used in combination with trastuzumab in current clinical practice in England and XP is preferred when patients are able to tolerate oral treatments. The company has also explored a scenario analysis in which the majority of patients receive XP, which the company considers better reflects chemotherapy usage in England based on clinical expert advice. The company has not included either triplet chemotherapy or doublet chemotherapy without trastuzumab as comparators in the economic model. The EAG's comments on this have been given previously in Table 4, but in summary, the EAG considers this to be reasonable as current practice is to offer trastuzumab with doublet chemotherapy, rather than doublet chemotherapy alone, in any HER2-positive patient where trastuzumab is not contraindicated. In addition, triplet chemotherapy is not widely used in the indication.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The company's approach is consistent with the NICE reference case. Health gains accrued by patients are valued in terms of QALYs gained. Health impacts on carers are not included.

Element	Reference case	EAG comments
Perspective on costs	NHS and PSS	The company's base case analysis adopts an NHS and PSS perspective. This is therefore consistent with the NICE reference case. However, the EAG notes that costs for social care do not appear to have been included except in the context of end-of-life costs.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company has not provided a fully-incremental analysis against each of the comparators specified in the NICE scope because they have argued that triplet chemotherapy and doublet chemotherapy without trastuzumab are not relevant comparators. They have therefore only provided a single comparison against trastuzumab with doublet chemotherapy. The company has also not provided an incremental comparison against trastuzumab combined with each possible combination of doublet chemotherapies (see Table 3 for the possible combinations). Instead, it has assumed that each fluoropyrimidine and platinum-containing doublet chemotherapy is clinically equivalent, and has used the mix of doublet chemotherapy treatments offered in KEYNOTE-811 in its base case. The company has explored the impact of altering the mix of doublet chemotherapies offered but this only affects estimates of costs.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A 40-year horizon has been adopted. This is considered by the EAG to be consistent with the NICE reference case in this population.
Synthesis of evidence on health effects	Based on systematic review	The company conducted a systematic review, but only one study, KEYNOTE-811, was identified to inform the clinical outcomes in the model. The company considered the feasibility of conducting an indirect comparison against doublet chemotherapy alone (i.e., without trastuzumab) using data from the TOGA study, but concluded that this was not feasible.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health gains are valued in terms of QALYs. Utility values obtained from the EQ-5D-5L in the KEYNOTE-811 study have been incorporated in the company's economic analysis. These have been mapped, using an appropriate approach, to a UK general population valuation set for the EQ-5D-3L.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	

Element	Reference case	EAG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	The company has presented evidence to support a severity modifier of 1.2x using estimates of expected QALYs in people treated with trastuzumab with chemotherapy based on estimates from TA208. In response to clarification, the company has presented ICERs both with and without the severity modifier applied. The company's evidence in support of the severity modifier is commented on in Section 5.
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	The company's base case cost-effectiveness analysis generally used appropriate estimates of resource use and unit costs that were consistent with the NICE reference case.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum. This is consistent with the NICE reference case.

4.3.3 Key issues identified from the EAG's critical appraisal

The main issues identified from the EAG's critical appraisal are summarised in Box 1 with cross references provided to the subsections where these are discussed in more detail. Items numbered 1, 2, 3, and 5 in Box 1 were identified as key issues in Section 1.

Box 1 Summary of the main issues identified within the company's health economic model

1. The model has been populated with data from the non-Asia CPS ≥1 cohort, which is a *post hoc* combination of data from two regions, and it is unclear if data from the Western Europe/Israel/North America/Australia region would be more generalisable to England than data from the Rest of World region (**Key Issue 1** –Section 3.2.3 and 4.3.3.1)
2. PFS and OS survival curves for the SoC arm use data from the global CPS ≥1 cohort instead of data from the non-Asia CPS ≥1 cohort, despite the company claiming that data from the non-Asia region are more generalisable to England (**Key Issue 2** – Section 4.3.3.2)
3. A proportional hazards modelling approach has been used to extrapolate OS and PFS in the pembrolizumab plus SoC arm and a constant HR has been applied life-long for both OS and PFS (**Key Issue 2** – Section 4.3.3.2)
4. Duration of treatment for each component of the intervention and control arms is capped by a maximum number of cycles resulting but this does not always correspond with usage in the KEYNOTE-811 study or expected usage in clinical practice in England (Section 4.3.3.3)
5. Use of utilities based on time-to-death utilities rather than a progression-based approach (**Key Issue 3** – Section 4.3.3.4)
6. Administration costs for trastuzumab are the same when given alone or in combination with pembrolizumab (Section 4.3.3.5)
7. Subsequent therapies based on KEYNOTE-811 do not reflect current practice (Section 4.3.3.6)
8. Disease management costs for patients who are progression-free overestimate follow-up visits and exclude costs for routine staging scans (Section 4.3.3.7)
9. Disease management costs for patients with progressed disease underestimate follow-up visits and costs for routine staging scans (Section 4.3.3.8)
10. End-of-life (terminal care) costs are based on estimates from an appraisal of urothelial cancer (Section 4.3.3.9)

4.3.3.1 Generalisability of the non-Asia cohort to patients being treated in England

As previously discussed in Section 3.2.3, the company considered that data from the Asia region were less generalisable to a UK setting and therefore used data from a non-Asia cohort which was generated by combining data from two regions: Europe/Israel/North America/Australia and Rest of World. Whilst each of the regions was prospectively defined as a subgroup of interest and region was a stratification factor in the randomisation, the combination of data from two regions into a non-Asia cohort was *post hoc*. The EAG agrees with excluding the Asia cohort from the analysis, but the EAG considers that the company has not adequately justified whether patients from the Rest of World region are as generalisable to eligible patients in England as patients from the Europe/Israel/North America/Australia region. The EAG considers that the Western Europe/Israel/North America/Australia cohort may be more applicable to clinical practice in England, and as this was a pre-specified subgroup and a stratification factor it would be valid to populate the model with data exclusively from the Europe/Israel/North America/Australia in CPS ≥ 1) cohort. However, the EAG were unable to do this using the data provided by the company.

4.3.3.2 Approach to modelling OS and PFS

The EAG disagrees with the company's survival extrapolation approach for the following reasons: (i) the extrapolated curve for the intervention arm for both OS and PFS does not fit the intervention arm data from the KEYNOTE-811 trial (see Figure 3 and Figure 4); (ii) data from the global cohort were used in the extrapolation when the company has claimed that data from the non-Asia cohort are more generalisable to the UK; (iii) a constant HR was assumed for a life-time which has not been justified by the company; (iv) a HR generated from a separate Cox model was applied.

In response to clarification question B6, the company provided survival extrapolation for OS and PFS based on the non-Asia CPS≥1 subgroup and joint modelling approach (i.e., with treatment as a covariate).[19] The company determined the most plausible model for OS is a 2-knot hazard spline model and for PFS is a log-logistic model. However, the results from these survival analyses have not been applied in the updated economic model. The EAG disagrees with the use of a joint modelling approach because either a constant HR was assumed for a life-time which has not been justified by the company, or a constant acceleration factor was assumed for a life-time which has not been justified by the company.

The EAG notes that in response to clarification question B6, the company also provided the results (estimated model coefficients, AIC and BIC) from the independent modelling approach (i.e., fitting a model to each arm independently).[19] Again these results have not been applied in the updated economic model and the company did not provide its view in terms of the most plausible model for OS and PFS when using an independent modelling approach.

As described in Section 4.3.1, the company's updated model does not allow the user to select options related to the choice of cohort (global versus non-Asia) separately from options related to the choice between using a proportional hazards modelling approach or independent parametric modelling approach.

The EAG's preferred approach to modelling OS and PFS, which incorporates curves fitted to data from the non-Asia (CPS ≥1) cohort using the independent modelling approach, is described in Sections 4.4.2.2 and 4.4.2.3.

4.3.3.3 Duration of treatment for each component of the intervention and control arms

Whilst the company's base case analysis assumed that the treatment duration for each drug would be capped as described in Section 4.2.2, this was inconsistent with the treatment durations permitted in the KEYNOTE-811 study for some drugs. The company clarified (response to question A8) that a second course of pembrolizumab (up to 17 cycles) was allowed following disease progression in patients who had either stopped treatment after 35 administrations for reasons other than disease progression or toxicity (i.e. they had completed the course), or had stopped treatment after attaining a complete response.[19] However, this only occurred in 1% (3/298) patients in the CPS≥1 global cohort. As the company also stated that all these patients were in the non-Asia region, the EAG infers that this occurred in 1.5% (3/202) patients in the CPS≥1 non-Asia cohort. Also, the mean duration of treatment for patients starting a second course was 8.8 weeks, with a range of 6.4 to 10.9 weeks suggesting that most patients only received 2 or 3 doses in their second course. As the second course was only taken up by a small proportion of patients and typically lasted a short duration, the EAG is satisfied with this not contributing to the costs of pembrolizumab in the model and has therefore kept the company's assumption that the maximum duration of treatment for pembrolizumab is 35 cycles.

The duration of trastuzumab is capped in the company's base case analysis at 35 cycles, although the CS notes that there is no restriction on duration of treatment in TA208, other than for disease progression or unacceptable toxicity.[10] The CS is inconsistent in reporting whether the duration of trastuzumab was restricted in KEYNOTE-811, stating on page 154 that a maximum of 35 doses could be given in the trial, and stating on page 35 that it could be given for up to a year after the 35 doses. The EAG's clinical advisors stated that they would continue to offer trastuzumab up to disease progression or unacceptable toxicity in clinical practice, but in practice most patients stopped before reaching 35 cycles. Based on this, the EAG preferred to use the TTD KM data to determine treatment duration for trastuzumab (see Section 4.4.2.4).

The EAG notes that the number of cycles for cisplatin and oxaliplatin was based on local guidance in KEYNOTE-811, with this being 6 cycles for cisplatin and 6 to 8 cycles for oxaliplatin (clarification

response A7).[19] The company states that the majority of patients in England receive 6 cycles of oxaliplatin based on clinical advice. The EAG's clinical advisors agreed that stopping chemotherapy at six cycles was a reasonable assumption for the majority of this patient group, although one clinical advisor noted that they often started patients on 4 cycles of chemotherapy, with the option to reassess and extend to 8 cycles, rather than starting with a 6-cycle course.

The duration of capecitabine and 5-FU was not restricted in KEYNOTE-811 to the same duration as the platinum-containing agent, with both being allowed up to 1 year after the 35 cycles of either pembrolizumab or placebo had been completed. The mean duration of each chemotherapy agent was shown previously in

Table 8. The EAG's clinical advisors noted that they do not generally extend capecitabine or 5-FU beyond the duration of the platinum-containing treatment in clinical practice because extended use is not thought to improve outcomes in this indication but is associated with AEs that might require hospital admission. The company has provided a scenario analysis in which the mean number of cycles was applied for each chemotherapy agent (see clarification response B35) and a scenario in which the actual TTD curve for each treatment given in KEYNOTE-811 was applied unrestricted (see clarification response B36).[19] As the EAG's clinical advisors advised that extended use of chemotherapy is unlikely to improve outcomes, and may overestimate the costs of treatment relative to clinical practice, the EAG prefers to assume in its base case that the duration of chemotherapy is capped, as in the company's base case. However, it has explored the impact of applying the mean number of chemotherapy cycles administered in KEYNOTE-811 as a scenario analysis. It has also explored the impact of restricting the maximum duration of chemotherapy to 4 cycles to determine how sensitive the model is to duration of chemotherapy given in standard care (see Section 4.4.2.4).

4.3.3.4 Utilities based on time-to-death instead of progression

There is considerable 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 EAG comments that neither approach overcomes the main limitation that the data collected have been heavily censored, either at the point of progression, or at treatment discontinuation.

The EAG's clinical advisors disagreed with the use of a time-to-death approach. They suggest that progression symptoms and AEs are key drivers for utility, and an analysis based on time without symptoms or toxicity (TWiST) may be a better approach to use.

Patients with a time-to-death ≥360 days or 180 to 360 days are assigned utility scores of [redacted] and [redacted], respectively. These values are very similar to the general population utility value for individuals aged [redacted] years and [redacted] years respectively (estimated general population utilities are [redacted] and [redacted] in the model at these ages respectively). The model may therefore overestimate HRQoL for patients in these time-to-death categories, given that the population has advanced gastric or GOJ cancer.

The company's utility analysis was based on descriptive statistics rather than modelling the data using a mixed effects model to consider the fact that data were repeatedly measured and to adjust for covariates which may be important confounders. In response to clarification question B16, the company investigated analysing utility data using a linear mixed effects regression model for both time-to-death based and progression based approaches.[43]

For the utility analysis with the time-to-death approach, the company explored the inclusion of age, sex, grade 3+ AEs and time-to-death as fixed effect covariates and concluded that both age and sex are not statistically significant, and these variables are not included in the final model. The mean and standard error based on the time-to-death approach are presented in Table 21.

Table 21 Mean (Standard Error) of EQ-5D utilities by time-to death using linear mixed effects model (reproduced from the company's additional analysis[43])

Time-to-death (days)	Without Grade 3+ AE	During Grade 3+ AE
<30	[redacted]	[redacted]
30-180	[redacted]	[redacted]
180-360	[redacted]	[redacted]
>360	[redacted]	[redacted]

Abbreviations: AE, adverse event.

For the utility analysis with progression status, the company also explored to include age, sex, grade 3+ AE and progression status as fixed effect covariates and concluded that both age and sex are not statistically significant, and these variables not are not included in the final model. The mean and standard error based on the progression-based approach are presented in Table 22.

Table 22 Mean (Standard Error) of EQ-5D utilities by progression status using linear fixed effects model (reproduced from the company's additional analysis [43])

Health state	Without Grade 3+ AE	During Grade 3+ AE
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

Abbreviations: AE, adverse event.

The EAG notes that the company's additional analyses also provide descriptive statistics for both time-to-death and progression-based approaches.[43] However, the number of patients and the estimated mean in each category are slightly different from the values presented in the CS. The EAG is unclear about the reasons for such discrepancy.

The EAG prefers to use the utility values estimated using a linear mixed effect model instead of descriptive statistics because the mixed effect modelling approach takes into account of the effect of covariates and correlations within a patient, and provides estimates with more face validity. The EAG therefore uses the data from Table 21 in its base case but has explored the use of data from Table 22 as scenario analysis.

4.3.3.5 Administration costs for trastuzumab alone versus pembrolizumab with trastuzumab

The company's base case applies the reference cost for health resource group (HRG) code SB13Z to trastuzumab whether given alone or with pembrolizumab after completion of CAPOX/XP. In response to clarification question B27, the company stated that it had explored a scenario analysis in which patients receiving trastuzumab monotherapy (i.e. those receiving SoC after completion of either CAPOX/XP) have an administration cost of SB12Z (Delivery simple chemotherapy at first attendance), whereas those receiving pembrolizumab in combination with trastuzumab after completion of CAPOX/XP continue to have SB13Z.[19] The results for this scenario are not provided by the company although it states that it resulted in a minor increase in the ICER which it described as negligible. The EAG considers that there should be some difference in administration costs for trastuzumab given alone versus trastuzumab given in combination with pembrolizumab. The EAG accepts that both are complex treatments but believes the company's scenario which applies a cost of £286.71 (HRG code SB12Z) for administering trastuzumab alone and £353.64 (HRG code SB13Z) for administering trastuzumab in combination with pembrolizumab is more appropriate when trying to capture the incremental impact of adding pembrolizumab to the existing treatment pathway (see Section 4.4.2.6).

4.3.3.6 Subsequent therapies

The EAG is concerned that the company has estimated subsequent therapies per patient completing or discontinuing study drug but has then applied the costs to those leaving the PFS state for any reason. Those leaving the PFS state due to death rather than progression are unlikely to incur costs for subsequent therapies. Equally, those stopping treatment for reasons other than progression or death, will incur subsequent therapy costs within the PFS state rather than at the time of exiting the PFS state. The company has implemented a scenario analysis, in which they increase the subsequent therapies costs to account for the fact that not all patients have either progressed or died at the time of the data cut. However, for this they have used the proportion of patients starting treatment who have progressed and not the proportion of patients completing or discontinuing treatment who have progressed.

In addition, the EAG was unable to verify the company's estimates of subsequent treatments from the drug utilisation report provided.[42] The data used in the company's model appear to analyse subsequent treatments according to the treatment combination received e.g. paclitaxel is separate from ramucirumab with paclitaxel, whereas the drug utilisation report only provides total usage of individual agent regardless of whether they were used alone or in combination.[42] The EAG understands that this means that the usage reported in the drug utilisation report and usage implemented in the model may not correlate exactly if some combinations were not frequent enough to be included in the top eight treatments. This means that some more commonly used drugs may have been excluded from the model where they were combined with other drugs in a combination that was used infrequently. This also

makes it impossible for the EAG to verify the data used in the model from the data provided in the drug utilisation report.

The EAG's clinical advisors said that there was no standard second line chemotherapy option for this patient group. One clinical advisor said that their most common treatment was docetaxel, but they were aware that some larger centres used paclitaxel, and some centres offered irinotecan. The other clinical advisor said that their preferred option was irinotecan with 5-FU and folinic acid (FOLFIRI), particularly if the patient had received a taxane containing regimen in the adjuvant or neoadjuvant setting. The EAG's clinical advisors noted that trastuzumab deruxtecan and nivolumab are not available outside of clinical trials. One clinical advisor said they would sometimes rechallenge with platinum but only if they had used less than the maximum dose at first-line and if the patient had been progression-free for more than a year. The other clinical advisor commented that they would not rechallenge with platinum if there had been progression on platinum-based chemotherapy. The EAG considered that these responses were not supportive of the company's scenario in which platinum rechallenge was used as commonly as docetaxel. The EAG also noted the conclusions of the committee in TA378 (TA of ramucirumab for treating advanced gastric cancer or GOJ adenocarcinoma previously treated with chemotherapy) which considered appropriate comparators for patients previously treated with chemotherapy.[57] In that appraisal, the committee heard from professional group submissions that taxanes are routinely used with irinotecan and FOLFIRI used less frequently. The committee concluded that both docetaxel and paclitaxel were relevant comparators with FOLFIRI and irinotecan not considered relevant because they are not in established use.[57] In addition, in TA852 (TA of trifluridine–tipiracil for treating metastatic gastric cancer or GOJ adenocarcinoma after 2 or more treatments), the committee heard that paclitaxel was generally used as second line treatment.[57] The EAG has conducted an exploratory analysis in which further treatment is equally split between docetaxel and paclitaxel and has included this assumption in their base case (see Section 4.4.2.7).

The EAG notes that the company's costing of paclitaxel does not capture the requirement for weekly intravenous infusions due to an error in the implementation. It appears that the company had intended to model second-line paclitaxel as infusions on days 1, 8, and 15 of a 28-day cycle but has instead only included one administration cost per 28-day cycle by selecting none for the resource use of doses given on days 8 and 15. Therefore, the EAG has also corrected this within its exploratory analysis (see Section 4.4.2.1). This increases the admin cost for paclitaxel from £88.41 per week to £273.27 per week.

4.3.3.7 Disease management for the progression-free state

The company stated at clarification that it was unclear how to interpret the expert opinion cited in the appraisal of trastuzumab with chemotherapy (TA208) regarding the frequency of follow-up visits during PFS.[19] It therefore considered that it was more conservative to apply both 3-weekly and 6-weekly

follow-up costs. However, based on the EAG report for TA208 (page 66) the EAG believes that the company applied follow-up visits once per 3-week cycle whilst receiving chemotherapy and once every other cycle (i.e., 6-weekly) for the remainder of their PFS regardless of whether they received trastuzumab or no further therapy.[58] Therefore, including both 3-weekly and 6-weekly follow up visits concurrently for the duration of PFS as in the company's approach is incorrect. The EAG therefore prefers to exclude the 3-weekly follow-up visits from the PFS costs, leaving the 6-weekly follow-up visits included, but has allowed for additional visits to account for 3-weekly follow-up during chemotherapy (see Section 4.4.2.8).

One clinical advisor stated that they would see patients 3-monthly after they completed chemotherapy, whilst the other stated that they would see patients 6-weekly after completing chemotherapy. Therefore, the PFS costs, which assumed continued 6-weekly throughout the period of PFS, may be overestimated relative to clinical practice in some NHS centres, although it is not possible to know the degree to which this might bias the ICER without having more comprehensive information from a range of centres.

The EAG notes that the CS does not include any routine computerised tomography (CT) scans for detecting progression whereas the EAG's clinical advisors stated that they would do 3-monthly CT scans with additional CT scans or endoscopies requested if patients had new symptoms. The EAG has included 3-monthly CT scans in its exploratory analysis (see Section 4.4.2.8)

The EAG's clinical advisors stated that they use cardiac monitoring less frequently than every 3 months in this population as this patient group are unlikely to be on trastuzumab for many years. They therefore use cardiac monitoring every 3 to 6 months during trastuzumab treatment and echocardiogram is used more than MUGA. Therefore, cardiac monitoring costs may also be overestimated in the company's base case, although the EAG expects the impact of this on the ICER to be small and therefore has not amended this.

The EAG's clinical advisors noted that specific blood tests are required to monitor patients receiving pembrolizumab to detect immune-related hepatitis, nephritis and endocrinopathies. This involves requesting blood tests for full blood counts, liver function tests and urea and electrolytes each cycle and cortisol tests every 8 weeks. Costs for these are not included in the company's model but were included for patients in the progression free health state in TA737.[51] However, the EAG notes that the costs for these blood tests are likely to be low, with costs in the progressed disease health state of £4.70 and £1.54 applied for full blood counts and biochemistry tests respectively. The EAG has therefore not explored this issue further.

4.3.3.8 Disease management for the progressed disease costs

The EAG considers that it is unlikely that resource use after disease progression should be less than resource use prior to disease progression. The EAG considers that this discrepancy is likely due to the company's assumption that only one incidence of resource use occurred per patient which potentially underestimates resource use, particularly for activities such as routine outpatient follow-up which may not occur as one-off outcomes. The company has excluded resource use types that were used in less than 5% of patients meaning that higher cost imaging tests such as magnetic resonance imaging (MRI) and positron emission tomography (PET) scans were excluded despite being reported in the UK cohort. The EAG notes that this study was restricted to patients starting second-line treatment options and therefore it does not capture typical resource use for patients who were too unwell to receive second-line chemotherapy treatment. Also, in many patients, the period of observation will overlap with the 3 months before death which the company has included as a separate end of life cost. The authors state that palliative care costs may be underestimated because they were not specifically captured in this study which was restricted to capturing "*hospitalizations, outpatient and emergency room visits, and laboratory and imaging tests performed*".[50] In addition, this paper is reporting resource use for 5 UK sites in the period 2013 to 2015 and may therefore not reflect current UK practice. The EAG's clinical advisors stated that whilst progressed patients who are not eligible for further treatment would be seen less by hospital oncologists, they may be seen more frequently in a community rather than a hospital setting to receive palliative care. The EAG notes that this community based palliative care would not have been captured in the Gómez-Ulloa *et al*. study.[50] Also, whilst the company's estimates of subsequent treatment costs capture administration costs for ongoing treatments, they do not capture the follow-up care required in patients with progressed disease who are receiving subsequent treatments and these appear to be potentially underestimated by Gómez-Ulloa *et al*. due to the assumption that each patient who reported a specific category of care only received that type of care once during the 6 months of follow-up. The EAG notes that in the appraisal of trastuzumab with chemotherapy (TA208) it was assumed that patients with progressed disease would receive supportive care at a cost of £542 per month in addition to the costs of subsequent treatment, although this was based on an estimate from a guideline for breast cancer rather than gastric cancer.[58] In addition, TA737 assumed 3-monthly consultations for patients with progressed disease which is higher than the 1.5 outpatient visits per annum applied by the company.[51] In response to clarification question B25, the company explored using the cost from TA208, (£679 when inflating the cost of £542 to current prices) and it reported that this increased the ICER by £3000.[19] Clinical advice to the EAG was that regular CT scans would not be used in patients no longer receiving active treatment and in these patients CT scans would only be required if there was an acute problem that might need intervention. However, as the model does not distinguish between progressed patients who are receiving subsequent therapy and those receiving only supportive care, it was not possible to properly reflect this advice in the model. The EAG has explored an assumption of applying 4 outpatient visits and 4 CT scans per year for progressed disease to see if

the cost-effectiveness is sensitive to assumptions regarding resource use post-progression (see Section 4.4.2.9).

4.3.3.9 End of life costs

The EAG identified the source of the terminal care cost from TA522 cited by the company.[52] It noted that while the company describes this as "*hospital care in the last 3 months of life*", according to Table 27 of the EAG report for TA522, the costs included both hospital and community care.[59] This included GP home consultations, community nursing hours, Macmillan nursing hours for terminal care at home as well as terminal care in a hospice or hospital. The majority of the resource use was based on a Marie Curie funded report which estimated the costs over 14 days of dying at home, in a hospital or hospice setting which was not specific to any type of cancer.[60] The estimate from TA522 also included costs for radiotherapy which amounted to 45% of the overall terminal care costs and these radiotherapy sessions were based on TA272 which was an appraisal of a treatment for advanced or metastatic urothelial cancer.[59] The EAG did not understand why the cost of radiotherapy sessions estimated for patients with urothelial cancer should be included in the cost of terminal care for patients with gastric or GOJ cancer. In TA737, the EAG queried the applicability of terminal care costs from TA522 to a population with gastro-oesophageal cancer patients and explored the impact of excluding radiotherapy costs.[51] The EAG in that appraisal also explored the impact of implementing the terminal care costs used in TA707 which were £8,974 over 3 months in 2019 prices.[51] However, as it was reported in the EAG report for TA737 that the ICER was not particularly sensitive to the end-of-life cost, the EAG has noted that this is an area of potential uncertainty but has not amended its base case analysis.

4.4 Exploratory analyses undertaken by the EAG

4.4.1 Overview of EAG's exploratory analyses

The methods for the EAG's exploratory analyses are provided in Section 4.4.2 with results provided in Section 4.4.3. The EAG has indicated in each case which changes are included in its base case and which are included only in its scenario analyses.

4.4.2 EAG's exploratory analyses – methods

4.4.2.1 Correction of errors in the company's model

The EAG corrected the company's implementation of administration costs for paclitaxel to match the intended weekly administration schedule. This was achieved by setting the resource use selection in N125 of the 'Subsequent Tx Costs' worksheet to "Deliver more complex parenteral chemotherapy at first attendance" so that this resource use is applied for each of the 3 doses given on days 1, 8, and 15, rather than just for the dose on day 1. This increased the administration cost for paclitaxel from £88.41 per week to £265.23 per week.

4.4.2.2 EAG's preferred survival extrapolation for OS

The EAG prefers to use an independent modelling approach for both OS and PFS, which avoids assuming either constant HR or constant acceleration factor for a life-time. The EAG uses the results from the company's independent modelling approach in response to clarification question B6 to determine its base case and scenario analysis.[19] These analyses use data from the non-Asia (CPS≤1) cohort. The EAG's choice of model was based on measures of statistical goodness-of-fit (AIC and BIC), visual inspection of the fitted curves in comparison to the KM data, the assessment of the empirical hazard function, and the assessment of long-term plausibility beyond the trial period using clinical expert opinion. The EAG notes that all models were fitted by the company (see clarification response B6).

For OS, the statistical goodness-of-fit of the standard parametric models and the spline models are summarised in Table 23. For the intervention arm, the log-logistic provides the lowest AIC and BIC scores. The log-normal, generalised gamma, one-knot hazard spline model, one-knot and three knots odds spline model all provide similar AIC scores (within three-point difference) to the log-logistic model, which indicates that these models fit the data equally well. The log-normal model provides similar BIC score to the log-logistic model, but the generalised gamma, one-knot hazard spline model, one-knot and three-knot odds spline model all have slightly worse BIC scores compared with the log-logistic model because these models are associated with a greater number of model parameters and BIC penalises more for the number of parameters in the model than AIC.

Visual assessments of the KM data and fitted models show that all spline models and standard parametric models fit the data well except for exponential model and Gompertz model (Figure 9 and Figure 10). The smoothed hazard function shows a unimodal shape (Figure 11), which indicates that the log-normal, log-logistic, generalised gamma and all spline models may be appropriate. The EAG notes that the shape of the unsmoothed hazard function is unclear as only part of the unsmoothed hazard function is presented by the company's empirical hazard plot.

The long-term predictions for the intervention arm using different models are summarised in

Table 24. The Weibull and Gompertz model provide 5 years and 10 years survival probabilities within the range provided by clinical experts (Table 25). The one-knot hazard spline model provides slightly higher 5 years survival probability (11% vs. <10%) but 10 years survival probability was within the range provided by the clinical experts (0%-1%, Table 25). The predictions from the other models are all higher than the range provided by clinical experts.

Based on the assessments above, the EAG's base case model for OS for the intervention arm is the one-knot hazard spline model with the log-logistic model (lowest AIC/BIC model) as a scenario analysis.

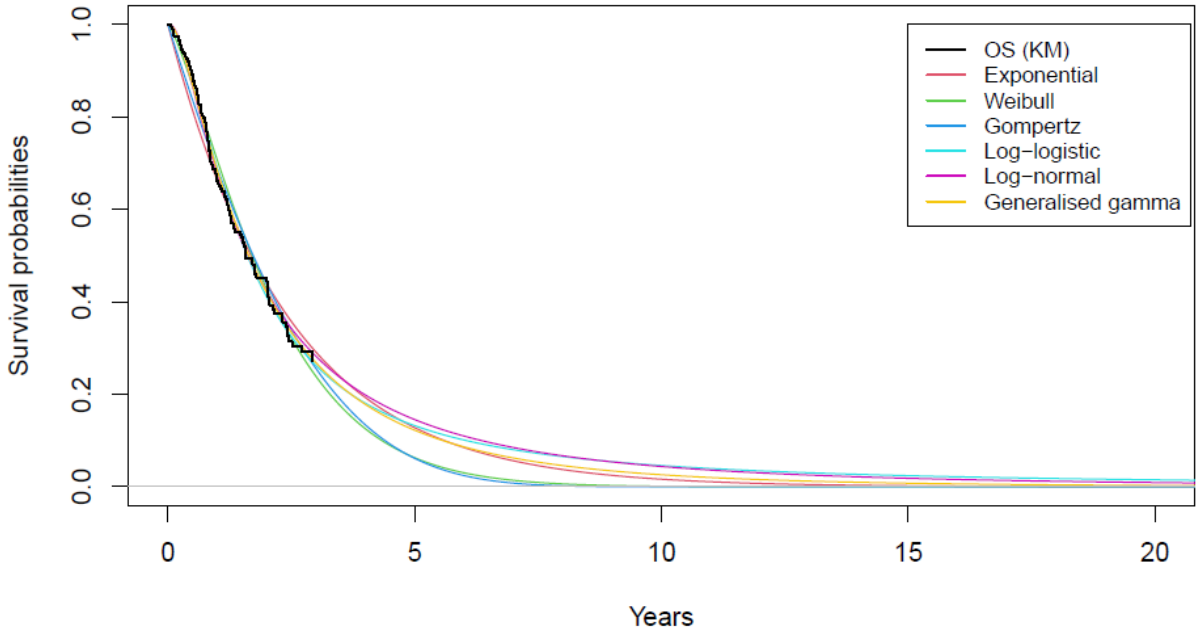
Table 23 Fit statistics of OS extrapolation in non-Asia CPS≥1 subgroup

Model	**Intervention**		**Comparator**	
	AIC	**BIC**	**AIC**	**BIC**
Standard parametric models				
Exponential	1404.19	1407.50	1549.44	1552.74
Weibull	1396.51	1403.12	1545.82	1552.41
Gompertz	1403.85	1410.46	1551.01	1557.61
Log-logistic	**1390.06**	**1396.68**	**1538.89**	**1545.49**
Log-normal	**1391.19**	**1397.81**	1546.38	1552.98
Generalised gamma	**1392.53**	1402.46	1543.73	1553.63
Spline models				
Hazard, 1 knot	**1392.47**	1402.39	1544.48	1554.37
Hazard, 2 knots	1393.41	1406.64	**1539.31**	1552.5
Hazard, 3 knots	1394.11	1410.65	**1539.52**	1556.02
Odds, 1 knot	**1391.61**	1401.54	**1540.12**	1550.01
Odds, 2 knots	1393.18	1406.41	**1540.05**	1553.24
Odds, 3 knots	**1392.86**	1410.41	**1539.35**	1555.84
Normal, 1 knot	1394.11	1402.22	**1541.81**	1551.71
Normal, 2 knots	1393.87	1406.09	**1540.70**	1553.89
Normal, 3 knots	1394.02	1410.56	**1539.01**	1555.50

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

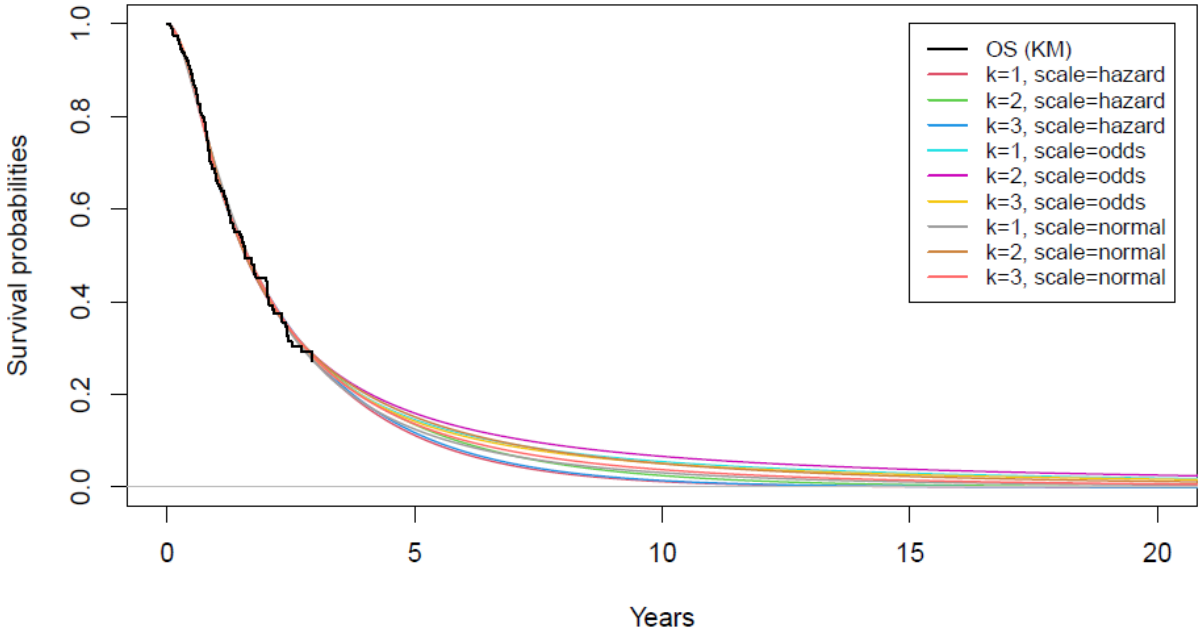
Bold: models with the lowest AIC/BIC (within three-point difference)

Figure 9 OS for the intervention arm, independently fitted standard parametric models



Abbreviations: OS, overall survival; KM, Kaplan-Meier.

Figure 10 OS for the intervention arm, independently fitted spline models



Abbreviations: OS, overall survival; KM, Kaplan-Meier.

Figure 11 Unsmoothed hazards versus smoothed hazards for OS, the intervention arm (reproduced from clarification response, Figure 8[19])

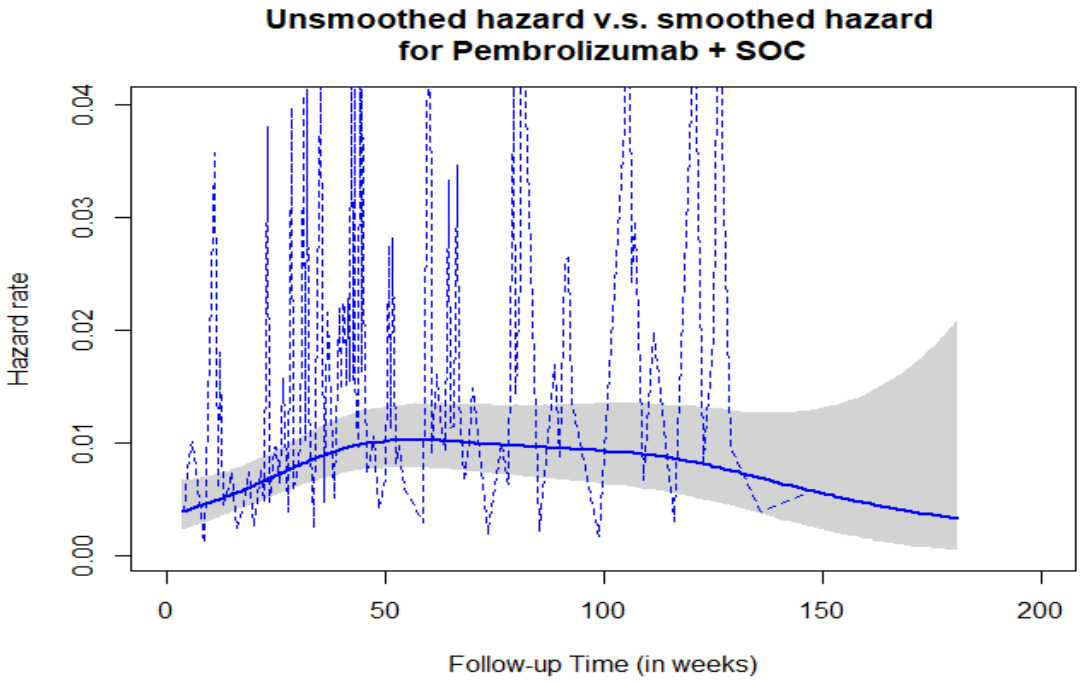


Table 24 OS predictions for the intervention in non-Asia CPS≥1 subgroup

Model	1-Year (KM estimation: 0.66)	2-Year (KM estimation: 0.44)	5-Year	10-Year	20-Year
Standard parametric models					
Exponential	0.66	0.44	0.13	0.02	0.00
Weibull	0.71	0.43	0.06	0.00	0.00
Gompertz	0.69	0.44	0.06	0.00	0.00
Log-logistic	0.69	0.41	0.13	0.05	0.02
Log-normal	0.68	0.42	0.15	0.04	0.01
Generalised gamma	0.68	0.42	0.12	0.03	0.00
Spline models					
Hazard, 1 knot	**0.68**	**0.42**	**0.11**	**0.01**	**0.00**
Hazard, 2 knots	0.68	0.41	0.14	0.02	0.00
Hazard, 3 knots	0.67	0.42	0.12	0.01	0.00
Odds, 1 knot	0.68	0.41	0.15	0.05	0.02
Odds, 2 knots	0.68	0.41	0.16	0.07	0.03
Odds, 3 knots	0.67	0.42	0.14	0.05	0.02
Normal, 1 knot	0.69	0.42	0.13	0.03	0.00
Normal, 2 knots	0.68	0.41	0.15	0.05	0.01
Normal, 3 knots	0.67	0.42	0.15	0.04	0.01

Bold: EAG's base case

Table 25 OS long-term plausibility informed by clinical expert opinion

	Expected survival probability for the intervention arm			
Timepoint	**Company's expert 1**	**Company's expert 2**	**EAG's expert 1**	**EAG's expert 2**
5 years	NA	NA	5-10%	0%
10 years	NA	NA	1%	0%
	Expected survival probability for the control arm			
5 years	5%	2-5%	≤5%	0%
10 years	2%	0-1%	0%	0%

For the control arm, the log-logistic provides the lowest AIC and BIC scores. All spline models apart from one-knot hazard spline model have similar AIC scores to the log-logistic model (within three-point difference, Table 23), indicating that these models fit the KM data equally well. No other models provide BIC scores which are within three-point difference to the log-logistic model BIC score.

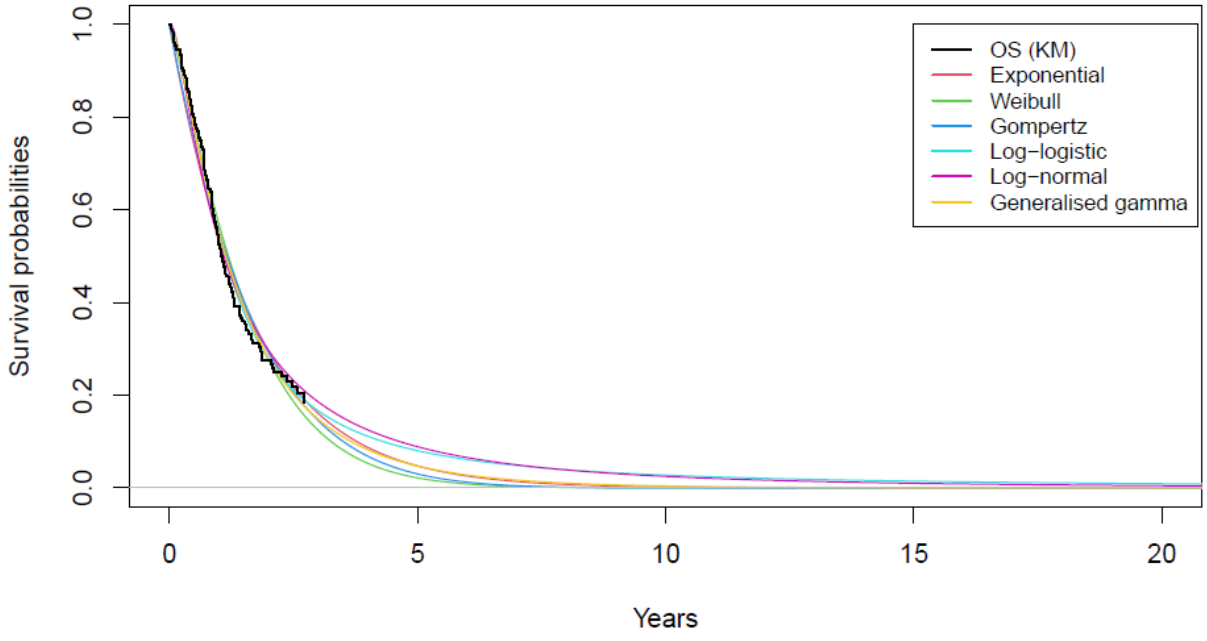
Visual assessments of the KM data versus the fitted models shows that log-logistic and all spline models provide a reasonable visual fit the observed KM data (Figure 12 and Figure 13). The smoothed hazard function shows a unimodal shape (Figure 14), which indicates that the log-normal, log-logistic, generalised gamma and all spline models may be appropriate. The EAG notes that the shape of the unsmoothed hazard function is unclear as only part of the unsmoothed hazard function is presented by the company's empirical hazard plot.

The long-term predictions for the control arm using different models are summarised in

Table 26. The exponential, Weibull, Gompertz, generalised gamma, one-knot hazard spline and one-knot normal spline models provide 5 years and 10 years survival probabilities within the range provided by clinical experts (Table 25). The predictions from the other models are all higher than the range provided by clinical experts either at 5 years or both 5 and10 years.

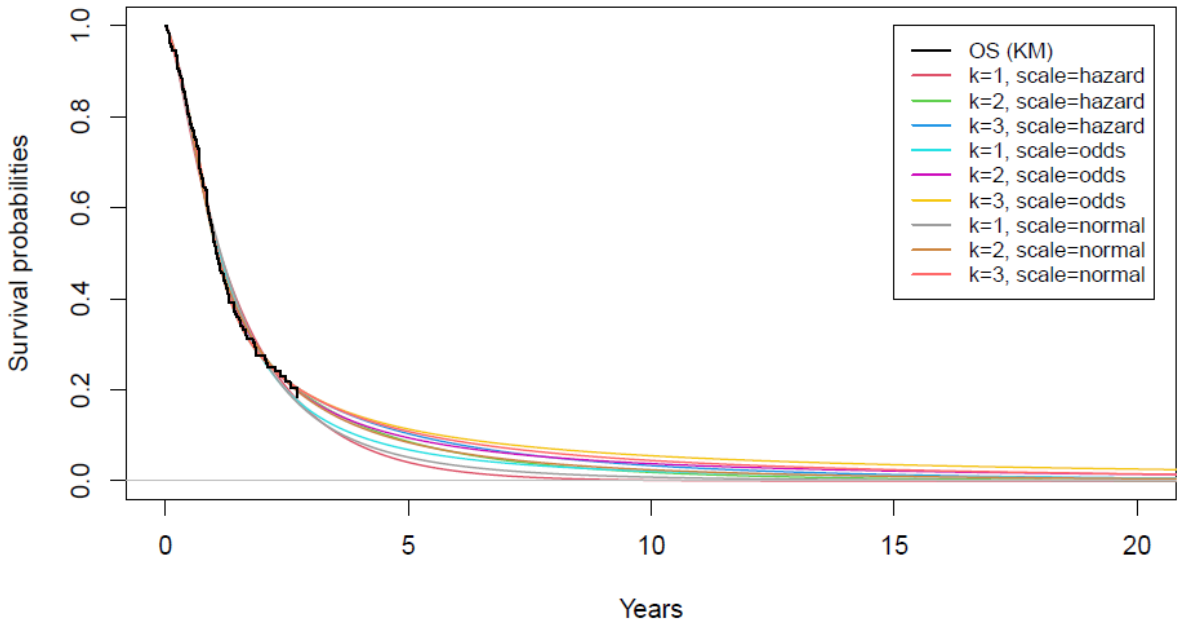
Based on the assessments above, the EAG's base case model for OS for the control arm is the one-knot normal spline model with the log-logistic model (lowest AIC/BIC model) as a scenario analysis.

Figure 12 OS for the comparator arm, independently fitted standard parametric models



Abbreviations: OS, overall survival; KM, Kaplan-Meier.

Figure 13 OS for the comparator arm, independently fitted spline models



Abbreviations: OS, overall survival; KM, Kaplan-Meier.

Figure 14 Unsmoothed hazards versus smoothed hazards for OS, the comparator arm (reproduced from clarification response, Figure 9)[19]

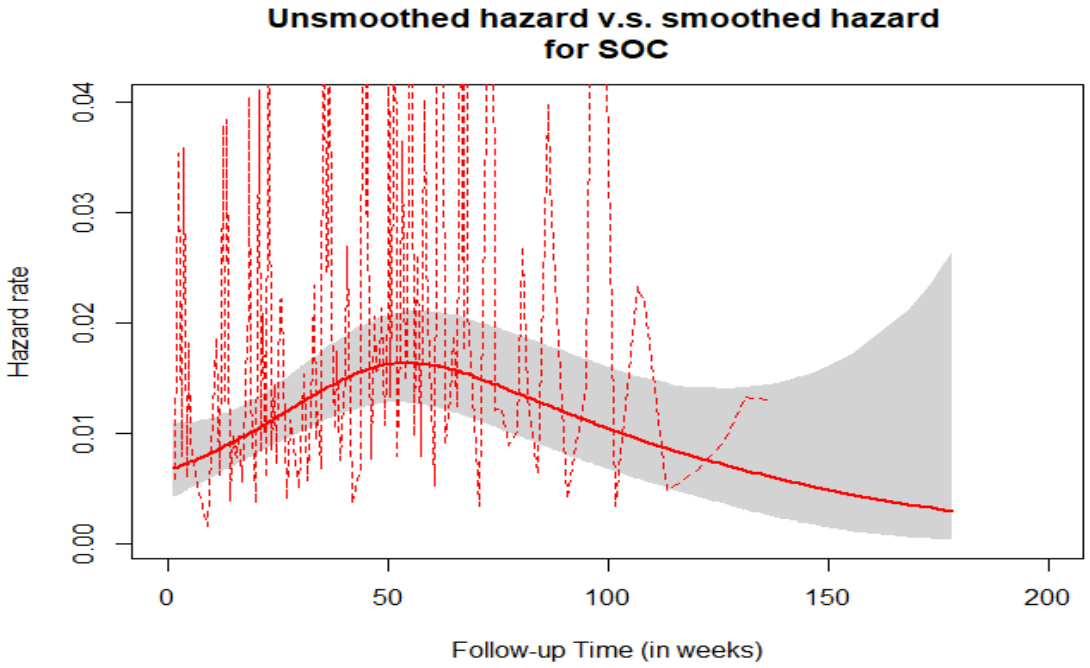


Table 26 OS predictions for the comparator in non-Asia CPS≥1 subgroup

Model	1-Year (KM estimation: 0.53)	2-Year (KM estimation: 0.28)	5-Year	10-Year	20-Year
Standard parametric models					
Exponential	0.54	0.30	0.05	0.00	0.00
Weibull	0.57	0.28	0.02	0.00	0.00
Gompertz	0.55	0.29	0.03	0.00	0.00
Log-logistic	0.54	0.28	0.08	0.03	0.01
Log-normal	0.53	0.30	0.09	0.02	0.00
Generalised gamma	0.55	0.28	0.05	0.00	0.00
Spline models					
Hazard, 1 knot	0.55	0.28	0.04	0.00	0.00
Hazard, 2 knots	0.53	0.28	0.09	0.02	0.00
Hazard, 3 knots	0.54	0.27	0.10	0.03	0.01
Odds, 1 knot	0.54	0.27	0.07	0.02	0.01
Odds, 2 knots	0.53	0.28	0.09	0.04	0.01
Odds, 3 knots	0.53	0.27	0.11	0.06	0.03
Normal, 1 knot	**0.55**	**0.27**	**0.05**	**0.01**	**0.00**
Normal, 2 knots	0.53	0.28	0.08	0.02	0.01
Normal, 3 knots	0.53	0.27	0.11	0.04	0.02

Bold: EAG's base case

4.4.2.3 EAG's preferred survival extrapolation for PFS

For PFS, the statistical goodness-of-fit of the fitted standard parametric models and spline models are summarised in Table 27. For the intervention arm, the three-knot normal spline model has the lowest AIC score. The spline models apart from the one-knot normal spline model all have similar AIC scores to the three-knot spline model (within three-point difference). In terms of BIC scores, the log-normal has the lowest BIC score of all the fitted models, and the log-logistic and one-knot odds spline model have similar BIC scores to the log-normal model (within three-point difference). Those models with similar AIC/BIC scores fit the KM data equally well.

The plots showing the intervention PFS KM curve versus the fitted curves using standard parametric models and spline models are presented in Figure 15 and Figure 16 separately. The EAG notes that there is a noticeable change in the gradient of the PFS KM curve around 1.5 years. All the standard

parametric models do not seem to fit the KM data well after around 1.5 years. The spline models fit the KM data better when compared with standard parametric models. The smoothed hazard function in Figure 17 has a unimodal shape, which indicates that the log-normal, log-logistic, generalised gamma and all spline models may be appropriate. The EAG notes that the shape of the unsmoothed hazard function is unclear as only part of the unsmoothed hazard function is presented in the company's empirical hazard plot.

The long-term predictions for the intervention arm using different models are summarised in

Table 29. All the standard parametric models, one-knot hazard spline, one-knot odds spline and one-knot normal spline models provide 5 years survival probabilities within the range provided by clinical experts (<10%,

Table 28). The exponential and Weibull models provide 10 years survival probabilities within the range provided by clinical experts (0%,

Table 28). The log-normal model provides slightly higher 10 years survival probability (1%).

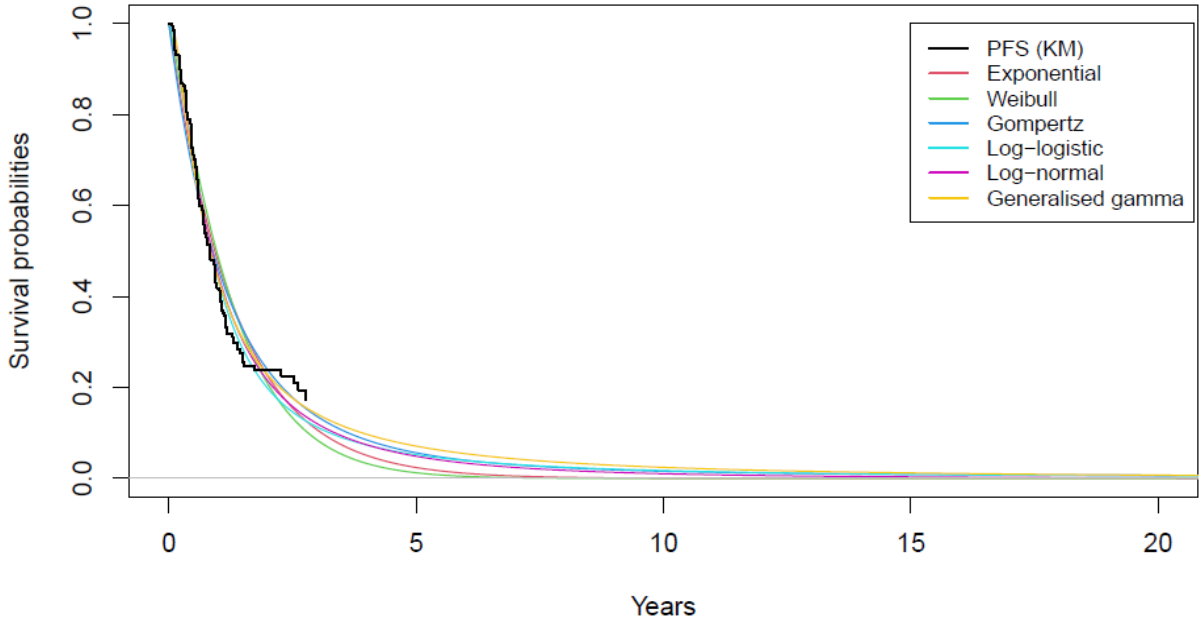
Based on the assessments above, the EAG's base case model for PFS for the intervention arm is the log-normal model with the log-logistic model as a scenario analysis.

Table 27 Fit statistics of PFS extrapolation in non-Asia CPS≥1 subgroup

Model	Intervention		Comparator	
	AIC	BIC	AIC	BIC
Standard parametric models				
Exponential	1481.71	1485.02	1491.32	1494.62
Weibull	1481.07	1487.69	1487.98	1494.58
Gompertz	1482.12	1488.73	1493.23	1499.83
Log-logistic	1458.93	**1465.55**	**1469.57**	**1476.17**
Log-normal	1458.17	**1464.79**	**1471.57**	**1478.16**
Generalised gamma	1458.50	1468.43	1473.34	1483.23
Spline models				
Hazard, 1 knot	**1457.96**	1467.88	1473.34	1483.23
Hazard, 2 knots	**1455.38**	1468.61	**1472.43**	1485.62
Hazard, 3 knots	**1456.18**	1472.72	1474.15	1490.64
Odds, 1 knot	**1457.40**	**1467.33**	**1471.56**	1481.45
Odds, 2 knots	**1456.58**	1469.82	1473.08	1486.27
Odds, 3 knots	**1456.57**	1473.11	1473.63	1490.12
Normal, 1 knot	1459.18	1469.11	1473.04	1482.94
Normal, 2 knots	**1455.66**	1468.89	**1472.43**	1485.63
Normal, 3 knots	**1455.14**	1471.68	1472.8	1489.29

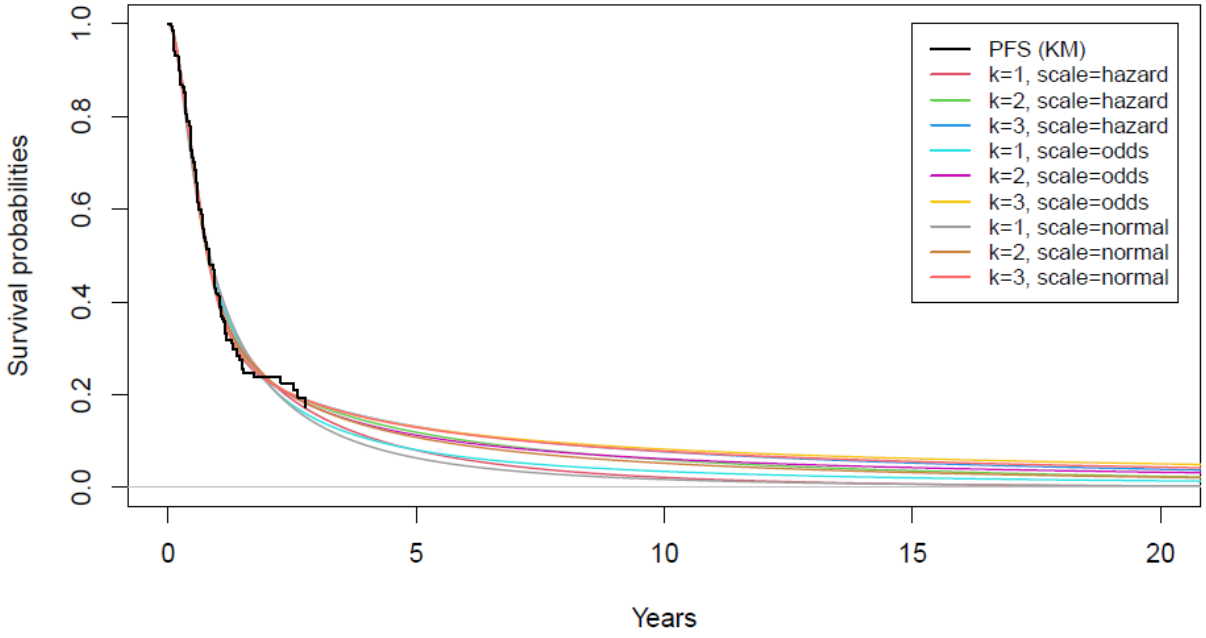
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.
Bold: models with the lowest AIC/BIC (within three-point difference)

Figure 15 PFS for the intervention arm, independently fitted standard parametric models



Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier.

Figure 16 PFS for the intervention arm, independently fitted spline models



Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier.

Figure 17 Unsmoothed hazards versus smoothed hazards for PFS, the intervention arm (reproduced from clarification response, Figure 18[19])

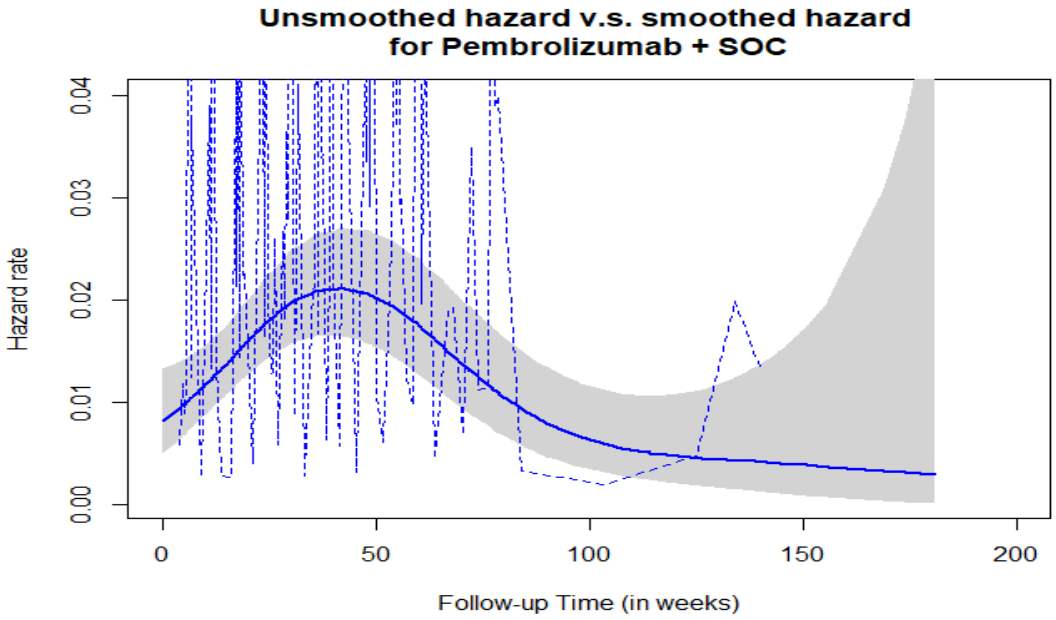


Table 28 PFS long-term plausibility informed by clinical expert opinion

	Expected survival probability for the intervention arm			
Timepoint	**Company's expert 1**	**Company's expert 2**	**EAG's expert 1**	**EAG's expert 2**
5 years	NA	NA	5-10%	0%
10 years	NA	NA	0%	0%
	Expected survival probability for the control arm			
5 years	NA	NA	0%	0%
10 years	NA	NA	0%	0%

Table 29 PFS predictions for the intervention in non-Asia CPS≥1 subgroup

Model	1-Year (KM estimation: 0.42)	2-Year (KM estimation: 0.24)	5-Year	10-Year	20-Year
Standard parametric models					
Exponential	0.47	0.22	0.02	0.00	0.00
Weibull	0.49	0.21	0.01	0.00	0.00
Gompertz	0.46	0.24	0.06	0.02	0.01
Log-logistic	0.43	0.20	0.05	0.02	0.01
Log-normal	**0.45**	**0.21**	**0.05**	**0.01**	**0.00**
Generalised gamma	0.44	0.23	0.07	0.02	0.01
Spline models					
Hazard, 1 knot	0.42	0.24	0.08	0.02	0.00
Hazard, 2 knots	0.40	0.23	0.12	0.06	0.02
Hazard, 3 knots	0.40	0.23	0.13	0.08	0.04
Odds, 1 knot	0.43	0.22	0.08	0.03	0.01
Odds, 2 knots	0.41	0.23	0.11	0.06	0.03
Odds, 3 knots	0.40	0.23	0.13	0.08	0.05
Normal, 1 knot	0.44	0.23	0.06	0.02	0.00
Normal, 2 knots	0.41	0.23	0.11	0.05	0.02
Normal, 3 knots	0.40	0.23	0.13	0.08	0.04

Bold: EAG's base case

For the control arm, the log-logistic model has the lowest AIC and BIC scores. The log-normal, two-knot hazard spline, one-knot odds spline and two-knot normal spline models have similar AIC scores to the log-logistic model (within three-point difference). The log-normal provides similar BIC score to the log-logistic model (within three-point difference).

Visual assessments of the KM data and fitted models show that all spline models and standard parametric models fit the data well except for Weibull and Gompertz models (

Figure 18 and

Figure 19). The smoothed hazard function shows a unimodal shape (see

Figure 20), which indicates that the log-normal, log-logistic, generalised gamma and all spline models may be appropriate. The EAG notes that the shape of the unsmoothed hazard function is unclear as only part of the unsmoothed hazard function is presented in the company's empirical hazard plot.

The long-term predictions for the comparator PFS using different models are summarised in

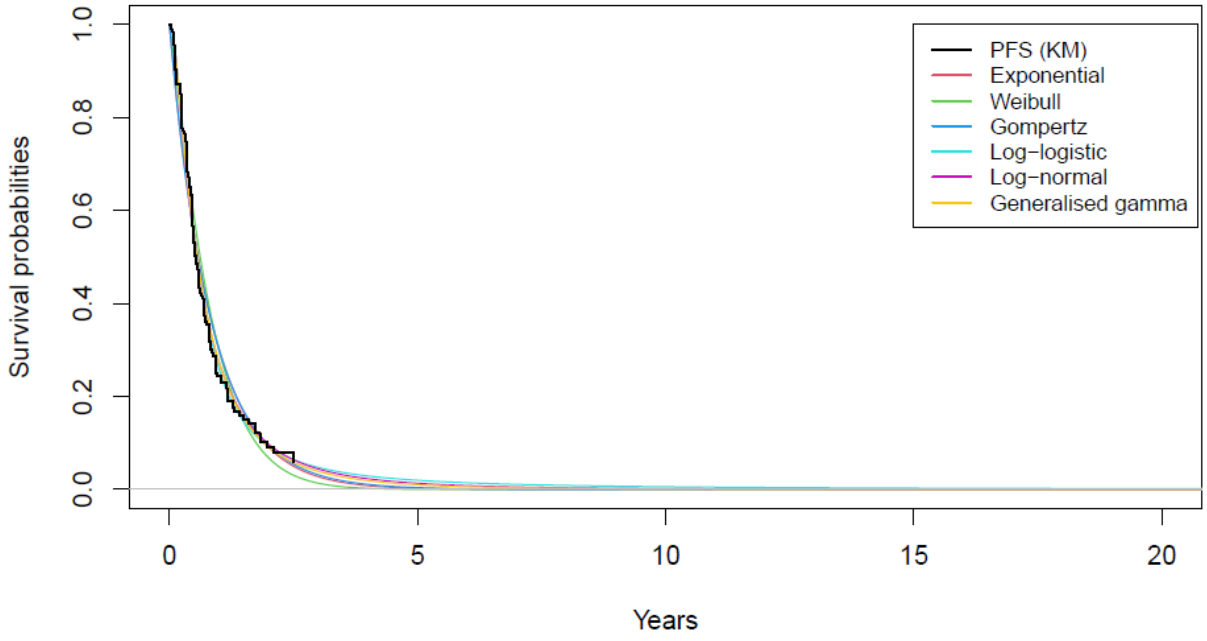
Table 30. The exponential, Weibull and Gompertz models provide 5 years and 10 years survival probabilities within the range provided by clinical experts (0%,

Table 28). The log-normal, generalised gamma, one-knot hazard spline, one-knot normal spline models provide slightly higher 5 years survival probability (1%), but 10 years survival probability was within the range provided by the clinical experts (0%,

Table 28). The predictions from the other models are all higher than the range provided by clinical experts.

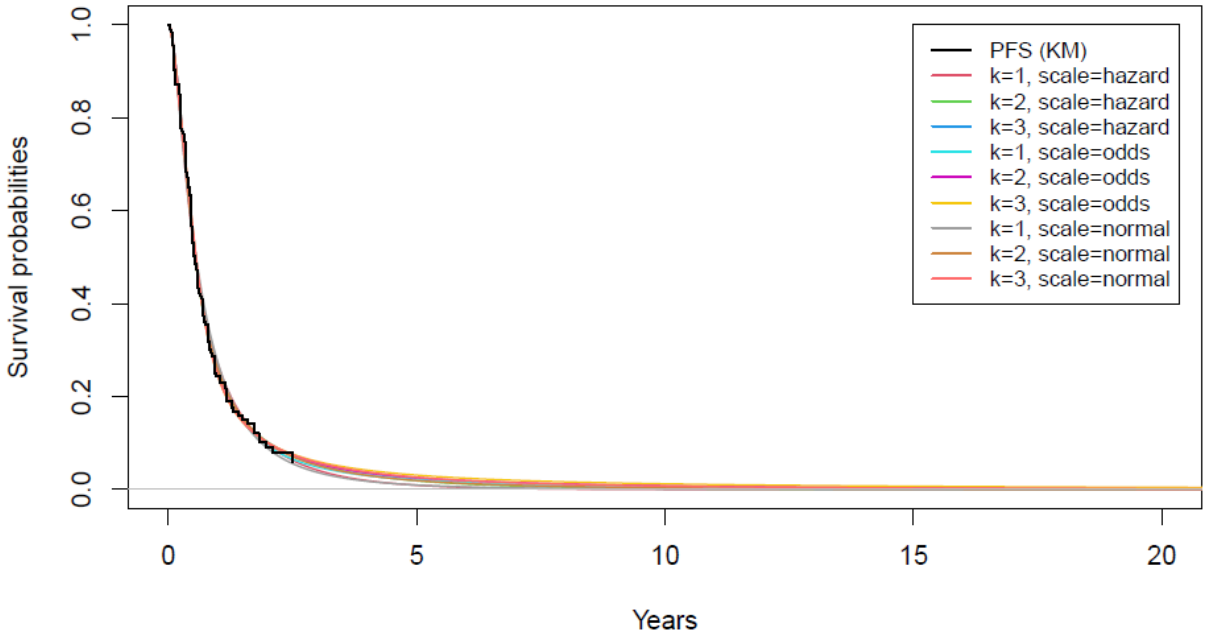
Based on the assessments above, the EAG's base case model for PFS for the comparator arm is the log-normal model with the log-logistic model (lowest AIC/BIC model) as a scenario analysis.

Figure 18 PFS for the comparator arm, independently fitted standard parametric models



Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier.

Figure 19 PFS for the comparator arm, independently fitted spline models



Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier.

Figure 20 Unsmoothed hazards versus smoothed hazards for PFS, the comparator arm (reproduced from clarification response, Figure 19[19])

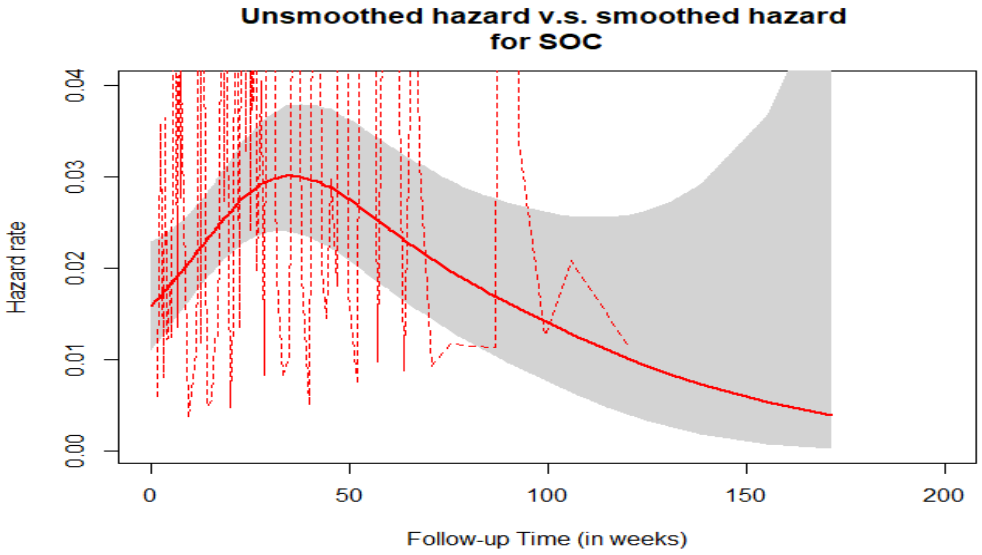


Table 30 PFS predictions for the comparator in non-Asia CPS≥1 subgroup

Model	1-Year (KM estimation: 0.24)	2-Year (KM estimation: 0.09)	5-Year	10-Year	20-Year
Standard parametric models					
Exponential	0.30	0.09	0.00	0.00	0.00
Weibull	0.30	0.07	0.00	0.00	0.00
Gompertz	0.30	0.10	0.00	0.00	0.00
Log-logistic	0.26	0.09	0.02	0.01	0.00
Log-normal	**0.27**	**0.10**	**0.01**	**0.00**	**0.00**
Generalised gamma	0.27	0.09	0.01	0.00	0.00
Spline models					
Hazard, 1 knot	0.27	0.10	0.01	0.00	0.00
Hazard, 2 knots	0.25	0.10	0.02	0.00	0.00
Hazard, 3 knots	0.25	0.10	0.02	0.00	0.00
Odds, 1 knot	0.26	0.09	0.02	0.01	0.00
Odds, 2 knots	0.26	0.10	0.03	0.01	0.00
Odds, 3 knots	0.24	0.10	0.03	0.01	0.00
Normal, 1 knot	0.27	0.09	0.01	0.00	0.00
Normal, 2 knots	0.26	0.10	0.02	0.00	0.00
Normal, 3 knots	0.24	0.10	0.03	0.01	0.00

Bold: EAG's base case

The KM curves and the extrapolated curves informed by the most plausible model as well as the model used in the scenario analysis are presented in

Figure 21 and Figure 22 below.

Figure 21 EAG's choices of extrapolations for OS in the non-Asia CPS≥1 subgroup

Figure 22 EAG's choices of extrapolations for PFS in the non-Asia CPS≥1 subgroup

4.4.2.4 Duration of treatments

The EAG has applied the company's assumption that the maximum number of cycles of chemotherapy is 6 cycles in its base case analysis. However, it has explored scenario analyses using the average number of cycles administered and using a maximum number of 4 cycles. The EAG has restricted the maximum number of cycles for pembrolizumab in its base case to 35 cycles, but it has allowed trastuzumab to be used according to the TTD curve from KEYNOTE-811 without any limit applied.

4.4.2.5 Utilities using a time-to-death approach

The EAG has included the company's time-to-death approach for utilities in its base case but has explored the impact of using the progression-based approach in its scenario analysis. The EAG prefers to use the company's utility analyses which used a linear mixed effect regression (provided in response to clarification question B16). The EAG therefore applied the data in Table 21 for its preferred base case and has explored using the data in Table 22 in its scenario analysis.

4.4.2.6 Resource use – administration costs

The EAG has incorporated the scenario analysis in which a lower HRG cost has been applied for administering trastuzumab alone (£286.71 for HRG code SB12Z)) versus trastuzumab with pembrolizumab (£353.64 for HRG code SB13Z) in the period after the chemotherapy element of the treatment has been completed. This is in addition to the correction described in Section 4.4.2.1 for the administration costs for paclitaxel as a subsequent therapy. This change has been included in the EAG's preferred base case.

4.4.2.7 Subsequent therapies

In any scenario in which the mix of subsequent therapies is based on KEYNOTE-811 (EAG exploratory analysis 10), the EAG has recalculated the proportions receiving subsequent therapies so they are estimated as a proportion of the progressed patients rather than as a proportion of those completing or discontinuing first-line therapy.

However, in the EAG's preferred base case it has assumed that 50% of progressed patients receive subsequent treatment and that subsequent treatment consists of either paclitaxel or docetaxel in equal proportions. This means that in the EAG's base case the distribution of subsequent treatment is not based on treatments received in KEYNOTE-811.

The EAG has also amended the model so that subsequent treatment costs are only applied to the proportion of patients leaving the progression-free state whose PFS event was progression rather than death. This is in keeping with the subsequent treatment costs having been calculated per progressed patient. This is applied both when using subsequent treatments based on KEYNOTE-811 and when using the EAG's assumption that subsequent treatment consists only of taxanes (EAG exploratory analyses 6 and 10).

4.4.2.8 Disease management for progression-free state

The EAG prefers to assume 3 weekly follow-up visits during doublet chemotherapy, with 6 weekly follow-up for the remainder of PFS to align with its understanding of what was modelled in TA208 (see Section 4.3.3.7). This was achieved by excluding the 3-weekly follow-up visits implemented by the

company for the duration of PFS, keeping the 6-weekly follow-up visits implemented by the company for the duration of PFS, and adding additional follow-up visits during the doublet chemotherapy phase of treatment to achieve an average of 3-weekly visits during the first 18 weeks.

The EAG has not updated the disease management costs for the progression-free health state to account for additional blood tests required for patients receiving pembrolizumab with trastuzumab relative to trastuzumab alone or to explore a different frequency for cardiac monitoring. This is because any changes to the ICER based on these are expected to be small. The EAG has included costs for 4 CT staging scans per year in the progression-free state.

4.4.2.9 Disease management for progressed-disease state

The EAG was concerned that the company's estimate of resource use in the progressed-disease state did not account for the frequency of activities that might occur more than once in the follow-up period (see Section 4.3.3.8). The EAG has therefore adjusted the resource use for the progressed-disease state to include 4 outpatient visits and 4 CT scans per year to determine the sensitivity of the model to changes in the costs for the progressed-disease state.

4.4.3 Results of the EAG's exploratory analyses

The EAG's exploratory analyses showing the impact of making individual changes to the company's base case model are provided in Table 31. The ICERs discussed in the following text are those generated when applying no QALY weighting, but the results when applying a QALY weighting of 1.2 are provided in Table 31 for reference. The exploratory analysis that has the most significant impact on the ICER is implementing the EAG's preferred survival extrapolation for OS, which increases the ICER from £[redacted] to £[redacted] per QALY. This change is driven by the EAG's preference for using the OS data from the non-Asia region, as the OS is lower when using data from the non-Asia region (see Figure 3). Implementing the EAG's preferred approach to modelling PFS does not have a large impact on the ICER because utilities are based on time-to-death and not progression-status. Therefore, changing PFS only affects costs and in this case it reduces the incremental cost resulting in a reduction in the ICER from £[redacted] to £[redacted] per QALY. Reducing the frequency of follow-up visits in the PFS and including 3 monthly CT scans also reduced the ICER bringing it down to [redacted] per QALY. Conversely increasing the frequency of outpatient visits and including 3 monthly CT scans in the progressed disease state increased the ICER to £[redacted] per QALY. Assuming that subsequent treatment is only received by 50% and consists only of taxanes reduced the ICER to £[redacted] per QALY. The scenarios which allowed trastuzumab treatment to extend beyond 35 cycles and allowed for a lower cost when it is given alone rather than combined with pembrolizumab both increased the ICER marginally. Implementing the time-to-death utilities from the linear mixed effects regression marginally increased the ICER to £[redacted] per QALY. The EAG's adjustment to the calculation of

subsequent therapies using the data from KEYNOTE-811 did not have a substantial impact on the ICER and was not included in its base case because the EAG preferred to assume that subsequent treatment consists of taxanes in its base case. The ICER for the EAG's preferred base case, which combined EAG's exploratory analyses 1 to 9, was substantially increased at £[redacted] per QALY, mainly due to the impact of the EAG's preferred OS extrapolation. The probabilistic ICER for the EAG's preferred base case was £[redacted] per QALY. Pembrolizumab with SoC had an ICER under £30,000 per QALY in [redacted]% of PSA runs both when using a QALY weight of 1.0 and when using a QALY weight of 1.2.

Table 31 EAG's exploratory analyses

Option	LYs	QALYs	Costs	Incremental		ICER (QALY weight x1)	ICER (QALY weight x1.2)
				QALYs	Costs		
Company base case – post-clarification (Deterministic)							
SoC*	3.03	[redacted]	[redacted]	-	-		
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1: correcting programming and implementation errors in the company's economic model							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2: Using the EAG's preferred survival extrapolation for OS							
SoC*	1.59	[redacted]	[redacted]	-	-	-	-
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3: Using the EAG's preferred survival extrapolation for PFS							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4: Removing the cap for TTD of trastuzumab							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 5: Applying lower administration costs for trastuzumab when administered without pembrolizumab							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 6: Assuming subsequent therapy to include only taxanes and applying that to only a proportion of PFS events who get progressed (25% get paclitaxel and 25% get docetaxel)							
SoC*	3.03	[redacted]	[redacted]	-	-		
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 7: Limiting outpatient visits to 6 weekly after chemotherapy and adding CT scans 4 times per annum for patients on PFS							

Option	LYs	QALYs	Costs	Incremental		ICER (QALY weight x1)	ICER (QALY weight x1.2)
				QALYs	Costs		
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 8: Increasing outpatient visits and CT scans to 4 times per annum for patients with progressed disease							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 9: Time-to-death utilities estimated using a linear mixed effects model							
SoC*	3.03	[redacted]	[redacted]	-	-	-	-
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 10: Subsequent therapies are estimated as a proportion of those progressing using KEYNOTE-811 and only applied to patient leaving PFS due to progression†							
SoC*	3.03	[redacted]	[redacted]	-	-		
Intervention**	4.94	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-9 (Deterministic)							
SoC*	1.59	[redacted]	[redacted]	-	-	-	-
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case applying analyses 1-9 (Probabilistic)							
SoC*	1.61	[redacted]	[redacted]	-	-	-	-
Intervention**	2.21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CT – computerised tomography; EAG – external assessment group, ICER – incremental cost-effectiveness ratio, OS – overall survival, LYs - life-years; PD – progressed disease, PFS – progression-free survival, QALYs- quality-adjusted life-years; TTD – time to treatment discontinuation

** SoC: Trastuzumab plus chemotherapy*

*** Intervention: Pembrolizumab with SoC*

† Not included in EAG base case because the EAG prefers subsequent therapies as described in exploratory analysis 6

The EAG has also conducted deterministic scenario analyses, shown in Table 32, using its preferred base case scenario as the starting point. The probabilistic model was not run for the scenario analyses as the results for the EAG's base case suggest that the deterministic ICER provides a close estimate of the expected probabilistic ICER. The ICER in these scenarios ranged from £[redacted] per QALY when using the log-logistic extrapolation for OS and PFS (still fitted separately to each arm of the non-Asia cohort) to £[redacted] per QALY when basing utilities on progression status rather than time-to-death. The scenario analyses also suggest that the ICER is not particularly sensitive to the choice of chemotherapy agent (scenario 5) or the duration of chemotherapy treatment (scenarios 2 and 3), although all of these scenarios alter only the cost of treatment and have no impact of clinical outcomes which are assumed to remain as observed in KEYNOTE-811.

Table 32 EAG's scenario analyses

Option	LYs	QALYs	Costs	Incremental		ICER (QALY weight x1)	ICER (QALY weight x1.2)
				QALYs	Costs		
EAG base case (Deterministic)							
SoC*	1.59	[redacted]	[redacted]	-	-	-	-
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 1 (Assuming a log-logistic curve for OS and PFS extrapolations)							
SoC*	1.84	[redacted]	[redacted]	-	-		
Intervention**	2.50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 2 (Using restricted mean duration to estimate costs for first-line chemotherapy)							
SoC*	1.59	[redacted]	[redacted]	-	-	-	-
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 3 (Reducing the cap applied to TTD of first-line chemotherapy to 4 cycles)							
SoC*	1.59	[redacted]	[redacted]	-	-		
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 4 (Using utility values based on progression status)							
SoC*	1.59	[redacted]	[redacted]	-	-		
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario 5 (Assuming 100% of doublet chemotherapy is with XP)							
SoC*	1.59	[redacted]	[redacted]	-	-		
Intervention**	2.17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG – external assessment group; ICER – incremental cost-effectiveness ratio; LYs - life-years, OS – overall survival, PFS – progression-free survival, QALYs- quality-adjusted life-years, TTD – time to treatment discontinuation; XP - cisplatin with capecitabine

** SoC: Trastuzumab plus chemotherapy*

*** Intervention: Pembrolizumab with SoC*

4.4.4 The EAG's estimate of the ICER

The EAG's exploratory analyses demonstrate that the ICER is highly sensitive to whether the data from the global cohort or the non-Asia cohort are used to estimate OS. The EAG's preferred approach of using parametric survival curves fitted separately to each arm of the non-Asia cohort provides a much higher ICER than the company's base case analysis. However, the EAG's preferred ICER was fairly robust to the choice of parametric curve when considering only curves fitted to the non-Asia cohort. The EAG considers that its base case ICER is somewhat uncertain due to uncertainty regarding the most appropriate method of capturing changes in utility over time as modelling utility based on progression status increased the ICER compared to the company's approach of using time-to-death.

5 SEVERITY MODIFIER

The company has presented an estimate of the proportionate and absolute QALY shortfall based on a comparison of the discounted QALYs generated in the control arm of the model (i.e., for trastuzumab with chemotherapy) and the discounted QALY expected for members of the general population who do not have gastric or GOJ cancer but otherwise have the same starting characteristics (i.e., age 60 and 21% females). Based on these data, the appropriate QALY multiplier would be x1 (see Table 33) because the proportional shortfall is [redacted] and the absolute short fall is [redacted]. The company originally stated that the Schneider *et al*. tool had been used to estimate the QALYs in the general population (see CS, page 149),[1] but it later stated, in response to clarification question B37, that this was not in fact the case and the model had been used instead to generate these estimates.[19] However, the company stated that they agreed with the principle of the Schneider *et al*. tool being used to provide consistency across appraisals. The EAG notes that when using the Schneider *et al*. tool, with the utility set described in the tool as being the reference case (Measurement and Valuation of Health [MVH] value set + Health Survey for England [HSE] 2014 Adjusted Limited Dependent Variable Mixture Model [ALDVMM] model, Hernandez Alava *et al*.), the discounted QALYs for the general population would be 12.62 rather than the 12.28 estimate provided by the company's model.[61] Combining this with the discounted QALY from the trastuzumab with chemotherapy arm estimated by in the company's base case model results in the same QALY multiplier as estimated by the company.

The company argues that the estimates of QALY in the SoC arm of the model are unrealistic because they are based on the whole CPS>=1 population which includes patients from the Asia region. It notes that the non-Asia region has shorter OS than the Asia region in KEYNOTE-811 and consider it implausible for the proportional QALY loss to be less than 85% for patients treated in current NHS practice. To address this concern, it prefers to use the QALYs estimated for trastuzumab with chemotherapy from TA208 which they report as being 0.980. When using this estimate of the QALYs under current practice, the appropriate QALY multiplier would be 1.2 (see Table 33) because the proportionate short fall is between 0.85 and 0.95. However, the EAG notes that the QALYs for the HER2-positive (IHC3+) subgroup range from 1.089 to 1.194 depending on whether trastuzumab is combined with XP or FP (ERG addendum dated 5th August 2010, Table 3c).[62] Whilst both of these provide smaller proportional QALY shortfalls than the company' estimate, they do still provide a figure compatible with a 1.2 QALY multiplier.

Overall, the EAG considers that a 1.2 multiplier is supported by the evidence if it is accepted that the data from the Asia region are not generalisable to the UK, whereas data from the other two regions are generalisable to the UK. This seems reasonable given the company's explanation that outcomes are expected to be better in the Asia region due to the widespread implementation of screening.

The EAG notes that both the ICER and the severity modifier are dependent on whether the data for OS from the non-Asia region are more generalisable to the population likely to receive treatment in England than the data from the global cohort. The EAG considers that it would be inconsistent to use the company's base case ICER, which is based on OS data from the global cohort including patients from the Asia region, and to then apply a severity modifier that has been calculated assuming that only data from the non-Asia region are applicable to patients receiving treatment in England

Table 33 Severity modifier calculations for various company and EAG scenarios

Analysis	Lifetime expected QALYs for the general population	Lifetime expected QALYs under current SoC	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
Company - modelled comparator arm and modelled general population*	12.277	[redacted]	[redacted]	[redacted]	1.0
Company - comparator arm from TA208 and modelled general population*	12.277	0.980	11.297	92.0%	1.2
EAG - modelled comparator arm for company base case and Schneider tool for general population	12.62	[redacted]	[redacted]	[redacted]	1.0
EAG - modelled comparator arm for EAG base case and Schneider tool for general population.	12.62	[redacted]	[redacted]	[redacted]	1.2
EAG - TA208 for comparator arm (trastuzumab +FP) and Schneider *et al.* tool for general population	12.62	1.089	11.53	91.4%	1.2
EAG - TA208 for comparator arm (trastuzumab +XP) and Schneider *et al.* tool for general population	12.62	1.194	11.43	90.6%	1.2

**CS, Table 60.*[1]

***The EAG notes that this figure appears to be based on a third comparator arm included in the model and not the trastuzumab with chemotherapy arm, however, the difference in absolute discounted QALYs between this estimate and the one for the trastuzumab with chemotherapy arm is -0.003 meaning that this error is unlikely to alter the conclusion regarding the appropriate QALY multiplier*

6 OVERALL CONCLUSIONS

The clinical evidence for pembrolizumab was based on one ongoing RCT, KEYNOTE-811. The EAG believes that no RCTs of pembrolizumab meeting the inclusion criteria of the NICE final scope have been missed. KEYNOTE-811 randomised 698 patients to either pembrolizumab in combination with trastuzumab and chemotherapy (CAPOX or FP), or placebo in combination with trastuzumab and chemotherapy (CAPOX or FP). According to clinical advice, patients in KEYNOTE-811 RCT were younger than would be seen in clinical practice in England but were generally representative in terms of primary location of disease at diagnosis, and the mix of locally advanced versus metastatic disease. The non-Asia cohort had a higher proportion of white patients than would be seen in clinical practice in England. Age may influence effectiveness, as patients under 65 years appeared to have more favourable treatment effect toward pembrolizumab for PFS and OS than older patients, however there is uncertainty in this as KEYNOTE-811 was not powered for subgroups.

The CS focused on the subgroup of patients with PD-L1 CPS ≥ 1 (in line with the anticipated marketing authorisation). For CPS≥1 participants, Grade ≥3 AEs were experienced by 73.2% of the pembrolizumab treated patients, and 65.1% of the comparator treated patients. Within the CPS ≥ 1 subgroup, the CS effectiveness outcomes concentrated on region, reporting the combined two subgroup regions of Western Europe/Israel/North America/Australia, and Rest of World (including South America); that is excluding the Asia region. The KEYNOTE-811 RCT was well-designed to give a low risk of bias. There is some concern that a *post hoc* analysis was used, that is combining West Europe/Israel/North America/Australia and Rest of the world, although it is noted that randomisation was preserved within each region.

At interim analysis 2 (IA2), for CPS≥1 participants excluding the Asia region, median OS for the pembrolizumab group (n=202) was 18.8 months (95%CI 15.5, 24.3), and for the comparator group (n=200) median OS was 12.6 months (95%CI 11.1, 14.9). The HR for OS significantly favoured the pembrolizumab group, HR 0.67 (95% CI 0.52, 0.85, p=0.0006). If considering region subgroups separately, OS for CPS≥1 participants, Western Europe/Israel/North America/Australia had a HR of 0.81 (95%CI 0.57, 1.15) whilst Rest of the World had a HR of 0.57 (95%CI 0.40, 0.80).

The CS provides an analysis of the cost-effectiveness of pembrolizumab plus SoC against SoC alone, where SoC is assumed to comprise of trastuzumab with chemotherapy. The addition of pembrolizumab to SoC is estimated to increase lifetime costs, largely through the increase in drug acquisition costs, but also through increased time spent in the progression-free health state. The addition of pembrolizumab to SoC is estimated to increase OS, resulting in additional time spent in the health state where time-to-

death is more than 1 year, which is associated with a greater health utility than time spent in health states with lower expected survival. This combination of increased survival and additional time spent in a state with higher utility results in an expected QALY gain for pembrolizumab plus SoC compared to SoC alone. The company's base case analysis provides a deterministic ICER of £[redacted] per QALY and a probabilistic ICER of £[redacted] per QALY when no QALY weighting is applied. The company's base case ICER when applying a QALY weighting of 1.2 is £[redacted] for the deterministic analysis and £[redacted] for the probabilistic analysis.

The EAG's primary concern regarding the company's economic analysis relates to the modelling of OS and PFS. The company claims that data from the Asia region of the KEYNOTE-811 study are less generalisable to clinical practice in England due to the widespread use of gastric cancer screening in Asia region countries which is not routinely offered in England. Therefore, the majority of the company's model inputs are informed by data from the non-Asia (CPS≥1) cohort. However, the company's approach to modelling OS and PFS uses data from the global (CPS≥1) cohort (including data from the Asia region) to model OS and PFS in the SoC arm. HRs from the non-Asia (CPS≥1) cohort are then applied to estimate OS and PFS for the pembrolizumab plus SoC arm. The EAG prefers to use parametric OS and PFS curves fitted separately to data from both the intervention and comparator arms of the non-Asia (CPS≥1) cohort. The EAG's exploratory analyses demonstrate that its alternative approach to modelling OS has a substantial impact on the ICERs, increasing it to £[redacted] (without QALY weighting) when applied as a single change to the company's base case. This is because OS was higher in the Asia region than in the two other regions which were combined to generate the non-Asia cohort. This has implications both for generating an appropriate estimate of the ICER and for determining the appropriate QALY weighting to account for the severity of the condition.

The EAG also noted that the time-to-death approach used by the company to model utilities provided a utility estimate for people with expected survival of over 1 year that was very similar to age-adjusted utility values in the general population. The EAG preferred to use the utility estimates from the company's linear mixed effects model, but this did not have a large impact on the ICER. The EAG also explored the impact of using a progression-based approach to estimate utilities and this demonstrated that the ICER is somewhat sensitive to the choice between a time-to-death and a progression-based approach to model utilities.

Overall, the EAG's preferred base case ICER was £[redacted] per QALY for the deterministic analysis and £[redacted] per QALY for the probabilistic analysis, when not applying any QALY weighing to account for severity. Using an alternative parametric extrapolation, but still modelling OS and PFS using parametric curves fitted separately to each arm of the non-Asia cohort, reduced the deterministic

ICER to £[redacted]. Using the progression-based approach to estimate utilities from the linear mixed effects model increased the EAG's preferred estimate of the ICER to £[redacted].

The company argues that the appropriate QALY weighting is 1.2 based on the lifetime QALYs estimated for trastuzumab with chemotherapy in the trastuzumab appraisal (TA208). The EAG prefers to use the QALYs from the SoC arm of the model to estimate the absolute and proportionate QALY shortfall and determine the corresponding QALY weighting. This approach would support a QALY weighting of 1.0 when using the company's base case analysis, and 1.2 when using the EAG's preferred base case analysis. The EAG's base case ICER when applying a QALY weighting of 1.2 is £[redacted] when using the deterministic analysis and £[redacted] when using the probabilistic analysis.

Overall, the EAG's estimate of the ICER is much higher than the company's estimate and is above £30,000 per QALY even when applying a QALY weighting of 1.2. This is largely due to the EAG preferring to exclude data from the Asia region when estimating OS and PFS in the cost-effectiveness analysis, which is consistent with the company's claim that this data is not generalisable to the UK. However, the EAG notes that the non-Asia cohort is a *post hoc* analysis combining data from two regions. The EAG considers that data from the Western Europe/Israel/North America/Australia region could be more applicable to England than data from the Rest of World region. The EAG also expects that populating the model with data from the Western Europe/Israel/North America/Australia region could have a substantial impact on the ICER, but this could not be explored by the EAG with the data provided by the company. This is therefore an additional uncertainty that is not captured within the EAG's exploratory analysis.

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8 APPENDICES

Appendix 1: Trial of comparator, ToGA

Study characteristics for ToGA trial

ToGA was a Phase III open-label RCT that compared chemotherapy with or without trastuzumab, for previously untreated HER2- positive locally advanced, recurrent, and/or metastatic cancer gastric or GOJ cancer (Bang *et al.*2010).[31] It was a multicentre study in 24 countries[31] across Europe (including the UK), Asia, North America, South America, African and Australia.[32] Randomisation was stratified by ECOG performance status, chemotherapy regimen, extent of disease, primary cancer site, and measurability of disease.[31] Cancers were histologically confirmed, and HER2 status was assessed with immunohistochemistry (HercepTest, Dako, Denmark]) and fluorescence in-situ hybridisation (FISH; HER2 FISH pharmDx, Dako).[31] Recruitment occurred between 2005 and 2008.[31]

The chemotherapy regimen[31] for both treatment groups was given every three weeks for six cycles, and consisted of cisplatin (80 mg/m² i.v. infusion day 1) plus either:
Capecitabine (1000 mg/m² orally twice a day for 14 days followed by one-week rest):
or 5-fluorouracil (800 mg/m² per day was given by continuous intravenous infusion on days 1–5 of each cycle).
The intervention group additionally received trastuzumab (8 mg/kg i.v. infusion day 1 of the first cycle, followed by 6 mg/kg every 3 weeks).[31]
Study treatment was continued until disease progression or unacceptable toxicity.[31] Dose adjustments for chemotherapy, or interruptions of trastuzumab were allowed.[31] The chemotherapy received by the majority of patients in both treatment groups was capecitabine plus cisplatin (XP) (Table 34).

The primary outcome was OS, defined as time from randomisation until death from any cause (assessment schedule days 1, 8, 15, 22, 43, 64, 85, 106, 127, and then every 21 days).[31,32] Secondary outcomes included: PFS defined as time from randomisation to progression (at least a 20% increase for target lesion, or unequivocal progression of existing non-target lesion) or death; ORR (RECIST criteria); and safety.[31,32]

Table 34 ToGA (NCT01041404) overview of study characteristics[31, 32]

Trial design	Population	Intervention N=294 in analysis	Comparator N=290 in analysis	Primary outcome
Phase III RCT, open-label	Adults (age >18) with previously untreated HER2-positive, histologically confirmed locally advanced, recurrent, and/or metastatic gastric or GOJ adenocarcinoma	Trastuzumab plus: capecitabine plus cisplatin (XP) n=256 (87%); or 5-fluorouracil plus cisplatin (FP) n=38 (13%)	Capecitabine plus cisplatin (XP) n=255 (88%) or 5-fluorouracil plus cisplatin (FP) n=35 (12%)	Overall Survival (OS) - Time to Event

Abbreviations: FP= cisplatin plus 5-FU; OS=overall survival;; HER2= human epidermal growth factor receptor 2; GOJ=gastro-oesophageal junction; RCT, randomised controlled trial

Risk of bias for ToGA trial

Risk of bias was assessed based on the Cochrane Risk of Bias tool 2.0. There was some similarity between assessment by the CS and EAG (Table 35). The EAG and CS differed in assessment of bias arising from the randomization process. The CS thought this was high risk because ToGA was not a double-blind study, however allocation concealment refers to preventing bias in intervention assignment by preventing trial personnel from knowing, or altering, the allocation sequence before and until assignment. Lack of blinding is captured in bias in measurement of the outcome. Lack of blinding can lead to a risk of performance and detection bias. The ToGA trial was open-label, and it was unclear who assessed the outcome measures. If outcome assessors are not blinded, then the potential for bias needs to be considered for each outcome assessed. Patient-reported outcome measures are more likely to be biased than objective measures such as OS, as assessment of OS would not have been influenced by knowledge of intervention received.[63] Both PFS and safety outcomes might have an element of subjectivity, and so are subject to bias in the ToGA trial. However, PFS and AEs are well-defined, which should reduce the effect of bias.

Table 35 Risk of bias ToGA trial

Type of bias	**ToGA**			
	Review authors' judgement	**Support for judgement**	**EAG judgement**	**Support for judgement**[31, 32 64]
Bias arising from the randomization process	High risk	Open-label study; participants were randomly assigned 1:1 to trastuzumab + chemotherapy or chemotherapy alone using a central interactive voice recognition system and assignment was *not* masked to either patients or investigators.	Low risk	Allocation sequence – stratified, randomised block design via interactive voice recognition system Allocation concealment – allocation was concealed, as randomisation performed centrally using an interactive voice recognition system Baseline characteristics –balanced between treatment groups
Bias due to deviations from intended interventions	Some concerns	Open-label study; patients and investigators were aware of assigned interventions. There were no deviations from the intended intervention because of trial context and appropriate analysis methods were employed to estimate treatment effects.	Some concerns	Participant awareness of assigned intervention – open-label Clinician/carer awareness of assigned intervention – open-label Trial context – no strong reason to believe, that the trial context led to failure to implement the protocol interventions Appropriate analyses - analyses were appropriate, modified ITT for effectiveness and HRQoL included all patients who received study medication at least once

Type of bias	ToGA			
	Review authors' judgement	**Support for judgement**	**EAG judgement**	**Support for judgement[31, 32 64]**
Bias due to missing outcome data	Low risk	Data for outcomes available represented all or nearly all randomized participants.	Low risk	Available outcome data – OS and PFS nearly all participants provided data
Bias in measurement of the outcome	High risk	Open-label study; assessment of the outcome may have been influenced by knowledge of intervention received.	OS – low risk PFS and AEs – some concerns	Method of measuring outcomes – appropriate Outcome measurement for treatment groups – same measurements at same time points across treatment groups Outcome assessor awareness – unclear Could assessment of the outcome have been influenced by knowledge of intervention received? – OS no; PFS might have an element of subjectivity, however the outcome is well-defined; AEs prone to influence, however the outcomes are well-defined
Bias in selection of the reported result	Low risk	Analysis was in accordance with a pre-specified analysis plan that was finalized before the outcome data were available for analysis.	Low risk	Analyses pre-specified – analyses were prespecified for OS and PFS Multiple outcome measurements – outcomes definitions pre-specified
Overall bias	Some concerns	Some concerns regarding bias due to open-label design.	Some concerns	

ToGA trial results

Of 594 patients randomised, 584 received study treatment and provided data for the effectiveness analyses.[31] Analyses occurred after 18.6 months median follow-up in the trastuzumab group, and 17.1 months in the comparator group.[31] In the trastuzumab plus chemotherapy group, the median number of cycles of trastuzumab therapy was eight (range 1–49), and the median number of chemotherapy cycles was six for cisplatin, capecitabine and 5-fluorouracil.[31] In the chemotherapy group, the median number of cycles of was five for cisplatin and capecitabine, and four for 5-fluorouracil.[31]

Median PFS for the trastuzumab plus chemotherapy group was 6.7 months (95%CI 6, 8), and for the chemotherapy group 5.5 months (95%CI 5, 6), HR 0.71 (95%CI 0.59, 0.85) p=0.0002, significantly favouring the trastuzumab plus chemotherapy group.[31]

Median OS for the trastuzumab plus chemotherapy group (n=294) was 13.8 months (95%CI 12, 16), and for the chemotherapy group (n=290) 11.1 months (95% confidence interval 10, 13), HR 0.74 (95%CI 0.60, 0.91) p=0.0046, significantly favouring the trastuzumab plus chemotherapy group.[31] Pre-planned subgroup analyses were reported for OS. For region subgroups, HRs for trastuzumab plus chemotherapy with reference chemotherapy were: Central or South America (n=52) HR 0.44 (95%CI 0.21, 0.90); Europe (n=190) HR 0.63 (95%CI 0.44, 0.89); Asia (n=319) HR 0.82 (95%CI 0.67, 1.11); Other (n=23) HR 1.22 (95%CI 0.48, 1.46).[31] The results showed the same direction of effect for OS for all regions except "Other" which had a small sample size and wide confidence intervals. It appeared that in the Europe region there was a more favourable treatment response to trastuzumab than in the Asia region, and that the most favourable trastuzumab response was in Central or South America, however subgroups were relatively small and not powered to detect treatment differences.[31]

In the Japanese region subgroup of ToGA, in which chemotherapy type was XP for all patients, median OS for the trastuzumab plus chemotherapy group (n=51) was 15.9 months (95%CI 12, 25), and for the chemotherapy group (n=50) 17.7 months (95% confidence interval 12, 24), HR 1.00 (95%CI 0.59, 1.69).[65] The Japanese region subgroup of ToGA had a median PFS for the trastuzumab plus XP (n=51) was 6.2 months (95%CI 5, 7), and for the XP group (n=50) 5.6 months (95% confidence interval 5, 7), HR 0.92 (95%CI 0.60, 1.43).[65] These were non-significant treatment group differences, however the direction of effect favoured the intervention group for PFS, but favoured the comparator group for OS, reflecting the pattern of the Asia region results of KEYNOTE-811.

Adverse events led to non-completion of the trials for 35/294 (11.9%) of the trastuzumab plus chemotherapy group, and 45/290 (15.5%) of the chemotherapy group.[32] Grade 3 or 4 AEs were experienced by 201/294 (68%) of the trastuzumab plus chemotherapy group, and 198/290 (68%) of the

chemotherapy group.[31] The most common grade 3 or 4 AEs were anaemia, neutropenia, diarrhoea, nausea, vomiting, thrombocytopenia and asthenia.[31] Any AE was experienced by 99% of the trastuzumab plus chemotherapy group, and 98% of the chemotherapy group.[31]

HRQoL was measured with the European Organization for Research and Treatment of Cancer (EORTC) quality of life QLQ-C30 (version 3.0) Global Health status (GHS). [64] The median time to 10% deterioration in the GHS score of the QLQ-C30 questionnaire was 10.2 months in the trastuzumab plus chemotherapy group, and 6.4 months in the chemotherapy group, significantly favouring the trastuzumab plus chemotherapy group ($p<0.0001$).[64]

ToGA and KEYNOTE-811comparison

Both ToGA and KEYNOTE-811 included a trastuzumab plus chemotherapy group. Chemotherapy type could be FP in either trial, however a minority of patients received this, with the majority in KEYNOTE-811 receiving CAPOX, and in ToGA, XP.

ToGA recruited between 2005 and 2008 [31], whereas KEYNOTE-811 started recruiting in 2018.[30] Both trials recruited adults with previously untreated HER2-positive, histologically confirmed locally advanced, recurrent, and/or metastatic gastric or GOJ adenocarcinoma. Both trials had a majority metastatic population (Table 36). ToGA did not report PD-L1 status. ToGA included ECOG 2, unlike KEYNOTE-811.

Outcomes of the trials are shown in Table 37. The trastuzumab plus chemotherapy group of the KEYNOTE-811 trial had longer OS and PFS than the trastuzumab plus chemotherapy group of the ToGA trial. This may have been due to patient characteristics (e.g., inclusion of ECOG2 in ToGA) or the influence of subsequent therapies. Adverse event rates were similar across trials.

Table 36 Participant Baseline Characteristics by Treatment Group [adapted from CS Section B Table 6, and ToGA references]

	KEYNOTE-811 CPS≥1 Participants global cohort Pembrolizumab plus trastuzumab plus chemotherapy		**KEYNOTE-811 CPS≥1 Participants global cohort Trastuzumab plus Chemotherapy**		**ToGA Trastuzumab plus Chemotherapy**		**ToGA Chemotherapy**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Participants in population	298		296		294		290	
PD-L1 status CPS ≥1	298	100	296	100	NR	NR	NR	NR
Sex								
Male	240	(80.5)	237	(80.1)	226	(77%)	218	(75%)
Female	58	(19.5)	59	(19.9)	68	(23)	72	(25)
Age (Years)								
Mean	60.6		61.4		59·4 (SD 10·8)		58·5 (SD 11·2)	
SE	0.7		0.6					
Race								
American Indian Or Alaska Native	5	(1.7)	6	(2.0)	NR	NR	NR	NR
Asian	97	(32.6)	97	(32.8)	151	(51)	158	(54)
Black Or African American	2	(0.7)	2	(0.7)	1	(<1)	2	(1)
Multiple	5	(1.7)	4	(1.4)	NR	NR	NR	NR
White	188	(63.1)	184	(62.2)	115	(39)	105	(36)
Missing	1	(0.3)	3	(1.0)	NR	NR	NR	NR
Geographic Region of Enrolling Site								
Western Europe/Israel/North America/Australia	97	(32.6)	96	(32.4)	NR Across both groups			

	KEYNOTE-811 CPS≥1 Participants global cohort Pembrolizumab plus trastuzumab plus chemotherapy		**KEYNOTE-811 CPS≥1 Participants global cohort Trastuzumab plus Chemotherapy**		**ToGA Trastuzumab plus Chemotherapy**		**ToGA Chemotherapy**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
					Europe n=190			
Asia	96	(32.2)	96	(32.4)	NR Across both groups Asia n=319			
Rest of the World	105	(35.2)	104	(35.1)	NR Across both groups Central or South America n=52			
ECOG Performance Scale								
0	127	(42.6)	121	(40.9)	NR, ECOG 0 or 1 264	(90)	NR, ECOG 0 or 1 263	(91)
1	171	(57.4)	174	(58.8)				
2	0	0	0	0	30	(10)	27	(9)
Missing	0	(0.0)	1	(0.3)	0	0	0	0
Primary Location at Diagnosis								
Adenocarcinoma of the GOJ	97	(32.6)	99	(33.4)	58	20	48	17
Adenocarcinoma of the stomach	201	(67.4)	197	(66.6)	236	80	242	83

	KEYNOTE-811 CPS≥1 Participants global cohort Pembrolizumab plus trastuzumab plus chemotherapy		KEYNOTE-811 CPS≥1 Participants global cohort Trastuzumab plus Chemotherapy		ToGA Trastuzumab plus Chemotherapy		ToGA Chemotherapy	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Disease Status								
Locally advanced	8	(2.7)	6	(2.0)	10	3	10	3
Metastatic	290	(97.3)	290	(98.0)	284	97	280	97
Chemotherapy Regimen								
CAPOX	251	(84.2)	253	(85.5)	0	0	0	0
FP	47	(15.8)	43	(14.5)	38	13	35	12
XP	0	0	0	0	256	87	255	88

Table 37 Outcomes of ToGA and KEYNOTE-811

	KEYNOTE-811 CPS≥1 Participants global cohort Pembrolizumab plus trastuzumab plus chemotherapy	**KEYNOTE-811 CPS≥1 Participants global cohort Trastuzumab plus Chemotherapy**	**ToGA Trastuzumab plus Chemotherapy**	**ToGA Chemotherapy**
N patients	298	296	294	290
Median OS (95%CI)	20.5 months (18.2-24.3)	15.6 months (13.5-18.6)	13.8 months (12-16)	11.1 months (10-13)
Median PFS (95%CI)	10.8 months (8.5-12.5)	7.2 months (6.8-8.4)	6.7 months (6-8)	5.5 months (5-6)
ORR n (%)	218 (73.2)	173 (58.4)	139 (47)	100 (35)
AEs N patients	298	295	294	290
Any AE	97.0	96.3	99.0	98.0
Grade ≥3 AEs	73.2%	65.1%	68%	68%

Summary of ToGA trial

ToGA was a Phase III open-label RCT that compared chemotherapy (XP or FP) with or without trastuzumab. The open-label nature of the trials meant there were some concerns of risk of bias. Median time to death for the trastuzumab plus chemotherapy group (n=294) was 13.8 months (95%CI 12, 16), and 11.1 months (95%CI 10, 13) for the chemotherapy group (n=290), favouring the trastuzumab plus chemotherapy group (HR 0.74 (95%CI 0.60, 0.91) p=0.0046). Median PFS for the trastuzumab plus chemotherapy group was 6.7 months (95%CI 6, 8), and for the chemotherapy group 5.5 months (95%CI 5, 6), favouring the trastuzumab plus chemotherapy group (HR 0.71 (95%CI 0.59, 0.85) p=0.0002). Grade 3 or 4 AEs were experienced by 201/294 (68%) of the trastuzumab plus chemotherapy group, and 198/290 (68%) of the chemotherapy group.

Single Technology Appraisal

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

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 the end of **7 August** 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 separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Report page 57, first bullet point: "Only grade ≥3 AEs that occurred in ≥3% of all CPS≥1 patients in either treatment group of KEYNOTE-811 are included in the company's model…"	"Only grade ≥3 AEs that occurred in ≥3% of all non-Asia CPS≥1 patients in either treatment group of KEYNOTE-811 are included in the company's model…"	The updated model provided with the clarification question responses included AE frequencies for the non-Asia cohort (see response to question B.29), as reflected in Table 11 of the EAG report.	The EAG has amended its text as proposed.

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Report page 78: error in description of scenario analysis: "…limiting the model's time horizon to 8 years (ICER increases to ~£[redacted]),…"	"…limiting the model's time horizon to 20 years (ICER increases to ~£[redacted]),…"	This ICER is reported in the scenario analysis where a 20-year time horizon is applied.	The EAG has amended its text as proposed.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Report page 111, Table 31 – first row: company base case deterministic ICER with QALY weight stated to be £[redacted]	Update to £[redacted]	This is the ICER presented in the clarification stage response.	The EAG has amended its text as proposed at Table 31 and also Table 2.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49, ORR results	Please remove word significant: This comprised of 29 patients with CR, and 144 with PR (CS Section B2.6.1 Table 19). The difference in ORR favoured the pembrolizumab group, estimate 14.7% (95%CI 7.1%, 22.2%) p=0.00008 (CS Section B2.6.1 Table 18)	ORR analysis is descriptive only in IA2.	The EAG has amended its text as proposed.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 4, typo	Please correct hazard ‘ration’ to ‘ratio’	Typo	The EAG has amended its text as proposed.

(please cut and paste further tables as necessary)

Location of incorrect marking	Description of incorrect marking	Amended marking
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Technical engagement response form

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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **15 September 2023**. 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 received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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.

Technical engagement response form

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

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Merck Sharp & Dohme Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key Issue 1: The use of a post hoc analysis of the non-Asia cohort which excluded data from the Asia region, but combined data from two other regions	No	*Differences in the treatment patterns across the regions* MSD and the EAG are in agreement that it is appropriate to exclude patients enrolled in KEYNOTE-811 from the Asian region, on the basis of generalisability to the England and Wales setting. This is due to differences in incidence, mortality, and clinical care including availability of screening in the Asian region. [1,2] In 2020, Asia accounted for approx. 75% of both newly diagnosed gastric cancer cases and gastric cancer mortality.[3] Given the higher rates or incidence and mortality within the Asia region, the implementation of screening programmes and biological differences, Asia has a higher proportion of non-cardia gastric cancer than non-Asia regions, and an impact on survival and other outcomes within the trial

[1] Wong M, Huang, J, Chan P et al *JAMA Netw Open.* 2021;4(7):e2118457.
[2] Morgan E, Arnold M, Camargo M et al eClinicalMedicine 2022;47:101404
[3] World Health Organisation International Agency for Research on Cancer Cancer Fact Sheets, Stomach Factsheet 7-Stomach-fact-sheet.pdf (iarc.fr) last accessed 15th September 2023

		is expected. Based on the differences highlighted, MSD believe the appropriate data set from the trial to inform the generalisable analysis is that pertaining to non-Asia region patients i.e. a combination of the two levels of the pre-specified non-Asia regions within the KEYNOTE-811 trial, i.e. "Western Europe/Israel/North America/Australia" and "Rest of World (ROW)". MSD acknowledge that there may be differences in healthcare systems and structures within the pre-specified regions. Although there is a paucity of data describing healthcare systems and standards within these countries, it could be reasonable to assume that in some countries, access to care may be a confounding issue. However, MSD believe that any differences would be mitigated in part due to the site selection for trial sites used for KEYNOTE-811 enrolment; all centres within the ROW region of KEYNOTE-811 were major cancer centres that are highly experienced in cancer care and provide similar care to that delivered in England and Wales. *Use of data informed by a post-hoc analysis of the non-Asia (region) cohort* The population included in the company submission is restricted to the PD-L1 CPS ≥1 subgroup of patients in KEYNOTE-811, in line with the population covered by the marketing authorisation. The PD-L1 CPS ≥1 population was a pre-specified subgroup of the KEYNOTE-811 trial. In their report, the EAG questioned the validity of the non-Asia (region) CPS ≥1 subgroup data presented in the company submission, which was generated post-hoc by combining CPS ≥1 data from two pre-specified regions ("Western Europe/Israel/North America/Australia" and "Rest of World (ROW)"). It is important to highlight that in the KEYNOTE-811 trial, in addition to the subgroup based on region, there was a pre-planned subgroup based on "race", defined as the split between Asia/non-Asia patients. In terms of patient numbers, the number of patients in the Asia subgroup based on race closely matches the number of patients in the Asia subgroup based on region; there is only a difference of two patients. Minimal difference in patient numbers

also can be seen when comparing the non-Asia subgroup based on race, with the number of patients in the pooled non-Asia subgroup based on region; again, the difference is just two patients – please see Table 1.

Hence, despite the post-hoc nature of the non-Asia region subgroup based on region, concern about the appropriateness of creating this pooled subgroup should be mitigated, given the comparability in patient numbers with the prespecified non-Asia subgroup based on race. The combination of stratification factors for randomisation ensures that the comparability between treatment groups in the CPS>=1 non-Asia patients is maintained.

Table 1. Participant Baseline Characteristics by Treatment Group, Race and Geographic Region (CPS≥1 Participants) (Global Cohort) (Intention-to-Treat Population)

	Pembrolizumab + SoC		SoC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	298		296		594	
Geographic Region of Enrolling Site						
Asia	96	(32.2)	96	(32.4)	192	(32.3)
Non-Asia	202	(67.8)	200	(67.5)	402	(67.7)
• Western Europe/Israel/North America/Australia	97	(32.6)	96	(32.4)	193	(32.5)
• Rest of the World	105	(35.2)	104	(35.1)	209	(35.2)
Race						
Asian	97	(32.6)	97	(32.8)	194	(32.7)

Non-Asia		201	(67.5)	199	(67.3)	400	(67.4)
• American Indian Or Alaska Native		5	(1.7)	6	(2.0)	11	(1.9)
• Black Or African American		2	(0.7)	2	(0.7)	4	(0.7)
• Multiple		5	(1.7)	4	(1.4)	9	(1.5)
• White		188	(63.1)	184	(62.2)	372	(62.6)
• Missing		1	(0.3)	3	(1.0)	4	(0.7)

In addition to comparability in patient numbers, efficacy results for pembrolizumab + trastuzumab + chemotherapy compared to trastuzumab + chemotherapy in the non-Asia subgroup based on race are also comparable with and those in the non-Asia subgroup based on region (previously reported in the company submission Appendix M). There is only one decimal point difference in the HRs which are almost equivalent: HR of 0.68, 95% CI [0.53; 0.87] for OS in non-Asia subgroup based on race and HR of 0.67, 95% CI [0.52; 0.85] for non-Asia subgroup based on region. PFS results are also similar: HR of 0.66, 95% CI [0.53; 0.82] in non-Asia race subgroup and HR of 0.62, 95% CI [0.49; 0.78] in non-Asia region subgroup.

The decision to combine the “Western Europe/Israel/North America/Australia” and “ROW” subgroups to create a post-hoc non-Asia subgroup by region (which mirrors the pre-specified non-Asia subgroup based on race in the KEYNOTE-811 trial) increases the sample size of the analysed population of interest while preserving the trial randomisation which makes the efficacy results more precise (standard error of estimates is smaller so estimates are more precise, with narrower CIs). If only results from “Western Europe/Israel/North America/Australia” cohort were used, the number of analysed patients

		is much lower, totalling just 193 participants (see Table 1) which could have potentially made results less reliable. MSD did not consider it appropriate to focus the company evidence submission on KEYNOTE-811 subgroup trial results based on a "race" subgroup, given that race is considered a protected characteristic under NICE's equality considerations). *Unmet need* MSD would like to take the opportunity to reiterate that patients with HER2 positive locally advanced unresectable or metastatic GC or GOJ adenocarcinoma have not benefitted from any new treatment options for over a decade. In 2010, NICE published TA208 which recommends trastuzumab, in combination with cisplatin and capecitabine or 5-fluorouracil, as an option for the treatment of people with HER2 positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction since 2010[4]. However, since then, patients with HER2 positive GC and GOJ adenocarcinoma have had no new effective treatment options come to market. Numerous HER2-targeting drugs such as the tyrosine kinase inhibitor lapatinib[5] [6], the antibody-drug conjugate trastuzumab-emtansine[7] and the addition of pertuzumab[8] to trastuzumab failed to demonstrate an improvement in OS in phase III studies in metastatic HER2 positive GC; therefore high unmet still persists in this patient

[4] National Institute for Health and Care Excellence. *Trastuzumab for the treatment of HER2-positive metastatic gastric cancer: Technology appraisal guidance [TA208]*. 2010 May 2023]; Available from: https://www.nice.org.uk/guidance/ta208.
[5] Satoh, T., et al., *Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study.* J Clin Oncol, 2014. **32**(19): p. 2039-49.
[6] Hecht, J.R., et al., *Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2–Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adenocarcinoma: TRIO-013/LOGiC—A Randomized Phase III Trial.* Journal of Clinical Oncology, 2016. **34**(5): p. 443-451.
[7] Thuss-Patience, P.C., et al., *Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study.* The Lancet Oncology, 2017. **18**(5): p. 640-653.
[8] Tabernero, J., et al., *Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study.* Lancet Oncol, 2018. **19**(10): p. 1372-1384.

		population[9]. Addition of pembrolizumab to trastuzumab and doublet chemotherapy is already recommended in the USA based on KEYNOTE-811 IA1 data[10] and recently it has been recommended across the EU based on IA2 data[11]. This appraisal aims to address this ongoing unmet need and potentially offers the first immuno-oncology (IO) treatment option for patients with unresectable advanced metastatic HER2 positive GC and GOJ adenocarcinoma, thereby broadening the available treatment options for clinicians to use for these patients.
Key issue 2: Method used to extrapolate overall survival (OS) and progression-free survival (PFS) in the economic model by applying a hazard ratio (HR) from the non-Asia (CPS ≥1) cohort to parametric curves fitted to the comparator (SoC) arm of the global (CPS ≥1) cohort	No	The method of applying a HR to the parametric curves fitted to the SoC arm was followed based on the non-rejection of the proportional hazards assumption following assessment for both OS and PFS. The EAG disagrees with this approach due to lack of justification of a constant HR or constant acceleration factor over a lifetime. The EAG's preferred approach to modelling these parameters is to fit independent models to both treatment arms.

[9] Haffner, I., et al., *HER2 Expression, Test Deviations, and Their Impact on Survival in Metastatic Gastric Cancer: Results From the Prospective Multicenter VARIANZ Study.* J Clin Oncol, 2021. **39**(13): p. 1468-1478.

[10] U.S. Food & Drug administration. *FDA grants accelerated approval to pembrolizumab for HER2-positive gastric cancer*. 2021 May 2023]; Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-her2-positive-gastric-cancer.

[11] European Commission Approves KEYTRUDA® (pembrolizumab) Plus Trastuzumab and Chemotherapy as First-Line Treatment for HER2-Positive Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Expressing PD-L1 (CPS ≥1) - Merck.com

		With the availability of subgroup analyses for the non-Asia region population (submitted in response to clarification questions), MSD acknowledge the inconsistency in applying the non-Asia population HR to SoC curves for the global cohort. Although, as outlined in the CS, the assessment of the proportional hazards assumption for OS revealed insufficient evidence to reject the assumption based on the log cumulative hazards plot, MSD acknowledges that a separately fitted approach is also plausible. Hence MSD has submitted a revised base case with this response (see Table 4 below) to reflect the preferred EAG approach. The revised base case is estimated using the non-Asia region dataset presented in the EAG model. **OS:** The 2-knot odds spline model is selected as the base case for the pembrolizumab plus SoC arm. MSD agree with the EAG's visual assessment that all spline models fit the trial data well, and that the unimodal shape demonstrated by the smoothed hazard function indicates the appropriateness of a spline model. Compared to the survival rates reported by the KEYNOTE-811 KM data (see EAR Table 24), the 2-knot odds model slightly

		overestimates survival at 1 year (68% vs 66%) but slightly underestimates survival at 2 years (41% vs 44%). The model predicts a 5-year survival of 16%, which exceeds that suggested by one of the clinical experts consulted by the EAG (reported in EAR Table 25 [5-10%]). The lack of immunotherapy precedent in the advanced HER2 positive GC treatment pathway may temper expectations of longer-term survival benefit for these patients, potentially resulting in 5-year survival estimations of a more conservative nature than are likely to be seen in practice. The established pattern of survival tails seen with pembrolizumab use in other cancers lends support to the plausibility of higher 5-year survival estimates[12]. For the SoC arm, the Weibull standard parametric model is selected in the base case. Survival rate predictions by experts are a more important driver of the selection of the appropriate parametric model for the SoC arm, given that these predictions are based on a greater wealth of data combined with clinical familiarity and experience of using SoC treatment regimens. The Weibull model reflects the KM rate at 2 years (28% of patients alive) and predicts an OS rate of 2% at 5 years. This aligns with the clinical experience of

[12] **de Castro G, Kudaba I, Wu Y, et al. Five-year outcomes with pembrolizumab versus chemotherapy as first-line therapy in patients with non–small-cell lung cancer and programmed death ligand-1 tumor proportion score ≥ 1% in the KEYNOTE-042 study. *J Clin Oncol*. 2023;41(11):1986-1991. doi:10.1200/JCO.21.02885**

		the clinical experts consulted by MSD and the EAG. The differing biological mechanisms of actions between an immunotherapy-containing intervention arm and SoC supports the use of different model types between treatment arms. The revised base case models and KM curves for both arms are presented in Figure 1 below. These model selections in the non-Asia population data estimate a proportional QALY shortfall of 0.908, which qualifies the model QALYs for a 1.2 weighting. Model results are presented in Table 4 below with this weighting applied. **PFS:** MSD acknowledge that, due to the completeness of the data for this outcome, the impact of the selected PFS model on the cost-effectiveness outcome is minor and the parameter is not a model driver. Based on the rationale of goodness-of-fit to the trial data, shape of the smoothed hazard function and long-term predictions compared to clinical expert opinion, MSD agree with the EAG selection of the lognormal parametric model for both treatment arms. The revised MSD base case reflects this.

Key issue 3: Utilities based on time-to-death rather than using utilities based on progression status (i.e., progressed disease versus progression-free)	No	The EAR describes this model assumption as an area of uncertainty, commenting that: "*neither approach overcomes the main limitation that the data collected have been heavily censored, either at the point of progression, or at treatment discontinuation."* Both approaches to estimating utility have been accepted by NICE committees in previous appraisals. MSD believes that the time-to-death approach to estimating utility is appropriate. In addition to the time intervals presented, a further time-to-death category was "unknown". For trial patients who had not died at database cut off (i.e. censored OS), their utility assessments taking place less than 360 days from date of censored death were assigned to the "unknown" category. 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. Given that there appears to be a link between time-to-death and utilities (i.e. utility is higher the further the patient is from their date of death), there is therefore potential for patients classified as "unknown" to live longer (because they have been censored rather than having a confirmed date of death) and for their utility values to be similar to or higher than the overall average utility in the study. But because the options available in the model are limited to the

		4 time-to-death category values, the only option for the assessments that take place more than 360 days before censoring date for these longer survivors is to be "downgraded" to the '≥360 days' value. If so, it could be that the utilities using the time-to-death approach are underestimated; and this would be more pronounced in the treatment arm with the higher number of "unknown" utility assessments. In KEYNOTE-811, there are [redacted] "unknown" utility assessments in the pembrolizumab plus SoC arm and [redacted] "unknown" utility assessments in the SoC arm, indicating a more conservative outcome may result in the pembrolizumab plus SoC arm compared to the SoC arm, with the time-to-death approach. As per the EAG report: *"The EAG prefers to use the utility values estimated using a linear mixed effect model instead of descriptive statistics because the mixed effect modelling approach takes into account of the effect of covariates and correlations within a patient, and provides estimates with more face validity."* Descriptive analyses, without adjustment for repeated measures, weight utility measurements in proportion to the number of measurements observed in each health state for each patient such that patients with longer time in a health state, and more measurements, receive greater weight than an individual in the health state for a short time and with only a single measurement.

		The MSD base case approach is to use descriptive statistics for the utility analysis, as described in the CS. MSD note that these values have not been presented in the EAR, instead the additional analyses using a mixed effects model have been presented (see EAR Table 21 and Table 22). MSD propose that the descriptive analysis method has the advantage of not effectively down-weighting values for subjects with multiple measurements, relative to those with a single measurement (by not adjusting for repeated measurement, as is the case in the linear mixed effect model). Furthermore, in the context of health economic modelling, it is logical that patients with multiple measurements spending longer time in a health state should receive proportionately greater weight for their health utilities than those with a single measurement, as they account for relatively more of the time and QALYs spent in that state within the model and are more representative of that health state experience. Regarding the effect of covariates, adjustment of utility values for age and gender within the cost-effectiveness model was applied using external data published by Hernandez Alava et al (2022). This is considered to be a suitable approach given the limited follow-up of the trial and is a common approach followed in previous oncology appraisals.

Key issue 4: Severity modifier is not based on the expected quality-adjusted life-years (QALYs) predicted by the company's cost-effectiveness analysis because this incorporates data from the Asia cohort which the company considers not generalisable to England	No	In the revised company base case, QALYs and proportional QALY shortfall are estimated using data from the non-Asia region, which MSD regard as the most generalisable to the England and Wales population. MSD agree with the EAG that the shortfall and the QALY weight should be estimated from the analysis (a weight of 1.2 is estimated based on the proportional shortfall method, as outlined above). MSD believe this Key Issue may be resolved before the Appraisal Committee Meeting on the grounds of no disagreement. MSD note that under NICE's previous methods for evaluating new medicines, this appraisal would have qualified for the higher willingness-to-pay threshold by meeting the end-of-life criteria (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). Even with the removal of the QALY weight associated with the severity modifier, the MSD revised base case is below this willingness-to-pay threshold.

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Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

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Table 3 Additional issues from the EAR

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Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Additional issue 1: Removal of treatment cap for trastuzumab TTD	4.3.3.3	No	EAR: "*The duration of trastuzumab is capped in the company's base case analysis at 35 cycles, although the CS notes that there is no restriction on duration of treatment in TA208, other than for disease progression or unacceptable toxicity… the EAG preferred to use the TTD KM data to determine treatment duration for trastuzumab*". The generalisabiltiy of the model's treatment cap to NHS clinical practice was investigated with clinical experts and it is not expected that any patient will receive more than this number of cycles, and the expected mean number of cycles is expected to be far less than 35 (with or without the addition of pembrolizumab). This was corroborated by the advice received from the EAG's clinical advisor.

			Whilst it was permitted for patients to receive more than 35 cycles of trastuzumab in KEYNOTE-811, a post-hoc analysis indicated the proportion to be minor, with [redacted] patients in the non-Asia pembrolizumab plus SoC arm and [redacted] patients in the non-Asia SoC arm exceeding 35 cycles. This is expected to have a low impact for costs and efficacy. Based on this low impact and the lack of generalisability to NHS clinical practice of exceeding 35 cycles of trastuzumab, MSD believe that the base case treatment cap of 35 cycles is appropriate.

Additional issue 2: Administration costs for trastuzumab alone versus pembrolizumab with trastuzumab	4.3.3.5	No	EAR: *"The company's base case applies the reference cost for health resource group (HRG) code SB13Z to trastuzumab whether given alone or with pembrolizumab after completion of CAPOX/XP… The EAG considers that there should be some difference in administration costs for trastuzumab given alone versus trastuzumab given in combination with pembrolizumab."* In this submission, MSD seek to accurately reflect the administration cost impact for the NHS of adding a treatment to an existing regimen. The assumption was made that the equivalent tariff would apply given the complex nature of the existing trastuzumab plus chemotherapy SoC, and SB13Z was chosen as the appropriate code. Based on the expert input provided in the NHSE BIA submission for this appraisal (page 8), MSD

			understand the following to be correct: "*The current Heregulin for trastuzumab + cisplatin + 5-fluourouracil is SB14Z (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance).*" MSD accept that this is the correct code and agree to update the base case appropriately. Furthermore, the NHSE submission states: *"Pembrolizumab will be added to day 1 and will not affect the Heregulin (i.e. will remain as SB14Z).*" The retention of the tariff of an equivalent value for the pembrolizumab plus SoC combination contradicts the EAR assertion that "…*there should be some difference in administration costs for trastuzumab given alone versus trastuzumab given in combination with pembrolizumab.*"

			Based on expert NHSE input, MSD believe that a tariff of equivalent values is appropriate to apply to trastuzumab when given alone or in combination with pembrolizumab.

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key Issue 2	• OS extrapolation as described in the CS • PFS extrapolation as described in the CS	• OS intervention arm: 2-knot odds model (no treatment waning) • OS SoC arm: Weibull model • PFS intervention arm: Lognormal model (no treatment waning) • PFS SoC arm: Lognormal model	Applying the pembrolizumab Patient Access Scheme, the revised base case ICER is [redacted]. Model settings have been programmed which reflect the additional issues from the EAR in Table 3 above (i.e. in EAG exploratory analyses sheet, switches 3, 8, 9 are set to "No")
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted] Incremental costs: [redacted] ICER: [redacted]	Incremental QALYs: [redacted] Incremental costs: [redacted] ICER: [redacted]	-

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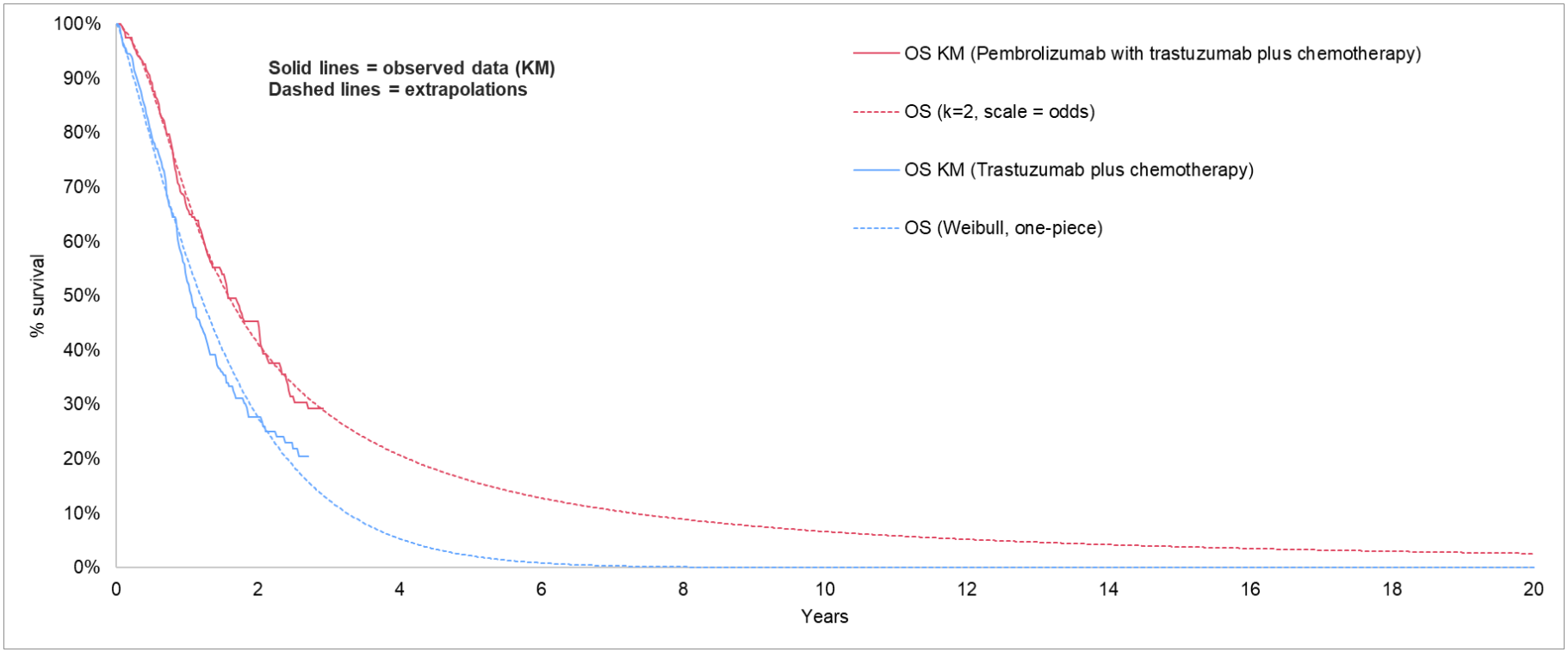
Figure 1: Revised base case models and KM data for treatment arms (OS)



Sensitivity analyses for revised base case

The results of the scenario analyses, ranked in descending order of impact, are presented in Table 2 .

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Table 2. Scenario analyses results (deterministic) vs. SoC

Rank	Scenario Name	Incremental Costs	Incremental QALYs	ICER	Difference vs. base case
1	Time horizon = 8 years	[redacted]	[redacted]	[redacted]	[redacted]
2	OS – gradual treatment waning between 7 & 9 years	[redacted]	[redacted]	[redacted]	[redacted]
3	0% discounting	[redacted]	[redacted]	[redacted]	[redacted]
4	Progression-based utility approach with PFS value = baseline and PD value = 0.732	[redacted]	[redacted]	[redacted]	[redacted]
5	1.5% discounting	[redacted]	[redacted]	[redacted]	[redacted]
6	Progression-based utilities	[redacted]	[redacted]	[redacted]	[redacted]
7	Time horizon = 20 years	[redacted]	[redacted]	[redacted]	[redacted]
8	Exclude RDI for 1L drugs	[redacted]	[redacted]	[redacted]	[redacted]
9	Exclude age-related gen pop utility multiplier	[redacted]	[redacted]	[redacted]	[redacted]
10	Pembrolizumab administration: 100% of patients on Q6W pembro	[redacted]	[redacted]	[redacted]	[redacted]
11	Exclude drug wastage (i.e. assume vial sharing)	[redacted]	[redacted]	[redacted]	[redacted]
12	Exclude terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]
13	Exclude AE disutility	[redacted]	[redacted]	[redacted]	[redacted]
14	UK chemotherapy regimen distribution - informed by clinical experts	[redacted]	[redacted]	[redacted]	[redacted]
15	Chemotherapy mean number of cycles as observed in trial	[redacted]	[redacted]	[redacted]	[redacted]
16	AE disutility of -0.053	[redacted]	[redacted]	[redacted]	[redacted]
17	Include half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PD, progressed disease; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; SoC, standard of care

The results of the one-way deterministic sensitivity analyses for the revised base case are presented in Table 3, and the tornado diagram is presented in Figure 2.

Technical engagement response form

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Table 3. One-way sensitivity analysis results

Rank	Parameter name	Lower bound ICER	Upper bound ICER	Difference vs. base case
1	RDI: Pembrolizumab with trastuzumab plus chemotherapy - Pembrolizumab, 200mg Q3W (43.6% - 100.0%)	[redacted]	[redacted]	[redacted]
2	RDI: Pembrolizumab with trastuzumab plus chemotherapy - Trastuzumab (42.7% - 100.0%)	[redacted]	[redacted]	[redacted]
3	RDI: Trastuzumab plus chemotherapy - Trastuzumab (42.7% - 100.0%)	[redacted]	[redacted]	[redacted]
4	Cost per administration: Deliver more complex parenteral chemotherapy at first attendance (£228.85 - £505.13)	[redacted]	[redacted]	[redacted]
5	RDI: Trastuzumab plus chemotherapy - Trastuzumab (loading dose) (42.7% - 100.0%)	[redacted]	[redacted]	[redacted]
6	RDI: Pembrolizumab with trastuzumab plus chemotherapy - Trastuzumab (loading dose) (42.7% - 100.0%)	[redacted]	[redacted]	[redacted]
7	Utility values ≥ 360 days to death (0.829 - 0.845)	[redacted]	[redacted]	[redacted]
8	Non-admitted face-to-face attendance, follow-up: unit cost (£143.33 - £316.36)	[redacted]	[redacted]	[redacted]
9	Non-admitted face-to-face attendance, follow-up: frequency of use (per week) (0.11 - 0.24)	[redacted]	[redacted]	[redacted]
10	Hospitalization/inpatient stay: unit cost (£1,411.06 - £3,114.53)	[redacted]	[redacted]	[redacted]

Figure 2. Tornado diagram presenting the results of the deterministic sensitivity analysis for the ten most sensitive variables vs. SoC

The results of the probabilistic sensitivity analyses for the revised base case are presented in Table 4 and the cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 3 and Figure 4 respectively.

Table 4. Incremental cost-effectiveness results based on PSA vs. SoC

Intervention	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER (£/QALY)
Trastuzumab plus chemotherapy	[redacted]	1.37	-	-	-
Pembrolizumab with trastuzumab plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years

Figure 3. Cost-effectiveness plane for PSA (1,000 simulations) vs. SoC

Figure 4. Cost-effectiveness acceptability curve (1,000 simulations) vs. SoC

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Single Technology Appraisal

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

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

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.

Do not include medical information about yourself or another person that could identify you or the other person.

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.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **15 September 2023.** 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.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating HER2-positive gastric or gastro-oesophageal junction adenocarcinoma and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	[redacted]
3. Job title or position	Professor of Medical Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma? ☐ A specialist in the clinical evidence base for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To increase oveall survival and to extend the progression free survival
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in median overall survival by >=3 months compared to CAPOX-Trastuzumab
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-positive gastric or gastro-oesophageal junction adenocarcinoma?	Yes, although Her-2 positive patients can on average do better than those who are her-2 negative, the survival still remains very poor (median survivan less than 1.5 years)
11. How is HER2-positive gastric or gastro-oesophageal junction adenocarcinoma currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Based on ESMO guidelines Her 2 3+ or FISH +ve patients are commenced on 6 cycles of platinum, 5FU (CAPOX or FP) + trastuzumab in 3 weekly cycles for 6 cycles. They are then continued on maintenance Trastuzumab 3 weekly until disease progression. This pathway is well defined and there is little varioation in practice across the NHS. There is some variation regarding when the Her-2 testing is done across the country (ie reflex versus on demand testing). This testing variation then results in variations in when the traztusumab is added into the chemotherapy regimen. Regarding impact on pathway of care: PD-L1 testing would have to be done as an extra test for patients who are Her-2 positive. This would require greater input from pathology departments. There would be greater work also within the chemotherapy delivery units and pharmacy as pembrolizumab would be an extra drug needed to be prepared and administered.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	It will bring about clinically meaningful benefits compared to current care and trial demonstrated >3 month benefit in mOS compared to SOC. In the third interim analysis, for patients with a PD-L1 score of >=1 the median survival was greater than 3 months compared to SOC and this was both clinically and statistically significant. HR QOL data awaited.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Based on the 3rd interim analysis, the treatment would be more effective for patients with a CPS PD-L1 score >=1 (where both mOS and PFS met prespecified criteria for significance).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Pembrolizumab will be an extra drug added into the current regimen. As per ESMO guideline CPS PD-L1 testing will need to be doen which is an extra test reliant on adequate tissue sampling and adequate capacity in our pathology departments. Adequate tissue sampling will require futher education / instruction within the diagnostic pathway. on occasion there maybe need for re-biospying if inadequate sample had previously been taken. Pathology capacity to do this test would be the main concern.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	To start: Her-2 +ve, CPS PD-L! >=1, PS 0 or 1 To stop: clinical or radiological (CT) progression. Number of CT scans would not alter compared to SOC.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	If QOL maintained for a longer duration than SOC, then delay in patients end of life needs (eg hospice or hospital admissions, requirement for best supportive care etc)
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	It has improved our current most beneficial regimen, therefore, is regarded as a step change.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	Yes – 62% of patients reflected a white Caucasian population, predominantly male and the median age was 62-63 which is in keeping with the UK population (median age 64?)

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	
23. How do data on real-world experience compare with the trial data?	There is no real world evidence for this regimen
24. NICE considers whether there are any equalities issues at each stage of an evaluation. 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. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	No

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. 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.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key Issue 1: The use of a post hoc analysis of the non-Asia cohort which excluded data from the Asia region, but combined data from two other regions (Western Europe/Israel/North America/Australia cohort and Rest of the World cohort) for patients with CPS≥1 **Which of these groups provides data that is most generalisable to NHS clinical practice:** • **Data from Western Europe, Israel, North America and Australia** only	The non Asian cohort as described but including rest of the world is representative of NHS clinical practice

Clinical expert statement

• Data from all regions **except** Asia (e.g. Western Europe, Israel, North America, Australia, South America)?	
Key issue 2: Method used to extrapolate overall survival (OS) and progression-free survival (PFS) in the economic model by applying a hazard ratio (HR) from the non-Asia (CPS ≥1) cohort to parametric curves fitted to the comparator (SoC) arm of the global (CPS ≥1) cohort A parametric survival model was fitted to the KM data for the comparator arm of the global (CPS≥1) cohort, and a HR estimate obtained from the non-Asia (CPS≥1) cohort was then applied to the extrapolated control arm to estimate the survival in the intervention arm. • **Is it appropriate to use KM data from global (CPS≥1) cohort for the comparator arm?** • **Is inclusion of evidence from an Asian population as part of the global cohort reflective of NHS clinical practice?**	
Key issue 3: Utilities based on time-to-death rather than using utilities based on	

progression status (i.e., progressed disease versus progression-free) Utility values were estimated based on a time-to-death approach (using four categorical groups, <30 days; 30 to 179 days; 180 to 359 days, and ≥360 days) rather than disease progression approach. • **Are changes in quality of life (represented by utility values) in people with gastric or gastro-oesophageal junction adenocarcinoma better reflected by on time to death or on whether someone has experience disease progression?** • **If the time to death approach is considered more appropriate, are the categories of time to death used appropriate to reflect changes in quality of life?** • **The quality of life for people who have greater than or equal to 360 days until death is similar to the age-matched general population. Does this reflect clinical practice in people with advanced gastric or gastro-oesophageal junction adenocarcinoma?**	

• **What factors impact quality of life in people with gastric or gastro-oesophageal junction adenocarcinoma?**	
Key issue 4: Severity modifier is not based on the expected quality-adjusted life-years (QALYs) predicted by the company's cost-effectiveness analysis because this incorporates data from the Asia cohort which the company considers not generalisable to England	
Are there any important issues that have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

For CPS PDL1>=1, Her 2 =ve patients there is a clinical and statistically meaningful improvement in OS and PFS at the 3rd interim analysis

Addition of pembrolizumab to SOC did not worsen the toxicity profile significantly compared to SOC

The Trial was representative of the NHS patients

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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 living with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma or caring for a patient with HER2-positive 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 **Monday 30 October 2023.** 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 trastuzumab and chemotherapy for untreated locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma [ID3742]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma

Table 1 About you, HER2-positive gastric or gastro-oesophageal junction adenocarcinoma, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
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) ☒ 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 submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☐ 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-positive gastric or gastro-oesophageal junction adenocarcinoma? **If you are a carer (for someone with HER2-positive gastric or gastro-oesophageal junction adenocarcinoma) please share your experience of caring for them**	I am an gastro-oesophageal junction adenocarcinoma cancer patient, treated in 2006 before HER2-positive was identified in this cancer, but I do run a support group network which includes HER2-positive patients, also my brother was diagnosed at a late stage last year, although treated he did not survive. Patients at diagnosis are made aware that is a less survivable cancer and that curative treatment is surgery with chemotherapy, or just palliative care treatment for 70% of patients. Talking to other patients any new treatment will give hope but are aware that sometimes quality of life and wellbeing is often more important when making treatment decisions. GUTS UK highlights the full range of problems these patients experience.
7a. What do you think of the current treatments and care available for HER2-positive 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?**	Current treatments are challenging for patients and not always effective, and it can even more challenging in different areas for various reasons, including staffing, nutrition, and prehabilitation and rehabilitation resources. Many patients are not able to communicate the extent of the side effects, some will just cope with them as know there is no other treatment and some will decide to just stop treatment as cannot cope.

8. If there are disadvantages for patients of current NHS treatments for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There are always going to be side effects which affect all patients differently, patients are aware of the side effects and do not feel it is advantageous. The additional treatment does not change treatment time as it is given consecutively with current treatment.
9a. If there are advantages of pembrolizumab with trastuzumab and 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 trastuzumab and 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**	The main advantage is the hope that this treatment will be more effective over current treatments. As many younger patients are being diagnosed with these cancers, their age and fitness will mean their bodies will be able to cope better and will ensure better QoL and increase QALYs.
10. If there are disadvantages of pembrolizumab with trastuzumab and chemotherapy over current treatments on the NHS please describe these. For example, are there any risks with pembrolizumab with trastuzumab and chemotherapy? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Only disadvantage with be a slight increase of possible side effects, but not every patient will be effected.

11. Are there any groups of patients who might benefit more from pembrolizumab with trastuzumab and chemotherapy or any who may benefit less? If so, please describe them and explain why 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	The younger patients diagnosed will benefit more, especially those that are diagnosed at a late stage. Patients who have other health conditions may not benefit. My brother had a stroke during treatment and I know of other patients in my support network who have had a stroke soon after, there are no known links or research that I know of so might be just coincidence.
12. Are there any potential equality issues that should be taken into account when considering HER2-positive gastric or gastro-oesophageal junction adenocarcinoma and pembrolizumab with trastuzumab and 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.	There are always going to be communities that we cannot reach, language barriers for the correct information and the potential of a younger patient being dismissed by GPs as only have vague symptoms.
13. Are there any other issues that you would like the committee to consider?	Nothing to further to add.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- These cancers are less survivable cancers, for which there are no screening tools to identify them which, so they are frequently diagnosed late, when the treatment options are limited.
- Younger patients are being diagnosed and this treatment may benefit them more.
- With a life limited condition, it is extremely important that people living with these cancers enjoy time with their family and this treatment could help people participate and provide them with valuable time.
- QoL is important to the patient, sometimes more than the treatment if side effects increase.
- This treatment offers another treatment pathway as there are only a few options available at the moment.

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Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer. A Single Technology Appraisal Addendum: EAG comments of the company's technical engagement response

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1. Introduction

In September 2023, the company submitted its response to technical engagement (TE) for the appraisal of pembrolizumab with trastuzumab and chemotherapy for untreated human epidermal growth factor receptor 2 (HER2)-positive advanced gastric or gastro-oesophageal junction (GOJ) cancer. The company's TE response includes a written response form which presents a brief discussion of each of the key issues identified in the External Assessment Group (EAG) report.[1] The TE response also includes a new company base case providing updated cost-effectiveness estimates for pembrolizumab with standard of care (SoC) versus SoC alone, where SoC is trastuzumab with doublet chemotherapy.

This addendum provides a brief commentary on the company's TE response and should be read in conjunction with the EAG report.[2] Section 2 provides a summary of the company's response and the EAG's critique of these points; whist Section 3 presents a fuller description of the EAG's critique on the company's response to particular issues. Section 4 provides a brief description of the changes in the updated model submitted by the company. Section 5 presents the methods for additional exploratory analyses undertaken by the EAG. Section 6 presents the results of additional exploratory analyses undertaken by the EAG.

There is a patient access scheme (PAS) in place for pembrolizumab. All results presented in this document include the PAS. This is unchanged from the discount offered at the time of the original company submission (CS).[3]

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

The main points discussed in the company's TE response and the EAG's comments are summarised in Table 1. Where further critique was considered necessary, this is provided in Section 3.

Table 1: Summary of company's TE response and EAG comments

Key issue	Headline points in company's TE response	EAG comments
Key issue 1: The use of a post hoc analysis of the non-Asia cohort which excluded data from the Asia region, but combined data from two other regions	• The company considers data from the non-Asia cohort to be most generalisable to the England and Wales setting as previously described in its original CS. The non-Asia cohort combines data from two pre-specified regions: Western Europe/Israel/North America/Australia; and 'rest of world'. • The company provides additional justification for the inclusion of data from the 'rest of world' region on the basis that all centres within this region were major cancer centres providing care similar to that delivered in England and Wales. • The company argues that whilst the non-Asia cohort was not pre-specified, it is very similar to the pre-specified subgroup analysis for race which compared Asian to non-Asian patients. • Using the non-Asia cohort maximises sample size without breaking randomisation and is therefore preferable to using the Western Europe/Israel/North America/Australia cohort.	The company has not provided any additional evidence on this point other than stating that all centres within the 'rest of world' region of KEYNOTE-811 were major cancer centres that are highly experienced in cancer care and provide similar care to that delivered in England and Wales. The EAG does not consider that the similarity of the results for the subgroup analysis on race and the post-hoc non-Asia geographic region is particularly relevant to the issue of whether the data from the Western Europe/Israel/North America/Australia region alone would be more applicable to patients being treated in England and Wales. The EAG notes that whilst the company has provided potential reasons for why the overall survival (OS) and progression-free survival (PFS) differ between the Asia region and the non-Asia region, they have not explained why the 'rest of world' region had more favourable midpoint HRs estimates for both OS and PFS than the Western Europe/Israel/North America/Australia region (see EAG report[2] pages 43 and 44).

Key issue	Headline points in company's TE response	EAG comments
Key issue 2: Method used to extrapolate OS and PFS in the economic model by applying a hazard ratio (HR) from the non-Asia (CPS ≥1) cohort to parametric curves fitted to the comparator (SoC) arm of the global (CPS ≥1) cohort	• The company has adopted the EAG's preferred approach of using OS and PFS curves separately fitted to each arm of the non-Asia (CPS ≥1) cohort. • The company prefers a two-knot odds spline model for OS in the pembrolizumab plus SoC arm and a Weibull model for OS in the SoC arm. • The company agreed with the EAG's selection of a lognormal parametric model for PFS for both arms, but notes that the choice of parametric model for PFS is not a key driver of cost-effectiveness due to the relative completeness of the PFS data.	The EAG does not consider that the company provided enough evidence to support its preferences for the two-knot odds spline model for OS in the pembrolizumab plus SoC arm and the Weibull model for OS in the SoC arm. The EAG maintains its position on choosing the one-knot hazard spline model for OS in the pembrolizumab plus SoC arm and one-knot normal spline model for OS in the SoC arm. The EAG has provided a more detailed critique on this issue in Section 3. The EAG considers the issue of PFS extrapolation resolved.
Key issue 3: Utilities based on time-to-death rather than using utilities based on progression status (i.e., progressed	• The company states that the censoring of patients with less than 360 days of survival (the "unknown" category) potentially underestimates the utility values for the time-to-death health states because the censoring is potentially informative with those surviving at the last available follow-up likely to have higher utility.	The company has not provided any additional evidence on this point to support the use of the time-to-event approach with descriptive analysis. The EAG notes that it is unclear which of the 4 existing categories that the data from the "unknown" category would belong to if the

Key issue	Headline points in company's TE response	EAG comments
disease versus progression-free)	• The company argues that the descriptive analysis which allows patients with multiple measurements to contribute more to the estimate of the utility than those with single measurement is preferable to the regression approach which allows for repeated measures, because those who spend longest in a health state should contribute more to the estimate of utility for that health state. • The company states that age and gender were adjusted for in an appropriate manner.	data were observed. Hence the impact of excluding the "unknown" category on the utility analysis is unclear. The EAG reiterates that there is considerable uncertainty related to whether using a time-to-death approach is preferred to a progression-based approach. The EAG disagrees with the company that patients with multiple measurements should receive greater weights in the utilities analysis as utility data are not missing at random. The EAG maintains its position on the use of the company's time-to-death approach for utilities in its base case and explores the impact of using the progression-based approach in its scenario analysis. The EAG also maintains its position to use the utility values estimated using a linear mixed effect model instead of descriptive statistics because the mixed effect modelling approach takes into account of the effect of covariates and correlations within a patient, and provides estimates with more face validity. The EAG also notes that there is a factual inaccuracy in the company's TE response: the EAG did present the company's descriptive utility values in Table

Key issue	Headline points in company's TE response	EAG comments
		12, Section 4.2.6.2 of the EAG report, where it describes the company's base case.[2] The EAG did not present any scenario analyses implementing the company's preferred utility values because it considered that they lacked face validity, as discussed in EAG report Section 4.3.3.4.[2] The EAG has provided a more detailed critique on this issue in Section 3.
Key issue 4: Severity modifier is not based on the expected quality-adjusted life-years (QALYs) predicted by the company's cost-effectiveness analysis because this incorporates data from the Asia cohort which the company considers not	• The company's preferred assumptions result in a proportional QALY shortfall of 0.908, which would support a 1.2x QALY weighting. • Company agrees with the EAG's assessment that a QALY weight of 1.2 is justified based on its updated survival modelling using parametric survival curves for OS fitted separately to the non-Asia cohort for both trial arms.	The EAG previously stated that its preference would be to use the QALYs from the cost-effectiveness model to estimate the QALY shortfall for patients receiving the current standard of care. As the company has now done this, the EAG considers this issue resolved. The EAG notes that both the company and the EAG's preferred base case analysis following TE (see Section 5) would support a proportionate QALY short fall of between 0.85 and 0.95 and therefore this would support a QALY multiplier of 1.2.

Key issue	Headline points in company's TE response	EAG comments
generalisable to England		
Additional issue 1:	• Company prefers to cap the maximum number of cycles of trastuzumab at 35. • It notes that only a small proportion of patients had more than this number of cycles in KEYNOTE-811 ([redacted] for pembrolizumab plus SoC; [redacted] for SoC) • It notes that this issue has a minor impact on the ICER.	The EAG accepts that this issue has minimal impact on the ICER, but based on clinical advice to the EAG that trastuzumab is not restricted to 35 cycles in current clinical practice, the EAG has maintained its original preference. Whilst the proportions having more than 35 cycles is small in both arms, the proportion is [redacted] in the pembrolizumab arm, which could be related to improvements in PFS relative to SoC, and the EAG therefore believes that it is appropriate for the model to capture this difference.
Additional issue 2:	• Company has maintained its previous base case assumption that the cost of administering trastuzumab should be the same whether given alone or in combination with pembrolizumab. • This is based on quotes taken from an NHS England submission stating that the addition of pembrolizumab will not change the administration cost.	The EAG notes that the statements from NHS England, quoted by the company, appear[a] to refer to the addition of pembrolizumab to the combination of trastuzumab, cisplatin and 5-FU (i.e. trastuzumab with FP) to which the HRG code SB14Z (Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance) is applied. Therefore, this refers to the addition of pembrolizumab to the early cycles where patients are also receiving doublet chemotherapy, for which the EAG has accepted the company's preferred approach; SB14Z when the regimen includes 5-FU and SB13Z (Deliver more Complex Parenteral Chemotherapy at First Attendance) otherwise.

Key issue	Headline points in company's TE response	EAG comments
		The issue the EAG raised previously (see EAG report 4.3.3.5[2]) relates to treatment rounds occurring after the completion/discontinuation of the doublet chemotherapy treatment. In these later treatment rounds the same HRG code (SB13Z) and therefore the same NHS resources have been assumed whether trastuzumab is given alone or in combination with pembrolizumab. The EAG believes that the additional administration time required to deliver two treatments versus one should be reflected in the model. The EAG therefore assumes that the HRG code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance) applies for trastuzumab given alone whereas the HRG code SB13Z applies for pembrolizumab given in combination with trastuzumab. The EAG therefore has not updated its preference based on the company's TE response. However, as it acknowledges that there is some uncertainty regarding the appropriate choice of HRG code, it has provided a scenario analysis in which it uses the company's preferred reference costs.

Abbreviations: 5-FU, fluoropyrimidine; EAG – external assessment group; CPS, combined positive score; CS, company submission; FP, 5-FU with cisplatin; HRG, healthcare resource group; ICER - incremental cost-effectiveness ratio; NHS - National Health Services; OS - overall survival; PFS - progression free survival; QALY - quality adjusted life year; SoC, standard of care – trastuzumab with chemotherapy; TE, technical engagement

[a] the EAG does not have access to the document from which the company is quoting to verify the context of the quotes

3. EAG's critique on key issues 2 and 3.

The EAG has already made brief comments in Table 1 on key issues 1 and 4 and additional issues 1 and 2, and does not consider it necessary to provide further commentary on these issues. However, additional critique is provided below on the company's responses to key issues 2 and 3.

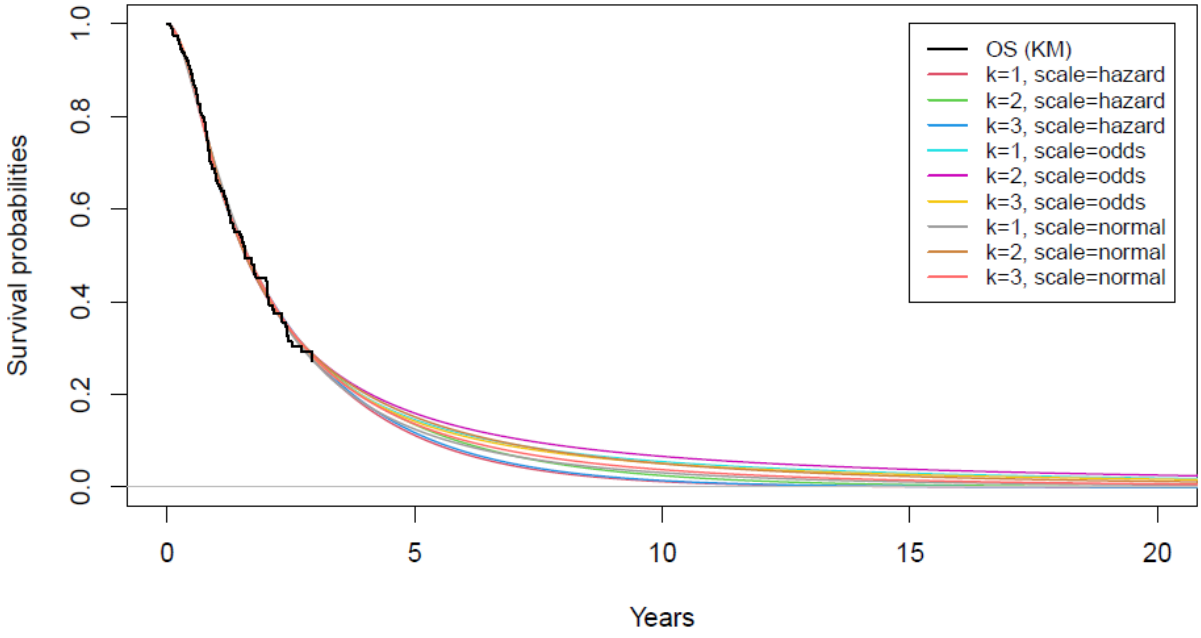
Key issue 2: Extrapolation of OS

For the OS extrapolation in the pembrolizumab plus SoC arm, the company prefers a two-knot odds spline model. The two-knot odds spline model predicts a 5-year survival of 16%, 10-year survival of 7% and 20-year of survival of 3%, and is associated with the highest predictions in all the fitted parametric and spline models (see Figure 1). The EAG notes that the predictions from the two-knot odds spline model are much higher than clinical advice provided by both EAG's clinical experts (see Table 2).

The company argues that "*The established pattern of survival trials seen with pembrolizumab use in other cancers lends support to the plausibility of higher 5-year survival estimates*."[1] The EAG notes that this relates to the 5-year survival outcome in the KEYNOTE-042 study (Pembrolizumab versus chemotherapy as first-line therapy in patients with non–small-cell lung cancer and programmed death ligand-1 tumor proportion score ≥ 1%). This study reports that 5-year OS is 16.6% - 21.9% for the pembrolizumab arm and 8.5% - 10.1% for the chemotherapy arm.[4] The EAG cautions extrapolating the long-term benefit of pembrolizumab for treating patients with non-small-cell lung cancer direct to the population in this appraisal as the natural history of the two diseases are not the same.

The EAG does not consider that the company provided enough evidence to support its preferences for the two-knot odds spline model for OS in the pembrolizumab plus SoC arm, and hence maintains its position of using a one-knot hazard spline model to extrapolate OS in the intervention arm which provides a more reasonable prediction, with 5-year survival of 11%, 10-year survival of 1% and 20-year of survival of 0% (see Table 2).

Figure 1 OS for the pembrolizumab plus SoC arm, independently fitted standard parametric models (reproduced from the EAG report Figure 9)[2]



Abbreviations: OS, overall survival; KM, Kaplan-Meier.

Table 2 OS long-term plausibility informed by clinical expert opinion (adapted from the EAG report Table 25)[2]

	Expected survival probability for the intervention arm				**Predicted survival probability for the intervention arm**	
Timepoint	**Company's expert 1**	**Company's expert 2**	**EAG's expert 1**	**EAG's expert 2**	**Company's TE base case**	**EAG's base case**
5 years	NA	NA	5-10%	0%	16%	11%
10 years	NA	NA	1%	0%	7%	1%
20 years	NE	NE	NE	NE	3%	0%
	Expected survival probability for the control arm				**Predicted survival probability for control arm**	
5 years	5%	2-5%	≤5%	0%	2%	5%
10 years	2%	0-1%	0%	0%	0%	1%
20 years	NE	NE	NE	NE	0%	0%

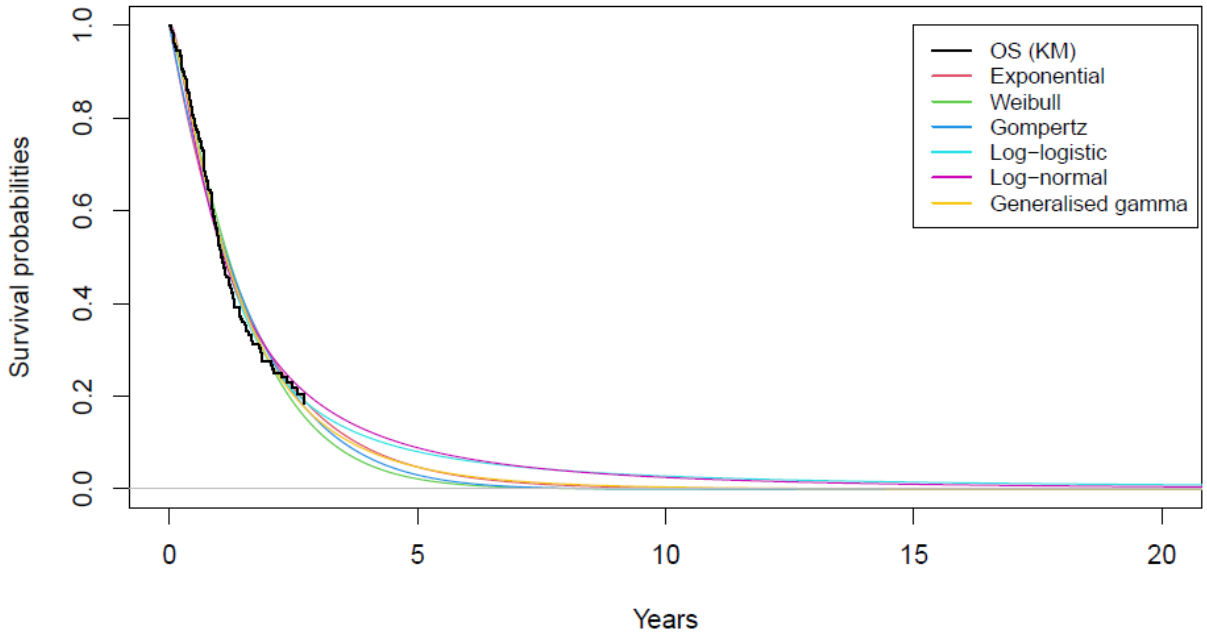
Abbreviations: NA, not applicable; NE, not evaluated.

For the OS extrapolation in the SoC arm, the company prefers a Weibull model. The EAG notes that the Weibull model provides the lowest predictions in all the fitted parametric and spline models (see

Figure 2). The EAG also notes that Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) score for the Weibull model are much higher (more than three-point differences) than the models with the lowest range of AIC and BIC scores (see Table 23 in the EAG report)[2] and this indicates that the Weibull model does not fit the Kaplan-Meier (KM) data well. Visual assessment comparing the fitted Weibull model and the KM curve also suggests that the Weibull model does not fit the data well, especially in the tail area (see Figure 2). Finally, the Weibull model is also unable to capture the unimodal shape shown in the hazard plot (see Figure 14 in the EAG report)[2].

The EAG maintains its position on the use of a one-knot normal spline model to extrapolate the SoC arm as it provides a low AIC score, a good visual fit to the KM data, a unimodal shape to the hazard function and a plausible long-term prediction (see Table 2).

Figure 2 OS for the SoC arm, independently fitted spline models (reproduced from the EAG report Figure 12)[2]



Abbreviations: OS, overall survival; KM, Kaplan-Meier.

Key issue 3: Health utility values

The EAG notes that there are two issues relate to the utility analysis: (i) time-to-death approach vs. progression-based approach; (ii) descriptive analysis vs. mixed effect regression analysis.

(i) time-to-death approach vs. progression-based approach

The company maintains its position and believes that the time-to-death approach to estimate utility is appropriate. The company explains that for patients who have censored OS and have utility assessments taking places less than 360 days from date of censored death were assigned to the "unknown" category,

and argues that there is potential for these patients to live longer and have either similar or higher utility values than the overall average utility in the study as the utility is higher the further the patient is from their date of death. The company believes that the utilities using the time-to-death approach could underestimate the true utility values because there are more "unknown" utility assessments in the pembrolizumab plus SoC arm than the SoC arm ([redacted] vs. [redacted]).

The EAG notes that the impact on excluding the "unknown" category in the utilities analysis is unclear because it is unclear which of the 4 existing categories that the data from "unknown" category would belong to if the data were observed.

The EAG reiterates the comments made in the EAG report "*There is considerable 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 EAG comments that neither approach overcomes the main limitation that the data collected have been heavily censored, either at the point of progression, or at treatment discontinuation*."[2]

(ii) descriptive analysis vs. mixed effect regression analysis

The company also maintains its position on preferring to use the descriptive analysis method rather than a mixed effect modelling approach. The company argues that the descriptive analysis method has the "*advantage of not effectively down-weighting values for subjects with multiple measurements, relative to those with a single measurement (by not adjusting for repeated measurement, as is the case in the linear mixed effect model)*" and "*in the context of health economic modelling, it is logical that patients with multiple measurements spending longer time in a health state should receive proportionately greater weight for their health utilities than those with a single measurement, as they account for relatively more of the time and QALYs spent in that state within the model and are more representative of that health state experience*".[1]

The EAG disagrees with the company that patients with multiple measurements should receive greater weights in the utilities analysis as utility data are not missing at random. Assigning more weights to patients with multiple measurements could bias the results. The EAG also highlights again that the company's time-to-death approach results in utility scores of [redacted] for patients with a time-to-death ≥360 days and [redacted] for patients with a time-to-death between 180 and 360 days. As commented in the EAG report that these values are very similar to the general population utility value for individuals aged [redacted] years and [redacted] years respectively (estimated general population utilities are [redacted] and [redacted] in the model at these ages respectively).[2] The model may therefore overestimate HRQoL for patients in these time-to-death categories, given that the population has advanced gastric or GOJ cancer.

The EAG maintains its position to use the utility values estimated using a linear mixed effect model instead of descriptive statistics because the mixed effect modelling approach takes into account of the effect of covariates and correlations within a patient, and provides estimates with more face validity.

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

Table 3 summarises the company's original base case model in the CS, the EAG's preferred analysis in the EAG report, and the company's updated base case model as presented in the company's TE response. It also indicates whether there is now agreement between the company's TE base case and the EAG's preferences or whether the EAG considers a particular issue to remain unresolved.

In response to key issue 2, the company has updated its base case analysis. These changes to the modelling of OS and PFS have been briefly described in Table 1, with further information provided in Section 3. With respect to key issue 3, the company's updated base case does not implement the EAG's preferred utility estimates, with both the company and EAG maintaining their original preferred utility estimates, as described in Table 1 with additional discussion in Section 3. The company also rejected the EAG's preferences to remove the treatment cap of 35 cycles for trastuzumab and the EAG's preferred administration costs for trastuzumab when given alone (after completion/discontinuation of doublet chemotherapy). However, the company accepted all other aspects of the EAG's preferred base case. The company has provided an updated set of scenario analyses and deterministic sensitivity analyses using their updated base case as the starting point. Results for the company's TE base case are provided in Section 4. The EAG has not reproduced the company's full scenario analyses in this addendum as these were the same set of scenario analyses presented in the CS and were not conducted specifically to address any of the key issues.

Table 3 Summary of company's original base case (CS[3]), EAG-preferred analysis (EAG report[2]) and company's updated base case (TE response[1])

Aspect of model/ issue identified in the EAG report Section 4.3.3	Company's original base case	EAG-preferred analysis	Company's updated TE base case	Agreement between EAG-preferred and updated company's base case
Correcting programming and implementation errors in the company's economic model	NA	Yes	Yes	Yes
Survival extrapolation for OS	Two-knot odds spline model fitted to SoC arm of global CPS ≥1 cohort; HR from non-Asia CPS ≥1 cohort applied to SoC arm to estimate OS in pembrolizumab plus SoC arm.	Curves fitted independently to both arms of non-Asia CPS ≥1 cohort; one-knot hazard spline model for pembrolizumab plus SoC; one-knot normal spline for SoC	Curves fitted independently to both arms of non-Asia CPS ≥1 cohort; 2-knot odds spline for pembrolizumab plus SoC; Weibull for SoC	No Company now uses curves fitted independently to non-Asia CPS ≥1 cohort, but company makes different choice of curves. EAG maintains their original preference
Survival extrapolation for PFS	Two-knot hazards spline model fitted to SoC arm of global CPS ≥1 cohort; HR from non-Asia CPS ≥1 cohort applied to SoC arm to estimate PFS in pembrolizumab plus SoC arm.	Log-normal curves fitted independently to both arms of non-Asia CPS ≥1 cohort	Same as EAG-preferred analysis	Yes
Removing the cap for TTD of trastuzumab	Capped at 35 cycles	No cap	Capped at 35 cycles	No EAG maintains their original preference
Administration costs for trastuzumab when administered without pembrolizumab after doublet chemotherapy	Complex chemotherapy cost for trastuzumab when given either with or without pembrolizumab	Complex chemotherapy cost for trastuzumab when given with pembrolizumab but simple chemotherapy cost when given alone	Company maintains their previous preference	No, EAG maintains their original preference
Mix of subsequent therapies	Proportions according to KEYNOTE-811	25% receive docetaxel and 25% receive paclitaxel	Same as EAG-preferred analysis	Yes

Aspect of model/ issue identified in the EAG report Section 4.3.3	Company's original base case	EAG-preferred analysis	Company's updated TE base case	Agreement between EAG-preferred and updated company's base case
Resource use during progression-free period	Outpatient visits both 3-weekly and 6-weekly during PFS but no routine CT scans	Outpatient visits 3-weekly during doublet chemotherapy and 6-weekly for remainder of PFS; quarterly CT scans	Same as EAG-preferred analysis	Yes
Resource use post-progression	Based on Gómez-Ulloa et al.[5] (~1.5 outpatient visits and ~1.6 CT scans per year)	4 outpatient visits and 4 CT scans per year	Same as EAG-preferred analysis	Yes
Method used to estimate utilities for health states from KEYNOTE-811 trial data	Time-to-death utilities estimated using descriptive statistics	Time-to-death utilities estimated using a linear mixed effects model	Company maintains its original preference	No, both company and EAG maintains their original preference.
Method used to estimate QALYs under SoC to inform severity modifier	Value from appraisal of trastuzumab with chemotherapy (TA208)	Comparator arm of company's model with EAG preferences	Comparator arm of company's TE base case	Both approaches provide a QALY multiplier of 1.2

Abbreviations: CPS, combined positive score; CT, computerised tomography; EAG – external assessment group; HR, hazard ratio; OS - overall survival; PFS - progression free survival; SoC, standard of care – trastuzumab with doublet chemotherapy; TE, technical engagement; TTD, time to treatment discontinuation

5. Methods of the EAG's TE exploratory analyses

The EAG has maintained all of its previous base case assumptions but has conducted some additional exploratory and scenario analyses.

Exploratory analyses 1 to 4

The EAG's preferred base case scenario differs from the company's TE base case in four ways (see Table 3). The impact of each of these has been explored individually by the EAG using the company's TE base case as the starting point (see Table 4). The changes explored are as follows:

- OS survival curves fitted independently to each arm of the non-Asia (CSP ≥1) cohort; one-knot hazard spline model for pembrolizumab plus SoC and one-knot normal spline for SoC
- Removal of 35 cycle cap for trastuzumab duration
- Lower administration cost when trastuzumab given alone (HRG code SB12Z) versus when given in combination with pembrolizumab (HRG code SB13Z) after completion/ discontinuation of doublet chemotherapy
- Time-to-death utilities estimated using a linear mixed effects model

The EAG's preferred base case, which is unchanged from the time of the EAG report, is equivalent to combining all these four changes.

EAG TE scenario analyses

The EAG also presents a scenario analysis (see Table 4) using the EAG's base case as the starting point. This scenario analysis applies the company's preference for the same administration cost (HRG code SB13Z) to be applied when trastuzumab is given either alone or in combination with pembrolizumab, after the completion/discontinuation of doublet chemotherapy.

The EAG notes that as the EAG's base case analysis has not been updated, all scenario analyses previously presented in the EAG report would still be relevant, but these are not reproduced here for brevity. Of note, these include a scenario analysis exploring the application of progression-based utilities using the results of linear mixed effects regression (see section 4.4.2.5 of the EAG report and EAG scenario 4 in Table 32[2]).

6. Results of the EAG's TE exploratory analyses

The EAG notes that the results presented in the company's TE response for its updated base case apply a QALY multiplier of 1.2 when presenting both incremental QALYs and ICERs. The EAG's preferred approach to presenting results, used in the EAG report and this addendum, is to present unweighted QALYs and then ICERs both with and without the QALY multiplier.

The results in Table 4 show that the key driver of the difference in the ICER between the EAG's preferred base case and the company's TE base case is the choice of parametric curves for extrapolation of OS. The other areas of difference between the company TE base case and the EAG's preferred base case have minimal impact on the ICER. The EAG notes that the proportionate QALY shortfall is between 0.85 and 0.95 in all the scenarios presented in Table 4, when using the comparator arm of the model to estimate lifetime expected QALYs for SoC and the EAG's preferred estimate for lifetime expected QALYs for the general population (12.62 as per EAG report Table 33[2]). Based on this, the EAG considers that a QALY multiplier of 1.2 is supported by both the company and the EAG's analyses.

Table 4: Results of the company's TE basecase and additional EAG analyses

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company TE base case (Deterministic)						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 1†: Choice of OS survival curves - one-knot hazard spline model for pembrolizumab plus SoC; one-knot normal spline for SoC						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 2†: Removal of cap for trastuzumab duration at 35 cycles						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 3†: Lower administration cost when trastuzumab given alone versus when given in combination with pembrolizumab (after doublet chemotherapy completed/discontinued)						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG exploratory analysis 4†: Time-to-death utilities estimated using a linear mixed effects model						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case (combines EAG exploratory analysis 1 to 4; unchanged from EAG report)						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG scenario analysis 1‡: Same administration cost both when trastuzumab given alone and when given in combination with pembrolizumab (after doublet chemotherapy)						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EAG – external assessment group; ICER – incremental cost-effectiveness ratio; OS – overall survival; QALYs - quality-adjusted life-year; TE, technical engagement

* *SoC: Trastuzumab plus chemotherapy*

** *Intervention: Pembrolizumab with SoC*

† *EAG exploratory analyses use the company's updated TE base case as their starting point*

‡ *EAG scenario analyses use the EAG's preferred base case as their starting point.*

7. Discussion

The EAG considers that it remains unresolved whether data from the single pre-specified region that includes Western Europe (Western Europe/Israel/North America/Australia region) is more applicable to the UK than data from the post-hoc non-Asia cohort preferred by the company which combines data from this region with data from the 'rest of world' region. The EAG would still prefer to see a scenario analysis using data from the single Western Europe/Israel/North America/Australia region.

The EAG considers that there remains significant uncertainty regarding the ICER due to uncertainty regarding long-term OS survival estimates. Whilst the company have accepted the EAG's preferred approach to modelling OS and PFS, which involved fitting curves independently to each arm of the non-Asia (CPS≥1) cohort, they have chosen different OS curves to those preferred by the EAG. The choice of OS curves has a very large impact on the ICER with the EAG's preferred choice of OS curves increasing the ICER for the company's TE base case from £[redacted] per QALY to £[redacted] per QALY (when applying a QALY weight of 1.2). The other differences between the EAG's and the company's preferred assumptions had minimal impact of the ICER. The EAG's base case ICER, when applying a QALY weighting of 1.2, remains as it was at the time of the EAG report; £[redacted] when using the deterministic analysis and £[redacted] when using the probabilistic analysis.[2]

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Pembrolizumab with trastuzumab and chemotherapy for untreated HER2-positive advanced gastric or gastro-oesophageal junction cancer. A Single Technology Appraisal
Second Addendum: EAG additional scenarios

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1. Introduction

In October 2023, NICE asked the EAG to provide some additional scenarios exploring the impact of using updated administration costs based on advice received from the Cancer Drugs Fund (CDF) Lead.[1] This addendum provides a description of the methods and results for those additional scenarios. This document should be read alongside the EAG report,[2] and the first addendum to the EAG report,[3] which provided a critique of the company' response to technical engagement (TE).[4]

There is a patient access scheme (PAS) in place for pembrolizumab. All results presented in this document include the PAS. This is unchanged from the PAS at the time of the original company submission (CS).[5] A confidential appendix is also provided which incorporates confidential prices for drugs other than pembrolizumab.

2. Methods for additional scenarios

The additional scenarios are based on advice provided by the CDF Lead regarding the Healthcare Resource Group (HRG) codes applied in clinical practice. Advice was requested by NICE from the CDF Lead after the EAG raised an issue regarding the company's application of the same HRG code (Deliver more Complex Parenteral Chemotherapy at First Attendance; SB13Z) when trastuzumab was offered either alone or in combination with pembrolizumab, after the completion of the doublet chemotherapy phase of treatment. In response to this request, the CDF Lead advised that the appropriate HRG code for maintenance trastuzumab monotherapy is, 'Deliver Simple Parenteral Chemotherapy at First Attendance,' (SB12Z).[1] In addition, the CDF Lead advised that because pembrolizumab in combination with trastuzumab is a new regimen, not previously allocated a HRG code, the appropriate HRG code for this combination would be 'Deliver Chemotherapy for Regimens not on the National List,' (SB17Z). The CDF Lead, directed NICE to the NHS payment scheme for relevant prices, which differ from the prices from the 2021/22 National Schedule of NHS Costs applied by the company and the EAG in their previous analysis (see Table 1). However, there is no NHS payment scheme price for SB17Z. Therefore, the CDF Lead provided an estimated average unit price across NHS Trusts of £320.[1]

The CDF Lead also advised that around 50% of NHS Trusts offered pembrolizumab on a 6-weekly cycle with trastuzumab continuing to be given on a 3-weekly cycle.[1] For those NHS Trusts using 6-weekly pembrolizumab, there is variation in whether the trastuzumab given alone on day 22 of a 6-week cycle is coded the same as trastuzumab monotherapy (SB12Z), or as 'Deliver Subsequent Elements of a Chemotherapy Cycle' (SB15Z). The CDF Lead advised that it would be reasonable to apply a 50:50 split between these two approaches.

Based on this advice, the EAG has provided two additional scenarios, one assuming 3-weekly pembrolizumab and the other assuming 6-weekly pembrolizumab. Both apply the 2023/24 NHS payment scheme prices instead of the previously used NHS reference costs. The costs applied in these additional scenarios, are summarised in Table 2.

The CDF Lead also noted that patients receiving trastuzumab and/or pembrolizumab will require outpatient review by the medical oncology service with reviews becoming less frequent overtime.[1] At TE the company accepted the EAG's preferred approach of assuming 3-weekly outpatient follow-up appointments during doublet chemotherapy, and 6-weekly outpatient follow-up appointments after completion of chemotherapy whilst patients remain progression-free and therefore continuing to receive either trastuzumab or pembrolizumab with trastuzumab.[4] The EAG has not updated this approach but has updated the unit cost to use the relevant price from the NHS payment scheme 2023/24.

Table 1 Unit costs using different sources for NHS prices

HRG Code	HRG Name	National Schedule of NHS Costs 2021/22[6]	NHS payment scheme, 2023/24 prices[7]
SB12Z	Deliver Simple Parenteral Chemotherapy at First Attendance	287	172
SB13Z	Deliver more Complex Parenteral Chemotherapy at First Attendance	354	343
SB14Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	475	515
SB15Z	Deliver Subsequent Elements of a Chemotherapy Cycle	387	343
SB17Z	Deliver Chemotherapy for Regimens not on the National List	NA	320 [a]
370; WF01A	Outpatient Medical Oncology Service; Follow Up Attendance - Single Professional	221	144

[a] No cost available in the published NHS Payment Scheme; source is personal communication from CDF Lead to NICE[1]

Table 2: Administration costs for chemotherapy applied in the scenarios available at TE and the EAG's additional scenarios

Treatment	**Company base case at TE**		**Company scenario 10 at TE**		**EAG base case at TE**		**EAG additional scenario 1 using CDF Lead advice**		**EAG additional scenario 2 using CDF Lead advice**	
Pembrolizumab dosing	**3-weekly**		**6-weekly**		**3-weekly**		**3-weekly**		**6-weekly**	
Source of unit cost	**National Schedule of NHS Costs 2021/22**						**NHS payment scheme, 2023/24 prices**			
Treatment combination	**Cost, £**	**HRG**	**Cost, £**	**HRG**	**Cost, £**	**HRG**	**Cost, £**	**HRG**	**Cost, £**	**HRG**
Pembrolizumab + trastuzumab	354	SB13Z	354	SB14Z	354	SB14Z	320	SB17Z[b]	320	SB17Z [a]
Trastuzumab on day 22 of 6-weekly pembrolizumab	NA	NA	354	SB14Z	NA	NA	NA	NA	258 [b]	50% SB12Z 50% SB15Z
Trastuzumab monotherapy	354	SB13Z	287	SB12Z	287	SB12Z	172	SB12Z	172	SB13Z
Pembrolizumab + trastuzumab + CAPOX [c]	354	SB13Z	354	SB14Z	354	SB14Z	343	SB13Z	343	SB13Z
Trastuzumab + CAPOX [c]	354	SB13Z	354	SB14Z	354	SB14Z	343	SB13Z	343	SB13Z
Pembrolizumab + trastuzumab + FP	475	SB14Z	475	SB14Z	475	SB14Z	515	SB14Z	515	SB14Z
Trastuzumab + FP	475	SB14Z	475	SB14Z	475	SB14Z	515	SB14Z	515	SB14Z

Abbreviations: CAPOX, capecitabine with oxaliplatin; FP, fluorouracil (5-FU) with cisplatin; HRG, healthcare resource group; TE, technical engagement

[a] No cost available in the published NHS Payment Scheme; source is personal communication from CDF Lead to NICE[1]

[b] average of £172 for SB12Z and £343 for SB15Z

[a] Same HRG applied to XP in any scenarios including XP

3. Results of the EAG's additional exploratory analyses

The EAG notes that the results presented in the company's TE response for its updated base case apply a QALY multiplier of 1.2 when presenting both incremental QALYs and ICERs. The EAG's preferred approach to presenting results, used in the EAG report and this addendum, is to present unweighted QALYs and then ICERs both with and without the QALY multiplier.

The results in Table 3 show that incorporating the updated administration costs has a minimal impact of the ICER increasing it from £[redacted] to £[redacted]. In both the EAG and the company's analyses, assuming 6-weekly administration of pembrolizumab, rather than 3-weekly administration, has a small impact on the ICER that is in the upward direction due to higher drug acquisition costs. This is because with 3-weekly administration, some patients discontinue treatment between day 1 and day 22, meaning the average dose across two cycles is less than the dose given on day 1 of a 6-week cycle. Assuming a 50% split between 3-weekly and 6-weekly administration would give an ICER of £[redacted].

Table 3: Results of the company's TE basecase and additional EAG analyses

Option	QALYs	Costs	Incremental		ICER (QALY weight of 1x)	ICER (QALY weight of 1.2x)
			QALYs	Costs		
Company TE base case (3-weekly pembrolizumab)						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company TE scenario 10 - 6-weekly pembrolizumab						
SoC*	[redacted]	[redacted]	-	-		
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG's preferred base case at TE (3-weekly pembrolizumab)						
SoC*	[redacted]	[redacted]	-	-	-	-
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG additional scenario† 1 using CDF Lead advice (3-weekly pembrolizumab)						
SoC*	[redacted]	[redacted]	-	-		
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG additional scenario† 2 using CDF Lead advice (6-weekly pembrolizumab)						
SoC*	[redacted]	[redacted]	-	-		
Intervention**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CDF, Cancer Drugs Fund; EAG – external assessment group; ICER – incremental cost-effectiveness ratio; QALYs - quality-adjusted life-year; TE, technical engagement

* *SoC: Trastuzumab plus chemotherapy*

** *Intervention: Pembrolizumab with SoC*

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

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