NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to consultees and commentators:

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

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 platinum-based chemotherapy for untreated, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma

[ID3741]

Document B

Company evidence submission

8th February 2021

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MSD Pembrolizumab [ID3741] DocB without Appendices [Fully redacted]	**1.0**	**No**	**8th February 2021**

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Tables and figures

Tables

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Abbreviations

AE	Adverse event
AEOSI	Adverse event of special interest
AIC	Akaike information criterion
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ASaT	All subjects 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
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
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

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

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication: KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults.

Please see Table 1 below for a summary of the National Institute for Health and Care Excellence (NICE) decision problem.

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, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma	Adults with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma.	The population described by MSD reflects the anticipated licence indication wording
Intervention	Pembrolizumab with platinum-based chemotherapy	Pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy	The intervention described by MSD reflects the anticipated licence indication wording
Comparator(s)	Platinum-based chemotherapy without pembrolizumab, such as: • doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin • triplet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin epirubicin	Platinum-based chemotherapy without pembrolizumab, such as: • doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin • triplet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin epirubicin	N/A
Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	N/A

B.1.2 Description of the technology being appraised

The draft summary of product characteristics (SmPC) has been included in Appendix C; however, the European Public Assessment Report (EPAR) that includes the indication under assessment in this submission was not available at the time of the submission. The technology being appraised (pembrolizumab) is described in the Table 2 below.

Table 2 Technology being appraised

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: Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. Keytruda as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. Keytruda as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations. Keytruda, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults. Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC 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. Keytruda as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma

	(cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV. Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy. Keytruda as monotherapy is indicated for 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. Keytruda, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a CPS ≥ 1. Keytruda, as monotherapy is indicated for the treatment of recurrent or metastatic HNSCC in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy. Keytruda, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma (RCC) in adults. Keytruda as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.
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 platinum and fluoropyrimidine based chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults
Method of administration and dosage	Pembrolizumab 200 mg every three weeks (Q3W); intravenous (IV) infusion (up to a maximum duration of 2 years). Chemotherapy 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle.
Additional tests or investigations	N/A
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.
Patient access scheme (if applicable)	A Patient Access Scheme (PAS) with a simple discount of [redacted][1], therefore 200 mg administration of pembrolizumab will cost [redacted]

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

Oesophageal cancer is the eighth most common type (1) of cancer in the world. The UK has the highest age-standardised incidence of oesophageal cancer in Europe (2), with approximately 9,000 people diagnosed annually in the UK (3). 80% of oesophageal cancers develop in adults aged 60 or over (4), with a higher prevalence in males than females (5).

The two main histology's of oesophageal cancer are:

- Squamous cell carcinoma: This develops in the thin, flat cells of the mucosa, which line the oesophagus, and most commonly originates in the upper two-thirds of the oesophagus (3). Squamous cell carcinoma accounts for approximately a third of cases of oesophageal cancers in the UK(6).
- Adenocarcinoma: This develops in the mucus-producing glandular cells of the submucosa, which line the oesophagus, and most commonly originates in the lower two-thirds of the oesophagus, including at the junction with the stomach (3). Adenocarcinoma accounts for approximately two-thirds of oesophageal cancers in the UK (6).

Lifestyle factors, such as obesity, alcohol consumption and smoking, are considered risk factors in 90% of oesophageal cancers (4). Obesity, defined as having a body mass index (BMI) ≥30, is linked to 25% of oesophageal cancers in men, and 10% in women (4). Smoking increases the risk of developing both the squamous cell carcinoma and adenocarcinoma forms of oesophageal cancer. Specific smoking related activities (smoking a pipe, chewing tobacco, using snuff, or using betel quid [paan / pan]) are also associated with an increased risk of oesophageal cancer (4). Alcohol consumption of more than 14 units of alcohol per week is linked to an increased risk of developing squamous cell oesophageal cancer (4).

Another risk factor is Barrett's oesophagus; a condition characterised by abnormalities developing in the cells lining the oesophagus and caused by long term indigestion (gastro-oesophageal reflux disease [GORD]). Barrett's oesophagus can cause an increased risk of developing oesophageal cancer – between 5-10% of people with this condition will subsequently develop oesophageal cancer within 10-20 years (7).

Symptoms of oesophageal cancer include difficulty in swallowing (dysphagia), persistent indigestion/heartburn, bringing up food soon after eating, loss of appetite and weight loss and pain/discomfort in the upper stomach/chest. The most common method for diagnosing oesophageal cancer is via a specific type of endoscopy, called gastroscopy(3,8). Occasionally

a barium swallow may be used, followed by an x-ray, to identify any oesophageal blockages which could potentially be a sign of cancer(3,8).

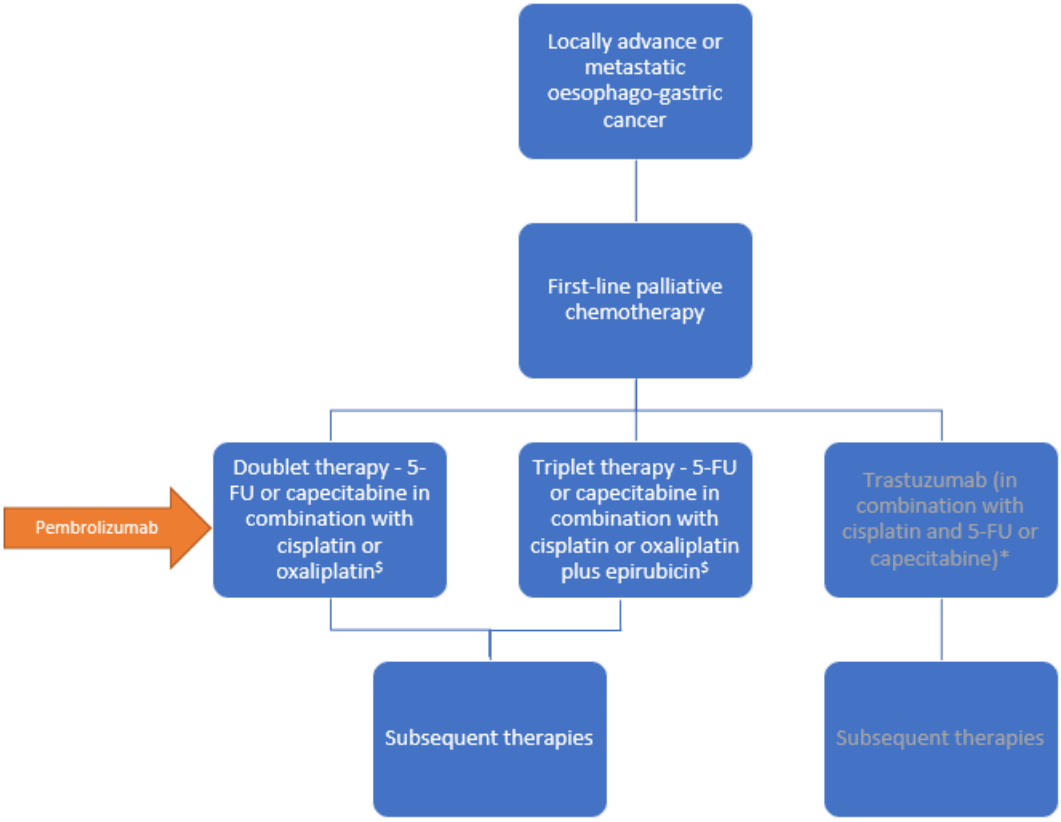
The treatment for oesophageal cancer is largely dependent on the stage at which the cancer is diagnosed. Locally advanced oesophageal cancers are either stage 2 or stage 3, and are defined as cancer that has spread into the tissues around the oesophagus, but not spread to other organs. For stage 1-3 oesophageal cancer, surgical resection of the affected section of the oesophagus (oesophagectomy) is the usual course of treatment (9). Advanced, metastatic cancers are stage 4. Stage 4 oesophageal cancer is unlikely to be cured, however chemotherapy and radiotherapy can slow the cancer spreading, and provide relief from other symptoms (9). According to CRUK, 30% of patients present with stage 4 Oesophageal cancer.

Survival rates for individuals with advanced oesophageal cancer are very low: most individuals with advanced oesophageal cancer live for only 3-12 months following their cancer diagnosis, and only 4% live for 5 years or more (10). Oesophageal cancer is now the fourth highest cancer killer in the UK, responsible for 4,000 deaths annually (11).

There is a high unmet need for first-line treatment options for patient with advanced oesophageal cancer, meaning that currently, treatment is restricted to doublet and triplet palliative chemotherapy options.

In England, the NICE guideline (12) on oesophageal and gastric cancer states that for locally advanced or metastatic oesophago-gastric cancer, treatment is restricted to palliative care only, as depicted in **Figure 1**. This figure also includes the proposed positioning of pembrolizumab as a first-line treatment option for adults with locally advanced or metastatic oesophageal cancer who have not been previously treated.

Figure 1: NICE pathway on locally advanced or metastatic oesophago-gastric cancer



**patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic adenocarcinoma of the stomach or gastro-oesophageal junction who have not received prior treatment for their metastatic disease and have tumours expressing high levels of HER2 as defined by a positive immunohistochemistry score of 3 (IHC3 positive).*

$ patients with performance status 0 to 2 and no significant comorbidities

B.1.4 Equality considerations

MSD does not envisage any equality issues with the use of pembrolizumab in combination with platinum-based chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults.

B.2. Clinical Effectiveness

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 appraised.

B.2.2 List of relevant clinical effectiveness evidence

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

The SLR was originally conducted in July 2020 and updated on 22 December 2020. As the manufacturer of the technology being appraised, MSD is aware of all relevant RCTs for pembrolizumab in combination with chemotherapy in this indication.

In total, 7 RCTs were identified (13–19): six trials reporting evidence for the relevant comparators and one reporting evidence for pembrolizumab in combination with chemotherapy: KEYNOTE-590 (20).

Please refer to Table 3 for a summary of the evidence coming from the pivotal clinical trial KEYNOTE-590 (20–22).

Table 3 Clinical effectiveness evidence

Study	Kato K, Shah MA, Enzinger P, Bennouna J, Shen L, Adenis A, et al. KEYNOTE-590: Phase III study of first-line chemotherapy with or without pembrolizumab for advanced oesophageal cancer. Future Oncol. 2019;15(10):1057-1066. (20)				
Study design	Phase III Randomized, Double-Blind, Placebo-Controlled Clinical Trial				
Population	Patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ • an ECOG PS of 0 or 1; • no active central nervous system metastases and/or carcinomatous meningitis; and • no active infection or autoimmune disease that required systemic therapy.				
Intervention(s)	Pembrolizumab + cisplatin + 5-fluorouracil (5-FU) Participants receive pembrolizumab 200 mg intravenously every 3 weeks with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion 4000 mg/m^2 per 3-week cycle). Completion of 35 administrations (approximately 2 years) of treatment with pembrolizumab.				
Comparator(s)	Placebo + cisplatin + 5-fluorouracil (5-FU) Participants receive saline placebo intravenously every 3 weeks with cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil (5-FU) 800 mg/m^2/day continuous IV infusion 4000 mg/m^2 per 3-week cycle).				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	KEYNOTE-590 [ref] is the pivotal clinical trial in this indication				
Reported outcomes specified in the decision problem	• **OS** • **PFS** • **ORR** • **Adverse effects (AEs) of treatment** • **HRQoL** Bolded outcomes are included in the economic model				
All other reported outcomes	• **Time to deterioration (TTD)** • **Duration of response (DOR)** • **Patient reported outcomes (PRO)** • **Disease control rate (DCR)** Bolded outcomes are included in the economic models				

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

B.2.3.1 KEYNOTE – 590 trial overview (21)

Pembrolizumab with platinum-based chemotherapy for untreated, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma [ID3741]

Trial design

KEYNOTE – 590 (21) is a randomised, double-blind, placebo-controlled multi-centre phase III trial to evaluate the efficacy and safety of pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU) versus placebo in combination with cisplatin and 5-FU as first-line treatment in subjects with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction (EGJ) (20).

The enrolment period was divided into 2 periods: Global Cohort and China Extension Study. In the Global Cohort, 749 subjects were enrolled in the study. Subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and to provide a tumour sample adequate for central laboratory analysis of biomarkers that may have been predictive of response to pembrolizumab.

Participants were randomised (1:1) to one of the following treatment arms, with allocation stratified by geographic region, histology, and ECOG performance score:

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

or

- Treatment arm 2: placebo administered IV Q3W combined with cisplatin 80 mg/m^2 IV Q3W and 5-FU 800 mg/m^2/day continuous IV infusion on each of days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle).

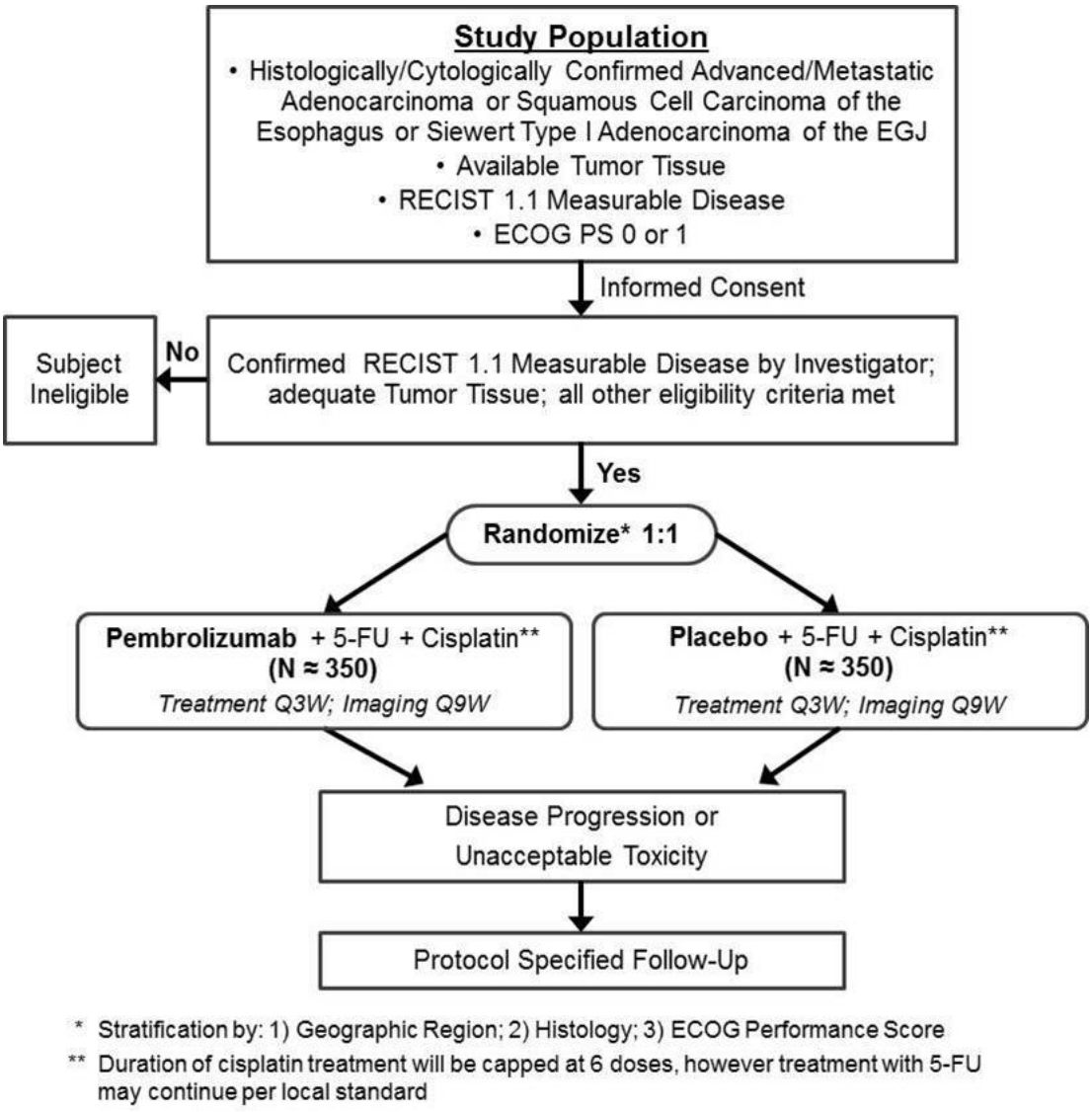
Treatment continued until confirmed progressed disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevented further administration of treatment, investigator's decision to withdraw the participant, participant withdrew consent, pregnancy of the participant, noncompliance with study treatment or procedure requirements, completion of 35 administrations (approximately 2 years) of treatment with pembrolizumab or achievement of a CR, or administrative reasons. No crossover from placebo arm to pembrolizumab arm was allowed.

106 eligible subjects from China were enrolled in the China Cohort which included subjects enrolled in China during the Global enrolment period as well as the China Extension Study

enrolment period. The China Extension study is identical to the Global Cohort with respect to key study characteristics (inclusion and exclusion criteria, study endpoints, primary and secondary objectives, study procedures). The Global Cohort and China Extension study were merged for the primary analyses, and henceforth will be referred to as the Global Study population.

A schematic of the trial design is provided below in Figure 2.

Figure 2 Schematic of KEYNOTE – 590 (21)



5-FU=5-fluorouracil; ECOG PS=Eastern Cooperative Oncology Group Performance Score; EGJ=Esophagogastric junction; Q3W=Every 3 weeks; Q9W=Every 9 weeks; RECIST 1.1=Response Evaluation Criteria in Solid Tumours Version 1.1.

Eligibility criteria

Male and female subjects with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ of at least 18 years of age were enrolled in this trial.

Inclusion criteria

- Has histologically- or cytologically-confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction (EGJ)
- Has measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment
- Eastern Cooperative Group (ECOG) performance status of 0 to 1
- Can provide either a newly obtained or archival tissue sample for PD-L1 by immunohistochemistry analysis
- Female participants of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to randomization and be willing to use an adequate method of contraception (e.g. abstinence, intrauterine device, diaphragm with spermicide, etc.) for the course of the study through 120 days after the last dose of study treatment and up to 180 days after last dose of cisplatin
- Male participants of childbearing potential must agree to use an adequate method of contraception (e.g. abstinence, vasectomy, male condom, etc.) starting with the first dose of study treatment through 120 days after the last dose of study treatment and up to 180 days after last dose of cisplatin, and refrain from donating sperm during this period
- Has adequate organ function.

Exclusion criteria

- Has locally advanced oesophageal carcinoma that is resectable or potentially curable with radiation therapy (as determined by local investigator).
- Has had previous therapy for advanced/metastatic adenocarcinoma or squamous cell cancer of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ.

- Has had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment.
- Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early-stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, in situ breast cancer that has undergone potentially curative therapy, and in situ or intramucosal pharyngeal cancer.
- Has known active central nervous system metastases and/or carcinomatous meningitis.
- Has an active autoimmune disease that has required systemic treatment in past 2 years.
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment, or has a history of organ transplant, including allogeneic stem cell transplant.
- Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis, or has an active infection requiring systemic therapy.
- Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study medication and up to 180 days after last dose of cisplatin.
- Has received prior therapy with an anti-programmed cell death protein-1 (anti-PD-1), anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor or has previously participated in a pembrolizumab (MK-3475) clinical trial.
- Has severe hypersensitivity (≥ Grade 3) to any study treatment (pembrolizumab, cisplatin, or 5-FU) and/or any of its excipients.
- Has a known history of active tuberculosis (TB; Mycobacterium tuberculosis) or human immunodeficiency virus (HIV) infection.
- Has known history of or is positive for hepatitis B or hepatitis C.
- Has received a live vaccine within 30 days prior to the first dose of study treatment.
- Has had radiotherapy within 14 days of randomization. Participants who received radiotherapy >14 days prior to randomization must have completely recovered from any radiotherapy-related AEs/toxicities.

The full list of inclusion/exclusion criteria are provided in the study protocol (21).

Settings and Locations where data were collected

The KEYNOTE-590 study was conducted at 168 centres in 26 countries: Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Denmark, France, Germany, Guatemala, Hong Kong, Japan, South Korea, Malaysia, Peru, Romania, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, United Kingdom, and United States. 22 subjects from 3 UK centres participated in KEYNOTE 590 trial.

Trial drugs and concomitant medication

Trial drugs

Study medications used in this trial are outlined below.

Table 4 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle	Experimental
Normal saline	NA	Q3W	IV infusion	Day 1 of each cycle	Placebo
Cisplatin	80 mg/m^2	Q3W	IV infusion	Day 1b of each cycle	Comparator regimen and combination agent
5FU	800 mg/m^2/day × 5 days (4000 mg/m^2 total per cycle)	Q3W	IV infusion	Continuous Days 1b to 5 of each cycle	Comparator regimen and combination agent

a Duration of cisplatin treatment will be capped at 6 doses, however treatment with 5-FU may continue per local standard.

b Administration of cisplatin and/or 5-FU may begin 1 to 2 days following pembrolizumab/placebo (eg, Day 2 or Day 3) as needed per local standard of care, with end day for 5-FU adjusted accordingly

c Or per local standard for 5-FU administration duration as long as total dose of 4000 mg/m2 per cycle Q3W is followed (eg, 1000 mg/m2/day on each of Days 1 to 4). 5-FU treatment is not to exceed a maximum of 35 cycles.

Abbreviations: 5-FU=5-fluorouracil, IV=intravenous, NA=not applicable, Q3W=every 3 weeks

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

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

Treatments were administered in the following order:

- Pembrolizumab or placebo infusion was administered first, followed by the cisplatin and 5-FU infusions. Administration of chemotherapy should have followed 1 to 2 days after pembrolizumab/placebo as needed per local standard of care. Treatment continued with pembrolizumab plus chemotherapy or placebo plus chemotherapy until documented confirmed PD, unacceptable AE(s), intercurrent illness that prevented further administration of treatment, investigator's decision to discontinue treatment, subject withdrew consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject received 35 administrations (approximately 2 years) of study medication, or administrative reasons requiring cessation of treatment. Regardless of clinical benefit, subjects only received 35 administrations (approximately 2 years) with pembrolizumab. Pembrolizumab 200-mg fixed dose was administered as a 30-minute IV infusion Q3W
- Placebo was normal saline solution prepared by the local pharmacist. Placebo was dosed and administered by blinded qualified trial site personnel in the same manner as pembrolizumab.
- Cisplatin 80 mg/m^2 was administered as a 60- or 120-minute IV infusion (or per site's standard practice) Q3W on Day 1 of each treatment cycle and after pembrolizumab/placebo administration. Duration of cisplatin treatment was capped at 6 doses.
- 5-FU was administered as a continuous IV infusion of 800 mg/m^2/day on each of Days 1 to 5 Q3W or per local standard for 5-FU administration duration as long as total dose of 4000 mg/m^2 per 3-week cycle was followed. 5-FU was administered after pembrolizumab/placebo administration. Duration of 5-FU treatment did not exceed 35 cycles.

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-590.

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

KEYNOTE-590 (21) objectives were pre-specified. In male and female adult subjects (≥18 years of age) with locally advanced/metastatic RCC, the objectives were as follows:

Primary objective(s)

1. To compare overall survival (OS) between treatment arms in subjects with oesophageal squamous cell carcinoma (ESCC) whose tumours are PD-L1 biomarker-positive (CPS≥10).
2. To compare OS between treatment arms in subjects with ESCC.
3. To compare OS between treatment arms in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10).
4. To compare OS between treatment arms in all subjects.
5. To compare progression free survival (PFS) per RECIST 1.1, as determined by investigator, in subjects with ESCC.
6. To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10).
7. To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms in all subjects.

OS was defined as the time from randomisation to death due to any cause. Subjects without documented death at the time of the final analysis were censored at the date of the last follow-up.

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

Secondary objective(s)

1. To evaluate objective response rate (ORR) per RECIST 1.1, as determined by investigator between treatment arms in all subjects.
2. Evaluate ORR per RECIST 1.1, as determined by investigator, between treatment arms in subjects with ESCC whose tumours are PD-L1 biomarker-positive (CPS ≥10), in subjects with ESCC, and in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10).
3. Evaluate DOR per RECIST 1.1, as determined by investigator, between treatment arms in all subjects, in subjects with ESCC whose tumours are PD-L1 biomarker-positive (CPS ≥10), in subjects with ESCC, and in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10).
4. Evaluate the safety and tolerability profile.
5. To evaluate changes from baseline in health-related quality of life using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the EORTC Quality Of Life Questionnaire Oesophageal Module (QLQ-OES18) in all subjects, in subjects with ESCC whose tumours are PD-L1 biomarker-positive (CPS ≥10), in subjects with ESCC, and in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10), treated with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.

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 is 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

To characterise patient reported outcome (PRO) utilities using EuroQoL 5-dimension 5-level (EQ- 5D-5L) questionnaire in all subjects, in subjects with SCC whose tumours are PD-L1 biomarker-positive (CPS ≥10), in SCC subjects, and in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10) treated with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.

1. Evaluate PFS per irRECIST as determined by investigator between treatment arms in subjects with ESCC whose tumours are PD-L1 biomarker-positive (CPS ≥10), in ESCC subjects, in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10), and in all subjects.
2. To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments. This could include the evaluation of microsatellite instability (MSI), whole exome sequencing (WES), and/or gene expression profiling (GEP) in available tumour tissue.

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 – 590 (21,22)
Location	This study was conducted at 168 centres in 26 countries: Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Costa Rica, Denmark, France, Germany, Guatemala, Hong Kong, Japan, South Korea, Malaysia, Peru, Romania, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, United Kingdom, and United States.
Trial design	A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with advanced/Metastatic Oesophageal Carcinoma (KEYNOTE-590). After a screening period of 28 days, participants were stratified by the following 3 factors: 1) geographic region (Asia vs Rest of the World), 2) histology (adenocarcinoma vs squamous cell carcinoma), and 3) Eastern Cooperative Oncology Group Performance Status (ECOG PS, 0 vs 1). After stratification, subjects were randomized in a 1:1 ratio to receive either pembrolizumab or saline placebo, both combined with cisplatin.
Eligibility criteria for participants	Key inclusion criteria: • Was ≥18 years of age on the day of signing informed consent. • Had histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ. • Had measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment. • Had an ECOG PS of 0 to 1. • Provided either a newly obtained or archival tissue sample for PD-L1 by IHC analysis.

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 concomitant medication	Intervention: n=373 Pembrolizumab 200 mg every 3 weeks plus cisplatin 80 mg/m2 IV Q3W Comparator: n=376 Placebo every 3 weeks plus cisplatin 80 mg/m^2 IV Q3W Subjects were prohibited from receiving the following during KEYNOTE – 590 (20) • Antineoplastic systemic chemotherapy or biological therapy • Immunotherapy not specified in the protocol • Chemotherapy not specified in the 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. • Brivudine, sorivudine analogues, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase should not be administered with 5-FU therapy.
Primary outcomes (including scoring methods and timings of assessments)	To compare OS between treatment arms in participants with oesophageal squamous cell carcinoma (ESCC) whose tumour expressed programmed cell death 1 ligand 1 (PD-L1) combined proportion score (CPS) ≥10, ESCC, PD-L1 CPS ≥10, and in all participants. To compare PFS per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1), as determined by investigator assessment between treatment arms in participants with ESCC, PD-L1 CPS ≥10, and in all participants.
Other outcomes used in the economic model/specified in the scope	N/A
Pre-planned subgroups	• Geographic region (Asia versus Rest of World) • Histology (adenocarcinoma versus squamous cell carcinoma) • ECOG performance scale (0 versus 1) • Age (<65 versus ≥65 years) • Sex (female versus male) • Disease status (locally advanced versus metastatic)

B 2.3.3 KEYNOTE-590: Participants baseline characteristics

Baseline characteristics are summarised in Table 6. The baseline demographic and disease characteristics of participants for the two groups were generally well balanced and representative of a patient population with metastatic oesophageal cancer. Most participants were male (83.4%) and had squamous cell carcinoma (73.2%). Among participants who either achieved an on-study CR or PR or were continuing in the study without PD per RECIST 1.1, 112 participants were evaluable for MSI status; none were MSI-H.

Table 6: **Subject Characteristics (ITT Population) – KEYNOTE-590** (22)

	Pembrolizumab + cisplatin + 5FU		**Cisplatin + 5FU**		**Total**	
	n	(%)	n	(%)	n	(%)
Subjects in population	373	(49.8)	376	(50.2)	749	(100)
Gender						
Male	306	(82.0)	319	(84.8)	625	(83.4)
Female	67	(18.0)	57	(15.2)	124	(16.6)
Age (Years)						
< 65	201	(53.9)	226	(60.1)	427	(57.0)
>= 65	172	(46.1)	150	(39.9)	322	(43.0)
Mean	62.8		62.0		62.4	
SD	9.8		9.2		9.5	
Median	64.0		62.0		63.0	
Range	28 to 94		27 to 89		27 to 94	
Race						
American Indian Or Alaska native	9	(2.4)	12	(3.2)	21	(2.8)
Asian	201	(53.9)	199	(52.9)	400	(53.4)
Black Or African American	5	(1.3)	2	(0.5)	7	(0.9)
Multiple	5	(1.3)	9	(2.4)	14	(1.9)
American Indian Or Alaska Native, White	3	(0.8)	6	(1.6)	9	(1.2)
Black Or African American, White	2	(0.5)	3	(0.8)	5	(0.7)
White	139	(37.3)	139	(37.0)	278	(37.1)
Missing	14	(3.8)	15	(4.0)	29	(3.9)
Ethnicity						
Hispanic Or Latino	42	(11.3)	57	(15.2)	99	(13.2)
Not Hispanic Or Latino	315	(84.5)	296	(78.7)	611	(81.6)
Not Reported	2	(0.5)	1	(0.3)	3	(0.4)
Unknown	12	(3.2)	20	(5.3)	32	(4.3)
Missing	2	(0.5)	2	(0.5)	4	(0.5)

Region						
Asia	196	(52.5)	197	(52.4)	393	(52.5)
Rest of World	177	(47.5)	179	(47.6)	356	(47.5)
Primary Diagnosis						
Squamous Cell Carcinoma of the Oesophagus	274	(73.5)	274	(72.9)	548	(73.2)
Adenocarcinoma of the Oesophagus	58	(15.5)	52	(13.8)	110	(14.7)
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	41	(11.0)	50	(13.3)	91	(12.1)
Metastatic Staging						
M0	29	(7.8)	37	(9.8)	66	(8.8)
M1	344	(92.2)	339	(90.2)	683	(91.2)
Brain Metastasis						
Yes	1	(0.3)	2	(0.5)	3	(0.4)
No	372	(99.7)	374	(99.5)	746	(99.6)
Current Disease Stage						
IB	0	(0.0)	1	(0.3)	1	(0.1)
IIB	1	(0.3)	0	(0.0)	1	(0.1)
III	4	(1.1)	6	(1.6)	10	(1.3)
IIIA	4	(1.1)	5	(1.3)	9	(1.2)
IIIB	8	(2.1)	12	(3.2)	20	(2.7)
IIIC	12	(3.2)	13	(3.5)	25	(3.3)
IV	268	(71.8)	289	(76.9)	557	(74.4)
IVA	9	(2.4)	7	(1.9)	16	(2.1)
IVB	65	(17.4)	41	(10.9)	106	(14.2)
IVC	1	(0.3)	1	(0.3)	2	(0.3)
IVE	1	(0.3)	1	(0.3)	2	(0.3)
ECOG Performance Scale						
0	149	(39.9)	150	(39.9)	299	(39.9)
1	223	(59.8)	225	(59.8)	448	(59.8)
2	1	(0.3)	1	(0.3)	2	(0.3)
Histology						
Adenocarcinoma	99	(26.5)	102	(27.1)	201	(26.8)
Squamous Cell Carcinoma	274	(73.5)	274	(72.9)	548	(73.2)
Disease Status						
Metastatic	344	(92.2)	339	(90.2)	683	(91.2)
Unresectable - Locally Advanced	29	(7.8)	37	(9.8)	66	(8.8)
PD-L1 Status						
CPS >= 10	186	(49.9)	197	(52.4)	383	(51.1)
CPS < 10	175	(46.9)	172	(45.7)	347	(46.3)
Not evaluable	6	(1.6)	6	(1.6)	12	(1.6)

Missing	6	(1.6)	1	(0.3)	7	(0.9)

Abbreviations: *n, sample size; SD, standard deviation; IMDC, International RCC Database Consortium; PD-L1, program death-ligand 1; CPS, combined positive score;*

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

This section reports the relevant statistical methodology of KEYNOTE-590 (21,22).

Table 7: Statistical analysis plan summary

Study Design Overview	A randomized, double-blind, placebo-controlled phase III clinical trial of pembrolizumab in combination with cisplatin and 5-fluorouracil versus placebo in combination with cisplatin and 5-fluorouracil as first-line treatment in subjects with advanced/metastatic oesophageal carcinoma (KEYNOTE-590)
Treatment Assignment	Subjects were randomised in a 1:1 ratio to receive pembrolizumab with 5-fluorouracil (5-FU) and cisplatin combination therapy or placebo with 5-FU and cisplatin.
Analysis Populations	Global Study Population N=749 Efficacy: Intention to Treat (ITT); Safety: All Subjects as Treated (ASaT)
Primary Endpoints/ Hypotheses	1. OS in subjects with ESCC whose tumours are PD-L1 biomarker positive (CPS≥10). 2. OS in subjects with ESCC. 3. OS in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10). 4. OS in all subjects. 5. PFS based on RECIST 1.1 as assessed by investigator in subjects with ESCC. 6. PFS based on RECIST 1.1 as assessed by investigator in subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10). 7. PFS based on RECIST 1.1 as assessed by investigator in all subjects.
Key Secondary Endpoints/Hypotheses	1. ORR based on RECIST 1.1 as assessed by investigator in all subjects.
Statistical Methods for Key Efficacy Analyses	The primary hypotheses were evaluated by comparing pembrolizumab in combination with chemotherapy arm to placebo in combination with chemotherapy arm on PFS and OS using a stratified Log-rank test. Estimation of the hazard ratio (HR) was done using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results followed a tiered approach. The tiers differed with respect to the analyses that were performed. There were no Tier I events in this study. Tier 2 parameters were assessed via point estimates with 95% CI provided for between-group comparisons; only point estimates by treatment group were provided for Tier 3 safety parameters. The between-treatment difference was analysed using the Miettinen and Nurminen method (23).

Interim Analyses	**Planned** One efficacy interim analysis was planned for the study. Results were reviewed by an external Data Monitoring Committee (eDMC).
	Interim Analysis (IA): Timing: performed after enrolment completion, once a 13 months minimum follow-up (i.e. 13 months since last subject is randomised) has been achieved and a minimum of 460 investigator assessed PFS events have been observed in SCC and 391 deaths have occurred in ESCC. Purpose: Final analyses for PFS and interim analysis for OS **Final analysis (FA):** Timing: performed when a minimum follow-up of 9 months after IA and 233 deaths have occurred in ESCC with PD-L1 CPS ≥10 and 455 deaths have occurred in SCC. Purpose: Final OS analysis
Multiplicity	The overall Type I error was strongly controlled at 2.5% (1-sided), with 1.2% initially allocated to OS in OSCC with PD-L1 CPS ≥10, 1.1% to OS in OSCC, 0 to OS in PD-L1 CPS ≥10, 0 to OS in all subjects, 0.2% to PFS in OSCC, 0 to PFS in PD-L1 CPS ≥10, and 0 to PFS in all subjects. Re-allocation of Type I error used the graphical approach of Maurer and Bretz (24).
Sample Size and Power	The sample size is 749 subjects. As per preliminary baseline characteristics, the prevalence of ESCC with PD-L1 CPS ≥10 is 38%, PD-L1 CPS ≥10 is 51%, and ESCC is 73%. A total of ~233 deaths were expected in ESCC with PD-L1 CPS ≥10 at the OS final analysis. With 233 deaths, the study has ~85% power for detecting an HR of 0.65 at an initially assigned 0.012 (1-sided) significance level. A total of approximately 455 deaths were expected in ESCC at the OS final analysis. With 455 deaths, the study has 88% power for detecting an HR of 0.72 at an initially assigned 0.011 (1-sided) significance level. A total of ~ 460 investigator assessed PFS events were expected in ESCC at the IA. With ~460 PFS events, the study has ~82.8% power for detecting a HR of 0.7 at an initially assigned 0.002 (1-sided) significance level.
Statistical methods for safety analyses	Adverse events (AEs) were coded using the standard MedDRA and grouped system organ class. AEs were graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

Abbreviations: *n, sample size; IV, intravenously; Q3W, every 3 weeks; BID, twice daily; QD, daily; PFS, progression free survival; OS, overall survival; ORR, objective response rate; CI, confidence interval, ESCC, oesophageal squamous cell carcinoma.*

Discontinuation of Treatment

Subjects were permitted to discontinue treatment at any time for any reason or be dropped from study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from study treatment by the investigator or the study

sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

In the event of any of the following reasons, a subject must have been discontinued from the study treatment, but would continue to be monitored in the trial:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Confirmed radiographic PD as outlined in the trial protocol
- Unacceptable adverse experiences as described in the trial protocol
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test
- Investigator decision to discontinue treatment
- Completion of 35 treatments (approximately 2 years) with pembrolizumab/placebo

Discontinuation of Trial Treatment after CR:

Discontinuation of treatment could be considered for subjects who had attained a confirmed CR and had been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of study treatment beyond the date when the initial CR was declared.

For subjects who were discontinued from treatment but continued to be monitored in the trial, all visits and procedures, as outlined in the study protocol, were to be completed. Discontinuation from treatment is considered "permanent." Once a subject was discontinued, he/she was not allowed to restart treatment.

B 2.4.1 Statistical methods used to compare groups for primary and secondary outcomes and approach to missing data

The statistical methods and analysis strategy for the primary and secondary efficacy endpoints are summarised in the Table 8 below.

Table 8: KEYNOTE-590– Analysis strategy for key efficacy endpoints (21)

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
PFS per RECIST 1.1 by investigator	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in the Table 9.
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at subject's last known alive date
Key Secondary Analyses			
ORR per RECIST 1.1 by investigator	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders

Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours.

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.

In order 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 9.

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 (25), 2-stage model, etc.,).

Table 9: 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, 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
Death or progression after ≥2 consecutive missed disease assessments without further valid non- PD disease assessments, or after new anti-cancer therapy	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
Abbreviations: PD = progressive disease			

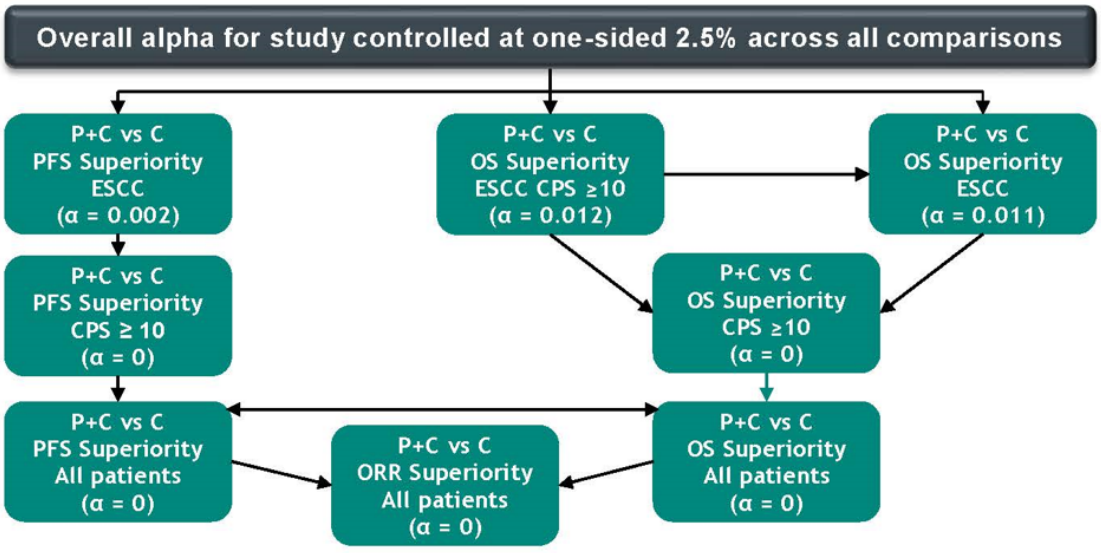
The proportional hazards assumption on PFS was examined using both graphical and analytical methods if warranted.

IA was performed after enrolment completion, when a minimum of 460 PFS events had accrued in ESCC and 391 deaths have occurred in ESCC subjects and all participants were followed for at least 13 months after randomisation.

Multiplicity strategy for PFS, OS and ORR

The study used the graphical method of Maurer and Bretz (24) 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 3 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. An assumption of 38% prevalence in ESCC subjects with PD-L1 CPS ≥10, 51% prevalence in subjects with PD-L1 CPS ≥10, and 73% prevalence in ESCC subjects was made in the calculations. Details of multiplicity strategy for the primary and key secondary endpoints are provided in Appendix D.

Figure 3. Maurer and Bretz multiplicity strategy approach used for hypothesis testing in KEYNOTE-590



Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival, ESCC, oesophageal squamous cell carcinoma

B 2.4.2 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 2.4.3 Statistical analysis

Table 10. Summary of statistical analyses

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
KEYNOTE-590 (21,22)	1. PFS, per RECIST 1.1 by investigator review 2. OS	The primary hypotheses for PFS and OS were evaluated by comparing pembrolizumab in combination with cisplatin and 5FU using a stratified log-rank test. Estimation of the HR was done 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 method. Stratified Miettinen and Nurminen's method with weights proportional to the stratum size was used for comparison of the ORR between the treatment arms.	The sample size was planned for 700 but the following power calculations are based on the actual final number of randomised subjects (N = 749). There were 2 primary endpoints for this study, PFS, and OS. The expected median PFS time in the control group was 6 months. Based on 487 PFS events, the study has ~84.9% power to detect a hazard ratio of 0.7 for PFS pembrolizumab+cisplatin+5FU combination vs. placebo) at alpha=0.002 (1-sided). The expected median OS time in the control group was 12 months. Based on 455 death events, the study had 88% power to detect a hazard ratio of 0.72 for OS at alpha=0.011 (1-sided).	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.

B 2.4.5 Participant flow in the relevant randomised controlled trials

Details of the participant flow in KEYNOTE-590 (22) are provided in Appendix D.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

2.5.1 & 2 Summary of quality assessment

Quality Assessment of KEYNOTE-590 (21,22) 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 11.

Table 11. Quality assessment results for KEYNOTE-590 (21,22)

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 randomized 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 finalized 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 trials

B 2.6.1. KEYNOTE-590 results

Early results are presented from the KEYNOTE-590 (22) study, based on the interim analysis (IA), which had a data cut-off date of 02 July 2020. 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 intention-to-treat (ITT) population. The study enrolment period was divided into 2 periods: Global Cohort and China Extension Study. The Global Cohort and China extension study were merged for the primary analyses and henceforth referred to as the Global Study population.

Interim analysis – data cut-off 02 July 2020

IA occurred after meeting the cut-off criteria of accruing at least 448 PFS events and with a minimum follow up of 13 months.
A total of 1020 participants were screened and 749 were randomised across 168 global study sites in 26 countries. 22 patients were recruited across 3 sites in the UK. A total of 740 randomised participants received at least 1 dose of study medication (pembrolizumab plus chemotherapy: 370; chemotherapy: 370). The participant flow and subject disposition from KEYNOTE-590 (22) are provided in Appendix D.

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

At IA, KEYNOTE-590 (22) had met both of its primary endpoints of PFS and OS, with p-values below the prespecified boundary for statistical significance of 0.02477 and 0.01421, respectively. As of the data cut-off date (02 July 2020) for IA, the median duration of follow up was 12.6 months (0.1 to 33.6 months) in the pembrolizumab plus chemotherapy group and 9.8 months (0.1 to 33.6 months) in the chemotherapy group.

There are different populations covered by the co-primary endpoints in the KEYNOTE-590 study:

- participants with ESCC whose tumours are PD-L1 biomarker-positive (CPS ≥10)
- participants with ESCC

- participants whose tumours are PD-L1 biomarker-positive (CPS ≥10)
- all participants

The focus of this submission (base case) is the population covering all study participants. In addition, cost-effectiveness analyses are presented for the sub-populations of participants whose tumours are PD-L1 biomarker-positive (CPS ≥10). The clinical efficacy and safety results relating to these sub-populations are also presented in the main body of the submission, with the results for the remaining sub-population assessed as a co-primary endpoint (participants with ESCC, participants with ESCC whose tumours are PD-L1 biomarker-positive (CPS ≥10) covered within the appendices).

OS: IA 02 July 2020 data-cut

All participants (ITT)

Pembrolizumab in combination with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS compared with chemotherapy for the 1L treatment of patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EJG. The OS HR of 0.73 (95% CI: 0.62, 0.0.86; p<0.0001), represents a 27% reduction in the risk of death for participants in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (Table 12).

The median OS was 12.4 months (95% CI: 10.5, 14.0) for the pembrolizumab plus chemotherapy group and 9.8 months (95% CI: 8.8, 10.8) for the chemotherapy group. OS results have demonstrated that pembrolizumab plus chemotherapy is superior to chemotherapy in all participants (Table 12). The KM curves for the OS separated early and remained separated throughout the evaluation period in favour of pembrolizumab plus chemotherapy (Figure 4).

The OS rates were higher in the pembrolizumab plus chemotherapy group at 12 (50.6% versus 9.4%) and 24 months (27.7% vs 16.3%) compared with the chemotherapy group (Table 13).

Table 12. Analysis of OS (ITT): IA July 2020 data cut

Treatment	N	Number of Events (%)	Person -	Event Rate/ 100	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % † (95% CI)

			Months	Person-Months		
Pembrolizumab + chemotherapy	373	262 (70.2)	4935.1	5.3	12.4 (10.5, 14.0)	50.6 (45.4, 55.6)
SOC	376	309 (82.2)	4301.2	7.2	9.8 (8.8, 10.8)	39.4 (34.4, 44.3)
Pairwise Comparisons					**Hazard Ratio‡ (95% CI)‡**	**p-Value**
Pembrolizumab + chemotherapy vs. SOC					0.73 (0.62, 0.86)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

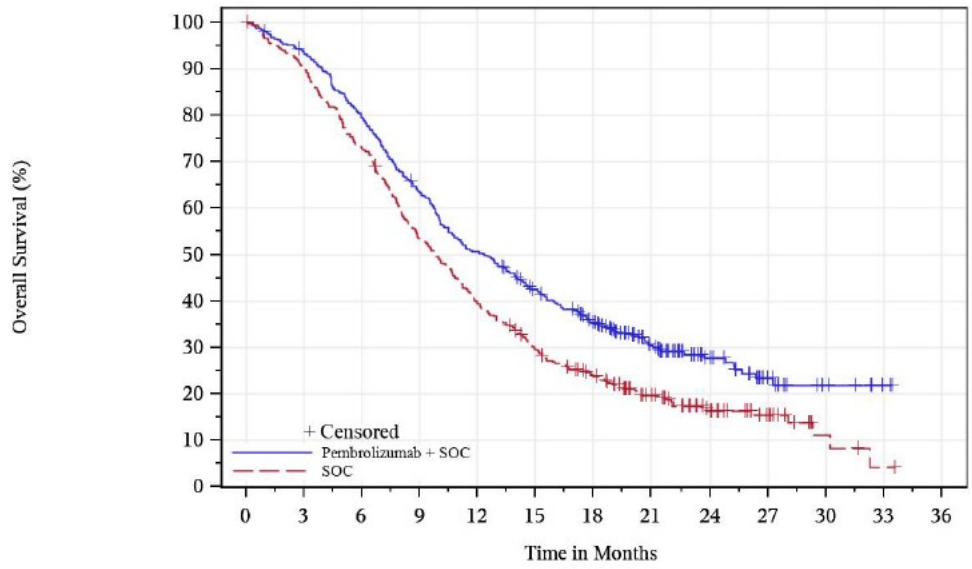
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Table 13. Summary of OS Rate Over Time (ITT): IA July 2020 data cut

	Pembrolizumab + chemotherapy (N=373)	**SOC (N=376)**
OS rate at 3 Months in (95% CI)†	93.8 (90.8, 95.9)	90.1 (86.6, 92.8)
OS rate at 6 Months in (95% CI)†	79.5 (75.1, 83.3)	73.1 (68.3, 77.3)
OS rate at 9 Months in (95% CI)†	63.6 (58.5, 68.3)	53.5 (48.4, 58.4)
OS rate at 12 Months in (95% CI)†	50.6 (45.4, 55.6)	39.4 (34.4, 44.3)
OS rate at 18 Months in (95% CI)†	35.3 (30.4, 40.2)	24.0 (19.8, 28.5)
OS rate at 24 Months in (95% CI)†	27.7 (22.7, 32.8)	16.3 (12.4, 20.6)

† From the product-limit (Kaplan-Meier) method for censored data.

Figure 4: KM Estimates of OS (ITT); IA July 2020 data-cut



Number of Subjects at Risk

Pembrolizumab + SOC	373	348	295	235	187	151	118	68	36	17	7	2	0
SOC	376	338	274	200	147	108	82	51	28	15	4	1	0

PD-L1 biomarker-positive (CPS ≥10)

Pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in OS compared with chemotherapy. The OS HR was 0.62 (95% CI: 0.49, 0.78; p<0.0001) represents a 38% reduction in the risk of death (Table 14). The median OS was 13.5 months (95% CI: 11.1, 15.6) for the pembrolizumab plus chemotherapy group and 9.4 months (95% CI: 8.0, 10.7) for the chemotherapy group (Figure 5). OS results have demonstrated that pembrolizumab plus chemotherapy is superior to chemotherapy in participants whose tumours express PD-L1 CPS ≥10.

Table 14. Analysis of Overall Survival (Subjects with PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median OS † (Months) (95% CI)	OS Rate at Month 12 in % †(95% CI)
Pembrolizumab + chemotherapy	186	124 (66.7)	2594.2	4.8	13.5 (11.1, 15.6)	53.8 (46.3, 60.6)
SOC	197	165 (83.8)	2201.1	7.5	9.4 (8.0, 10.7)	37.1 (30.3, 43.8)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + chemotherapy vs. SOC					0.62 (0.49, 0.78)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.

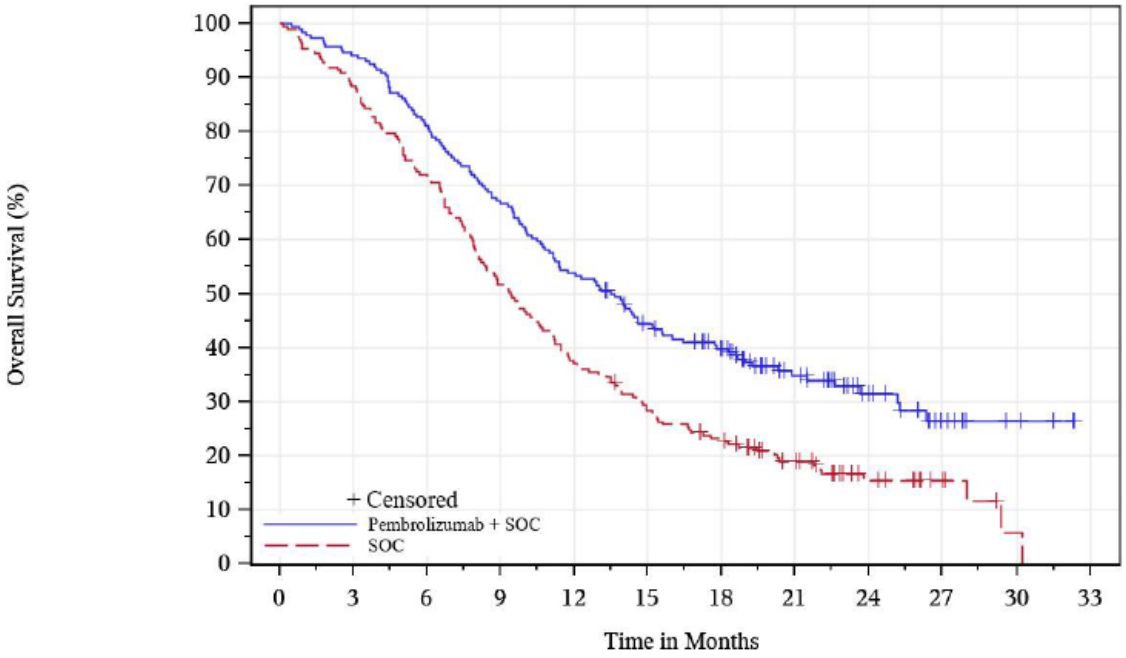
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Table 15. Overall Survival Rate (Subjects with PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + chemotherapy (N=186)	SOC (N=197)
OS rate at 3 Months in (95% CI)†	94.1 (89.6, 96.7)	88.3 (83.0, 92.1)
OS rate at 6 Months in (95% CI)†	81.2 (74.8, 86.1)	72.1 (65.3, 77.8)
OS rate at 9 Months in (95% CI)†	67.2 (60.0, 73.4)	51.8 (44.6, 58.5)
OS rate at 12 Months in (95% CI)†	53.8 (46.3, 60.6)	37.1 (30.3, 43.8)
OS rate at 18 Months in (95% CI)†	39.8 (32.7, 46.8)	22.6 (17.0, 28.7)
OS rate at 24 Months in (95% CI)†	31.4 (24.2, 38.9)	15.4 (10.3, 21.4)
† From the product-limit (Kaplan-Meier) method for censored data.		

Figure 5. Kaplan-Meier Estimates of Overall Survival (Subjects with PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	186	175	151	125	100	79	66	40	23	10	4	0
SOC	197	174	142	102	73	55	42	28	13	6	1	0

PFS: IA 02 July 2020 data-cut

All participants (ITT)

Pembrolizumab in combination with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in PFS based on investigator assessment per RECIST 1.1 compared with chemotherapy for the 1L treatment of patients locally advanced

unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction. The PFS HR of 0.65 (95% CI: 0.55, 0.76; p<0.0001) represents a 35% reduction in the risk of progression or death for participants in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (Table 16).

The median PFS was 6.3 months (95% CI: 6.2, 6.9) for the pembrolizumab plus chemotherapy group and 5.8 months (95% CI: 5.0, 6.0) for the chemotherapy group. PFS results have demonstrated that pembrolizumab plus chemotherapy is superior to chemotherapy in all participants.

In the pembrolizumab plus chemotherapy group, the PFS rates at 12 and 18 months were higher compared with the chemotherapy group (

Table 17). The KM curves separated early and remained separated for the duration of the evaluation period (Figure 6).

Table 16. Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule): IA July 2020 data cut

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + chemotherapy	373	297 (79.6)	2981.5	10.0	6.3 (6.2, 6.9)	62.4 (57.1, 67.3)
SOC	376	333 (88.6)	2235.1	14.9	5.8 (5.0, 6.0)	48.7 (43.4, 53.7)
Pairwise Comparisons					**Hazard Ratio‡ (95% CI)‡**	**p-Value**
Pembrolizumab + chemotherapy vs. SOC					0.65 (0.55, 0.76)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

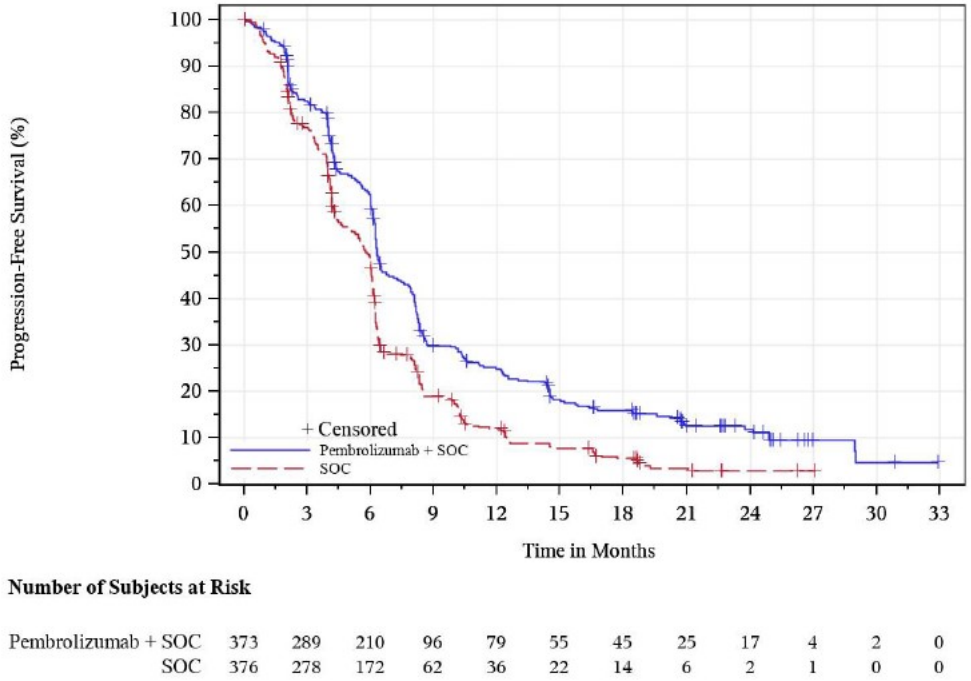
§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Table 17. Summary of PFS Rate Over Time Based on Investigator Assessment per RECIST 1.1: IA July 2020 data cut

	Pembrolizumab + chemotherapy (N=373)	SOC (N=376)
PFS rate at 3 Months in (95% CI)†	82.5 (78.2, 86.1)	76.9 (72.3, 80.9)
PFS rate at 6 Months in (95% CI)†	62.4 (57.1, 67.3)	48.7 (43.4, 53.7)
PFS rate at 9 Months in (95% CI)†	29.9 (25.1, 34.8)	18.9 (15.0, 23.2)
PFS rate at 12 Months in (95% CI)†	24.9 (20.4, 29.6)	11.9 (8.7, 15.7)
PFS rate at 15 Months in (95% CI)†	18.2 (14.2, 22.5)	7.8 (5.1, 11.1)
PFS rate at 18 Months in (95% CI)†	15.8 (12.0, 20.0)	5.5 (3.3, 8.5)
† From the product-limit (Kaplan-Meier) method for censored data.		

Figure 6. KM Estimates of PFS (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT): IA July 2020 data-cut



PD-L1 biomarker-positive (CPS ≥10) (ITT)

Pembrolizumab plus chemotherapy provided a statistically significant and clinically meaningful improvement in PFS based on investigator assessment per RECIST 1.1 compared with chemotherapy. The PFS HR was 0.51 (95% CI: 0.41, 0.65; p<0.0001) in favour of pembrolizumab plus chemotherapy compared to chemotherapy, representing a 49% reduction in the risk of death and disease progression (Table 18). The median PFS was 7.5 months (95% CI: 6.2, 8.2) for the pembrolizumab plus chemotherapy group and 5.5 months (95% CI: 4.3, 6.0) for the chemotherapy group. PFS results have demonstrated that pembrolizumab

plus chemotherapy is superior to chemotherapy in participants whose tumours express PD-L1 CPS ≥10.

Table 18. Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 primary Censoring Rule) (Subjects with PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + chemotherapy	186	140 (75.3)	1618.4	8.7	7.5 (6.2, 8.2)	65.6 (58.0, 72.1)
SOC	197	174 (88.3)	1125.6	15.5	5.5 (4.3, 6.0)	45.9 (38.6, 52.8)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + chemotherapy vs. SOC					0.51 (0.41, 0.65)	<0.0001§

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma).

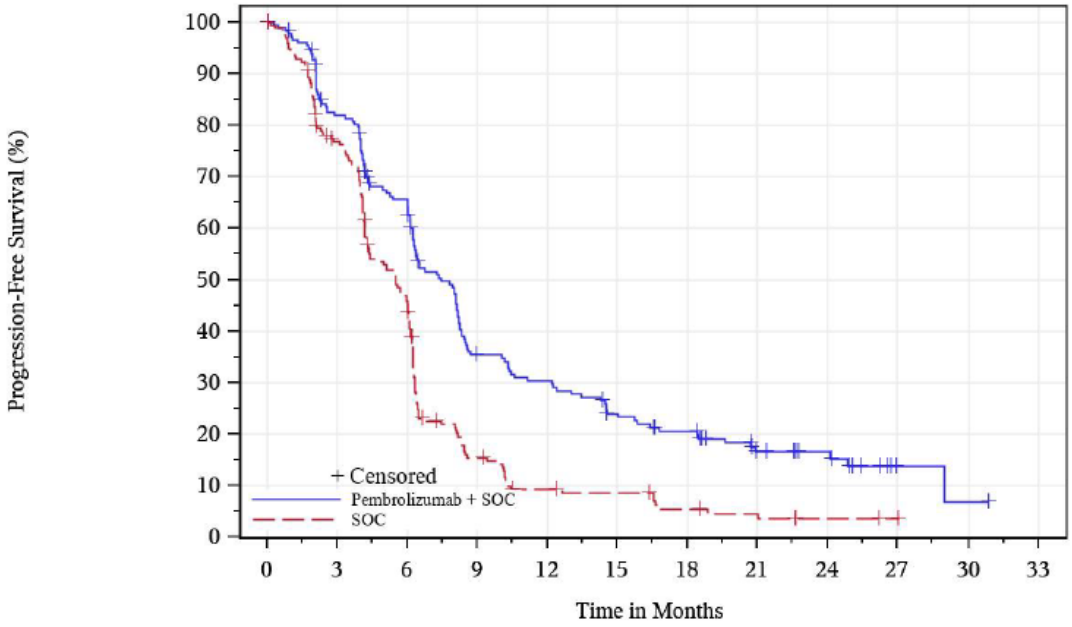
Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Table 19. Summary of PFS Rate Over Time Based on Investigator Assessment per RECIST 1.1 (Subjects with PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + chemotherapy (N=186)	SOC (N=197)
PFS rate at 3 Months in (95% CI)†	81.9 (75.4, 86.9)	76.8 (70.2, 82.1)
PFS rate at 6 Months in (95% CI)†	65.6 (58.0, 72.1)	45.9 (38.6, 52.8)
PFS rate at 9 Months in (95% CI)†	35.4 (28.2, 42.7)	15.4 (10.5, 21.1)
PFS rate at 12 Months in (95% CI)†	30.3 (23.5, 37.5)	9.2 (5.5, 14.2)
PFS rate at 15 Months in (95% CI)†	24.0 (17.7, 30.8)	8.5 (4.9, 13.4)
PFS rate at 18 Months in (95% CI)†	20.6 (14.7, 27.2)	5.4 (2.6, 9.9)

† From the product-limit (Kaplan-Meier) method for censored data.

Figure 7. Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) (Subjects with PD-L1 CPS >= 10, ITT Population)



Number of Subjects at Risk

Pembrolizumab + SOC	186	143	109	56	48	36	29	17	12	2	1	0
SOC	197	145	85	26	14	12	7	5	2	1	0	0

Secondary Efficacy Endpoints

The results of key secondary endpoints ORR and DOR in all participants, subjects with ESCC and subjects whose tumours are PD-L1 biomarker-positive [CPS ≥10]) are presented below. The results of the key secondary endpoints in the subgroups and subpopulations (subjects with ESCC, subjects with ESCC whose tumours are PD-L1 biomarker-positive [CPS ≥10]; are presented in Appendix L.

ORR: IA 02 July 2020 data-cut

All participants (ITT)

Pembrolizumab with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in ORR compared with SOC for the 1L treatment of participants with untreated, unresectable locally advanced or metastatic oesophageal cancer or GEJ adenocarcinoma. The confirmed ORR (based on investigator assessment per RECIST 1.1) was substantially higher with pembrolizumab plus chemotherapy than SOC (45.0% vs 29.3%),

reflecting a clinically meaningful and statistically significant 15.8% difference (p<0.0001) (Table 20).

A total of 24 (6.4%) participants treated with pembrolizumab plus chemotherapy achieved a CR (investigator-assessed), while 9 (2.4%) participants treated with SOC achieved a CR (investigator-assessed) (Table 21). Participants receiving pembrolizumab plus chemotherapy were more likely to experience a reduction in tumour size than those receiving SOC alone.

Table 20. Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (ITT); IA July 2020 data-cut

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + chemotherapy vs. SOC	
				Estimate (95% CI)†	p-Value††
Pembrolizumab + chemotherapy SOC	373 376	168 110	45.0 (39.9, 50.2) 29.3 (24.7, 34.1)	15.8 (9.0, 22.5)	<0.0001

† Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).
†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.

Table 21. Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 with Confirmation (ITT); IA July 2020 data-cut

	Pembrolizumab + chemotherapy		SOC	
	n	%	n	%
Number of Subjects in Population	373		376	
Complete Response (CR)	24	6.4	9	2.4
Partial Response (PR)	144	38.6	101	26.9
Best Overall Response (CR+PR)	168	45.0	110	29.3
Stable Disease (SD)	128	34.3	174	46.3
Disease Control (CR + PR + SD)	296	79.4	284	75.5
Progressive Disease (PD)	42	11.3	59	15.7
Not Evaluable (NE)	4	1.1	2	0.5
No Assessment	31	8.3	31	8.2

Responses are based on Investigator Assessment best assessment across timepoints, with confirmation.
NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).
No Assessment: no post-baseline assessment available for response evaluation.

PD-L1 biomarker-positive (CPS ≥10)

In participants whose tumours express PD-L1 CPS ≥10, the confirmed ORR based on investigator assessment per RESCIST 1.1 was substantially higher with pembrolizumab plus

chemotherapy than chemotherapy (51.1% v 26.9%), reflecting a clinically meaningful 24.0% improvement relative to chemotherapy (Table 22).

Table 22. Analysis of Objective Response with Confirmation Based on Investigator Assessment per RECIST 1.1 (Subjects whose tumours are PD-L1 biomarker-positive (CPS ≥10), ITT Population)

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % Pembrolizumab + chemotherapy vs. SOC	
				Estimate (95% CI)†	p-Value††
Pembrolizumab + chemotherapy	186	95	51.1 (43.7, 58.5)	24.0 (14.3, 33.2)	<0.0001
SOC	197	53	26.9 (20.8, 33.7)		

† Based on Miettinen & Nurminen method stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma).

†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0. Responses are based on Investigator Assessment per RECIST 1.1 with confirmation.

Table 23. Summary of Best Overall Response Based on Investigator Assessment per RECIST 1.1 with Confirmation (Subjects with PD-L1 CPS ≥ 10, ITT Population)

	Pembrolizumab + chemotherapy		SOC	
	n	%	n	%
Number of Subjects in Population	186		197	
Complete Response (CR)	11	5.9	5	2.5
Partial Response (PR)	84	45.2	48	24.4
Best Overall Response (CR+PR)	95	51.1	53	26.9
Stable Disease (SD)	55	29.6	98	49.7
Disease Control (CR + PR + SD)	150	80.6	151	76.6
Progressive Disease (PD)	21	11.3	27	13.7
Not Evaluable (NE)	3	1.6	1	0.5
No Assessment	12	6.5	18	9.1

Responses are based on Investigator Assessment best assessment across timepoints, with confirmation.

NE: post-baseline assessment(s) available however not being evaluable (i.e., all post-baseline assessment(s) being NOT EVALUABLE or CR/PR/SD < 6 weeks from randomization).

No Assessment: no post-baseline assessment available for response evaluation.

DOR: IA July 2020 data-cut

All participants

The responses in the pembrolizumab plus chemotherapy group for the untreated, unresectable locally advanced or metastatic oesophageal cancer or GEJ adenocarcinoma were more durable compared with the chemotherapy group (Appendix L), based on data from

the July 2020 data cut-off. The median DOR in the pembrolizumab plus chemotherapy group was numerically longer (8.3 months; range: (1.2+ - 31.0+) chemotherapy group (6.0 months; 1.5+ to 25.0+) (Appendix L) In the pembrolizumab plus chemotherapy group, a 3-fold higher percentage of participants had extended responses for ≥24 months by KM estimation (18.1% versus 6.1%) (Appendix L).

PD-L1 biomarker-positive (CPS ≥10)

In participants whose tumours express PD-L1 CPS ≥10, responses were more durable in the pembrolizumab plus chemotherapy group compared with the chemotherapy group. Median DOR in the pembrolizumab plus chemotherapy group was numerically longer (10.4 months; range: 1.9 to 28.9+) compared with the chemotherapy group (5.6 months; 1.5+ to 25.0+) (Appendix L). The median time to response was the same in the pembrolizumab plus chemotherapy group and chemotherapy group.

Exploratory objectives

PRO Compliance Rate and Completion Rate – IA July 2020 data-cut

PROs were analysed in the PRO FAS population (n=730), 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 18 in both treatment groups (Appendix L). As expected, completion rates generally decreased at each time point as more participants discontinued the study treatment.

EQ-5D-VAS Health Status/Quality of Life change from baseline to Week 30: IA July 2020 data-cut

All participants

In the PRO FAS population, the compliance and completion for the EQ-5D at baseline was 98.1% for both the pembrolizumab plus chemotherapy and the chemotherapy groups. Compliance at Week 18 was 90.4% for the pembrolizumab plus chemotherapy group and 92.7% for the chemotherapy group. Completion at Week 18 was 61.6% for the pembrolizumab plus chemotherapy group and 56.7% for the chemotherapy group. There were no clinically meaningful differences from baseline to week 18 in the EQ-5D-VAS health status/QoL score for participants in both the pembrolizumab plus chemotherapy group and the chemotherapy group based on data from the July 2020 data-cut (Table 24). Changes from baseline to week 18 were generally similar between the treatment groups at week 18 (Table 24).

Table 24. Analysis of Change from Baseline in EQ-5D VAS to Week 18; IA July 2020 data-cut

Treatment	Baseline		Week 18		Change from Baseline to Week 18	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + chemotherapy	360	72.59 (18.65)	226	72.41 (18.55)	367	-2.29 (-4.35, -0.24)
SOC	353	74.43 (17.14)	204	74.03 (16.59)	359	-3.49 (-5.61, -1.37)
Pairwise Comparison					Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + chemotherapy vs. SOC					1.20 (-1.61, 4.01)	0.4016

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

PD-L1 biomarker-positive (CPS ≥10) (ITT)

Table 25. Analysis of Change from Baseline in EQ-5D VAS to Week 18 (Subjects with PD-L1 CPS ≥ 10, FAS Population)

Treatment	Baseline		Week 18		Change from Baseline to Week 18	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + chemotherapy	180	74.02 (17.00)	110	71.94 (16.88)	184	-3.38 (-6.42, -0.35)
SOC	183	74.59 (16.84)	103	73.97 (17.01)	187	-3.78 (-6.87, -0.69)
Pairwise Comparison					Difference in LS Means† (95% CI)	p-Value†
Pembrolizumab + chemotherapy vs. SOC					0.40 (-3.70, 4.49)	0.8490

† Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma).

For baseline and Week 18, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

B.2.7 Subgroup analysis

B 2.7.1. Subgroup analyses carried out

Subgroup analyses were pre-specified in the KEYNOTE-590 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:

- Stratification factor: histology (adenocarcinoma versus squamous cell carcinoma)
- Stratification factor: geographic region (Asia versus Rest of World)
- Stratification factor: ECOG performance scale (0 versus 1)
- Disease status (locally advanced versus metastatic)
- Age category (< 65 versus ≥ 65)
- Sex (male versus female)

The results of subgroup analyses for all sub-populations are presented in Appendix E.

OS by Subgroup: IA: July 2020 data-cut

The improvement in OS for pembrolizumab plus chemotherapy compared with SOC in all subjects (based on the July 2020 data-cut) was consistent across all subgroups and sub-populations analysed (Appendix E). Subgroup analyses of OS for the sub-populations covered by the other co-primary endpoints of KEYNOTE-590 (subjects with ESCC whose tumours are PD-L1 biomarker-positive [CPS ≥10]; subjects with ESCC; subjects whose tumours are PD-L1 biomarker-positive [CPS ≥10]) are presented in Appendix E.

PFS by Subgroup: IA: July 2020 data-cut

The improvement in PFS for pembrolizumab plus chemotherapy compared with chemotherapy (based on the July 2020 data-cut) was observed across all subgroups and sub-populations analysed (Appendix E.) Subgroup analyses of PFS for the sub-populations covered by the other co-primary endpoints of KEYNOTE-590 (subjects with ESCC whose tumours are PD-L1 biomarker-positive [CPS ≥10]) 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 plus chemotherapy compared with a relevant comparator, in our specific population of interest (patients with patients with oesophageal cancer): KEYNOTE-590 (20–22). Therefore, it was not possible to conduct a meta-analysis.

B.2.9 Indirect and mixed treatment comparisons

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

Given that pembrolizumab in combination with cisplatin and 5-FU have only been compared head-to-head to placebo plus cisplatin and 5-FU, an indirect treatment comparison is needed to obtain estimates of the relative efficacy and safety of pembrolizumab versus other regimens relevant to the UK context, including capecitabine plus cisplatin and epirubicin with cisplatin and 5-FU; however, because these interventions have generally only been evaluated in non-comparative studies, performing an anchored network meta-analysis (NMA) of pembrolizumab plus 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 26. An overview of the patients' characteristics in all included studies is provided in Table 27, Table 28 and Table 29.

Table 26. Summary of the trials of relevance identified through the SLR

Trial ID	N	Treatment 1	Treatment 2
KEYNOTE-590	749	Pembrolizumab + 5-FU + cisplatin	Placebo + 5-FU + cisplatin
Lorenzen 2009	62	Cisplatin + 5-FU	Cetuximab + cisplatin + 5-FU
POWER	146	Cisplatin + 5-FU	Panitumumab + cisplatin + 5-FU
Wang 2017	150	Cisplatin + 5-FU	Cisplatin + 5-FU + 10μg/m^2 or 20μg/m^2 rhLTα-DA
Lee 2008	45	Capecitabine + cisplatin	--
Lee 2015	94	Capecitabine + cisplatin	Capecitabine + paclitaxel
Ross 2002	580	Epirubicin + cisplatin + 5-FU	Mitomycin + cisplatin + 5-FU

Table 27: Treatment characteristics of included trials

Trial		Regimen	Agent
KEYNOTE-590	Pembrolizumab + cisplatin + 5-FU	Pembrolizumab	Pembrolizumab, IV (200mg; D1, Q3W; UDP)
		Cisplatin	Cisplatin, IV (80mg/m^2; D1; Q3W; UDP)
		5-FU	5-FU, IV (800mg/m^2; D1-5; Q3W; UDP)
	Placebo + cisplatin + 5-FU	Cisplatin	Cisplatin, IV (80mg/m^2; D1; Q3W; UDP)
		5-FU	5-FU, IV (800mg/m^2; D1-5; Q3W; UDP)
Lorenzen 2009	Cisplatin + 5-FU	Cisplatin	Cisplatin, IV (100mg/m^2; D1; 29-day cycle; UDP or max. 6 cycles)
		5-FU	5-FU, IV (1000mg/m^2; D1-5; 29-day cycle; UDP or max. 6 cycles)
POWER	Cisplatin + 5-FU	Cisplatin	Cisplatin, IV (100mg/m^2; D1; Q3W; UDP)
		5-FU	5-FU, IV (1000mg/m^2; D1-4; Q3W; UDP)
Wang 2017	Cisplatin + 5-FU	Cisplatin	Cisplatin, IV (15mg/m^2; D1-D5; Q3W; UDP or max. 6 cycles)
		5-FU	5-FU, IV (750mg/m^2; D1-5; Q3W; UDP or max. 6 cycles)
Lee 2008	Capecitabine + cisplatin	Capecitabine	Capecitabine, PO (1250mg/m^2; D1-14 BID; Q3W; UDP)
		Cisplatin	Cisplatin, IV (60mg/m^2; D1; Q3W; UDP)
Lee 2015	Capecitabine + cisplatin	Capecitabine	Capecitabine, PO (1000mg/m^2; D1-14 BID; Q3W; UDP)
		Cisplatin	Cisplatin, IV (75mg/m^2; D1; Q3W; UDP)
Ross 2002	Epirubicin + cisplatin + 5-FU	Epirubicin	Epirubicin, IV (50mg/m^2; D1; Q3W; Max. 8 cycles)
		Cisplatin	Cisplatin, IV (60mg/m^2; D1; Q3W; Max. 8 cycles)
		5-FU	5-FU, IV (200mg/m^2/day; D1; Max. duration 6 months)

Abbreviations: 5-FU, fluorouracil; BID, twice daily; IV, intravenous; PO, oral; Q3W, every 3 weeks; UDP, until disease progression.

Table 28. Patient characteristics of trials identified through the SLR (age, sex, region, performance score)

Trial ID	Treatment	N	Age, Median (Range)	Male, n (%)	Region		Performance score		
					Asia, n (%)	Europe, n (%)	ECOG 0, n (%)	ECOG 1, n (%)	ECOG 2, n (%)
KEYNOTE-590	Pembrolizumab + cisplatin + 5-FU	373	64 (28-94)	306 (82)	196 (52.5)	--	149 (39.9)	223 (59.8)	1 (0.3)
	Placebo + cisplatin + 5-FU	376	62 (27-89)	319 (84.8)	197 (52.4)	--	150 (39.9)	225 (59.8)	1 (0.3)
Lorenzen 2009	Cisplatin + 5-FU	30	62 (40-74)	29 (96.7)	--	30 (100)	15 (50)	15 (50)	--
POWER	Cisplatin + 5-FU	73	59.6*	58 (79.5)	--	73 (100)	34 (47.2)	38 (52.8)	--
Wang 2017	Cisplatin + 5-FU	48	60 (41-74)	42 (87.5)	48 (100)	--	--	--	--
Lee 2008	Capecitabine + cisplatin	45	62 (47-72)	44 (97.8)	45 (100)	--	--	--	4 (8.9)
Lee 2015	Capecitabine + cisplatin	46	62 (46-76)	45 (97.8)	46 (100)	--	--	--	--
Ross 2002**	Epirubicin + cisplatin + 5-FU	289	58 (28-78)	218 (75.4)	--	289 (100)	58 (20.1)	166 (57.4)	59 (20.4)

*Notes: * Only mean age was reported and presented here; ** Ross 2002 had a mixed cancer population of esophageal, EGJ, and gastric cancer patients with no subgroup characteristics by cancer type; patient characteristics of the overall population is presented. Abbreviations: 5-FU, fluorouracil; ECOG, Eastern Cooperative Oncology Group.*

Table 29. Patient characteristics of trials identified through the SLR (disease stage, cancer type, histology)

Trial ID	Treatment	N	Extent of disease		Cancer type			Histology	
			Locally advanced n, (%)	Metastatic, n (%)	Oesophageal, n (%)	EGJ, n (%)	Gastric, n (%)	Squamous cell carcinoma, n (%)	Adenocarcinoma, n (%)
KEYNOTE-590	Pembrolizumab + cisplatin + 5-FU	373	29 (7.8)	344 (92.2)	332 (89)	41 (11)	--	274 (73.5)	99 (26.5)
	Placebo + cisplatin + 5-FU	376	37 (9.8)	339 (90.2)	326 (86.7)	50 (13.3)	--	274 (72.4)	102 (27.1)

Lorenzen 2009	Cisplatin + 5-FU	30	4 (13.3)	26 (86.7)	30 (100)	--	--	30 (100)	--
POWER	Cisplatin + 5-FU	73	43 (58.9)	--	73 (100)	--	--	73 (100)	--
Wang 2017	Cisplatin + 5-FU	48	--	48 (100)	48 (100)	--	--	48 (100)	--
Lee 2008	Capecitabine + cisplatin	45	37 (82.2)	--	45 (100)	--	--	45 (100)	--
Lee 2015	Capecitabine + cisplatin	46	43 (93.4)	3 (6.5)	46 (100)	--	--	46 (100)	--
Ross 2002*	Epirubicin + cisplatin + 5-FU	289	130 (52)	154 (53.3)	95 (33)	61 (21.1)	125 (43.3)	20 (6.9)	243 (84.1)

Note: * Ross 2002 had a mixed cancer population of esophageal, EGJ, and gastric cancer patients with no subgroup characteristics by cancer type; patient characteristics of the overall population is presented. Abbreviations: 5-FU, fluorouracil; EGJ, esophagogastric junction

Feasibility assessment

A feasibility assessment for an NMA is a well-established process and typically involves determining whether the evidence from RCTs for the interventions of interest form a network, followed by an assessment of the differences in study, treatment, patient, and outcomes characteristics within or between treatment comparisons. As illustrated in Error! Reference source not found., there was a lack of network connectivity between the three studies included in feasibility assessment. Hence the NMA feasibility assessment process was adapted to the context of an unanchored MAIC as summarised in Appendix D. In the context of an MAIC, the validity of estimates depends on the degree of overlap in the study populations and the extent that it is possible to up or down-weight patients to achieve an appropriate match to the external trial. Beyond exploring the between-study differences based on the study-level data, descriptive statistics based on the index trial can be performed, and the extent of the overlap in the study populations can be assessed based on diagnostic criteria of the MAIC.

Studies included in feasibility assessment

Of the seven trials identified in the SLR and deemed relevant to the UK context, four were not considered for the feasibility assessment. Three of these trials Lorenzen 2009 (15), POWER (16,17), and Wang 2017 (19) were excluded for using cisplatin with 5-FU, which is already captured in the population of interest in the index trial, KEYNOTE-590. One additional trial Ross 2002 (18) was excluded due to a lack of reported patient characteristics for the population of interest. As a result, three trials were included in the feasibility assessment: KEYNOTE-590, an RCT comparing pembrolizumab plus cisplatin and 5-FU to placebo plus cisplatin and 5-FU and two trials that administered capecitabine plus cisplatin 2008 and Lee et al 2015 (13,14). A summary of each included study is presented in Table 30.

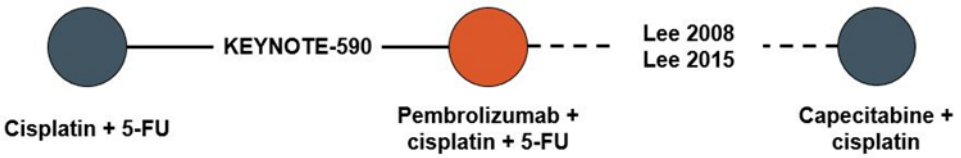
Table 30. Summary of trials included in the UK feasibility assessment

Trial	Description
Pembrolizumab plus cisplatin and 5-FU versus placebo plus cisplatin and 5-FU	
KEYNOTE-590	KEYNOTE-590 is an ongoing phase III double-blind, multicentre, randomized controlled trial evaluating the efficacy and safety of pembrolizumab with cisplatin and 5-FU as compared to placebo with cisplatin and 5-FU (22).
Capecitabine plus cisplatin	
Lee 2008	A phase II single-arm trial evaluating capecitabine plus cisplatin as first-line chemotherapy in 45 patients with advanced oesophageal squamous cell carcinoma. Patients were recruited from a single centre in South Korea. The primary objective was to evaluate the response rate per WHO and secondary objectives were OS, TTP, and safety. The ORR was 57.8% with 0 CR and 26 PRs. The median duration of response in responders was 4.6 months. Median follow-up was 25.7 months, median TTP was 4.7 months, and median survival was 11.2 months. The most common grade 3/4 non-haematological adverse events was anorexia (9.4%) and the most common grade 3/4 haematological adverse events were neutropenia (17.3%) (13).
Lee 2015	A phase II, open-label trial evaluating capecitabine plus cisplatin as first-line treatment in 46 patients with metastatic oesophageal squamous cell carcinoma. Patients were recruited from a single centre in South Korea. The primary objective of this study was to assess the response rate per RECIST 1.0 and secondary objectives included assessment of PFS, OS, toxicity and HRQoL. The ORR was 57% with a median follow-up of 23 months. Median PFS was 5.1 months and median OS was 10.5 months (14).

***Abbreviations**: 5-FU, fluorouracil; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGJ, esophagogastric junction; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TTP, time-to-progression; WHO, World Health Organization.*

The network of evidence identified in the SLR is depicted in Figure 8 – as can be seen, it was not possible to form a connected network.

Figure 8. Network diagram of studies identified through SLR



Recommendation

Upon reviewing the inclusion criteria and patient characteristics for the three trials included in the feasibility assessment, key differences were observed between the patient populations of

KEYNOTE-590 (21,22) and the two external trials as described in Table 30. Unlike KEYNOTE-590, which was carried out in multiple centres internationally, Lee 2008 (13) and Lee 2015 (14) were both conducted in a single centre in South Korea. Lee 2008 and Lee 2015 only enrolled ESCC patients whereas KEYNOTE-590 enrolled ESCC, oesophageal adenocarcinoma, and EGJ Siewert type I adenocarcinoma patients. By virtue of these differences, non-Asian patients as well as those Asian patients without ESCC will automatically receive a weight of 0 within an MAIC, which will likely to lead to large reductions in effective sample size (ESS) and a high degree of uncertainty around the estimated treatment effects due to these being heavily influenced by relatively few individuals. In addition, patients with locally advanced disease would also receive a null weight in a comparison with Lee 2015 (14), further reducing the ESS and increasing the associated uncertainty.

A major source of potential bias in MAIC estimates stems from imbalances in prognostic factors/effect modifiers post-matching. As IPD are not available from Lee 2008 (13) and Lee 2015 (14), it is only possible to adjust for those factors reported in the associated publications. A targeted literature review was performed to identify studies of prognostic factors in oesophageal cancer (see details in Appendix D). Although some of the prognostic factors identified in the review are reported in Lee 2008 (13) and Lee 2015 (14), other factors such as tumour size/length and weight loss/BMI are not. The following potential effect modifiers were also identified by examining result of RCTs within the target population: sex/gender, performance status, disease stage (metastatic versus locally advanced), tumour location (oesophagus versus GEJ), histology (squamous cell carcinoma versus adenocarcinoma), ethnicity (Asian versus non-Asian), PD-L1 status (relevant for immunotherapies only). While the majority of these can be accounted for, performance status cannot as only Lee 2008 (13) reported this characteristics but not with sufficient granularity to allow for adjustment; the split reported in the study is between ECOG 0-1 and 2, but all patients in KEYNOTE 590 fell into the former category. The presence of ECOG 2 patients, which although only reported to be a small proportion of the Lee 2008 (13) trial (8.9%), would further introduce bias into any comparisons.

Even if a sufficiently large ESS could be achieved and the bias due to potential residual imbalances between populations were assumed to be minimal, there are also questions over the generalisability of results from a comparison of KEYNOTE-590 with the Lee 2008 (13) and Lee 2015 (14) trials to the population relevant to the decision problem. In an MAIC, treatment effects are estimated for the population as specified in the external comparator trials, which in

this context would be patients of Asian ethnicity with (metastatic) ESCC. Ethnicity, histology, and tumour location have all been identified as effect modifiers, although the role of ethnicity is subject to some controversy (26), meaning these may not hold within the more broader population specified in the decision problem. This along with the other issues noted above leads to the recommendation that indirect comparisons are not conducted.

B.2.10 Adverse reactions

The primary safety analyses of IA were based on data from the ASaT population of 740 participants as of the cut-off date of 02 July 2020. In all tables, individuals are counted only once for a specific AE term by the worst severity recorded.

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

- Drug Related AEs
- Grade 3-5 AEs
- Serious AEs
- Death to AEs
- Discontinuation due to AEs
- Interruptions due to AEs
- AEs of special interest

IA: July 2020 data-cut

The median exposure to study drug was similar between the pembrolizumab plus chemotherapy and the chemotherapy groups (Table 31). However, the mean exposure and mean number of cycles received was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group. Participants in the pembrolizumab plus chemotherapy group remained on treatment longer as compared with the chemotherapy group. The rate of drug-related AEs was similar between the groups.

Table 31. Extent of Exposure - Summary of Duration on Therapy (ASaT Population)

	Pembrolizumab + chemotherapy (N=370)	**SOC (N=370)**
Duration on Therapy (months)		
Mean	7.7	5.8
Median	5.7	5.1
SD	6.84	4.76
Range	0.0 to 26.0	0.1 to 26.6
Number of Cycles		

Mean	**11.0**	**8.5**
Median	**8.0**	**7.0**
SD	**9.35**	**6.43**
Range	**1.0 to 35.0**	**1.0 to 35.0**
† For Pembrolizumab + chemotherapy arm, if any drug was administered during a cycle, it is counted as one cycle of administration.		

In the pembrolizumab plus chemotherapy group, more participants had a duration of exposure of ≥6, ≥12, ≥18 and ≥24 months compared with participants in the chemotherapy group (Table 32).

Table 32. Exposure by duration (ASaT population)

	Pembrolizumab + chemotherapy (N=370)		**SOC (N=370)**	
	n	**(%)**	**n**	**(%)**
Duration of Exposure				
>0 m	370	(100.0)	370	(100.0)
≥ 1 m	326	(88.1)	325	(87.8)
≥ 3 m	269	(72.7)	260	(70.3)
≥ 6 m	167	(45.1)	131	(35.4)
≥ 9 m	105	(28.4)	72	(19.5)
≥ 12 m	79	(21.4)	39	(10.5)
≥ 18 m	50	(13.5)	13	(3.5)
≥ 24 m	13	(3.5)	2	(0.5)
Each subject 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.				

Adverse events

The overall incidence of AEs was similar in the two groups. The incidences of 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 discontinuation due to SAEs were similar between treatment groups. The number of reported deaths due to AE was similar between the 2 treatment groups (pembrolizumab plus chemotherapy: 7.6%; chemotherapy: 10.3%). One death from the pembrolizumab plus chemotherapy group was due to COVID-19. There were no trends identified in the overall incidences of AEs by age, sex, race, baseline ECOG PS, and geographic region (Table 33).

Table 33. Disposition of Subjects (ITT Population)

	Pembrolizumab + chemotherapy	SOC		Total
	n (%)	n	(%)	n (%)

Subjects in population	373		376		749	
Status for Trial						
Discontinued	265	(71.0)	311	(82.7)	576	(76.9)
Death	260	(69.7)	308	(81.9)	568	(75.8)
Associated With Covid-19	1	(0.3)	0	(0.0)	1	(0.1)
Withdrawal By Subject	5	(1.3)	3	(0.8)	8	(1.1)
Not Associated With Covid-19, No Further Information	3	(0.8)	2	(0.5)	5	(0.7)
Not Associated With Covid-19, Subsequently Died	2	(0.5)	1	(0.3)	3	(0.4)
On-Going	108	(29.0)	65	(17.3)	173	(23.1)
Status for Study Medication						
Started	370		370		740	
Completed	15	(4.1)	1	(0.3)	16	(2.2)
Discontinued	328	(88.6)	359	(97.0)	687	(92.8)
Adverse Event	49	(13.2)	44	(11.9)	93	(12.6)
Clinical Progression	36	(9.7)	41	(11.1)	77	(10.4)
Complete Response	0	(0.0)	1	(0.3)	1	(0.1)
Physician Decision	9	(2.4)	10	(2.7)	19	(2.6)
Progressive Disease	204	(55.1)	239	(64.6)	443	(59.9)
Protocol Violation	0	(0.0)	1	(0.3)	1	(0.1)
Withdrawal By Subject	30	(8.1)	23	(6.2)	53	(7.2)
On-Going	27	(7.3)	10	(2.7)	37	(5.0)

If the overall count of subjects is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, subjects in population is used as the denominator for the percentage calculation.

Table 34. Adverse Event Summary (ASaT Population)

	Pembrolizumab + chemotherapy	**SOC**
	n (%)	**n (%)**
Subjects in population	370	370
with one or more adverse events	370 (100.0)	368 (99.5)
with no adverse event	0 (0.0)	2 (0.5)
with drug-related† adverse events	364 (98.4)	360 (97.3)
with toxicity grade 3-5 adverse events	318 (85.9)	308 (83.2)
with toxicity grade 3-5 drug-related adverse events	266 (71.9)	250 (67.6)
with non-serious adverse events	368 (99.5)	367 (99.2)
with serious adverse events	205 (55.4)	204 (55.1)
with serious drug-related adverse events	117 (31.6)	97 (26.2)
who died	28 (7.6)	38 (10.3)
who died due to a drug-related adverse event	9 (2.4)	5 (1.4)
discontinued drug due to an adverse event	90 (24.3)	74 (20.0)
	72 (19.5)	43 (11.6)

discontinued drug due to a drug-related adverse event **discontinued drug due to a serious adverse event** **discontinued drug due to a serious drug-related adverse event**	58 (15.7) 38 (10.3)	47 (12.7) 17 (4.6)

† Determined by the investigator to be related to the drug. Grades are based on NCI CTCAE version 4.03.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Table 35: Exposure-Adjusted Adverse Event Summary (Including Multiple Occurrences of Events) (ASaT Population)

	Event Count and Rate (Events/100 person-years)†			
	Pembrolizumab + chemotherapy		**SOC**	
Number of Subjects exposed	370		370	
Total exposure‡ in person-years	266.55		209.74	
Total events (rate)				
adverse events	7,383	(2769.86)	6,733	(3210.23)
drug-related§ adverse events	4,661	(1748.65)	4,167	(1986.78)
toxicity grade 3-5 adverse events	1,141	(428.07)	1,105	(526.85)
toxicity grade 3-5 drug-related adverse events	722	(270.87)	642	(306.10)
serious adverse events	399	(149.69)	379	(180.70)
serious drug-related adverse events	179	(67.15)	154	(73.43)
adverse events resulting in dose modification"	1,029	(386.05)	835	(398.12)
adverse events leading to death	31	(11.63)	38	(18.12)
drug-related adverse events leading to death	9	(3.38)	5	(2.38)
adverse events resulting in drug discontinuation	116	(43.52)	84	(40.05)
drug-related adverse events resulting in drug discontinuation	89	(33.39)	49	(23.36)
serious adverse events resulting in drug discontinuation	69	(25.89)	52	(24.79)
serious drug-related adverse events resulting in drug discontinuation	44	(16.51)	19	(9.06)

*† Event rate per 100 person-years of exposure = event count *100/person-years of exposure.*

‡ Drug exposure is defined as the between the first dose date + 1 day and the earlier of the last dose date + 30 or the database cut-off date.

§ Determined by the investigator to be related to the drug.

" Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded

Overall AEs

The overall incidence of AEs was similar in the pembrolizumab plus chemotherapy (100%) and chemotherapy (99.5%) arms (Table 36). The most frequently reported AEs (those reported in ≥40% of participants in either treatment group) were nausea, anaemia, decreased appetite, fatigue, and constipation (Table 36).

Table 36: Subjects With Adverse Events By Decreasing Incidence (Incidence ≥ 10% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + chemotherapy		SOC	
	n	(%)	N	(%)
Subjects in population	370		370	
with one or more adverse events	370	(100.0)	368	(99.5)
with no adverse events	0	(0.0)	2	(0.5)
Nausea	249	(67.3)	232	(62.7)
Anaemia	187	(50.5)	208	(56.2)
Decreased appetite	164	(44.3)	141	(38.1)
Fatigue	149	(40.3)	126	(34.1)
Constipation	148	(40.0)	149	(40.3)
Neutrophil count decreased	139	(37.6)	111	(30.0)
Diarrhoea	135	(36.5)	123	(33.2)
Vomiting	126	(34.1)	117	(31.6)
Stomatitis	100	(27.0)	95	(25.7)
Neutropenia	97	(26.2)	90	(24.3)
White blood cell count decreased	97	(26.2)	69	(18.6)
Weight decreased	87	(23.5)	90	(24.3)
Blood creatinine increased	79	(21.4)	78	(21.1)
Hyponatraemia	68	(18.4)	77	(20.8)
Hypokalaemia	67	(18.1)	71	(19.2)
Platelet count decreased	62	(16.8)	62	(16.8)
Asthenia	60	(16.2)	45	(12.2)
Dysphagia	60	(16.2)	63	(17.0)
Cough	59	(15.9)	56	(15.1)
Mucosal inflammation	59	(15.9)	68	(18.4)
Hiccups	56	(15.1)	53	(14.3)
Alopecia	55	(14.9)	39	(10.5)
Pyrexia	55	(14.9)	44	(11.9)
Pneumonia	54	(14.6)	52	(14.1)
Insomnia	49	(13.2)	44	(11.9)
Malaise	48	(13.0)	43	(11.6)
Rash	44	(11.9)	26	(7.0)
Hypothyroidism	40	(10.8)	24	(6.5)
Dysgeusia	38	(10.3)	32	(8.6)
Neuropathy peripheral	37	(10.0)	37	(10.0)
Hypoalbuminaemia	35	(9.5)	49	(13.2)
Thrombocytopenia	28	(7.6)	37	(10.0)

Every subject is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

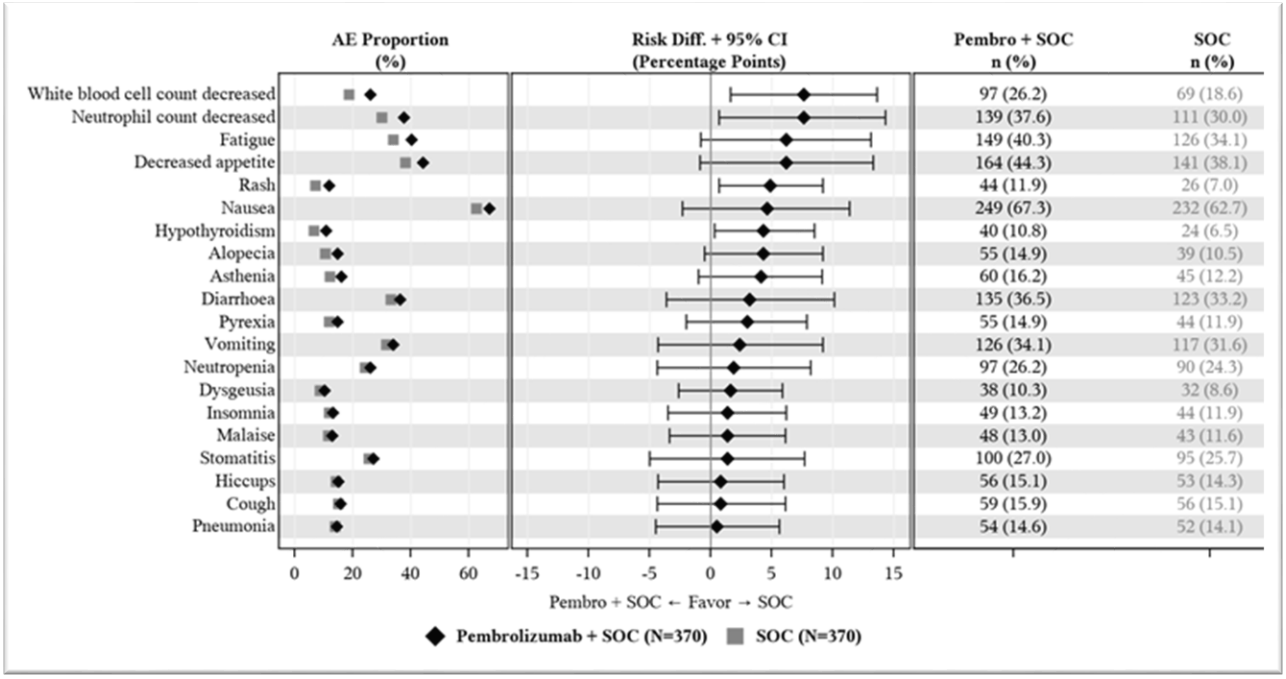
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

A rainfall plot comparing commonly reported AEs (incidence ≥10% in either treatment group) showed higher rates of WBC count decreased, neutrophil count decreased, rash, and hypothyroidism in the pembrolizumab plus chemotherapy group than in the chemotherapy group (Figure 9). These events were predominantly Grades 1 to 3 and manageable.

After adjustment for exposure, decreased WBC count, rash, and hypothyroidism remained higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group (Table 37). However, neutrophil count decreased was lower in the pembrolizumab plus chemotherapy group than the chemotherapy group after adjustment for exposure.

Figure 9: Between-Treatment Comparisons in Adverse Events Selected Adverse Events (>= 10% Incidence) and Sorted by Risk Difference (ASaT Population)



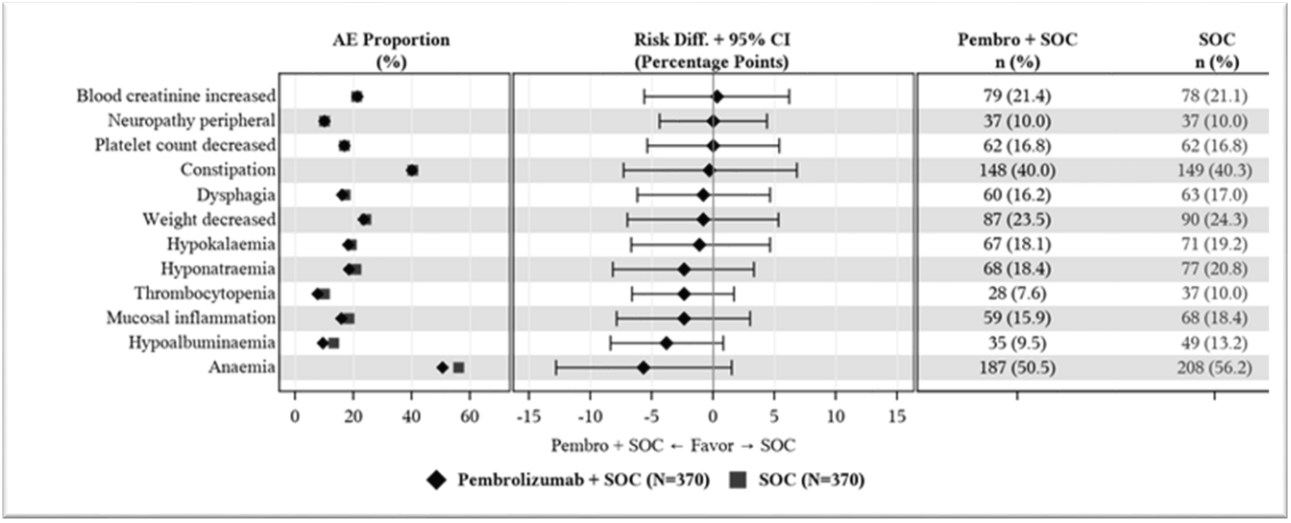


Table 37: Exposure-Adjusted Adverse Events (Including Multiple Occurrences of Events) (Incidence ≥ 10% in One or More Treatment Groups) (ASaT Population)

	Event Count and Rate (Events/100 person-year) †	
	Pembrolizumab + chemotherapy	**SOC**
Number of Subjects exposed‡	370	370
Total exposure§ person-years	266.55	209.74
Total events (rate)	4521(1696.13)	4128(1968.19)
AE Category		
Blood and lymphatic system disorders	536(201.1)	546(260.3)
Anaemia	288(108.1)	309(147.3)
Neutropenia	193(72.4)	180(85.8)
Thrombocytopenia	55(20.6)	57(27.2)
Endocrine disorders	46(17.3)	27(12.9)
Hypothyroidism	46(17.3)	27(12.9)
Gastrointestinal disorders	1468(550.8)	1345(641.3)
Constipation	238(89.3)	209(99.7)
Diarrhoea	233(87.4)	191(91.1)
Dysphagia	76(28.5)	79(37.7)
Nausea	522(195.8)	510(243.2)
Stomatitis	164(61.5)	150(71.5)
Vomiting	235(88.2)	206(98.2)
General disorders and administration site conditions	604(226.6)	503(239.8)
Asthenia	105(39.4)	72(34.3)
Fatigue	229(85.9)	187(89.2)
Malaise	78(29.3)	64(30.5)
Mucosal inflammation	114(42.8)	120(57.2)
Pyrexia	78(29.3)	60(28.6)

Infections and infestations	59(22.1)	59(28.1)
Pneumonia	59(22.1)	59(28.1)
Investigations	829(311.0)	736(350.9)
Blood creatinine increased	131(49.2)	116(55.3)
Neutrophil count decreased	281(105.4)	242(115.4)
Platelet count decreased	104(39.0)	109(52.0)
Weight decreased	96(36.0)	111(52.9)
White blood cell count decreased	217(81.4)	158(75.3)
Metabolism and nutrition disorders	545(204.5)	539(257.0)
Decreased appetite	285(106.9)	245(116.8)
Hypoalbuminaemia	44(16.5)	67(31.9)
Hypokalaemia	113(42.4)	114(54.4)
Hyponatraemia	103(38.6)	113(53.9)
Nervous system disorders	86(32.3)	78(37.2)
Dysgeusia	45(16.9)	35(16.7)
Neuropathy peripheral	41(15.4)	43(20.5)
Psychiatric disorders	59(22.1)	56(26.7)
Insomnia	59(22.1)	56(26.7)
Respiratory, thoracic and mediastinal disorders	178(66.8)	166(79.2)
Cough	69(25.9)	64(30.5)
Hiccups	109(40.9)	102(48.6)
Skin and subcutaneous tissue disorders	111(41.6)	73(34.8)
Alopecia	55(20.6)	40(19.1)
Rash	56(21.0)	33(15.7)

*† Event rate per 100 person-year of exposure=event count *100/person-year of exposure.*

‡ Number of subjects exposed to drug at the start of indicated time interval.

§ Drug exposure is defined as the interval of min (last dose date + 30, Cutoff Date) – first dose date + 1.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Grade 3-5 AEs

The overall incidence of Grade 3 to 5 AEs was similar for pembrolizumab plus chemotherapy (85.9%) compared with chemotherapy (83.2%) (Table 38). The most frequently reported Grade 3 to 5 AEs (incidence ≥5%) for both treatment arms were: decreased neutrophil count, anaemia, neutropenia, hyponatremia, pneumonia, white blood cell count decrease.

Table 38: Subjects with Grade 3-5 Adverse Events by Decreasing Incidence (Incidence ≥ 5% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + chemotherapy	SOC

	n	(%)	n	(%)
Subjects in population	370	(100)	370	(100)
with one or more grade 3-5 adverse events	318	(85.9)	308	(83.2)
with no grade 3-5 adverse events	52	(14.1)	62	(16.8)
Neutrophil count decreased	89	(24.1)	64	(17.3)
Anaemia	63	(17.0)	81	(21.9)
Neutropenia	54	(14.6)	61	(16.5)
Hyponatraemia	45	(12.2)	41	(11.1)
Pneumonia	35	(9.5)	35	(9.5)
White blood cell count decreased	34	(9.2)	18	(4.9)
Dysphagia	29	(7.8)	26	(7.0)
Fatigue	29	(7.8)	25	(6.8)
Nausea	27	(7.3)	26	(7.0)
Vomiting	27	(7.3)	20	(5.4)
Hypokalaemia	24	(6.5)	32	(8.6)
Stomatitis	21	(5.7)	14	(3.8)
Decreased appetite	15	(4.1)	20	(5.4)
Weight decreased	11	(3.0)	19	(5.1)
Platelet count decreased	7	(1.9)	20	(5.4)

Every subject is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades are based on NCI CTCAE version 4.03.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Drug-related Grade 3-5 AEs

The types and frequencies of drug-related Grade 3 to 5 AEs reported in the pembrolizumab plus chemotherapy group were generally consistent with the known safety profiles of pembrolizumab monotherapy and 5-FU/cisplatin chemotherapy.

The overall incidence of drug-related Grade 3 to 5 AEs was similar between pembrolizumab plus chemotherapy (related to at least one drug or both) (71.9%) and chemotherapy (67.6%) (Table 39). The most frequently reported drug-related Grade 3 to 5 AEs (incidence ≥5%) in both treatment groups were: Neutrophil count decrease, neutropenia, anaemia, white blood cell count decrease.

The largest between-treatment difference was noted in the incidence of neutrophil count decreased in the pembrolizumab plus chemotherapy group (22.7%) compared with the chemotherapy group (16.8%).

Table 39: Subjects with drug-related grade 3-5 adverse events by decreasing incidence (Incidence ≥ 5% in One or More Treatment Groups) (ASaT Population)

	Pembrolizumab + chemotherapy		SOC	
	n	(%)	n	(%)
Subjects in population	370	(100)	370	(100)
with one or more drug-related grade 3-5 adverse events	266	(71.9)	250	(67.6)
with no drug-related grade 3-5 adverse events	104	(28.1)	120	(32.4)
Neutrophil count decreased	84	(22.7)	62	(16.8)
Neutropenia	53	(14.3)	60	(16.2)
Anaemia	46	(12.4)	54	(14.6)
White blood cell count decreased	32	(8.6)	18	(4.9)
Nausea	26	(7.0)	24	(6.5)
Fatigue	23	(6.2)	20	(5.4)
Vomiting	23	(6.2)	18	(4.9)
Stomatitis	21	(5.7)	14	(3.8)
Hyponatraemia	20	(5.4)	20	(5.4)
Hypokalaemia	17	(4.6)	19	(5.1)

Every subject is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Grades are based on NCI CTCAE version 4.03.

Non-serious adverse events up to 30 days of last dose and serious adverse events up to 90 days of last dose are included.

Drug-related Serious AEs

The overall incidence of drug-related SAEs was similar between pembrolizumab plus chemotherapy (31.6%) and chemotherapy alone (26.21%). The most frequently reported drug-related SAEs were pneumonia (pembrolizumab plus chemotherapy: 3.5%; chemotherapy: 0.8%), pneumonitis (pembrolizumab plus chemotherapy: 3.2%; chemotherapy: 0.0%), and febrile neutropenia (pembrolizumab plus chemotherapy: 2.4%; chemotherapy: 3.2%).

B.2.11 Ongoing studies

The KEYNOTE-590 (21,22) study is ongoing, with an estimated study completion date of May 2023. There are no other ongoing clinical trials for pembrolizumab in this indication other than KEYNOTE-590.

B.2.12 Innovation

Currently in the UK, there is no innovative immuno-oncology treatment available for the first-line treatment of patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma. Data from KEYNOTE-590 (22) show that pembrolizumab in combination with chemotherapy is a promising treatment option which has demonstrated efficacy, including significant survival benefits, in all oesophageal patients, and has an acceptable tolerability profile.

Pembrolizumab, a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity. As evident by clinical and safety data presented, pembrolizumab offers a durable and well tolerated treatment option for patients with oesophageal cancer.

For decades, cytotoxic chemotherapies have remained the main treatment options for metastatic oesophageal cancer. For patients who have not received previous treatment, combination chemotherapies are routinely used, as palliative treatment options. Various palliative chemotherapy regimens have been investigated in oesophageal cancer studies and have been shown to have at least some activity in the first-line setting, with response rates ranging from 19% to 52% and 5-year survival rates of approximately 5%, with significant toxicity rates (27). Current National Comprehensive Cancer Network (NCCN) (28), European Society for Medical Oncology (ESMO) (29), and NICE NG83 (12) guidelines recommend the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), either alone or in combination with a third drug such as epirubicin or a taxane, as the most effective first-line treatment option.

In 2018, the results of the interim analysis of KEYNOTE-180 demonstrated that pembrolizumab showed clinically meaningful anti-cancer activity as a third-line therapy in patients with oesophageal cancer, with an ORR of 9.9% (95% CI: 5.2, 16.7) (30). In addition, pembrolizumab monotherapy was approved for patients with ESCC whose tumours express PD-L1 CPS ≥10 in the US, Japan, China, and other countries based on KEYNOTE- 181, which used pembrolizumab as second line therapy in participants with advanced metastatic oesophageal cancer. Median OS for patients with ESCC whose tumours express PD-L1 CPS ≥10 was 10.3 months compared with 6.7 months with chemotherapy, 12-month OS was 48% versus 23%, respectively (31). As a result of the findings of KEYNOTE-180 and KEYNOTE-181, pembrolizumab was granted FDA approval as monotherapy for the treatment of recurrent

locally advanced, metastatic, ESCC whose tumours express PD-L1 CPS ≥10 with disease progression after 1 or more systemic treatments.

The majority of patients are diagnosed with advanced/metastatic cancer, and in this setting, response to chemotherapeutic agents is poor. Given the high incidence and mortality worldwide and lack of effective therapeutic options, oesophageal cancer patients represent a patient population with a high unmet need for drug development.

B.2.13 Interpretation of clinical effectiveness and safety evidence

KEYNOTE-590 (22) met the predefined criteria for statistical significance for both of its primary endpoints of OS and PFS, as well as its key secondary endpoint of ORR. The results from the interim analysis of KEYNOTE-590 (22) provide evidence that treatment with pembrolizumab plus chemotherapy is superior to SOC alone for patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma and provides a clinically meaningful improvement in OS, PFS and ORR. Results for OS, PFS, and ORR showed consistent benefit of pembrolizumab plus chemotherapy across all sub-populations analysed under the co-primary endpoints, and for all protocol specified subgroups that were considered. Pembrolizumab in combination with chemotherapy has generally acceptable safety profile.

In the all-comer population (the population reflected within the base-case of this submission), OS HR was 0.73 (95% CI: 0.62, 0.86; $p<0.0001$) in favour of pembrolizumab plus chemotherapy, reflecting a 27% reduction in the risk of death. The median OS was 12.4 months (95% CI: 10.5, 14.0) for the pembrolizumab plus chemotherapy group compared to 9.8 months (95% CI: 8.8, 10.8) for the placebo plus chemotherapy group.

PFS HR in all participants was 0.65 (95% CI: 0.55, 0.76; $p<0.0001$) in favour of pembrolizumab plus chemotherapy, reflecting a 35% reduction in the risk of death or disease progression based on the investigator assessment per RECIST 1.1. The median PFS was 6.3 months (95% CI: 6.2, 6.9) for the pembrolizumab plus chemotherapy group and 5.8 months (95% CI: 5.0, 6.0) for the chemotherapy group.

Confirmed ORR in all participants was substantially higher in the pembrolizumab plus chemotherapy group than the chemotherapy group (45.0% vs 29.3%) reflecting a clinically meaningful 15.8% difference ($p<0.0001$), based on investigator assessment per RECIST 1.1.

Median DOR in all participants in the pembrolizumab plus chemotherapy group was numerically longer (8.3 months; range: 1.2 to 31.0+) compared with the chemotherapy group (6.0 months; 1.5+ to 25.0+) based on investigator assessment per RECIST 1.1.

In all participants and other subpopulations, the differences in LS means from global health status/QoL were similar between the both treatment groups.

Incidences of 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 discontinuation due to SAEs were similar between treatment groups. Incidences of discontinuation of any drug within the treatment regimen due to drug- related AEs and drug-related SAEs were higher in the pembrolizumab plus chemotherapy group than in the chemotherapy group. The incidence of AEOSI was higher in the pembrolizumab plus chemotherapy group compared with the chemotherapy group. The most common AEOSI categories in the pembrolizumab plus chemotherapy group were hypothyroidism (10.8%), pneumonitis (6.2%), and hyperthyroidism (5.7%).

It was not feasible to conduct an indirect treatment comparison between pembrolizumab and other treatments relevant to the UK population (capecitabine plus cisplatin and epirubicin with cisplatin and 5-FU) due to studies differences and lack of connected network between the studies identified in the SLR.

Internal validity

KEYNOTE-590 (21,22) is a robust, multi-centre, randomised, double-blind, placebo controlled phase III trial of pembrolizumab plus chemotherapy versus chemotherapy in patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EJG who have not received prior therapy. Prior to randomisation, eligible subjects were first stratified by histology (adenocarcinoma vs squamous cell carcinoma), geographic region (Asia versus Rest of the world) and ECOG PS, (0 vs 1).

The primary endpoints were to compare OS and PFS (per RECIST 1.1 as assessed by investigator) in subjects treated with pembrolizumab plus chemotherapy versus chemotherapy. OS is a clinically relevant endpoint, that was directly referenced in the final scope for this appraisal and the decision problem. This selected endpoint is consistent with that used in studies of other therapeutic agents in the population of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EJG. The definition of

progression when evaluating PFS in KEYNOTE-590 (21,22) followed an established response evaluation criterion (RECIST 1.1), in line with European Guidance (32).

HRQoL was explored under exploratory endpoints in the KEYNOTE-590 (21,22) study, with changes from baseline in patients treated with pembrolizumab plus chemotherapy compared to chemotherapy recorded using both the preferred measure of EQ-5D according to the NICE reference case, in addition to the cancer specific EORTC QLQ-C30 and EORTC QLQ-OES18. KEYNOTE-590 (21,22) 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-590 (21,22) is a global study conducted in 168 centres in 26 countries, including 29 sites in Europe. Of the patients participating in the study, 162 were enrolled at sites in Europe, including 22 from the UK.

Baseline characteristics of patients enrolled in KEYNOTE-590 (22) were as expected for patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EJG. Most patients were male, 68.9 % of participants were Asian and 21.7% white, median age of the participants was 63 years. Subgroup analyses confirm the benefit of pembrolizumab plus chemotherapy versus chemotherapy in patients of all histologies (please see section 2.6.1 and Appendix E for more detailed discussion). The treatment arms were generally well balanced by all baseline characteristics.

The observed safety profile of pembrolizumab plus chemotherapy in KEYNOTE-590 (22) 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 chemotherapy group were generally consistent with the established pembrolizumab safety profile. No new safety signal was identified.

Table 40. End-of-Life Criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: • Patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma, have a short life expectancy with median survival measured in less than 10 months (12). • Median OS in KEYNOTE-590, for patients in the ITT analysis treated with SOC, was 9.4 months. Clinical experts confirmed this was in line with UK clinical practice.	B.1.3 page 14-15 B.2.6.2 page 41 - 46
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Pembrolizumab in combination with chemotherapy offers an extension to life of at least 3 months compared to SOC: • ITT – In the ITT population of KEYNOTE-590, the median OS for pembrolizumab in combination with chemotherapy was 12.4 months (95% CI, 10.5, 14.0) compared to 9.8 months (95% CI 8.8, 10.8) for SOC. Although this is <3 months, in the context of the poor outcomes of this patient population, it is a clinically significant increase in median OS. – The estimated mean months gained in the economic model, in the ITT population, with pembrolizumab in combination with chemotherapy is 20.3 months compared to 12.7 months with SOC. An expected increase in mean OS of 7.5 months. • CPS≥10 – The median OS difference is greater within the CPS≥10 sub-population. The median OS for pembrolizumab in combination with chemotherapy was 13.5 months (95% CI, 11.1, 15.6) compared to 9.4 months (95% CI 8.0, 10.7) for SOC. This demonstrates an increase in OS of 4.1 months. – The estimated mean months gained in the economic model, in the CPS≥10 population, with pembrolizumab in combination with chemotherapy is 23.0 months compared to 12.4 months with SOC. This is an expected increase in mean OS of 10.6 months.	B.2.6.1 page 41-46

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

An SLR was conducted in two phases; an original search and a subsequent update, to identify relevant cost-effectiveness studies from the published literature. The initial search was conducted on 30th April 2020. An updated search employing the same search strategy of all previously searched bibliographic databases and grey literature was conducted on 24th November 2020.

The search did not identify any cost-effectiveness studies evaluating pembrolizumab in combination with chemotherapy in the specified population. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

B.3.2 Economic analysis

A cost-effectiveness study that met the relevant inclusion criteria for this appraisal was not identified, therefore a de novo cost-effectiveness model was built to assess the cost-effectiveness of pembrolizumab in combination with chemotherapy compared with the relevant comparators.

Patient population

The patient population included in the economic evaluation consisted of patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma. This is in line with the anticipated licence and with the NICE final scope. The patient characteristics were based on the European patients from the KEYNOTE-590 trial and are presented in Table 41, below.

As outlined in Section 2.6, MSD consider the CPS≥10 sub-population to be of particular clinical significance. The base-case population is reflective of the anticipated marketing authorisation, however analyses in the CPS≥10 sub-population is presented within section B.3.9, with the assumptions used within the economic model outlined within Appendix M.

Table 41. Baseline characteristics of patients included in the model

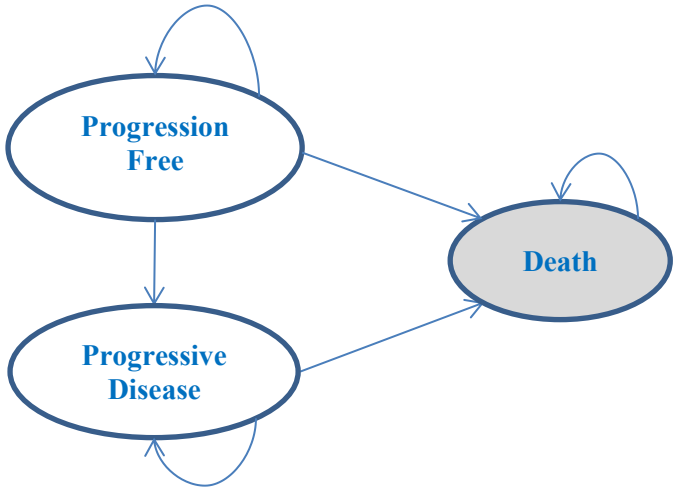
Patient Characteristics	Mean	Measurement of uncertainty and distribution	Reference / Source
Average age (years)*	61.4	SD = 9.3	KEYNOTE-590
Proportion male*	80.7	-	
Average patient weight (kg) *	71.2	SD = 13.5	
Body Surface Area (m^2)	1.84	SD = 0.20	

**These values refer to patients recruited from European sites participating in KEYNOTE-590*

Model structure

The modelling approach for this appraisal is consistent with economic models developed for recent NICE oncology submissions in an advanced cancer setting (33–35), as well as advanced oesophageal cancer in the second-line setting (36). A partitioned survival cohort simulation model was developed to estimate health outcomes and costs for pembrolizumab in combination with chemotherapy and comparator regimens in the target patient population. The transition diagram of the cohort simulation model is presented in Figure 10, below.

Figure 10. Model structure

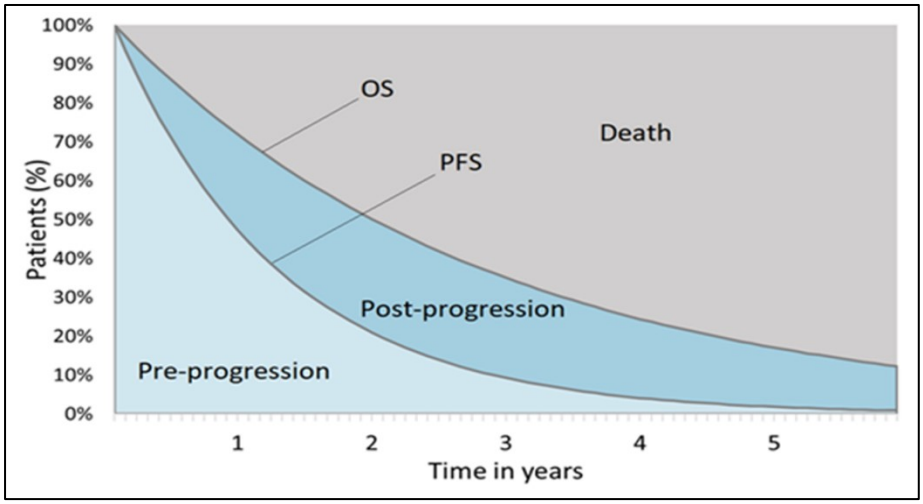


There are three mutually exclusive health states in the model:

- Pre-progression, which is the starting health state, with patients staying in this state until disease progression or death
- Post-progression, which encompasses patients alive after progression and before death
- Death, which is an absorbing health state

Partitioned survival modelling uses an overall survival curve to estimate the proportion of people alive over time directly- either from a parametric distribution or directly from KM trial data (37). The area under the (extrapolated) OS curve provides an estimate of mean life expectancy. OS may be further partitioned into different health states to allow these health states to have different HRQoL and cost implications (37). The model used requires two survival curves to estimate state membership for the model; the area underneath the OS curve represents the proportion of patients that were still alive (both in pre-progression and post-progression) at different points in time, while the proportion of patients in the pre-progression state were identified by the patients located underneath the PFS curve; where progression is defined by the primary censoring rule in KEYNOTE-590 trial (21), i.e. assessment per RECIST 1.1 assessed by investigator (21). Hence, the area between the PFS and the OS represents the proportion of post-progression patients, i.e. those who were in the 'post-progression' health state. Please see Figure 11 below.

Figure 11. Partitioned survival 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 is unlike 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.

For each health state, a specific cost and quality-of-life adjustment weight (i.e. utility) is assigned within each time period 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% in line with NICE reference case (38).

Please see Table 42 below comparing features of economic analysis between this appraisal and previous appraisals. Please note that NICE ID1249 (36) (Nivolumab for previously treated unresectable, advanced oesophageal cancer) is within a different patient population to that of this appraisal and has only been referred to due to the sparsity of Technology Appraisals conducted within an untreated advanced oesophageal population.

Table 42. Features of the economic analysis

	Previous Appraisal	**Current Appraisal**	
	NICE ID1249 (36)	**Chosen values**	**Justification**
	Nivolumab for previously treated unresectable advanced oesophageal cancer	NICE ID3741 Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer	
Time horizon	40 years	20 years	Lifetime horizon for the defined population (NICE reference case)
Treatment waning effect?	None	None- explored within scenario analyses	Due to the short life expectancy and quick progression in these patients, a treatment waning effect is deemed inappropriate. Also, any treatment waning effect is reflected in the extrapolation of OS. In line with NICE ID1249
Source of utilities	ATTRACTION-3 provides EQ-5D-3L data that can be used to derive utility inputs for use in nivolumab and comparator arms.	Utility values collected in KN590 trial using the EQ-5D-5L questionnaire, mapping to EQ-5D-3L using the crosswalk method as per NICE preference (21,22,38,39)	Consistent with NICE reference case
Source of costs	TA378 (40), MIMS (41), NHS reference costs 2018/19 (42), PSSRU (43)	TA378 (40), eMIT (44), NHS reference costs 2018/19 (42)	Resource use was based on previous NICE TAs in oesophageal/gastric cancer (TA378 (40), ID1249 (36)). Unit costs were taken from recognised databases as per the NICE reference case.

Intervention technology and comparators

The intervention (pembrolizumab in combination with chemotherapy) was included in the model as per the proposed licensed dosing regimen (i.e. pembrolizumab administered

intravenously at a fixed dose of 200 mg over 30 minutes up to 35 administrations combined with cisplatin administered intravenously at a dose of 80 mg/m^2 every 3 weeks (Q3W) for 6 doses and 5-FU administered as continuous IV infusion on days 1 to 5 at a dose of 800mg/m^2/day (4000 mg/m^2 total per cycle) Q3W, up to 35 administrations).

The proposed licence states that pembrolizumab has to be administered until PD or unacceptable toxicities or for a maximum of 35 doses (2 years).

The decision problem outlined within the final scope issued by NICE determined the following to be comparators of relevance:

Platinum-based chemotherapy without pembrolizumab, such as:

- *doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin*
- *triplet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin epirubicin*

This includes the KEYNOTE-590 trial comparator, cisplatin in combination with 5-FU.

The NICE Guideline in the assessment and management of Oesophago-gastric cancer in adults (NG83)(12) outlines the difference in evidence between the different combinations (see Section 9.2.6). Comparisons 2, 7 and 8 are the most relevant for this appraisal:

Table 43 Summary of NG83 Section 9.2.6

Comparison Number	Comparison	Overall Survival	Progression Free Survival
2	5-FU/cisplatin combinations with or without anthracycline	Moderate quality evidence from 2 RCTs with 167 people with oesophago-gastric cancer indicate there is no clinically significant difference in overall survival in groups treated with 5FU/cisplatin/anthracycline versus 5-FU/cisplatin alone (HR 0.70, 95% CI: 0.43-1.15).	Moderate quality evidence from 1 RCT with 91 people with oesophago-gastric cancer indicate there is no clinically significant difference in progression-free survival in groups treated with 5-FU/cisplatin/anthracycline versus 5-FU/cisplatin alone (HR 0.95, 95% CI: 0.58-1.57).
7	Cisplatin versus oxaliplatin combinations	Moderate quality evidence from 2 RCTs with 1222 people with oesophago-gastric cancer indicated no clinically significant difference in overall	Low quality evidence from 2 RCTs with 1222 people with oesophago-gastric cancer indicated there is no clinically significant difference in

		survival in groups treated with oxaliplatin combinations compared with cisplatin combinations (HR 0.91, 95% CI: 0.80-1.04).	progression-free survival in groups treated with oxaliplatin combinations compared with cisplatin combinations (HR 0.90, 95% CI: 0.79-1.02).
8	5-FU combinations versus non-5-FU combinations	Moderate quality evidence from 2 RCTs with 400 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in overall survival in groups treated with 5-FU combinations compared to non-5-FU based combinations (HR 0.59, 95% CI 0.46-0.75).	Low quality evidence from 1 RCT with 146 people with oesophago-gastric cancer indicated a clinically significant beneficial effect in overall survival in groups treated with 5-FU combinations compared to non-5-FU cisplatin based combinations (HR 0.56, 95% CI 0.39-0.81).

As evidenced by NG83, comparison 2 shows the addition of an anthracycline (e.g. epirubicin) is not associated with a clinically significant difference in OS. Comparison 7 suggests that there is no clinically significant difference in overall survival in groups treated with oxaliplatin combinations compared with cisplatin combination. Furthermore, comparison 8 suggests that treatment with 5-FU combinations indicated a clinically significant benefit in OS when compared with groups treated with non-5-FU based combinations. The REAL-2 study further evidenced that capecitabine is similar to flurouracil, and oxaliplatin is similar to cisplatin, in terms of efficacy.

MSD sought clinical expert opinion to gain a greater understanding of the relative efficacies of the different combination therapies recommended by NICE. The clinical experts agreed that there was no difference in terms of efficacy between the doublet therapies. Furthermore, the addition of epirubicin (an anthracycline) added little efficacy benefit, with a considerable impact on toxicity. This was further verified at an advisory board, held virtually on the 29th January 2021.

As stated in section B.2.9, due to the difficulties in conducting an NMA, the approach undertaken to compare versus non-trial comparators which are used within UK clinical practice, is to assume clinical equivalency with the trial comparator (cisplatin in combination with 5-FU). This simplifying assumption is supported by NG83 and clinical expert opinion, given the clinician advice, the impact of this assumption is anticipated to be minimal and is investigated within scenario analyses. The base case comparison will be conducted versus the trial comparator, with comparisons versus each therapy as outlined by the NICE Final

Scope (45), and a blended comparator (assuming equal distribution) investigated within scenario analyses.

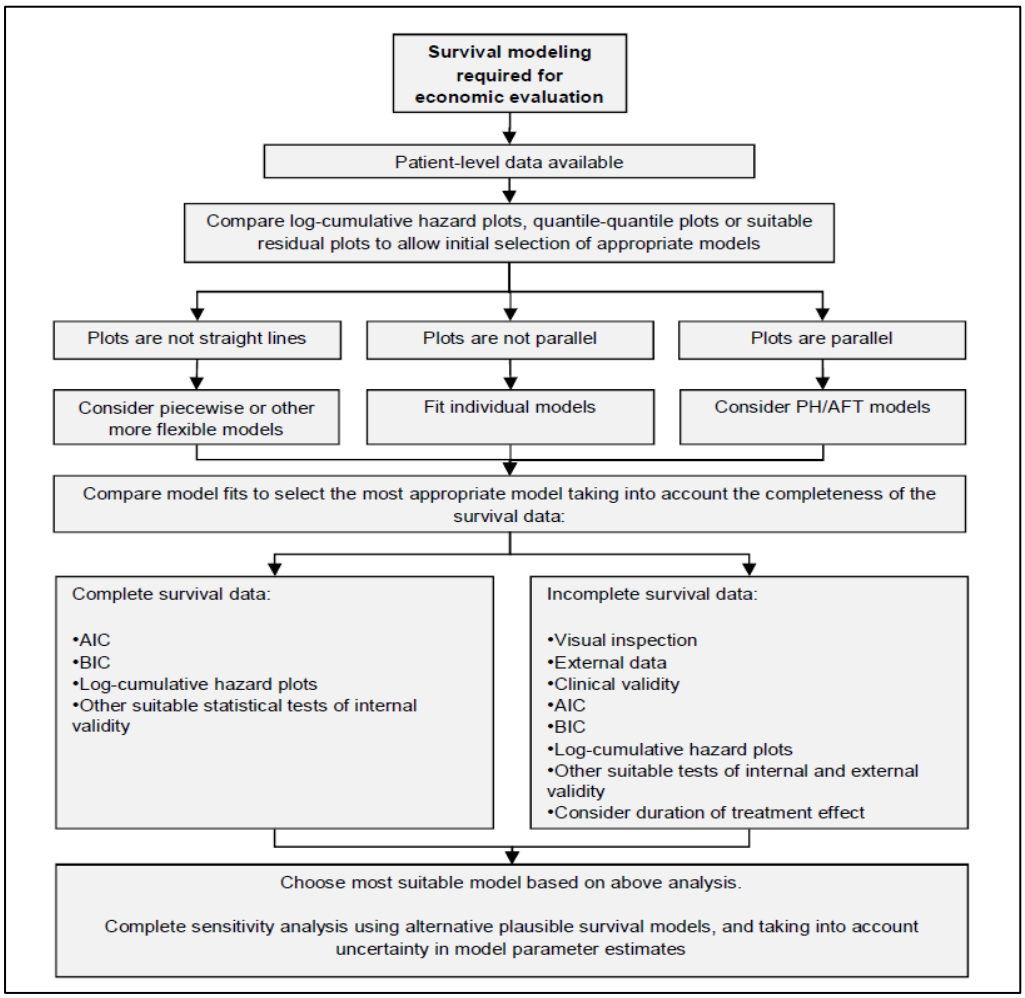
B.3.3 Clinical parameters and variables

Method of modelling effectiveness

The clinical effectiveness parameters for pembrolizumab in combination with chemotherapy and SOC in the cost-effectiveness model were estimated from the KEYNOTE-590 patient-level data on OS, PFS and adverse event rates.

The follow-up period of KEYNOTE-590 was shorter than the time horizon of the economic model, therefore, extrapolation of the OS and PFS curves was required. Parametric models were fitted to the KEYNOTE-590 KM data. The survival curve fitting was carried out in line with NICE Decision Support Unit (DSU) guidelines outlined in Technical Support Document 14 (46). In summary, the steps that were followed are presented in Figure 12 below.

Figure 12. Survival model selection process algorithm (adapted from TSD 14)(46)



AFT: Accelerated failure time; AIC: Akaike information criterion; BIC Bayesian information criterion; PH: Proportional hazards

Modelling OS

As KEYNOTE-590 (21) is a comparative phase III trial, patient-level data are available for both arms of the study. The cumulative and log cumulative hazard plots can be found in Figure 13 and Figure 14, respectively.

The log-cumulative hazard plots allow an assessment of whether the proportional hazards assumption is reasonable (37). As seen in Figure 14, the plots of the two arms are not parallel, as the plots cross, suggesting the proportional hazard assumption does not hold; hence a pooled parametric curve was deemed inappropriate. Furthermore, given the availability of IPD and the different mechanisms of action of pembrolizumab in combination with chemotherapy and SOC, parametric survival models were fitted separately to each treatment arm, as this approach required fewer assumptions than jointly fitted models.

Figure 13. Cumulative hazard plot of OS for pembrolizumab in combination with chemotherapy and SOC

Key: Pembrolizumab + Chemotherapy red; SOC blue

Figure 14. Log-cumulative hazard plot of OS for pembrolizumab + chemotherapy and SOC

Key: Pembrolizumab + Chemotherapy red; SOC blue

Two modelling approaches were used to estimate OS. The fully fitted modelling approach fits parametric models to the entirety of the KM data. Conversely, in the piecewise modelling approach, KM data is used directly within the model up to the point of the cut-off (week 32 or week 40), after which a parametric curve is fitted to the remaining KM data and used to estimate OS beyond the trial period. Both approaches utilised IPD from KEYNOTE-590.

The fully fitted parametric models have poor visual fit versus piecewise models. All fully fitted parametric models, including the statistically best-fitting log-logistic curve based on AIC/BIC statistics, underestimated the observed OS KM data in the first 8 months for both arms. Literature suggests that 5-year overall survival for stage IV oesophageal cancer is around 5% (47,48). The best-fitting one-piece log-logistic distribution underestimated 5-year survival for the trial comparator arm.

The two cut-offs at week 32 and week 40 for the piecewise models were identified based on structural changes observed by the Chow tests (see Figure 15), with higher Chow test statistics indicating a higher likelihood of structural change (49,50). Please note the Chow test statistics for the SOC arm proved inconclusive for determining an appropriate cut-off. The peak for the Chow test statistic was observed around week 40, the statistics are observed a smaller peak at around week 32. The piecewise model using the week 40 cut-off was selected as the base case given it is associated with the highest Chow test statistics. The Week 32 cut-off was explored in the scenario analysis.

Figure 15. Plot of multiple Chow test statistics for OS in KEYNOTE-590: pembrolizumab in combination with chemotherapy, overall population

For consistency, the Week 40 cut-off was selected for both the pembrolizumab in combination with chemotherapy and the SOC arms. Parametric survival extrapolations and the observed Kaplan–Meier data within the trial period are presented in

Figure **16** for the pembrolizumab in combination with chemotherapy arm and in Figure 17 for the SOC arm.

Figure 16. OS KM curve with fitted piecewise model, 40-week cut-off, for pembrolizumab + chemotherapy based on KEYNOTE-590

Figure 17. OS KM curve with fitted piecewise model, 40-week cut-off, for SOC based on KEYNOTE-590

Statistical tests using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to help select the best-fitting parametric distribution based on internal validity. Table 44 below details the AIC/BIC statistics for both pembrolizumab in combination with chemotherapy and SOC.

Table 44. Summary of goodness-of fit qualities of OS models for pembrolizumab in combination with chemotherapy and SOC

Arm	Functional form	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized Gamma	Best Fitting
Pembrolizumab + chemotherapy	AIC	1310.17	1307.14	1306.59	1306.10	1306.34	1307.13	**Log-logistic**
	BIC	1313.62	1314.03	1313.49	1312.99	1313.23	1317.47	**Log-logistic**
SOC	AIC	1306.55	1307.53	1302.00	1302.97	1305.08	1303.64	**Log-normal**
	BIC	1309.83	1314.10	1308.57	1309.54	1311.64	1313.49	**Log-normal**

Key: 5-FU, fluorouracil; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.
Source: KEYNOTE-590 (data cut-off date: July 2, 2020).

The AIC/BIC statistics suggested that for pembrolizumab in combination with chemotherapy the best fitting distribution is the log-logistic function. For the SOC arm the best fitting distribution is the log-normal function. Notably, the gompertz distribution leads to clinically implausible outcomes.

However, as the modelled period is longer than the length of KM data, the external validity is also important for considering parametric curve selection. To help with the selection and validation of base case parametric survival models for extrapolation, a targeted literature search was conducted to identify studies reporting long-term OS for advanced and metastatic oesophageal cancer (47,51):

- A pan-European study based on oesophageal patients diagnosed between 1995 and 1999 and followed up to 2003 in 66 cancer registries in 24 European countries, including the UK, reported a 5-year survival rate of 3.8% for patients with distant stage oesophageal cancer (52).
- A 5-year survival rate of 5% for distant oesophageal cancer was reported by the American Cancer Society based on the US Surveillance, Epidemiology, and End Results (SEER) database for people diagnosed with oesophageal cancer between 2009 and 2015 (47,51). Similar estimates were reported by other publications using

stage IV oesophageal patients in the SEER database between 2010 and 2014 (53). Based on metastatic oesophageal patients in the SEER database between 1988 and 2012, Wu et al. reported 5-year and 10-year survival rates of 5.4% and 3.5% (54).

- In a small single-site retrospective study in Japan of 80 ESCC patients with distant organ metastasis, the 5-year survival rate of less than 5% was reported (55).

Table 45. Long term Overall Survival estimates for SOC

	KM	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized Gamma
3 month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 year		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 year		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 year		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 46. Long term Overall Survival estimates for pembrolizumab in combination with chemotherapy

	KM	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized Gamma
3 month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20 year		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the pembrolizumab in combination with chemotherapy arm, the log-logistic model has the best AIC and BIC and good visual fit within the trial period when compared with the observed Kaplan–Meier data. For the SOC arm, the log-logistic model has the second best-fitting AIC and BIC (with a difference of less than 1 versus the log-normal model that has the best-fitting AIC and BIC) and good visual fit. The log-logistic curve's tail was considered by clinical experts to be more credible based on the expectation that a percentage of patients would derive a

long-term survival benefit from treatment with pembrolizumab in combination with chemotherapy.

The log-logistic curve with a cut-off at 40 weeks provides the most clinically plausible prediction for a survival rate of 4.8% and 2.0% at 5-years and 10-years for the SOC arm compared with available external data (see Table 45)(47,48). The long-term extrapolation for the pembrolizumab in combination with chemotherapy arm (5-year OS of 11.4% see Table 46) was also considered as clinically plausible by clinical experts, based on the mechanism of action for immunotherapy where a subgroup of patients are expected to receive long-term survival benefit.

Taking all of these factors into consideration; visual fit, statistical fit, clinical plausibility of long-term OS estimates, the piecewise log-logistic model with a cut-off at week 40 was used to model OS for both the intervention and comparator arms.

Figure **18** and Figure 19 below show the extrapolated OS over a 5-year period and a lifetime horizon of 20 years. Please see Appendix M for a description of modelling OS in the CPS≥10 sub-population.

Figure 18. OS KM curves with fitted piecewise parametric models with a 40-week cut-off for the OS of pembrolizumab in combination with chemotherapy and SOC based on KEYNOTE-590 over a 5-year period

Figure 19. OS KM curves with fitted piecewise parametric models with a 40-week cut-off for the OS of pembrolizumab in combination with chemotherapy and SOC based on KEYNOTE-590 over a lifetime horizon (20-year period)

Modelling PFS

PFS data from KEYNOTE-590 was relatively complete with over 90% of patients in each arm having reach the PFS endpoint. Based on the KEYNOTE-590 trial protocol (21), the first post-randomisation imaging was conducted at week 9 (± 1 week) with subsequent imaging being performed every 9 weeks (± 1 week) or more frequently if clinically indicated. Visual inspection of the KM PFS curves revealed a steep drop at around week 9 in both arms of KEYNOTE-590 data (22), reflecting the first protocol-scheduled tumour imaging assessment at 9 weeks (± 1 week). Prior to the first imaging only a small proportion of patients enrolled in KEYNOTE-590 reached the PFS endpoint, therefore, piecewise models with 10-week cut-off were selected as the base case approach for extrapolating PFS. In this approach the hazards rates for PFS failure are obtained directly from the KM curve up to week 10 followed by parametric models fitted to the post- week 10 data. To identify the most plausible PFS curve extrapolation among the standard parametric curves, the guidance from the NICE DSU was followed (46). Figure 20 and Figure 21 below display the PFS 10-week piecewise models for pembrolizumab in combination with chemotherapy and SOC.

Figure 20. PFS KM curve vs. fitted piecewise parametric curves for pembrolizumab in combination with chemotherapy

Figure 21. PFS KM curve vs fitted piecewise parametric curves for chemotherapy

Statistical tests based on the AIC and the BIC, combined with visual inspection were used to help select the best-fitted parametric distribution based on internal validity. Table 47 reports the AIC/BIC statistics for the PFS curve extrapolations for both pembrolizumab in combination with chemotherapy and chemotherapy alone.

Table 47. Summary of goodness-of-fit qualities of the piecewise PFS models for pembrolizumab in combination with chemotherapy and chemotherapy

Arm	Functional form	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalized Gamma	Best Fitting
Pembrolizumab + chemotherapy	AIC	2264.06	2264.88	2242.46	2227.85	2261.66	2241.97	Log-logistic
	BIC	2267.75	2272.26	2249.84	2235.23	2269.04	2253.04	Log-logistic
SOC	AIC	2157.88	2149.25	2172.01	2127.63	2159.82	2141.98	Log-normal
	BIC	2161.55	2156.59	2197.34	2134.97	2167.15	2152.98	Log-normal

Key: 5-FU, fluorouracil; AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Source: KEYNOTE-590 (data cut-off date: July 2, 2020).

The best statistical fit according to AIC/BIC criterion for both treatment therapies is the log-logistic distribution (see Table 47), the second-best fitting curve for both arms being the generalised gamma distribution. Given that the KEYNOTE-590 PFS data is sufficiently mature, the primary method for the validation of the KM curve extrapolation is visual inspection and the AIC/BIC statistical tests, therefore the curves with the lowest scores were considered.

The base case for modelling PFS was a piecewise modelling approach; using KM data up to a cut-off of 10 weeks, followed by a log-logistic distribution. From Figure 20 and Figure 21 above, it is evident that the different extrapolation methods yield similar results due to the maturity of the data, as a result, the progressed proportion of patients is relatively insensitive to the choice of distributions used to extrapolate the KM data.

The modelled PFS curves used in the base-case analysis described above are presented in Figure 22 below. Please see Appendix M for a description of modelling PFS in the CPS≥10 sub-population.

Figure 22. PFS KM curves fitted with log-logistic curves from 10 weeks (base case)

Adverse Events

The AEs considered in the economic model include grade 3+ all-cause adverse events occurring in at least 5% of patients. The approach used to identify the relevant AEs to be included in the economic model has been previously validated by clinical experts.

The incidence of AEs was ascertained from the KEYNOTE-590 trial (22). Table 48 below presents the AEs included in the model and the proportion of patients who experience them. The AE profile for the blended chemotherapy arm was assumed to be equivalent to that of the comparator arm in the KEYNOTE-590 trial. MSD considers this to be a conservative approach given that clinical expert opinion suggests that triplet therapies (a proportion of which makes up the blended comparator arm) are associated with an increased incidence of adverse events. The unit costs and disutilities associated with each of the individual AEs were assumed to be the same across the different treatment arms; therefore, the difference in costs and disutilities associated with AEs in the model is driven by the AE rates displayed in Table 48 below. This approach is consistent with methods used in previous oncology submissions (33,34) and ensures that the full cost and HRQoL impact associated with AEs are captured within the model for all treatment arms without discounting.

In the base case, the impact of AEs was incorporated by estimating weighted average costs per patient, applied as a one-off cost. These were then applied in the first cycle of the model for each treatment arm, the same approach was taken for disutility associated with AEs.

Table 48. Grade 3+ AE rates for AEs included in the model

AEs (Grades 3+)	Pembrolizumab + chemotherapy	SoC	Blended chemotherapy		
N=	370	370	Yoon 2016 (56)	Cleary 2019 (57)	Waddell 2013 (58)
Anaemia	17.0%	21.9%	0.0%	0.0%	5.6%
Decreased appetite	4.1%	5.4%	0.0%	0.0%	0.0%
Dysphagia	7.8%	7.0%	4.8%	0.0%	0.0%
Fatigue	7.8%	6.8%	4.8%	15.0%	0.0%
Hypokalaemia	6.5%	8.6%	0.0%	0.0%	0.0%
Hyponatraemia	12.2%	11.1%	4.8%	2.5%	0.0%
Nausea	7.3%	7.0%	19.1%	36.3%	27.8%
Neutropenia	14.6%	16.5%	4.8%	0.0%	0.0%
Neutrophil count decreased	24.1%	17.3%	0.0%	2.5%	4.1%
Platelet count decreased	1.9%	5.4%	0.0%	0.0%	0.0%
Pneumonia	9.5%	9.5%	0.0%	0.0%	0.0%

Stomatitis	5.7%	3.8%	0.0%	0.0%	8.7%
Vomiting	7.3%	5.4%	0.0%	1.3%	0.0%
Weight decreased	3.0%	5.1%	0.0%	0.0%	0.0%
White blood cell count decreased	9.2%	4.9%	0.0%	0.0%	5.6%

Mean durations of the all-cause AEs were based on KEYNOTE-590 and were used together with AE rates and AE disutility to estimate the QALY decrements of each modeled arm due to AEs. The all-cause AE durations are assumed to be the same for all modelled arms and are presented in Table 49 below.

Table 49. Duration of Grade 3+ AEs in KEYNOTE-590

	Mean duration (weeks)	SD	N
All-cause AEs	8.24	15.8	2246
Key: AE, adverse event; SD, standard deviation; N, number. Source: KEYNOTE-590 (data cut-off date: July 2, 2020).			

B.3.4 Measurement and valuation of health effects

Health-related quality-of-life (HRQoL) data from clinical trials

HRQoL of patients with advanced oesophageal cancer

The health-related quality-of-life of patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma is likely to be heavily impaired due to the debilitating nature of the disease. Often patients have difficulty eating, and swallowing can also become difficult- leading to weight loss (59). Furthermore, as the cancer grows it can block or partially block the oesophagus, preventing food entry through the gut and hence the absorption of nutrients and calories. If patients are not able to eat and drink, they become more susceptible to other problems such as infection. Patients can also often feel fatigued and lacking in energy, with the emotional and physical changes affecting patients' relationships (59). These factors exacerbate as a patient comes closer to death, alongside other physical changes such as being semi-conscious, loss of bladder and bowel control, restlessness, changes in breathing and confusion (60,61).

Evaluating HRQoL in KEYNOTE-590

HRQoL was evaluated in the KEYNOTE-590 trial using EuroQoL EQ-5D-5L. The latest position statement on the use of EQ-5D-5L value set for England by the National Institute for Health and Care Excellence (NICE) does not recommend using the EQ-5D-5L value set for English technology appraisals (62), and prefers utility values to be calculated by mapping the EQ-5D-5L descriptive system data onto the EQ-5D-3L value set using the mapping function developed by van Hout et al. (2012) in the reference (39). This approach was taken, and the results of this analysis have been used to inform inputs for the cost-effectiveness model.

In KEYNOTE-590, for both arms, the EQ-5D-5L questionnaire was administered on day 1 of every cycle from cycles 1 to 9, after which it was administered every 3 cycles for up to 1 year or until the end of treatment, whichever occurred first (21). The EQ-5D-5L data were also collected at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit. A visit window of ±7 days were applied to EQ-5D-5L visit assessments.

The analyses of the EQ-5D-5L utilities were based on the Full Analysis Set (FAS) population for EQ-5D-5L questionnaire. The FAS population comprised of subjects who were randomized, received a study treatment, and completed at least one EQ-5D-5L questionnaire. Subjects were analysed in the treatment group allocated at randomization. The EQ-5D-5L FAS population included a total of 713 subjects.

HRQoL Utility approaches

The base-case used within the economic model is to apply time-to-death utilities. This approach is the most valid in such a rapidly progressing cancer, where patients deteriorate quickly as they get closer to death, hence a single utility value to homogeneously represent the post-progression period is less appropriate than in a cancer with a slower deterioration We recognise that health state based utilities according to progression status will also be of interest to the NICE committee; these have been included in a scenario analysis. The methodology employed is described below.

- Estimation of utilities based on time-to-death

  This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. This approach to define health state utilities based on time to death was developed by Batty et al. (2011) (63) and Hatswell et al. (2014) (64), which reflects the decline in the quality of life for patients with advanced or metastatic cancer as they approach death. It has previously been used in the estimation of

HRQoL in patients with advanced NSCLC who had previously received platinum-based chemotherapy or palliative radiotherapy (65–68) and in advanced melanoma (63,64) patients.

A time-to-death approach more accurately capturing the decrease in health-related quality of life over time (versus standard progression-based utilities) for patients with advanced oesophageal cancer. Hatswell et al (64) noted that disease progression may not fully capture all predictive factors of patient utility and time-to-death provides a good fit to patient data.

The time to death utility approach was accepted and deemed appropriate in multiple metastatic cancer HTA submissions to NICE and in a number of other pembrolizumab submissions to NICE in other metastatic cancer settings (e.g. TA531 (69), originally TA447 (70)).

Moreover, the utility estimate for progressed disease in the standard progression-based approach is limited in reflecting the patient experience. EQ-5D utility data collected were collected within KEYNOTE-590 for up to one year, or until the end of treatment, whichever came first; the EQ-5D data were also collected at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit. Therefore, data were collected for newly progressed patients but not for those whose condition had deteriorated. The application of time-to-death utilities mitigates this issue by basing utility valuations on time-to-death (regardless of whether death arises from a progression-free or progressive disease state) rather than by progression status.

An important limitation of the time-to-death approach is that the records measured within 360 days from OS censoring date cannot be assigned to a time-to-death category due to uncertain death date. However, for KEYNOTE-590 (22), by the data cut-off date of July 2, 2020, 571 of 749 patients (76.2%) in the intention-to-treat population had a known death date. Amongst all 5744 EQ-5D-5L measures, only 318 (5.54%) had unknown time-to-death category. For this analysis, the uncertainty in the utility by time-to-death approach due to unknown death dates is relatively low and hence the results can be deemed to be largely representative of the patient population.

In this analysis, the linear mixed-effects regression model included indicators for time to death (i.e. 0-29, 30-89, 90-179, 180-359, or ≥ 360 days until death) and the

presence/absence of any Grade 3+ AEs, as well as patient-level random effects to account for correlation between repeated measurements of the same patient.

In the model, utilities were applied based on the distribution of patients across different categorizations 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.

- Estimation of utilities based on progression-free and progressed disease states.

This approach, commonly seen in previous oncology economic modelling literature, defines health states based on time relative to disease progression (33,71). This approach generates results to be used in the economic model by health state. As previously mentioned, a limitation of this approach is attributed to the distribution and collection of EQ-5D questionnaires within KEYNOTE-590. EQ-5D utility data post-progression were only collected at the point of treatment discontinuation and at the 30-day post-treatment discontinuation follow-up visit. Therefore, post-progression utility data is limited, and unlikely to accurately reflect the rapid deterioration of patients' quality of life in this cancer. Due to the paucity of data within this disease area, it is not possible to substitute utility values from the literature to alleviate this issue. The reference case asserts a preference for using utility data ascertained from the relevant clinical trial, hence using utility values sourced from the literature, as a substitute, would require substantial justification as utility data from KEYNOTE-590 is available. Due to this limitation, the post-progression utility is not representative of the lived experience of patients in their terminal month; hence utilities reported by the time-to-death approach are considered a more accurate measure of HRQoL.

The date of progression was determined via RECIST 1.1 per investigator assessment (21). To estimate utilities:

  - for the progression-free health state, EQ-5D scores collected at all visits before the progression date were used.
  - for the progressive disease health state, EQ-5D scores collected at all visits after the progression date were used.

Utility in both the progression-free state and the progressive disease were estimated by the linear mixed-effects model. The model included indicators for progression-based health states (progression-free vs progressive disease) and the

presence/absence of any Grade 3+ AEs. The same utilities were applied to all treatment arms in the model and also for all subgroups.

Please see the results of both methods in Table 50 and Table 51 below.

Table 50. EQ-5D health utility scores by time-to-death

	Pooled (N=**713**), number of observations: 5744		
	Estimate	SE	95% confidence interval
≥360 days	[redacted]	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]	[redacted]
90 to 180 days	[redacted]	[redacted]	[redacted]
30 to 90 days	[redacted]	[redacted]	[redacted]
0 to 30 days	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]

Table 51. EQ-5D health utility scores by progression status (pooled)

	Pooled (N=**713**), number of observations: 5744		
	Estimate	SE	95% confidence interval
Progression-free	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]

Collection of EQ-5D questionnaires

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab in combination with chemotherapy and SOC arms), and pooled for both arms. In addition, 95% CIs were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested. The level of EQ-5D compliance through time is presented in Table 52.

Table 52. Compliance of EQ-5D by visit and by treatment (FAS Population)

Treatment Visit	Category	Pembrolizumab + Cisplatin + 5-FU	Cisplatin + 5-FU
		N = 367	N = 360
Baseline	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 3	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 6	Expected to complete questionnaires	[redacted]	[redacted]

Treatment Visit	Category	Pembrolizumab + Cisplatin + 5-FU	Cisplatin + 5-FU
		N = 367	N = 360
	Completed		
	Compliance(completed per protocol)*		
Week 9	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 12	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 15	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 18	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 21	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 24	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 33	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 42	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 51	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 60	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 69	Expected to complete questionnaires		
	Completed		
	Compliance(completed per protocol)*		
Week 78	Expected to complete questionnaires		
	Completed		

Treatment Visit	Category	Pembrolizumab + Cisplatin + 5-FU	Cisplatin + 5-FU
		N = 367	N = 360
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 87	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 96	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 105	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]
Week 114	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance(completed per protocol)*	[redacted]	[redacted]

**Compliance is the proportion of subjects who completed the PRO questionnaire among those who are expected to complete it at each time point (excludes those missing by design).*
Missing by design includes: death, discontinuation, translations not available, and no visit scheduled.
(Database Cut-off Date: 2nd July 2020).

Mapping

In KEYNOTE-590 (21), the EQ-5D-5L (72) instrument was used to measure generic health status. It contains five health state dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension is rates on a 5-point scale from 1 (no problems) to 5 (extreme problems).

The latest position statement on the use of EQ-5D-5L value set for England by NICE does not recommend using the EQ-5D-5L value set for England. The EQ-5D-5L data collected in the trial can be converted to population-based utility valuations using published algorithms, and the NICE position statement recommends calculating utility values by mapping the EQ-5D-5L descriptive system data onto the EQ-5D-3L value set using the mapping function developed by van Hout et al. (2012). In this analysis, health state utilities were estimated based on

mapping EQ-5D-5L data collected in KEYNOTE-590 to EQ-5D-3L value set using the mapping function from van Hout et al. (2012), as per NICE's recommendation (39,62).

Health-related quality-of-life studies

Please see Appendix H for a list of the studies identified through the SLR.

Adverse reactions

AE-related disutility was applied as a one-time QALY decrement in the first model cycle (i.e. Week 0). Disutility associated with AEs per patient was calculated in each treatment arm as a function of: the rates of included AEs in the treatment arm (Table 48), the mean duration of AEs (Table 49), and the estimated disutility associated with Grade 3+ AE based on the time-to-death approach.

Table 53. One-off QALY decrements due to Grade 3+ AEs by treatment arm

	Pembrolizumab + chemotherapy	SOC
Average disutility per patient due to Grade 3+ AEs	[redacted]	[redacted]

Key: 5-FU, fluorouracil; AE, adverse event; QALY, quality-adjusted life year.

Age-related disutility

The model considered additional age-related utility decrements as the modelled population ages over the modelled time horizon. The age decrements were calculated as the relative change of the general population utility at the modelled age compared with the utility at the starting age (Table 41). The calculated age adjustments were then applied to the estimated time to deaths or progression-based utility values in the model. The UK age-related general population utility were derived from the literature (73).

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

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

Time to death (days)	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
≥360	[redacted]	[redacted]	3	Utility values from KEYNOTE-590 (Data cut: July 2020), in line with NICE reference case
[180, 360)	[redacted]	[redacted]		
[90, 180)	[redacted]	[redacted]		
[30, 90)	[redacted]	[redacted]		
<30	[redacted]	[redacted]		
Disutility for Grade 3+ AE	[redacted]	[redacted]		

AE, adverse Event

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

Details of the systematic review conducted as part of the appraisal for the identification of relevant cost and health care resource use data to populate the model can be found in Appendix I.

Intervention and comparators' costs and resource use

Drug Costs

The drug acquisition costs per treatment are presented below, with the unit costs for comparators being taken from the electronic market information tool (eMit)(44) which provides information about prices for generic drugs based on the average price paid by the NHS over the last four months. If comparators' drug costs were not available from eMIT, the costs from the British National Formulary (BNF)(74) were used. When multiple vial/package sizes were available, the lowest price per mg was applied as a conservative assumption.

Intervention – Pembrolizumab in combination with chemotherapy

- **Pembrolizumab**

As per the anticipated licence, the model uses a 200mg fixed dose of pembrolizumab, administered as a 30-minute IV infusion every three weeks (Q3W), this is the current dose of pembrolizumab that is available in clinical practice for other indications (75). The list price of a 100mg vial of pembrolizumab is £2,630.00. Therefore, the drug cost for pembrolizumab per administration is £5,260 based on two 100mg vials using the list price. [redacted]

- **Cisplatin**

As per the anticipated licensed dosing regimen for the proposed indication, the model incorporates the administration of cisplatin (in combination with pembrolizumab and 5-FU). The dose of cisplatin administered to patients within the model is 80mg/m^2 intravenously on a Q3W basis. The cost of cisplatin per cycle is £9.06, the calculation to derive this cost is shown

in Table 55 below and is based on the average patient BSA observed in KEYNOTE-590 (see Table 41).

- **5-FU**

As per the anticipated licensed dosing regimen for the proposed indication, the model incorporates the administration of 5-FU (in combination with pembrolizumab and cisplatin). The dose of cisplatin administered to patients within the model is 800mg/m^2/day intravenously on each of days 1 to 5 of a Q3W cycle. The cost of 5-FU per cycle is £5.11, the calculation to derive this cost is shown in Table 55 below and is based on the average patient BSA observed in KEYNOTE-590 (see Table 41).

Comparators

The comparators considered in the cost-effectiveness model are cisplatin in combination with 5-FU (KEYNOTE-590 trial comparator) and blended chemotherapy. The doses of cisplatin and 5-FU are the same as the doses seen in the pembrolizumab/chemotherapy combination.

A blended chemotherapy arm is included in the model which accounts for all therapies listed in the NICE scope. An assumption has been made such that the costs of the each of the components within the blended chemotherapy arm is weighted equally. In addition to this, comparisons between pembrolizumab in combination with chemotherapy and the individual regimens included in the blended chemotherapy arm has been explored as a scenario analysis.

The dosing of the regimens in the model is based on the KEYNOTE-590 trial protocol whenever available. Dosing of the non-trial comparators was based on the SmPC (76–80) and other relevant guidelines. The drug costs per administration are calculated based on body surface area (BSA), which is assumed to be 1.84m^2. This is based on the mean BSA for patients recruited in the KEYNOTE-590 trial. A conservative assumption made in the model is that full vial sharing takes place for all comparators hence wastage costs are not incorporated. Table 55 below shows the calculation of the costs for the therapies included in the model.

Table 55. Acquisition costs for drugs considered in first-line therapy

Drug	Dose per administration	Dose frequency	Total dose	Cost per mg	Cost per administration	Dose reference	Cost reference
Pembrolizumab	200mg	Q3W	200mg	£26.30	£5,260.00	SmPC	BNF

Cisplatin	80mg/m^2	Q3W	147.2mg	£0.07	£9.80	SmPC	eMIT
5-FU	800mg/m^2/day (for 5 days)	Q3W	7,360mg	£0.001	£5.53	SmPC	eMIT
Oxaliplatin	130mg/m^2	Q3W	239.2mg	£0.09	£20.74	CAPOX Regimen	eMIT
Capecitabine*	1000mg/m^2 twice a day	Q3W	51,520 mg	£0.0004	£20.78	SmPC	eMIT
Epirubicin	50mg/m^2	Q3W	92mg	£0.10	£8.87	SmPC	eMIT
Leucovorin$	200mg/m^2	Q2W	368mg	£0.01	£1.85	SmPC	eMIT

* Capecitabine is administered for 14 days of each cycle with a 7-day break (21 day cycle).

$ Leucovorin is prescribed as part of the FOLFOX regimen

Time-on-treatment

As per the anticipated licensed indication, patients treated with pembrolizumab in combination chemotherapy are expected to be treated until disease progression or unacceptable toxicity. In line with the KEYNOTE-590 protocol (21), a stopping rule has been implemented in the model whereby patients do not receive pembrolizumab therapy beyond 35 cycles (approximately 2 years). To align with the KEYNOTE-590 trial protocol the duration of treatment for cisplatin and 5-FU has been capped at 6 cycles and 35 cycles, respectively. To estimate the treatment duration of the intervention and comparator arms, time-on-treatment (ToT) KM data from KEYNOTE-590 was used. The use of ToT allows the model to reflect both early discontinuation caused by AEs, alongside other reasons for discontinuation before progression, as well as any additional weeks of treatment received by patients whilst awaiting confirmation of progression.

The ToT data from KEYNOTE-590 is mature, as a result, the base case applied in the model utilises the observed ToT Kaplan-Meier data directly. In scenario analysis, one-piece parametric curves were fitted to the pembrolizumab and 5-FU arms; the best fitting curve based on AIC/BIC and visual inspection was used in the scenario analysis. The ToT for the individual drugs within the blended chemotherapy arm are either assumed to be equivalent to 5-FU or cisplatin from the chemotherapy arm as observed in KEYNOTE-590. Figure 23 and Figure 24 below display ToT for both treatment arms within the KEYNOTE-590 trial.

Figure 23. ToT KM curves for pembrolizumab in combination with chemotherapy based on KEYNOTE-590

Figure 24. ToT KM curve for chemotherapy based on KEYNOTE-590

Blended chemotherapy

As well as comparing to the trial comparator, a comparison was made against a blended comparator arm, assuming equal distribution across each treatment outlined within the NICE Final Scope. Individual comparisons versus each treatment are also presented in section B.3.7.

Relative dose intensity

The model accounts for missed doses and dose reductions for all therapies included in the model, and this is accounted for using the relative dose intensity (RDI), interpreted as a proportion of the protocol dose that participants actually received. An assumption was made that the RDI for capecitabine and epirubicin was equivalent to the RDI of 5-FU in comparator of the KEYNOTE-590 trial. The RDI for oxaliplatin in the model is assumed to be equivalent to that of cisplatin in the comparator arm of KEYNOTE-590 trial arm. Table 56 below displays the RDI for each of the therapies included in the cost-effectiveness model.

Table 56. Relative dose intensities for treatments included in the economic model

Drug	Relative Dose Intensity	Source
Pembrolizumab	[redacted]	KEYNOTE-590 experimental arm
Cisplatin (with pembrolizumab + 5-FU)	[redacted]	KEYNOTE-590 experimental arm
5-FU (with pembrolizumab + cisplatin)	[redacted]	KEYNOTE-590 experimental arm
Cisplatin	[redacted]	KEYNOTE-590 control arm
5-FU	[redacted]	KEYNOTE-590 control arm
Oxaliplatin	[redacted]	Assumed equivalence to cisplatin
Capecitabine	[redacted]	Assumed equivalence to 5-FU
Epirubicin	[redacted]	Assumed equivalence to 5-FU

Administration costs

Drug administration costs include the cost of therapy administration required at each treatment cycle. Costs were sourced from the NHS reference costs 2018-19 (42). Administration costs are applied in the model such that drug administration costs are incurred based on the time on treatment (obtained from KEYNOTE-590) for each therapy included within the model. The relevant cost codes and their associated costs are listed in Table 57 below.

Table 57. Administration costs for regimens included in the economic model

Regimen	Code	Description	Cost
Pembrolizumab + cisplatin + 5-FU	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	£322.88
Cisplatin + 5-FU	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	£322.88
Cisplatin + capecitabine	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	£322.88
Oxaliplatin + 5-FU	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	£322.88
Oxaliplatin + capecitabine	SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance	£263.28
Cisplatin + 5-FU + epirubicin	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	£322.88
Cisplatin + capecitabine + epirubicin	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	£322.88
Oxaliplatin + 5-FU + epirubicin	SB14Z	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance	£322.88
Oxaliplatin + capecitabine	SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance	£322.88

Health-state unit costs and resource use

A comprehensive literature search was conducted on April 30th 2020 with a subsequent update on November 24th 2020 to identify costs and resource use in the treatment and management of oesophageal cancer. Please see appendix I for details of the search strategy and literature identified.

Patients incur different disease management costs dependent on their progression status. Frequency of resource use for the progression-fee health state was based on the expert opinion of UK clinicians whilst the frequencies of resource use for progressive disease were

based on resource use frequencies for a progression-free health state reported in the previous NICE appraisal TA378 (40). The unit costs for the resource use elements were obtained from 2018/19 NHS reference costs (42).

Table 58. Resource use and unit costs of progression-free, progressed health states within the model

	Resource Use	Resource use (per cycle)	Justification	Unit Cost	Reference
PFS	CT Scan	0.08	Clinical expert opinion	£104.36	RD25Z Computerised Tomography, NHS reference costs 2018-19
	Full blood count	0.33		£2.83	DAPS05, NHS reference costs 2018-19
	Renal function test	0.33		£29.47	WH15Z, NHS reference costs 2018-19
	Hepatic function test	0.33		£29.47	WH15Z, NHS reference costs 2018-19
	Consultation visit	0.25		£197.32	WF01A Service code 370, NHS reference costs 2018-19
	Total cost per week			**£78.62**	
PPS	Consultation visit	0.08	TA378	£197.32	WF01A Service code 370, NHS reference costs 2018-19
	Total cost per week			**£16.44**	

Adverse reaction unit costs and resource use

A description of the AEs included in the model and the corresponding frequencies are presented in section B.3.3. The impact of adverse events on HRQoL as part of the cost-effectiveness analysis is described in section B.3.4.

The management costs for each of the AEs is derived from the NHS reference costs 2018-19 (42), with previous NICE appraisals of pembrolizumab being used as a guide to allocate an accurate HRG code (33,71). The costs of treating each AE with and the associated HRG codes and description are provided in Table 59.

Table 59. Unit costs of adverse events

Adverse Event	Code	Description	Cost
Anaemia	SA01G	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	£623.25

Decreased Appetite	FD04A	Nutritional Disorders with Interventions, with CC Score 2+	£301.33
Dysphagia	A13A1	Speech and Language Therapist, Adult, One to One	£108.24
Fatigue	SA01G	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+	£623.25
Hypokalaemia	KC05H	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4	£963.30
Hyponatraemia	KC05H	Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4	£963.30
Nausea	FD10M	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2	£418.64
Neutropenia	SA35A	Agranulocytosis with CC Score 13+	£728.33
Neutrophil Count Decreased	WJ11Z	Other Disorders of Immunity	£474.18
Platelet count decrease	SA12	Thrombocytopenia with CC Score 8+	£620.79
Pneumonia	DZ11P	Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12	£3,449.89
Stomatitis	CB02A	Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 5+	£669.91
Vomiting	FD10M	Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2	£418.64
Weight decrease	N16AF	Specialist Nursing, Enteral Feeding Nursing Services, Adult, Face to face	£108.15
White blood cell count decrease	WJ11Z	Other Disorders of Immunity	£474.18

The cost-effectiveness model applies a one-off AE cost at the beginning of the model. The one-off cost is calculated based on the costs of the adverse events shown in Table 59 weighted by the incidence values set out in Table 48. The weighted one-off cost applied in the model is presented in

Table **60** below.

Table 60. One-off costs of AEs within the model

	Pembrolizumab + chemotherapy	SoC
One-off adverse event cost	£1,061.82	£1,062.08

Miscellaneous unit costs and resource use

Subsequent therapy costs

The economic model applies a one-off cost to account for subsequent therapies, as per the distribution seen with KEYNOTE-590 (22). Both drug acquisition and drug administration costs have been accounted for in the model. Subsequent treatment options were assessed across all subsequent treatment lines and were included if they were received by ≥5% of the patients, the therapies included are presented in Table 61. The previous NICE assessment of TA378 did not recommend ramucirumab for previously treated oesophageal cancer, therefore the distribution of subsequent therapies was reweighted to exclude ramucirumab.

Table 61. Proportion of patients who receive each subsequent treatment (across all subsequent lines ≥5% in any arm)

	Pembrolizumab + chemotherapy	SoC
Patient number	**370**	**370**
Cisplatin	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
5-FU	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]

Table **62** below presents the costs, dosing schedules and treatment duration of each subsequent treatment option. For simplicity, RDIs were not considered and vial sharing was assumed for subsequent treatments, constituting a conservative approach.

Table 62. Dosing schedules, drug acquisition costs, drug administration costs and treatment duration by subsequent therapy

Drug	**Dose** (74)	**Drug Cost** (44)	**Cost per mg**	**Administration Cost (per week)** (42)	**Mean duration of treatment post pembrolizumab + SOC(weeks)** (22)	**Mean duration of treatment post SOC (weeks)** (22)
Cisplatin	80mg/m^2 Q3W	£6.66	£0.07	£107.63	[redacted]	[redacted]
Docetaxel	75mg/m^2 Q3W	£20.96	£0.13	£62.17	[redacted]	[redacted]
5-FU	800mg/m^2 Q3W days 1-5	£1.88	£0.00	£62.17	[redacted]	[redacted]
Irinotecan	180mg/m^2 Q2W	£16.78	£0.03	£93.26	[redacted]	[redacted]
Oxaliplatin	130mg/m^2 Q2W/Q3W	£8.67	£0.09	£129.15	[redacted]	[redacted]
Paclitaxel	90mg/m^2 Q4W, days 1, 8 and 15	£18.88	£0.13	£65.82	[redacted]	[redacted]
Nivolumab*	240mg Q3W	£1,097.00	£10.97	£93.26	-	[redacted]

* The use of nivolumab as subsequent therapy is explored in a scenario analysis.

Table 63 below presents the one-off subsequent therapy costs included in the economic model. The cost is based on the acquisition and administration costs and weighted according to the distribution of subsequent therapies observed in Table 61.

Table 63 One-off subsequent costs applied in the model

Therapy	**Pembrolizumab + cisplatin + 5-FU**	**Cisplatin + 5-FU**	**Blended chemotherapy***
Acquisition Costs	[redacted]	[redacted]	[redacted]
Administration Costs	[redacted]	[redacted]	[redacted]
Total Costs	[redacted]	[redacted]	[redacted]

* Assumed to be equivalent to the cisplatin + 5-FU subsequent therapies

Subsequent therapy (scenario analysis 13)

The NICE appraisal for nivolumab in combination with platinum-based chemotherapy [ID1249] is currently in progress (36). The combination may become available as a treatment option for patients in the second line oesophageal cancer setting. Therefore, a scenario analysis will be conducted whereby all patients who received subsequent therapy post treatment with SOC, will be assumed to received nivolumab monotherapy. The PFS reported in the [ID1246] appraisal has been used as a proxy to apply the mean treatment duration of nivolumab in the second line.

Terminal care costs

The economic model includes an end-of-life cost of £7,630.19. This cost is applied to all patients at the point of death and is reflection of the costs of terminal care. The cost was obtained from TA522 (81) and inflated using indices from the PSSRU (43).

B.3.6 Summary of base-case analysis inputs and assumptions

Summary of base-case analysis inputs

Table 64. Summary of variables applied in the economic model

Parameters	Mean / Deterministic value	Lower	Upper	Distribution used in PSA	Section in the submission document
General Information					
Model cycle length (weeks)	1	-	-	Not varied in PSA	See Section B.3.2
Model time horizon (years)	20	-	-	Not varied in PSA	
Discount rate: Costs	3.5%	-	-	Not varied in PSA	
Discount rate: Health outcomes	3.5%	-	-	Not varied in PSA	
Patient Information					
Patient Age	61.4	59.69	63.11	Normal	See Section B.3.2
Proportion male	80.7	73.0	87.4	Beta	
Average patient weight (kg)	71.2	68.8	73.7	Not varied in SA	
Patient Body Surface Area (m2)	1.84	1.80	1.84	Lognormal	
Utility Inputs					
Utility by time-to-death					
Utility time to death >=360 days	[redacted]	Multivariate Normal			See Section B.3.4
Utility time to death days [180,360)	[redacted]	Multivariate Normal			
Utility time to death days [90,180)	[redacted]	Multivariate Normal			
Utility time to death days [30,90)	[redacted]	Multivariate Normal			
Utility time to death <30 days	[redacted]	Multivariate Normal			
AE-related disutility (pembrolizumab + chemotherapy)	[redacted]	Multivariate Normal			
AE-related disutility (SOC)	[redacted]	Multivariate Normal			
Regimen Related Costs					
Drug costs (per administration)					
Pembrolizumab + 5-FU + cisplatin					See Section B.3.5
Pembrolizumab	£5,260	-	-	Not varied in SA	
5-FU	£3.97	-	-	Not varied in SA	
Cisplatin	£5.71	-	-	Not varied in SA	
5-FU + cisplatin					
5-FU	£4.26	-	-	Not varied in SA	
Cisplatin	£6.39	-	-	Not varied in SA	
5-FU + oxaliplatin + leucovorin					

5-FU	£2.77	-	-	Not varied in SA	
Oxaliplatin	£8.84	-	-	Not varied in SA	
Leucovorin	£1.43	-	-	Not varied in SA	
Capecitabine + cisplatin					
Capecitabine	£15.98	-	-	Not varied in SA	
Cisplatin	£6.39	-	-	Not varied in SA	
Capecitabine + oxaliplatin					
Capecitabine	£15.98	-	-	Not varied in SA	
Oxaliplatin	13.52	-	-	Not varied in SA	
5-FU + cisplatin + epirubicin					
5-FU	£4.47	-	-	Not varied in SA	
Cisplatin	£4.79	-	-	Not varied in SA	
Epirubicin	£6.82	-	-	Not varied in SA	
5-FU + oxaliplatin + epirubicin					
5-FU	£4.47	-	-	Not varied in SA	
Oxaliplatin	£4.79	-	-	Not varied in SA	
Epirubicin	£6.82	-	-	Not varied in SA	
Capecitabine + cisplatin + epirubicin					
Capecitabine	£14.98	-	-	Not varied in SA	
Cisplatin	£4.79	-	-	Not varied in SA	
Epirubicin	£6.82	-	-	Not varied in SA	
Capecitabine + oxaliplatin + epirubicin					
Capecitabine	£14.98	-	-	Not varied in SA	
Oxaliplatin	£13.52	-	-	Not varied in SA	
Epirubicin	£6.82	-	-	Not varied in SA	
Relative Dose Intensities					
Pembrolizumab + 5-FU + cisplatin					See Section B.3.5
Pembrolizumab	[redacted]	[redacted]	[redacted]	Beta	
5-FU	[redacted]	[redacted]	[redacted]	Beta	
Cisplatin	[redacted]	[redacted]	[redacted]	Beta	
SOC					
5-FU	[redacted]	[redacted]	[redacted]	Beta	
Cisplatin	[redacted]	[redacted]	[redacted]	Beta	
Oxaliplatin	[redacted]	[redacted]	[redacted]	Beta	
Capecitabine	[redacted]	[redacted]	[redacted]	Beta	
Epirubicin	[redacted]	[redacted]	[redacted]	Beta	
Leucovorin	[redacted]	[redacted]	[redacted]	Beta	
Administration cost for IV					
Deliver Simple Parenteral Chemotherapy at First Attendance	£186.51	£151.75	£224.80	Gamma	See Section B.3.5
Deliver more complex parenteral chemotherapy at first attendance	£263.28	£214.21	£317.33	Gamma	
Deliver Complex Chemotherapy, including Prolonged Infusional	£322.88	£262.71	£389.16	Gamma	

Treatment, at First Attendance					
Disease Management Costs					
Weekly cost in progression-free state	£78.62	63.97	94.76	Gamma	See Section B.3.5
Weekly cost in progressive disease state	£16.44	13.38	19.82	Gamma	
Cost of PD-L1 test	£42.61	34.67	51.35		
Subsequent treatment cost (following intervention)	£1,809.99	1472.68	2181.56	Gamma	
Subsequent treatment cost (following comparator)	£2,357.46	1918.12	2841.42	Gamma	
Cost of terminal care (one-off cost)	£7,630.19	6208.23	9196.59	Gamma	
% AE Pembrolizumab + chemotherapy					
Anaemia	17.0%	-	-	Not varied in SA	See Section B.3.3
Decreased appetite	4.1%	-	-	Not varied in SA	
Dysphagia	7.8%	-	-	Not varied in SA	
Fatigue	7.8%	-	-	Not varied in SA	
Hypokalaemia	6.5%	-	-	Not varied in SA	
Hyponatraemia	12.2%	-	-	Not varied in SA	
Nausea	7.3%	-	-	Not varied in SA	
Neutropenia	14.6%	-	-	Not varied in SA	
Neutrophil count decreased	24.1%	-	-	Not varied in SA	
Platelet count decreased	1.9%	-	-	Not varied in SA	
Pneumonia	9.5%	-	-	Not varied in SA	
Stomatitis	5.7%	-	-	Not varied in SA	
Vomiting	7.3%	-	-	Not varied in SA	
Weight decreased	3.0%	-	-	Not varied in SA	
White blood cell count decreased	9.2%	-	-	Not varied in SA	
% AE SOC					
Anaemia	21.9%	-	-	Not varied in SA	See Section B.3.3
Decreased appetite	5.4%	-	-	Not varied in SA	
Dysphagia	7.0%	-	-	Not varied in SA	
Fatigue	6.8%	-	-	Not varied in SA	
Hypokalaemia	8.6%	-	-	Not varied in SA	
Hyponatraemia	11.1%	-	-	Not varied in SA	
Nausea	7.0%	-	-	Not varied in SA	
Neutropenia	16.5%	-	-	Not varied in SA	
Neutrophil count decreased	17.3%	-	-	Not varied in SA	
Platelet count decreased	5.4%	-	-	Not varied in SA	
Pneumonia	9.5%	-	-	Not varied in SA	
Stomatitis	3.8%	-	-	Not varied in SA	
Vomiting	5.4%	-	-	Not varied in SA	
Weight decreased	5.1%	-	-	Not varied in SA	

White blood cell count decreased	4.9%	-	-	Not varied in SA	
AE Mean duration					
All Cause AE Mean Duration (weeks)	8.24	7.59	8.60	Normal	
AE Management costs					
Pembrolizumab + chemotherapy	£1,061.82	863.94	1279.80	Gamma	See Section B.3.5
SOC	£1,062.08	864.15	1280.11	Gamma	
Survival Models					
PFS parametric curve fitting – piecewise model, 10-week cut-off					
Pembrolizumab + chemotherapy					
PFS - Piecewise log-logistic Intercept	[redacted]	Multivariate Normal			See section B.3.3
PFS - Piecewise log-logistic Log(scale)	[redacted]	Multivariate Normal			
SOC					
PFS - Piecewise log-logistic Intercept	[redacted]	Multivariate Normal			See section B.3.3
PFS - Piecewise log-logistic Log(scale)	[redacted]	Multivariate Normal			
OS parametric curve fitting – piecewise model, 40-week cut-off					
Pembrolizumab + chemotherapy					
OS – Log-logistic Intercept	[redacted]	Multivariate Normal			See section B.3.3
OS - Log-logistic Log(scale)	[redacted]	Multivariate Normal			
SOC					
OS – Log-logistic Intercept	[redacted]	Multivariate Normal			See section B.3.3
OS - Log-logistic Log(scale)	[redacted]	Multivariate Normal			

Assumptions

Table 65 summarises the assumptions used in the economic model.

Table 65. List of assumptions used in the economic model

Area	Assumption	Justification
Clinical efficacy of comparators	The clinical efficacy of external comparators, analysed alongside the base case comparisons in Section B.3.7, assumes equal clinical efficacy to that of cisplatin in combination with 5-FU seen in KEYNOTE-590.	Although the trial comparator (cisplatin in combination with 5-FU) is not frequently used within UK clinical practice, NG 83 and clinical expert opinion suggest that there is minimal difference in efficacy outcomes when either comparing between different doublet therapies, and also when comparing doublet therapies with triplet therapies.
Treatment pathway	Once patients progress they receive subsequent therapies in line with those administered to patients in KEYNOTE-590.	The use of subsequent treatments as observed in KEYNOTE-590 is reflected within the OS efficacy inputs used within the economic model. Therefore, to best reflect the treatment pathway of patients with locally advanced or metastatic oesophageal cancer, and to accurately attribute costs to the subsequent treatments received, subsequent therapies were assumed as per KEYNOTE-590. These second line treatments are generalisable to the UK.
PFS efficacy	Use KM data for the first 10 weeks from the KEYNOTE-590 trial, followed by a log-logistic distribution to model PFS for pembrolizumab + chemotherapy and SOC.	Based on the trial protocol of KEYNOTE-590, the first tumour assessment was performed at week 9.
OS efficacy	Use KM data for the first 40 weeks from the KEYNOTE-590 trial, followed by a log-logistic distribution to model OS for pembrolizumab + chemotherapy and SOC.	Following guidance from TSD 14, the piecewise modelling approach with a 40-week cut-off (es established using the Chow test statistics) and log-logistic extrapolation (as established by AIC/BIC statistics and clinical validity of long-term OS estimates) was considered the most appropriate method for modelling OS.
Safety	The incidence of AEs from KEYNOTE-590 were used to reflect that observed in UK clinical practice	Assumption based on the results of the KEYNOTE-590 trial (i.e. All-cause grade 3-5 AEs (incidence≥5% in one or more treatment groups)). The same method and criteria were applied in recent NICE oncology appraisals of pembrolizumab (34).

Area	Assumption	Justification
HRQoL	The quality of life of patients is appropriately captured by considering time-to-death utilities	Clinical opinion suggests there is a decline in HRQoL in the final months of life of patients. This may not be accurately captured by using a progression-based health-state approach due to the lack of EQ-5D questionnaires undertaken post-progression. This approach has been previously accepted by NICE committees in other oncology indications (34). Given the limitations of the progression-based approach to appropriately reflect utilities post-progression, a time to death approach was considered in the base case.
Age-related disutility	Utilities were adjusted by UK general population utility where utility decreases with age	Based on the Ara and Brazier study describing the impact of age on HRQoL (73).
Healthcare resource use costs	Resource use is assumed to be equal between pembrolizumab + chemotherapy and SOC comparators	Due to paucity of data, resource use was assumed to be equivalent between treatment arm in the pre- and post-progression health states.
Stopping rule	In the economic model, pembrolizumab will not be administered beyond a maximum of 35 cycles (~24 months), cisplatin will be administered for a maximum of 6 cycles and 5-FU a maximum of 35 cycles.	This assumption is in line with the KEYNOTE-590 clinical trial.

B.3.7 Base-case results

Base-case incremental cost-effectiveness analysis results

The results of the economic model are presented in Table 66 below. Table 66 presents analysis vs cisplatin in combination with 5-FU, the trial comparator in the ITT population, as per the anticipated marketing authorisation. As outlined in Section 2.6, MSD consider the CPS≥10 sub-population to be of particular clinical significance. Analyses in the CPS≥10 sub-population is presented within section B.3.9, with the assumptions used within the economic model outlined within Appendix M.

In the base case analysis vs. SOC, the estimated mean overall survival was [redacted] years with pembrolizumab in combination with chemotherapy and [redacted] years with SOC. Patients treated with pembrolizumab in combination with chemotherapy accrued [redacted] QALYs compared to [redacted] among patients in the SOC cohort. This gives an incremental life year gain of 0.76 years and an incremental QALY gain of 0.63 QALYs. MSD considers this to be a substantial and clinically meaningful improvement in both LYs gained, and QALYs gained, considering the vast unmet need within this patient population.

Table 66 presents the base case cost-effectiveness results for pembrolizumab versus SoC, incorporating the discount of the PAS. The results show pembrolizumab to be cost-effective compared to SoC when considering a willingness to pay threshold of £50,000 per QALY.

Table 66. Base-case results versus trial comparator SOC (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	2.13	[redacted]	-	-	-
SOC	[redacted]	1.37	[redacted]	27,165	0.63	43,225
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

As mentioned in section B.3.2. our approach to non-trial comparators assumes equivalent efficacy (as per the SOC arm of KEYNOTE-590).

The base case comparison will be conducted versus the trial comparator, with comparisons versus each therapy as outlined by the NICE Final Scope (please see Table 67)(45), and a blended comparator assuming equal distribution across therapies (please see Table 68).

Table 67. Base-case results versus selected non-trial comparator (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus selected comparator (QALYs)
Pembrolizumab + chemotherapy	[redacted]	2.13	[redacted]	-	-	-
5-FU+cisplatin	[redacted]	1.37	[redacted]	27,165	0.63	43,225
5FU + oxaliplatin + leucovorin	[redacted]	1.37	[redacted]	25,995	0.63	41,364
Capecitabine + Cisplatin	[redacted]	1.37	[redacted]	27,065	0.63	43,066
Capecitabine + oxaliplatin	[redacted]	1.37	[redacted]	27,480	0.63	43,727
5-FU + cisplatin + epirubicin	[redacted]	1.37	[redacted]	27,108	0.63	43,135
5-FU + oxaliplatin + epirubicin	[redacted]	1.37	[redacted]	27,066	0.63	43,068
Capecitabine + cisplatin + epirubicin	[redacted]	1.37	[redacted]	27,029	0.63	43,009
Capecitabine + oxaliplatin + epirubicin	[redacted]	1.37	[redacted]	26,987	0.63	42,941

Table 68. Base-case results versus non-trial blended comparator (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	2.13	[redacted]	-	-	-
SOC	[redacted]	1.37	[redacted]	26,987	0.63	42,942
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

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.

B.3.8 Sensitivity analyses

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. The mean values, distributions around the means and sources used to estimate the parameters are detailed in B.3.6.

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 69, and the corresponding scatterplot and cost-effectiveness acceptability curve are presented in Figure 25 and Figure 26.

Table 69. Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator SOC (discounted price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
SOC	[redacted]	[redacted]	27,200	0.64	42,752

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

The cost-effectiveness acceptability curve shows that, for the base case, there is approximately a 69.8% of chance of pembrolizumab in combination with chemotherapy being cost-effective when compared to SOC at the £50,000 per QALY threshold. This suggests the modelling approach is stable, with high levels of certainty in the efficacy expectations, and that pembrolizumab in combination with chemotherapy is likely to be the most cost-effective treatment.

Figure 25. Scatterplot of PSA results (1,000 simulations) versus trial comparator SOC (discounted price)

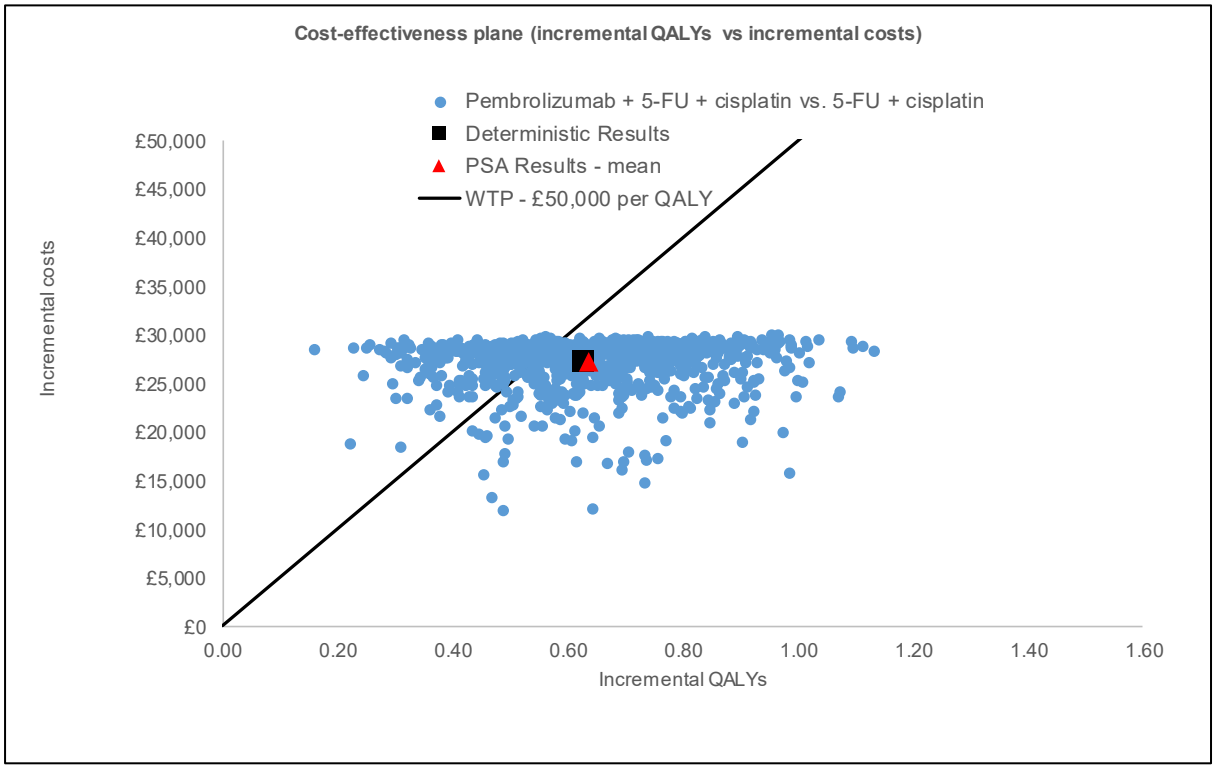
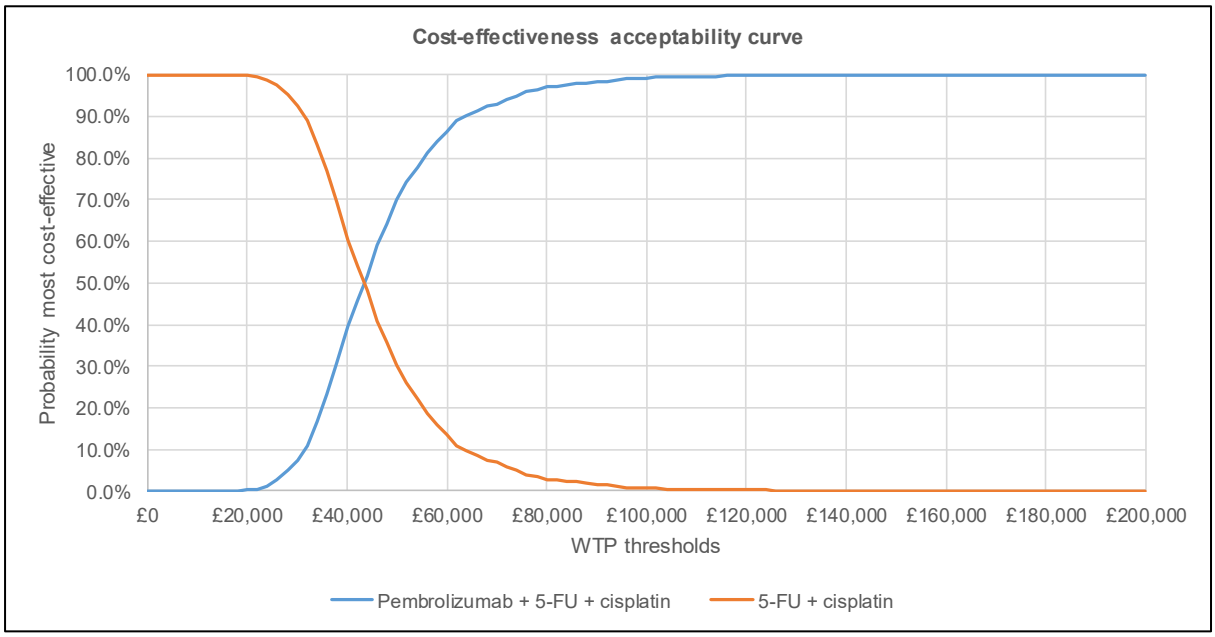


Figure 26. Cost-effectiveness acceptability curve versus trial comparator SOC (discounted price)



Deterministic sensitivity analysis

Deterministic sensitivity analyses 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 are as follows:

- Baseline characteristics (i.e. age, % female)
- Annual discount of costs and effectiveness
- Drug acquisition and administration costs
- Drug relative dose intensity
- Resource utilisation
- Subsequent treatment cost
- Health state-based utility and time-to death-based utility
- AE costs and AE-related disutility
- Background mortality
- Parameters of the parametric curves fitted to OS, PFS and ToT.

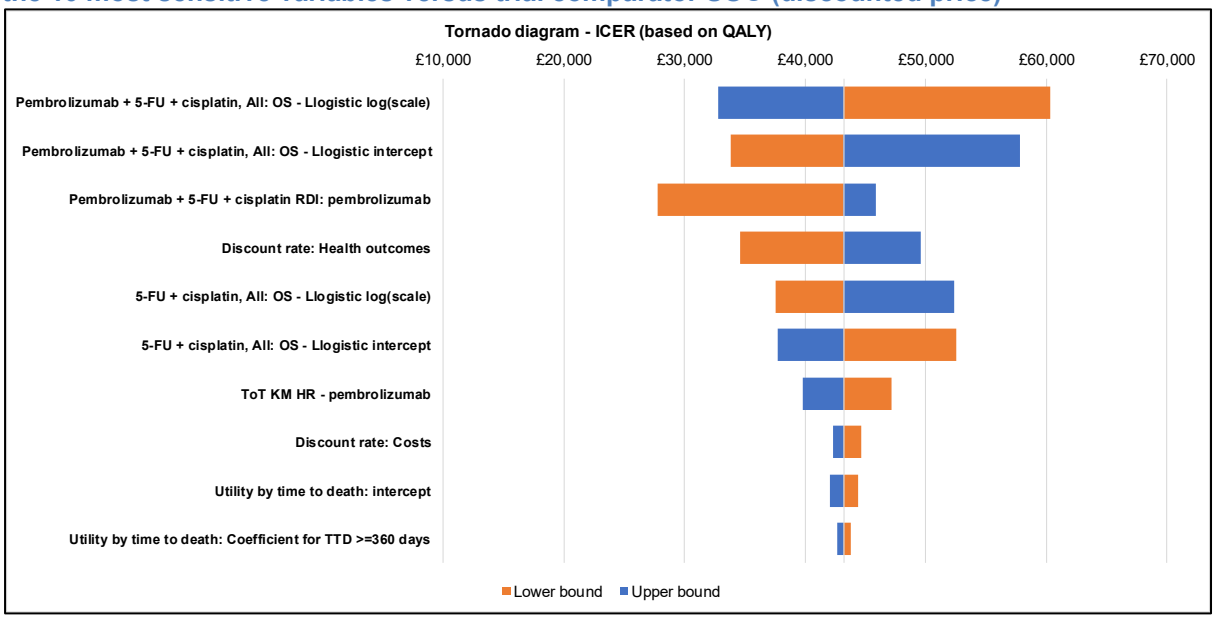
The results of the deterministic sensitivity analyses for pairwise comparisons of pembrolizumab combination vs. SoC are presented in Figure 27 below.

The tornado diagram below shows the parameters the ICER is most sensitive to; whilst there is movement in the ICER estimate, this is modest and relatively stable.

The inputs that most affect the ICERs are those related to the extrapolation of the OS (i.e. the parameters of the log-logistic distributions used for extrapolation), followed by the relative dose intensity of pembrolizumab and the annual discount rate of effectiveness (see Figure 27).

The parameters of the log-logistic are fitted to the KM data and offer the best statistic fit of any parametric distribution to the pembrolizumab in combination with chemotherapy arm. The pembrolizumab RDI was observed directly within KEYNOTE-590. Hence the deterministic values used for these parameters are the most appropriate.

Figure 27. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensitive variables versus trial comparator SOC (discounted price)



Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions:

Scenario 1: Alternative parametric distribution for the extrapolation of OS; using a piecewise modelling approach, cut-off at 40-weeks, with the log-normal curve to extrapolate OS (third best fitting based on AIC/BIC for pembrolizumab + chemotherapy)

Scenario 2: Alternative parametric distribution for the extrapolation of OS; using a piecewise modelling approach, cut-off at 40-weeks, with the Weibull curve to extrapolate OS (fourth best fitting based on AIC/BIC for pembrolizumab + chemotherapy)

Scenario 3: Alternative cut-off point for the estimation of OS; using a piecewise modelling approach, cut-off at 32-weeks, with the log-logistic curve to extrapolate OS (best-fitting based on AIC/BIC for pembrolizumab + chemotherapy)

Scenario 4: Introducing a treatment waning effect, initiating at 5 years and completing at 7 years, at which point the hazard rate for pembrolizumab in combination with chemotherapy is equal to SOC

Scenario 5: Alternative parametric distribution for the extrapolation of PFS; using a piecewise modelling approach, cut-off at 10-weeks, with the log-normal curve to extrapolate PFS (second best fitting based on AIC/BIC for pembrolizumab + chemotherapy)

Scenario 6: Alternative cut-off point for the estimation of PFS and alternative distribution for the extrapolation of PFS; using a piecewise modelling approach, cut-off at 37-weeks, with the exponential curve to extrapolate PFS (best fitting based on AIC/BIC for pembrolizumab + chemotherapy)

Scenario 7: Alternative approach for the estimation of ToT; using a fully fitted parametric approach. For pembrolizumab + chemotherapy, fully parametric generalised-gamma for pembrolizumab, Weibull for 5-FU and KM for cisplatin. For SOC, fully parametric Weibull for 5-FU and KM for cisplatin (best fitting curves based on AIC/BIC)

Scenario 8: Removing the relative dose intensity for pembrolizumab + chemotherapy and SOC, assuming 100%

Scenario 9: Alternative approach for utility description; using pooled health state based utilities to estimate QALYs

Scenario 10: Using a time horizon of 10 years

Scenario 11: Using a time horizon of 30 years

Scenario 12: Using a time horizon of 40 years

Scenario 13: Alternative approach for estimating subsequent therapy costs after SOC; considering the ongoing appraisal ID1249, assuming that all patients who receive subsequent therapy after SOC receive nivolumab monotherapy

Scenario 14: Removing AE related disutility

Scenario 15: Removing Age-adjusted utility

Scenario 16: Removing vial sharing assumption

Scenario 17: Removing Half Cycle Correction

Table 70. Results from the scenario analyses versus trial comparator SoC (discounted price)

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,165	0.63	43,225
Scenario 1	OS piecewise 40-week cut-off, log-normal distribution	[redacted]	2.20	[redacted]	[redacted]	1.34	[redacted]	27,211	0.71	38,265
Scenario 2	OS piecewise 40-week cut-off, Weibull distribution	[redacted]	1.57	[redacted]	[redacted]	1.11	[redacted]	27,058	0.39	69,985
Scenario 3	OS piecewise 32-week cut-off, log-logistic distribution	[redacted]	2.05	[redacted]	[redacted]	1.44	[redacted]	27,103	0.50	54,085
Scenario 4	OS treatment waning initiated at 5-years, completed at 7-years	[redacted]	2.06	[redacted]	[redacted]	1.37	[redacted]	27,157	0.58	47,125
Scenario 5	PFS piecewise 10-week cut-off, log-normal distribution	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,134	0.63	43,176
Scenario 6	PFS piecewise 37-week cut-off, exponential distribution	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,166	0.63	43,226
Scenario 7	Alternative TOT approach using fully fitted parametric distributions	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	26,606	0.63	42,336
Scenario 8	Assuming 100% dose intensity	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	28,920	0.63	46,019
Scenario 9	Health state based utilities	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,165	0.53	50,803
Scenario 10	Time horizon 10-years	[redacted]	1.88	[redacted]	[redacted]	1.29	[redacted]	26,885	0.50	54,025
Scenario 11	Time horizon 30-years	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,277	0.67	40,595
Scenario 12	Time horizon 40-years	[redacted]	2.22	[redacted]	[redacted]	1.40	[redacted]	27,307	0.68	40,320

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Scenario 13	Assumption of nivolumab monotherapy as subsequent therapy post-SOC	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	6,098	0.63	9,703
Scenario 14	Removing AE disutility	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,165	0.63	43,216
Scenario 15	Removing Age-adjusted utility	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,165	0.65	41,752
Scenario 16	Removing vial sharing assumption	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,166	0.63	43,226
Scenario 17	Removing Half Cycle Correction	[redacted]	2.14	[redacted]	[redacted]	1.38	[redacted]	27,164	0.63	43,238

Summary of sensitivity analyses results

The probability of pembrolizumab in combination with chemotherapy being the most cost-effective treatment at a threshold of £50,000 per gained QALY is 70.5%.

One-way sensitivity analyses showed that the inputs that most affect the ICERs are those related to the extrapolation of the OS (i.e. the parameters of the log-logistic distributions used for extrapolation), followed by the relative dose intensity of pembrolizumab and the annual discount rate of effectiveness.

Scenario analyses showed that the most sensitive scenarios relate to the chosen parametric distribution for OS, the choice of utility approach, the presence of treatment waning, time horizon and assumption of nivolumab monotherapy in the second-line setting. This ranged from £9,703 to £69,985 with the assumption of nivolumab in the second line post SOC, and a piecewise modelling approach for OS using KM data up to 40-weeks and extrapolating with the Weibull distribution, respectively. Multiple variables were tested with the results remaining under the £50,000 WTP threshold across a number of plausible scenarios (with 2 exceptions) This gives confidence that the results from the economic model are stable under reasonable assumptions.

B.3.9 Sub-population analysis

The results of the cost-effectiveness analyses on the CPS≥10 sub-population are presented below. As stated in Section B.2.7, OS in the CPS≥10 sub-population was a prespecified primary endpoint of KEYNOTE-590, and derived additional benefit attributed to the mechanism of action of the innovative combination therapy of pembrolizumab in combination with chemotherapy. Further detail on the statistical analysis and characteristics of the sub-population can be found in Section B.2.7.

The assumptions informing the cost-effectiveness analyses for this sub-population are outlined below. Please see Appendix **M** for a more detailed justification of these selections.

CPS≥10 assumptions

- Overall Survival extrapolation: piecewise modelling approach, using KM data up to 40-weeks, after which extrapolating with the log-logistic distribution

- Progression-free Survival extrapolation: piecewise modelling approach, using KM data up to 10-weeks, after which extrapolating with the log-logistic distribution
- Time on Treatment: utilising the mature KM data to accurately reflect drug acquisitions costs from KEYNOTE-590
- Utilities: using the TTD approach

Table 71. Incremental cost-effectiveness results for pembrolizumab in combination with chemotherapy vs. SOC for patients with CPS≥10 (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	2.41	[redacted]	-	-	-
SOC	[redacted]	1.34	[redacted]	30,296	0.88	34,440
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years						

B.3.10 Validation

Validation of cost-effectiveness analysis

Clinical benefit

The efficacy outcomes of pembrolizumab in combination with chemotherapy observed in the KEYNOTE-590 trial have been compared to the outcomes from the cost-effectiveness model. For more details comparing the results generated from the model to the outcomes from the model please refer to Appendix J.

Expert validation

The modelling approach is in line with multiple metastatic oncology appraisals and has been validated by clinical experts to be an appropriate structure for this population.

The model was quality-assured extensively by the internal processes of the economists who produced the economic model in addition to an external vendor, CHEORS, who quality checked the model.

As an external validation, for a comprehensive quality check, CHEORS reviewed the model and report based on the set parameters. These include verifying the formulae and control settings,

checking the lower and upper bounds of various parameters used in the model, checking the graphs and formatting errors in the model, consistency of the report with the model, testing the macros used in the excel model, and verifying the results of the model. After a thorough review, and updates made to the economic model, CHEORs found no major implementation errors or bugs.

B.3.11 Interpretation and conclusions of economic evidence

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab in combination with chemotherapy for the treatment of untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma. The economic evaluation reflects patients assessed in KEYNOTE-590 and is relevant to all groups of patients who could potentially benefit from use of the technology, as identified in the decision problem.

No study assessing the cost-effectiveness of pembrolizumab in combination with chemotherapy for the target population specified above was identified from the systematic literature review. It was therefore not possible to compare the results of the economic model developed in this submission with any available publication.

Relevance of the economic evaluation for all patient groups

The population included in the economic evaluation was consistent with the untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma eligible for pembrolizumab in combination with chemotherapy as per the anticipated licence. As mentioned previously, clinical efficacy estimates from the KEYNOTE-590 trial, which assessed patients in line with the anticipated licenced indication, were used in the model. Therefore, the economic evaluation is relevant to all patients who could potentially use pembrolizumab in combination with chemotherapy in the patient population under consideration.

Generalisability of the analysis to the clinical practice in England

The analysis is directly applicable to clinical practice in England since:

- The patient population in KEYNOTE-590 and the de novo economic evaluation are reflective of patients with untreated advanced oesophageal cancer in the UK.
- While the trial comparator is not routinely used in the UK, validation with UK clinical experts alongside NICE Guideline 83 suggests the results are generalizable on the basis that doublet and triplet therapy are assumed to be equally efficacious.
- The economic model structure is consistent with other oncology models submitted to NICE.
- The resource utilitisation and unit costs are reflective of UK clinical practice and were mainly derived from the NHS Reference Costs and previous NICE submissions, incorporating the feedback provided by the ERGs in recent NICE appraisals. These cost inputs are considered most appropriate to model the cost-effectiveness of pembrolizumab in combination with chemotherapy.
- Extensive sensitivity analyses were conducted, considering alternative approaches to extrapolation and different data sources and scenarios related to the estimation of QALYs and costs.

Strengths of the evaluation

Partitioned survival analysis is a well-established modelling approach and has been commonly used in prior HTA submissions for treatments of advanced oesophageal cancer and other oncology indications.

Direct, head-to-head comparative data were available from the Phase III KEYNOTE-590 trial to inform the economic evaluation of pembrolizumab in combination with chemotherapy versus SOC. Observed data from the trial showed that pembrolizumab in combination with chemotherapy reduced the hazards of death by 27% (HR = 0.73, 95% CI: 0.62-0.86; p<0.00001) and reduced the hazards of disease progression or death by 35% (HR = 0.65, 95% CI: 0.55-0.76; p<0.0001) compared with SOC. The finding of large, statistically significant benefits on the dual endpoints of OS and PFS provide strong support to the extension of life expectancy projected by the economic model. The inputs for this economic evaluation were based on data from KEYNOTE-590 whenever possible and appropriate.

Treatment options for this indication are limited and current standard of care palliative chemotherapy has poor outcomes. Pembrolizumab in combination with chemotherapy is the first immunotherapy-based treatment of its kind which provides statistically significant, and clinically meaningful, benefits for OS and PFS. It will have a profound impact on the treatment landscape for advanced and metastatic oesophageal cancer.

Efficacy and treatment duration inputs for the pembrolizumab in combination with chemotherapy and SOC arms were based on patient-level data from the KEYNOTE-590 trial. For these treatment arms, the selection of parametric survival models for OS and PFS were based on goodness-of-fit with the observed data, visual inspection and long-term clinical plausibility. OS data in the KEYNOTE-590 trial are relatively mature and therefore there is less uncertainty in long term extrapolation of OS. ToT Kaplan–Meier data in the KEYNOTE-590 trial are mature (reaching 0% survival probability within the trial period) and therefore the base case utilised the Kaplan–Meier data directly for ToT to reduce uncertainty.

Utility and AE-related disutility inputs were based on EQ-5D data collected from the KEYNOTE-590 trial, and EQ-5D is the preferred health utility measure by NICE and other HTA bodies. The utility inputs were assumed to be the same for all treatment arms. The utility decrement associated with AEs was considered in each treatment arm, based on the mean duration of AEs observed in KEYNOTE-590. The economic evaluation also appropriately accounted for subsequent-line therapies by incorporating the weighted drug acquisition and administration costs of subsequent therapies based on the distribution of subsequent treatments observed in KEYNOTE-590.

Importantly, key model assumptions and choice of model base case settings, especially parametric survival curves, were validated by clinical experts, including UK clinicians.

Limitations of the evaluation

As with any economic evaluation, the cost-effectiveness analyses is associated with some limitations.

The uncertainty associated with the long-term extrapolation of fitted parametric survival curves is a limitation of the study, especially for the OS for pembrolizumab in combination with chemotherapy arm, where there is no external long-term data to validate. The choice of base case

survival curve was based on statistical fit, visual inspection, long-term clinical plausibility, and validation by clinical experts.

One limitation of this evaluation was the lack of specific inputs for subgroups, which led to the use of inputs such as disease management costs, terminal care costs from the overall population for the subgroups. These inputs were explored in sensitivity analyses, and most were found to have no significant impact on the ICER.

Another limitation was the lack of head-to-head trials for pembrolizumab in combination with chemotherapy versus non-trial comparators (i.e. the blended chemotherapy comparator). Due to the lack of clinical evidence, the efficacy and safety of the blended chemotherapy were assumed to be equivalent to the 5-FU + cisplatin trial comparator in the model base case.

Conclusion

The KEYNOTE-590 trial demonstrates superior OS and PFS with pembrolizumab in combination with chemotherapy versus SOC as first-line treatment for patients with advanced and metastatic oesophageal cancer. For the overall population, pembrolizumab + 5-FU + cisplatin was estimated to extend life expectancy by 0.76 years compared with 5-FU + cisplatin over a lifetime horizon.

This cost-effectiveness analysis shows that pembrolizumab in combination with chemotherapy offers benefits to patients with advanced and metastatic oesophageal cancer in terms of LY and QALY gains, in comparison with relevant comparators. Based on this evaluation, when incorporating the discounted price for pembrolizumab, the base-case ICER for pembrolizumab in combination with chemotherapy vs chemotherapy is lower than the WTP threshold of £50,000 in the UK.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with platinum-based chemotherapy for untreated, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma [ID3741]

MSD response to clarification questions

March 2021

File name	Version	Contains confidential information	Date
ID3741 Pembro for OC Clarification Letter for ERG v0.1 10.2.2021	1	Yes	23-Feb-21

Section A: Clarification on effectiveness data

Literature searches

A1. Please can you provide further detail of the grey literature searches for the clinical effectiveness SLR described on p. 89 (Appendix D), including conference proceedings and years checked?

Manual searches of clinicaltrials.gov and conference proceedings were conducted to identify trials that had not been published at the time the review was conducted but were still eligible for inclusion.

The following conference proceedings were searched:

- American Society of Clinical Oncology (ASCO; 2018, 2019 and 2020)
- Gastrointestinal Cancers Symposium (ASCO-GI; 2018, 2019 and 2020)
- European Society for Medical Oncology (ESMO; 2018 and 2019)
- World Congress on Gastrointestinal Cancer (ESMO-GI; 2018, 2019 and 2020)
- ESMO Asia (2018 and 2019)
- American Association for Cancer Research (AACR; 2018, 2019 and 2020)

A2. Please confirm the source of the filters used to identify RCTs in MEDLINE and Embase? What steps were taken to ensure the clinical effectiveness searches also identified single arm trials?

The study design filters recommended by the Scottish Intercollegiate Guidelines Network (SIGN) for MEDLINE and EMBASE were used to identify clinical trials (https://www.sign.ac.uk/what-we-do/methodology/search-filters/). The search results were cross-referenced with the most recent guidelines published by the National Comprehensive Cancer Network and European Society for Medical Oncology to ensure the search captured all relevant evidence, including single arm trials.

A3. Please confirm if citation chasing (forwards or backwards) was completed on the included studies in Table 5.

Citation chasing was not completed; however, clinical trial registries for all included studies (if available) were cross-referenced to ensure all corresponding publications were captured.

A4. Were any specific searches completed for adverse events (in addition to the searches for the clinical effectiveness SLR)?

No searches were conducted specifically for adverse events; however, adverse events and serious adverse events were included in the PICOS inclusion criteria for the clinical SLR. Specifically, the clinical SLR included the following outcomes: drug related adverse events, grade 3-5 adverse events (overall and drug related), discontinuations due to adverse events, and serious adverse events.

A5. Please provide further details on the exclusion of

(i) Cunningham 2008 (Table 6). This trial was listed for exclusion on 'outcome' but presents e.g. overall survival (OS) and progression-free survival (PFS).

(ii) Similarly for Jatoi (2006) (excluded on outcome)

Cunningham 2008 and Jatoi 2006 were excluded for not reporting subgroup outcomes for esophageal or esophagogastric junction Siewert type I cancer patients. Both studies only report aggregate outcomes for esophageal, esophagogastric junction, and gastric cancer patients.

A6. Please comment on the rationale for not incorporating the term 'gastric' in association with cancer terms within the search strategies for the clinical effectiveness SLR.

The population terms relating to oesophageal or oesophagogastric junction were considered most suitable to capture studies of relevance to this appraisal. Using gastric cancer would have introduced too many non-relevant studies in terms of location of the primary tumour.

A7. Please comment on the rationale for not incorporating alternative spellings for oesophagus and oesophageal, as well as further free-text search terms to capture the EGJ population (such as gastroesophageal, gastro-oesophageal, esophagogastric, oesophagogastric) within the search strategies for the clinical effectiveness SLR.

The combinations of subject headings and free-text terms relevant to the population of interest used within the search strategies were deemed sufficiently sensitive to capture all relevant citations. As mentioned in the response to questions A2 and A3, this assumption was tested by cross referencing the results with information included in clinical trial registries and clinical

guidelines. These checks confirmed that no relevant trials were missed therefore no updates were made to search strings.

Comparators

A8. The company submission states (section B2.9) "these interventions [capecitabine plus cisplatin and epirubicin with cisplatin and 5-FU] have generally only been evaluated in non-comparative studies".

The ERG is aware of the following studies cited by Guo et al. (2019); please comment on their applicability to the decision problem and in particular within a network meta-analysis.

A randomized, comparative study of combination chemotherapies in advanced gastric cancer: 5-fluorouracil and cisplatin (FP) versus 5-fluorouracil, cisplatin, and 4′-epirubicin (FPEPIR). Kyoto Research Group for Chemotherapy of Gastric Cancer (KRGCGC). Anticancer Res. 1992;12(6B):1983–8.

Kim T, Choi SJ, e.a. Ahn JH. A prospective randomized phase III trial of 5-fluorouracil and cisplatin (FP) versus epirubicin, cisplatin, and 5FU (ECF) in the treatment of patients with previously untreated advanced gastric cancer (AGC). Eur J Cancer. 2001;37(Suppl 6):S314.

Yun J, Lee J, Park SH, Park JO, Park YS, Lim HY, et al. A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer. Eur J Cancer. 2010;46(5):885–91.

All of the above studies were conducted in gastric cancer patients and did not include oesophageal or esophagogastric junction Siewert type I patients, therefore are not relevant to the current decision problem.

A9. The company submission states (Doc B, p61) "the NMA feasibility assessment process was adapted to the context of an unanchored MAIC as summarised in Appendix D". Please elaborate on this adaptation (and/or further identify the location of the explanation).

The process for assessing the feasibility of an NMA where there is a connected network of RCTs has been well established, and involves an investigation of whether there are differences within or between direct treatment comparisons in terms of a) treatment or

outcome definitions, b) the distribution of study and patient characteristics, c) baseline risk associated with treatment effect, and d) observed treatment effects. Since there is no parallel explicit process specific to MAIC, the NMA feasibility assessment process was adapted to the context of an unanchored MAIC for this study, as summarized in Table 1.

***Table 1*: Comparison of feasibility assessment steps for network meta-analysis versus unanchored matching-adjusted indirect comparisons, and rationale for changes given underlying assumptions of unanchored matching-adjusted indirect comparisons**

Steps	Feasibility assessment steps for NMA	Feasibility assessment steps for unanchored MAIC	Description of change and rationale
a	Assessment of the treatment (doses/schedules) or outcome definitions that are expected to modify relative treatment effects	Assessment of outcome definitions that are expected to modify relative treatment effects • Should index trial definitions be adapted to align with external source(s)?	**Remove treatments and align outcome definitions** • In unanchored MAIC the treatment network is disconnected or includes single-arm studies; therefore, it is not necessary to compare intervention characteristics since no 'connecting' comparators • MAIC cannot adjust for differences in treatment administration co-treatments, or treatment switching, which are confounded with treatment; therefore, comparisons of treatments across external studies are not necessary • May be feasible to change outcome definitions in index trial to align with external source
b	Assessment of the distribution of study and patient characteristics that are expected to modify relative treatment effects	Assessment of the distribution of study and patient characteristics that are expected to modify absolute or relative treatment effects • Should patients from the index trial be excluded to align with inclusion from external source(s)? • Is it possible to adjust for all known effect modifier and prognostic factors?	**Assessment of not only effect modifiers but also prognostic factors** • A standard NMA of RCTs assumes 'constancy of relative effects' on linear predictor scale (since patients only randomized within trials); assumes balance in all effect modifiers (differences in distribution of prognostic factors does not affect inference) • An unanchored MAIC assumes 'conditional constancy of absolute effects'; assumes absolute treatment effect is constant at any level of effect modifiers and prognostic factors (assumes all effect modifiers and prognostic factors to be known); assumes outcome does not depend on correlations between covariates (or consistent with IPD) ○ Therefore, unanchored MAICs should adjust for all effect modifiers *and prognostic factors*
C	Assessment of the baseline risk (placebo-response) that is also associated with the relative treatment effects	--	**Not applicable** • Comparisons of baseline risk across the trials in an NMA require multiple trials with a placebo, which is not applicable to unanchored MAIC
d	Assessment of observed treatment effects	Assessment of how the observed absolute effects are reported • For which outcomes is it possible to conduct comparisons based on reporting?	Unlike with an NMA where evaluation of relative effects may be helpful to justify model choice (i.e. fixed versus random effects), for an unanchored MAIC the way the aggregate data are published will inform what comparisons are possible (which outcomes can be evaluated) and/or what assumptions are necessary (e.g., if only medians are reported rather than Kaplan-Meier curves)

***Abbreviations**: IPD, individual patient data; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; RCT, randomized controlled trial.*

Systematic review methods

A10. Please can you provide further details of the methods you used when conducting your systematic review, specifically relating to how you performed screening and data extraction.

Two reviewers, working independently, reviewed all abstracts and proceedings identified by the search according to the selection criteria, with the exception of outcome criteria, which were only applied during the screening of full-text publications. All studies identified as eligible during the abstract screening phase were then screened at the full-text stage by the same two reviewers. The full-text studies identified at this stage were included for the data extraction. Following reconciliation between the two investigators, a third reviewer was included to reach consensus for any remaining discrepancies during abstract screening or full-text screening.

Similarly, for the data extraction, two reviewers, working independently, extracted data on study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies. Following reconciliation between the two reviewers, a third reviewer was included to reach consensus for any remaining discrepancies.

Trial data and analysis

A11. Please clarify how the documented testing hierarchy and p-value redistribution methods were used in the context of this interim analysis focused on specific populations.

The testing hierarchy is provided in Section 8.8.1 of the protocol and section B2.4.1 and appendix D. As illustrated in Figure XX, at the interim analysis all the hypotheses (H1-H8) were tested. Figure XX 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.

Table 2 below provides a summary of the results for all the 8 primary and key secondary hypotheses tested under the pre-specified plan. The p-values at the boundary were calculated as per the details provided in the appendix D of the submission. The observed p-values were compared with the p-value boundaries to conclude statistical significance for all of the hypotheses tested.

Table 2 **Topline Results of Testing for All Primary and Key Secondary Hypotheses**

Primary Hypotheses	Observed HR (95% CI)	Number of events observed	p-value observed	p-value boundary	Outcome
H1: OS in ESCC PD-L1+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H2: OS in ESCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H3: OS in PD-L1+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H4: OS in All Subjects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H5: PFS in ESCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H6: PFS in PD-L1+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
H7: PFS in All Subjects	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key Secondary Hypotheses	**Difference (95% CI)**		**p-value**	**p-value boundary**	**Outcome**
H8: ORR in All Subjects	[redacted]		[redacted]	[redacted]	[redacted]

Figure 1 Multiplicity Diagram for Type I Error Control

Abbreviations: ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

A12. Please can you provide a summary of demographic baseline data for KEYNOTE-590 trial subjects with adenocarcinoma, similar to the demographic

data provided for subjects with Squamous Cell Carcinoma in table 3. P.30 Appendix E.

A summary of demographic baseline data for KEYNOTE-590 trial subjects with adenocarcinoma is provided in the table below.

Table 3 Participant Characteristics Participants with Adenocarcinoma (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gender						
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]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian Or Alaska Native, White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American, White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region						
Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A13. Please can you provide a summary of BMI and smoking status for both populations of squamous and adenocarcinoma KEYNOTE-590 trial participants at baseline

The BMI of the participants with adenocarcinoma and with squamous cell carcinoma are presented in Table 4 and Table 5 respectively. Information regarding the smoking status was not collected for the participants of KEYNOTE-590.

Table 4 Participant Characteristics Participants with Adenocarcinoma (Intention-to-Treat Population)

	Pembrolizumab + SOC	SOC	Total
Participants in population	[redacted]	[redacted]	[redacted]
Body Mass Index (kg/m^2)			
Subjects with data	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 02JUL2020			

Table 5 Participant Characteristics Participants with Squamous Cell Carcinoma (Intention-to-Treat Population)

	Pembrolizumab + SOC	SOC	Total
Participants in population	[redacted]	[redacted]	[redacted]
Body Mass Index (kg/m^2)			
Subjects with data	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Database Cutoff Date: 02JUL2020			

A14. Please can you provide numbers of deaths between start date of first administration of investigational product and a) 28 days b) 3 months c) 6

months d)12 months e)18 months and f) 2 years for both active and control arms of KEYNOTE-590

A summary of the number of events and overall survival rates by treatment for the post-randomization timepoints of 1 month, 3 months, 6 months, 12 months, 18 months and 2 years is presented in Table 6.

Please note that there is no death between 28 days and 1 month in either treatment arm. It was therefore communicated to ERG to display 1 month instead of 28 days, which was accepted during the meeting with ERG on 9th Mar 2021.

Table 6 Summary of Number of Events and Overall Survival Rate Over Time (ITT Population)

	Pembrolizumab + SOC (N=373)		SOC (N=376)	
	Number of events	OS rate (95% CI)[a]	Number of events	OS rate (95% CI)[a]
Month 1	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]

[a] From the product-limit (Kaplan-Meier) method for censored data.
Database Cutoff Date: 02JUL2020

A15. Please can you provide subgroup analyses of Overall Survival, similar to table 4, p.136, Appendix E, but for KEYNOTE-590 trial participants with adenocarcinoma whose tumours express PD-L1 (PS more than or equal to 10)

The subgroup analyses of OS for all subgroup factors of interest for participants with adenocarcinoma and PD-L1 CPS ≥ 10 are summarized in Table 7..

Table 7 Subgroup Analysis of Overall Survival (Subjects with Adenocarcinoma and PD-L1 CPS >= 10, ITT Population)

	Pembrolizumab + SOC			SOC			
	(N=43)			(N=54)			Pembrolizumab + SOC vs. SOC
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)[†]
Overall	[redacted]						
Age Category							
< 65 years	[redacted]						
>= 65 years	[redacted]						
Disease Status							
Metastatic	[redacted]						
Unresectable - Locally Advanced	[redacted]						
ECOG							
0	[redacted]						
1	[redacted]						
2	[redacted]						
Geographic Region							
Asia	[redacted]						
Rest of World	[redacted]						
Sex							
Male	[redacted]						
Female	[redacted]						

[†] For overall analysis, estimates are based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1). For subgroup analysis, estimates are based on unstratified Cox regression model with treatment as a covariate.

NA: Not Analyzed.

If any level of a subgroup variable has fewer than 10% of the total population, subgroup analysis is not performed for this level of the subgroup variable.

Database Cutoff Date: 02JUL2020

A16. Please can you provide a forest plot of OS hazard ratio by subgroup factors for subjects with adenocarcinoma, similar to Fig 2, p.133 Appendix E which focuses on KEYNOTE-590 trial subjects with squamous cell carcinoma

A forest plot of OS hazard ratio by subgroup factors for subjects with adenocarcinoma is provided in the figure below.

Figure 2 Forest Plot of OS Hazard Ratio by Subgroup Factor (Subjects with Adenocarcinoma, ITT Population)

A17. Please can you provide a forest plot of OS hazard ratio by subgroup factor similar to Fig 3, p.135, Appendix E but for KEYNOTE-590 trial subjects with adenocarcinoma and PD-L1 expression

A forest plot of OS hazard ratio by subgroup factor for KEYNOTE-590 trial subjects with adenocarcinoma and CPS>=10 expression is provided in the figure below.

Figure 3 Forest Plot of OS Hazard Ratio by Subgroup Factor (Subjects with Adenocarcinoma and PD-L1 CPS >= 10, ITT Population)

A18. Please can you provide a subgroup analysis of PFS based on investigator assessment per RECIST 1.1 at July 2020 data-cut similar to Table 7, p 136, Appendix E but for adenocarcinoma subjects in the KEYNOTE-590 trial

Subgroup analysis of PFS based on investigator assessment per RECIST 1.1 at July 2020 data-cut for adenocarcinoma subjects in the KEYNOTE-590 trial is provided in the table below.

Table 8 Subgroup Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) (Subjects with Adenocarcinoma, ITT Population)

	Pembrolizumab + SOC (N=99)			SOC (N=102)			Pembrolizumab + SOC vs. SOC
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)†
Overall	[redacted]						
Age Category							
< 65 years	[redacted]						
>= 65 years	[redacted]						
Disease Status							
Metastatic	[redacted]						
Unresectable - Locally Advanced	[redacted]						
ECOG							
0	[redacted]						
1	[redacted]						
2	[redacted]						
Geographic Region							
Asia	[redacted]						
Rest of World	[redacted]						
Sex							

Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† For overall analysis, estimates are based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1). For subgroup analysis, estimates are based on unstratified Cox regression model with treatment as a covariate.

NA: Not Analyzed.

If any level of a subgroup variable has fewer than 10% of the total population, subgroup analysis is not performed for this level of the subgroup variable.

Database Cutoff Date: 02JUL2020

A19. Please can you provide a forest plot of PFS hazard ratio by subgroup factor based on investigator assessment per RECIST 1.1 at July 2020 cut off similar to Fig 6, p.136 of Appendix E, but for subjects with adenocarcinoma in the KEYNOTE-590 trial

A forest plot of PFS hazard ratio by subgroup factor based on investigator assessment per RECIST 1.1 at July 2020 cut off for subjects with adenocarcinoma in the KEYNOTE-590 trial is provided in the figure below.

Figure 4 Forest Plot of PFS Hazard Ratio by Subgroup Factor Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) (Subjects with Adenocarcinoma, ITT Population)

A20. Please can you provide a subgroup analysis of PFS based on investigator assessment per RECIST 1.1 at July 2020 data cut, similar to Table 8, p.142, Appendix E, but for KEYNOTE-590 trial subjects with adenocarcinoma and PD-L1 CPS >=10)

A subgroup analysis of PFS based on investigator assessment per RECIST 1.1 at July 2020 data cut for KEYNOTE-590 trial subjects with adenocarcinoma and PD-L1 CPS >=10) is provided in the table below.

Table 9 Subgroup Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) (Subjects with Adenocarcinoma and PD-L1 CPS >= 10, ITT Population)

	Pembrolizumab + SOC			SOC			
	(N=43)			(N=54)			Pembrolizumab + SOC vs. SOC
	N	Number of Events	(%)	N	Number of Events	(%)	Hazard Ratio (95% CI)†
Overall	[redacted]						
Age Category							
< 65 years	[redacted]						
>= 65 years	[redacted]						
Disease Status							
Metastatic	[redacted]						
Unresectable - Locally Advanced	[redacted]						
ECOG							
0	[redacted]						
1	[redacted]						
2	[redacted]						
Geographic Region							

Asia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† For overall analysis, estimates are based on Cox regression model with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1). For subgroup analysis, estimates are based on unstratified Cox regression model with treatment as a covariate.

NA: Not Analyzed.

If any level of a subgroup variable has fewer than 10% of the total population, subgroup analysis is not performed for this level of the subgroup variable.

Database Cutoff Date: 02JUL2020

A21. Please can you provide a forest plot of PFS hazard ratio by subgroup factor based on investigator assessment per RECIST 1.1, similar to Fig 7, p.143, Appendix E, but for KEYNOTE-590 trial subjects with adenocarcinoma and PD-1 CPS>=10)

A forest plot of PFS hazard ratio by subgroup factor based on investigator assessment per RECIST 1.1 for KEYNOTE-590 trial subjects with adenocarcinoma and PD-1 CPS>=10) is provided in the figure below.

Figure 5 Forest Plot of PFS Hazard Ratio by Subgroup Factor Based on Investigator Assessment per RECIST 1.1 (Primary Censoring Rule) (Subjects with Adenocarcinoma and PD-L1 CPS >= 10, ITT Population)

A22. Please can you confirm whether the subsequent treatment percentages that appear in Table 61 of the company submission are the direct observed values from the KEYNOTE-090 trial, and if so, are they from the intention to treat (ITT) population?

Please see question B21.

A23. Please provide relevant estimates of PFS across all relevant subgroups using each of the sensitivity analysis censoring rules.

The analyses of progression-free survival based on investigator assessment per RECIST 1.1 for the sensitivity censoring rules 1 and 2 are presented in Appendix A.

Stopping rule

A24. Please can you clarify regarding the source of information for the pembrolizumab stopping rule. In the company submission, it is stated that "the proposed licence states that pembrolizumab has to be administered until PD or unacceptable toxicities or for a maximum of 35 doses (2 years)", and that this is based on the SmPC. However, the ERG has been unable to identify any information on the stopping rule in the SmPC (Appendix C).

The information regarding pembrolizumab stopping rule provided in the submission is incorrect. The SmPC does not define a stopping rule for pembrolizumab in this indication. However, in KEYNOTE 590 pembrolizumab was administered until PD or unacceptable toxicities or for a maximum of 35 administrations (approximately 2 years).

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Please confirm the source of the filter used in the Medline and Embase searches (via Embase.com) for the utility review (p. 194)?

The filters used for searches for the utility review were based on those developed by ISSG and CADTH, please see the links below for further information:

Inter TASC Information Specialists' Sub-Group (ISSG group): *https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/*

Canadian Agency for Drugs and Technologies in Health (CADTH): *https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#health/*

Model settings

B2. The model time horizon is set to 20 years in the base case with alternative time points of 10, 30 and 40 years tested in scenario analysis. At 20 years there is estimated to be 2.9% still alive in the pembrolizumab + chemotherapy treatment arm using the company's base case overall survival curves. Please justify why 20 years was selected as the time horizon in the base case?

MSD's original base time horizon selection of 20 years was informed by the current survival estimates of patients treated within UK clinical practice.

MSD have chosen to update the base case time horizon to 30 years to fully capture the expected costs and benefits of pembrolizumab in combination with chemotherapy within this indication. Please see Appendix C for the updated cost effectiveness analyses.

Comparators

B3. PRIORITY QUESTION: On page 84, Document B, the company states:

"As stated in section B.2.9, due to the difficulties in conducting an NMA, the approach undertaken to compare versus non-trial comparators which are used within UK clinical practice, is to assume clinical equivalency with the trial comparator (cisplatin in combination with 5-FU). This simplifying assumption is supported by NG83 and clinical expert opinion, given the clinician advice, the impact of this assumption is anticipated to be minimal and is investigated within scenario analyses."

Please clarify how this has been investigated within scenario analysis and present the results of these scenarios.

Clinical experts advised MSD that non-trial doublet therapies could be considered equivalent to the KEYNOTE-590 trial comparator (cisplatin +5-FU) and that the addition of epirubicin added no efficacy benefit, but worsened the safety profile. On that basis MSD did not formally explore the impact of the clinical equivalence assumption within scenario analyses. This approach is further supported by NICE Guidance 83.

MSD did explore the impact of comparing pembrolizumab in combination with chemotherapy versus non-trial comparators by applying the relevant costs as reported in Tables 67 and 68 of the Company Submission. Tables 67 and 68 show the ICER is not sensitive to the choice of comparator. Efficacy inputs were varied together for trial and non-trial comparators assuming equivalent efficacy in the sensitivity analysis.

MSD have also explored the impact of AE's by sourcing AE rates from the literature, please see Question B12 for these analyses.

Effectiveness

B4. PRIORITY QUESTION: The KEYNOTE-590 study includes 52.5% patients from Asia, versus 47.5% from the rest of the world (ITT population, company submission Table 6). Region has an apparent impact on the hazard ratio (HR) for OS as shown in the Clinical Study Report forest plots (OS HR: [redacted] for Asian patients versus [redacted] for the rest of the world patients). Please provide an analysis using only the rest of the world patients including; a table of baseline patient characteristics (also by treatment arm), Kaplan-Meier plots for OS, PFS and time on treatment (ToT), and cost-effectiveness results.

The KEYNOTE-590 study includes 52.5% patients from Asia, versus 47.5% from the rest of the world (ITT population, company submission Table 6). Region has an apparent impact on the hazard ratio (HR) for OS as shown in the Clinical Study Report forest plots (OS HR: [redacted] for Asian patients versus [redacted] for the rest of the world patients). Please provide an analysis using only the rest of the world patients including; a table of baseline patient characteristics (also by treatment arm), Kaplan-Meier plots for OS, PFS and time on treatment (ToT), and cost-effectiveness results. MSD have presented the requested analyses of the Rest of World population within Appendix B.

In KEYNOTE-590, 393 (52.5%) participants were enrolled in Asia. Based on subgroup analyses, improvements in OS were observed in participants from Asia and ROW who received pembrolizumab plus chemotherapy compared with chemotherapy, consistent with the overall ITT patient population.

MSD notes the apparent impact of region on efficacy results with the OS HR being numerically better in the Asia region compared to the ROW region. However, the 95% CIs around the point estimates for OS HRs for participants from both Asia and ROW regions overlapped substantially. KEYNOTE-590 was not powered to detect differences by region therefore this apparent interaction needs to be interpreted with care. Feedback from clinicians MSD has consulted is that there is no clinical rationale for the difference. MSD are also aware of ID1249, Nivolumab for previously treated unresectable advanced oesophageal cancer, the Appraisal Consultation Document states, "*The clinical expert commented that although the trials were mainly done in Asia, there is no difference in the underlying biology of oesophageal squamous cell cancer compared with people in the UK… The committee agreed with the clinical expert and concluded that the clinical trial was broadly generalisable to people with advanced*

oesophageal squamous cell cancer in the UK." Although this is in relation to the second-line setting, MSD consider this to also be applicable to the first-line setting.

MSD have not updated the economic model to include this analysis. As mentioned, the KEYNOTE-590 trial was not powered to estimate the treatment effect in the ROW population as no alpha was allocated to this subgroup, therefore interpretation of this analysis should be undertaken with caution.

B5. PRIORITY QUESTION: Please provide the following diagnostic plots:

a. ***On page 87 of the company submission, in Figure 13 and Figure 14, with the application of the commercial in confidence formatting it is unclear which line refers to which treatment arm. Please provide new figures, such that it is clear which line refers to which treatment after formatting is applied. In the revised Figure 13, please align the x-axis increments with those used for Figure 15 (Chow test)***

MSD delivered an updated submission changing the confidentiality markings of diagrams on the 25th February.

Please see Figure 6 - Figure 11, which has time points overlaid on the cumulative and log-cumulative hazard plots.

Figure 6. Cumulative hazard plot of OS for pembrolizumab in combination with chemotherapy and SOC (32 week marked)

Key: Pembrolizumab + Chemotherapy red; SOC blue

Figure 7. Cumulative hazard plot of OS for pembrolizumab in combination with chemotherapy and SOC (40 week marked)

Key: Pembrolizumab + Chemotherapy red; SOC blue

Figure 8. Cumulative hazard plot of OS for pembrolizumab in combination with chemotherapy and SOC (60 week marked)

Key: Pembrolizumab + Chemotherapy red; SOC blue

Figure 9. Log-cumulative hazard plot of OS for pembrolizumab in combination with chemotherapy and SOC (32 week marked)

Key: Pembrolizumab + Chemotherapy red; SOC blue

Figure 10. Log-cumulative hazard plot of OS for pembrolizumab in combination with chemotherapy and SOC (40 week marked)

Key: Pembrolizumab + Chemotherapy red; SOC blue

Figure 11. Log-cumulative hazard plot of OS for pembrolizumab in combination with chemotherapy and SOC (60 week marked)

Key: Pembrolizumab + Chemotherapy red; SOC blue

b. As recommended in NICE DSU TSD 14, please provide a quantile-quantile (Q-Q) plot for the observed OS data to assess the acceleration failure time (AFT) assumption.

Please see the requested Q-Q plot in

Figure **12** below.

The Q-Q plots suggested that the observed data was bending away from the straight line (slope became smaller over time). This suggests that the hazards of death for the pembrolizumab + chemotherapy arm was decreasing faster than the SOC arm and the trend cannot be captured by an AFT model.

Figure 12. Overall Survival Q-Q plot for pembrolizumab + chemotherapy vs SOC

c. ***Please provide additional diagnostic plots to assess the visual fit of the parametric survival distributions using the observed OS data; smoothed hazard versus time and LN(smoothed hazard) versus time. Please also provide a plots of LN(odds of survival) (i.e., LN(S(t)/(1-S(t))) versus LN(time) and LN(inv. normal probability of death) (i.e., LN(Φ^{-1}(1-S(t)))) versus LN(time).***

Pembrolizumab + chemotherapy

Figure 13. Smoothed Hazard of Death for Pembrolizumab + chemotherapy (One-piece fitting)

All fitted one-piece models poorly described the trend in hazard of death and overestimated the hazard for Pembrolizumab + SOC after week 75. The structural change in hazard around 40 weeks was also evident based on the non-parametric smoothed hazard plot.

Figure 14. Smoothed Hazard of Death for Pembrolizumab + chemotherapy (piecewise fitting with 40-week cut-off)

The log-logistic model with 40 weeks cut-off was shown as the best fitted curve to describe the trend in hazard of death.

Figure 15. Ln(Smoothed Hazard of Death) for Pembrolizumab + SOC

Figure 16. Log(Odds of Survival) for pembrolizumab + chemotherapy

The observed log(odds of survival) curve was relatively straight after week 40, indicating that the piecewise log-logistic model is appropriate.

Figure 17. Log(Inv. Normal Prob of Death) for pembrolizumab + SOC

Several piecewise parametric extrapolation curves, including the selected base-case log-logistic function, closely fit the observed log(inverse normal probability of death) curve.

SOC

Figure 18. Smoothed Hazard of Death for SOC (piecewise fitting with 40-week cut-off)

Figure 19. Ln(Smoothed Hazard of Death) for SOC

Figure 20. Log(Odds of Survival) for SOC

The observed log(odds of survival) curve was relatively straight after week 40, indicating that the piecewise log-logistic model is appropriate.

Figure 21. Log(Inv. Normal Prob of Death) for SOC

Several piecewise parametric extrapolation curves, including the selected base-case log-logistic function, closely fit the observed log(inverse normal probability of death) curve.

d. Please provide the above plots additionally for PFS (cumulative hazard versus time; LN(cumulative hazard) versus time; Q-Q plot; smoothed hazard versus time and LN(smoothed hazard versus time)

Please see the diagnostic plots provided below.

Figure 22. Cumulative hazard of PFSINV and Ln(Cumulative hazard of PFSINV)

Figure 22 above shows the ln(cumulative hazard) plots were not parallel.

Figure 23. Progression Free Survival Q-Q plot for pembrolizumab + SOC vs SOC

The Q-Q plot shows a large deviation from the straight dotted line, therefore an AFT model for PFS is not appropriate.

Figure 24. Smoothed hazard of PFSINV for Pembrolizumab + SOC

The log-logistic model with 10 weeks cut-off was shown as the best fitted curve to describe the trend in hazard of progression for pembrolizumab + SOC.

Figure 25. Ln(Smoothed hazard of PFSINV) for Pembrolizumab + SOC

Figure 26. Smoothed hazard of PFSINV for SOC

The log-logistic model with 10 weeks cut-off was shown as the best fitted curve to describe the trend in hazard of progression for SOC.

Figure 27. Ln(Smoothed hazard of PFSINV) for SOC

B6. The company interpret Figure 14 on page 87 to suggest that the proportional hazard assumption does not hold for OS. However, the log-cumulative hazard plot shows [redacted], and therefore the interpretation is subjective.

a. ***Please provide scenario analysis in the cost-effectiveness model where joint parametric models have been fit to the observed OS data after the identified cut-point with a covariate for treatment arm.***

b. ***Please provide the same scenario analysis using joint parametric models for the PFS observed data, if the diagnostic plots requested in B4d show support for proportional hazard or AFT models.***

MSD consider a joint parametric modelling approach for both OS and PFS to be inappropriate. As outlined within NICE TSD 14,

"When a parametric model is fitted to survival data two broad approaches may be taken. One option is to split the data and fit an individual or piecewise parametric model to each treatment arm. The second option is not to split the data and to fit one parametric model to the entire dataset, with treatment group included as a covariate in the analysis and assuming

proportional hazards. The approach taken is very often likely to reflect the nature of the comparison being drawn…

Generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach – the assumption should be tested which will indicate whether it may be preferable to separately fit parametric models to each treatment arm, or to allow for time-varying hazard ratios. Fitting separate parametric models to each treatment arm involves fewer assumptions, although it does also require the estimation of more parameters… Hence if the proportional hazards assumption does not seem appropriate it is likely to be most sensible to fit separate parametric models of the same type, allowing a two-dimensional treatment effect on both the shape and scale parameters of the parametric distribution."

The underlying assumption of applying a joint parametric model is that the two comparators will maintain a constant/proportional hazard ratio over time. This assumption would be inappropriate for the following reasons:

1) As outlined in the text above, when IPD is available, fewer assumptions are required when fitting separate parametric models, the assumption being that the proportional hazard assumption is met. On review of the quantile-quantile plots provided in question B5 (b) and B5 (d), MSD note that the observed data deviates from the constant over the time period, especially after week 40 the trajectory of the plot is very different. Therefore, this is supportive of the proportional hazard assumption not being met and fitting models separately being more appropriate.

2) MSD considers the mechanism of action of an immune checkpoint inhibitor in combination with chemotherapy to be substantially different from chemotherapy alone. Hence, MSD consider a joint parametric modelling approach (which would not allow a two-dimensional treatment effect on both the shape and scale parameters) would be unjustified. Chemotherapeutic agents such as cisplatin and 5-fluorouracil enhance immunogenicity of cancer cells and increase susceptibility to immune-mediated cytotoxicity (1). This is described by Antonia et al 2014 (2), "*Existing treatment modalities, (e.g., chemotherapy, radiotherapy, and molecularly targeted therapies) cause tumor reduction, not only through cytotoxic/cytostatic effects, but also through mechanisms that may potentiate immune activity, including modification of the tumor microenvironment and release of tumor antigens. This activity may be complementary, even synergistic, to the immunotherapies designed to support an antitumor immune response.*" This is supported by the higher objective response rate, and longer duration

of response observed with pembrolizumab in combination with chemotherapy in KEYNOTE-590.

B7. The cut-offs for the OS piece-wise models were identified based on structural changes identified via Chow tests. The Chow test statistics plot for the OS of the pembrolizumab in combination with chemotherapy arm is presented on page 89 (Figure 15). Please provide the Chow test statistics plot for the OS standard of care arm.

Please see Figure 28 below for the Chow test statics plot for the OS standard of care arm.

Figure 28. Plot of multiple Chow test statistics for OS in KEYNOTE-590: SOC, overall population

B8. The base case cut-off for the PFS piece-wise models (Week 10) was chosen based on the timing of the post-randomised imaging conducted at week 9. An alternative cut-off of 37-weeks is also provided in scenario analysis and in the cost-effectiveness model. Please justify why Week 37 was chosen as an alternative cut-off point and provide any associated plots used to inform this decision for both treatment arms (e.g., Chow test statistics).

Figure 29 below presents the PFS curve for pembrolizumab in combination with chemotherapy. The curve shows the last drastic drop (as shown by the vertical line) in PFS is

at 37 weeks which is in-line with tumour imagine schedule. Furthermore, the Chow test plot presented in Figure 30 shows that the 37-week time point is in close proximity to the peak of the Chow test plot thus signifying the structural change at this time point. Finally, MSD would like to note that PFS is not a major driver of cost-effectiveness in the model.

Figure 29. Progression Free Survival (INV) pembrolizumab + chemotherapy

Figure 30. Plot of multiple Chow test statistics for PFS in KEYNOTE-590: pembrolizumab in combination with chemotherapy, overall population

B9. The base case assumes a lifetime treatment effect for pembrolizumab in combination with chemotherapy versus chemotherapy alone. Please provide evidence supporting this assumption and justify the time points in the scenario exploring a 5- to 7-year treatment waning effect.

The pembrolizumab data currently available for this indication do not indicate a treatment waning effect. We acknowledge there may be insufficient long-term data to be conclusive that a treatment waning effect would not be present within pembrolizumab in combination with chemotherapy for oesophageal cancer. However, KEYNOTE trials with longer follow-up do not exhibit evidence of a loss of treatment effect after stopping treatment at 2 years. NICE TSD 14 states that in the absence of clinical evidence, an approach with clinically valid and justifable assumptions which are informed by clinical expert opinion and biological plausibilty should be undertaken and explored within scenario analysis.

The basis for assuming a sustained treatment effect is according to biological/clinical plausibility and longer-term follow-up data from KEYNOTE trials in different indications:

Biological/clinical plausibility

From a biochemical point of view, the mechanism of action of PD-1 inhibitors like pembrolizumab enable cytotoxic CD8+ T-cells avoid an exhausted state, thereby allowing them to keep the disease in a state of cancer-immune equilibrium, which can potentially be maintained for up to several decades even in the absence of continued therapy:

- Cytotoxic CD8+ T-cells (CTLs) are considered to be one of the main effector cell types of the adaptive immune system responsible for combating cancer cells. Functional tumour-reactive T-cells are able to proliferate, produce effector cytokines, and differentiate into memory T-cells that can successfully keep tumours dormant/subclinical for long periods of time, without eradicating the malignant cells completely, in a state termed cancer-immune equilibrium which can potentially be maintained for prolonged periods of time, possibly up to several decades(3,4).
- When effector CTLs enter the tumour microenvironment they encounter a complicated network of cells and cytokines including chronic antigen encounter from the tumour which can induce them to enter an “exhausted state” state in which T-cell effector functions and differentiation into memory T-cells are impaired (5). PD-L1 is one of the major factors in the tumour microenvironment because of its high expression in many cancer tissues and its capability to down-regulate and induce apoptosis in CTLs, the typical sign of T cell exhaustion is expression of the inhibitory receptor PD-1 and so the PD-1/PD-L1 pathway is a central regulator of T-cell exhaustion (5).

- Blockade of the PD-1:PD-L1 pathway can “reinvigorate” exhausted CTLs, restoring effector functions, increasing cell numbers, and generation of functional memory T-cells that can provide an ongoing anti-tumour effect for months to years, even in the absence of continued therapy (6,7).

Longer term KEYNOTE data

Longer term data from other KEYNOTE clinical trials has shown a continued treatment effect post discontinuation of pembrolizumab treatment at 2 years. In KEYNOTE-006 a long-term survival benefit has been observed in patients with advanced melanoma who were treated with pembrolizumab for up to 2 years (8). In patients who ceased treatment after completing 35 doses of pembrolizumab at 2 years, 78.4% remained in progression-free survival for at least 24 months (censored) following discontinuation (8). The long-term outcome seen in KEYNOTE-006 is generally consistent with the outcome seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year stopping rule (9). The cumulative and log-cumulative hazard plots below show that there is no structural difference between the hazards in these two trials. This can also be seen in the digitised KM data shown in Figure 31, Figure 32 and Figure 33. This data points towards a sustained treatment effect post discontinuation of pembrolizumab in melanoma patients.

These data are also the justification for the conservative approach undertaken within Scenario 4 of the company submission; whereby a sustained treatment effect is experienced up to 5 years, followed by a gradual treatment wane to 7 years.

Figure 31. Cumulative and log-cumulative hazard plots for OS in KEYNOTE-001

Figure 32. Cumulative and log-cumulative hazard plots for OS in KEYNOTE-006

Figure 33. Comparison of Overall Survival curves of KEYNOTE-001 and KEYNOTE-006 in melanoma

B10. Please present evidence to test whether the choice of censoring rule for PFS impacts method of extrapolation.

For the primary analysis, any subject who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any subject who initiates new anti-cancer therapy will be censored at the last disease assessment prior to the initiation of new anti-cancer therapy. Subjects who do not start new anti-cancer therapy and who do not experience an event will be censored at the last disease assessment. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by investigator assessment, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than complete response or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analyses are summarised in the trial protocol (10).

Sensitivity Analyses 1 and 2 for investigator assessments [Appendix A Table 1, Table 2] [Appendix A Figure 1, Figure 2] were consistent with the results of the primary analysis of PFS.

B11. The model considers two types of extrapolation method for estimating OS, and one type of extrapolation method for PFS. These methods are a single parametric model (OS only), and piece-wise models (with a Kaplan-Meier component and a parametric component; OS and PFS).

a. ***Please can the company provide explanation for why other flexible modelling approaches (e.g., spline-based models) were not considered, and, if deemed suitable, provide other approaches as an option within the model.***

Based on the NICE DSU TSD14, more flexible models should be considered when the hazard functions are observed or expected to have complex shapes. For this submission, the diagnostic plots for the hazard function (e.g., log-cumulative hazard plot, nonparametric smoothed hazard function) showed a relatively simple trend. The piecewise models with

standard parametric functions fit the observed data sufficiently well, especially with the selected base-case (Figure 18 in the company submission). In addition, at the time of database cut-off, most patients (70.2% in the pembrolizumab in combination with chemotherapy arm, 82.2% in the SOC arm) had died. The observed data were sufficiently mature to inform the standard parametric extrapolations. In some cases, more flexible models are useful when standard parametric fitting cannot provide adequate options to explore uncertainties in the extrapolation (e.g., very few curves generate plausible long-term OS estimates). For this submission, multiple standard functions (with the base-case cut-point at 40 weeks and alternative cut-points) provided clinically plausible long-term OS estimates, which allowed us to reasonably explore uncertainties associated with the curve selection.

More flexible models often require additional assumptions (11). For example, the assumption on the number and location of knots can significantly affect the extrapolation using spline-based models. More importantly, although a more flexible model may fit the observed data extremely well, it is not guaranteed that the extrapolation will be reliable (11). Considering the maturity of the observed data and the satisfactory performance of the standard parametric extrapolation methods, we decided not to explore more flexible models which would require additional assumptions.

b. Please can the company justify the exclusion of single parametric models for the outcome of PFS; or alternatively, please provide single parametric models for PFS for consideration within the model for completeness.

MSD have updated the economic model with fully fitted parametric models for PFS. Please see Figure 34 and Figure 35 below. A scenario analysis has been included within Appendix C using a fully fitted parametric curve approach for PFS, with the log-logistic distribution selected on the basis of best statistical fit.

Figure 34. Fully fitted parametric Progression Free Survival (INV) curves for pembrolizumab + chemotherapy

Figure 35. Fully fitted parametric Progression Free Survival (INV) curves for SOC

Adverse events

B12. On page 98 in Table 48, three literature sources (Yoon 2016; Cleary 2019; Waddell 2013) are presented as options to inform the adverse events rates for the blended comparator arm. However, these are not discussed within the company submission. Please provide further details on these sources and reasons why these are not considered for the base case for the blended comparator.

MSD presented the data from the three trials to show the similarity between KEYNOTE-590 AE data and that which is published in the literature. However, the data were not considered in the base case for several reasons. Firstly, the three trials listed in table 48 all included gastric cancer patients in their analysis which is not representative of the patient population observed in KEYNOTE-590. Secondly, the population numbers in the Yoon and Cleary phase II trials are small with n=80 and n=21, respectively. Thirdly, all the trials relate to the adenocarcinoma population whilst the KEYNOTE-590 includes both the squamous cell carcinoma and adenocarcinoma patients. Finally, there is a paucity in AE data from the three listed trials. None of the publications provide AE data for decreased appetite, hypokalemia, platelet count decrease, pneumonia and weight decrease and therefore will lead to an underestimation of AE costs and disutilities if used in the base case cost-effectiveness analysis.

Please see Appendix C for scenario analyses investigating the impact of sourcing AE rates from the literature for the blended chemotherapy comparison.

Health-related quality of life

B13. In KEYNOTE-590, the EQ-5D-5L questionnaire was administered on day 1 of every cycle from cycle 1 to 9, after which it was administered every 3 cycles for up to 1 year or until the end of treatment, whichever occurred first. The EQ-5D data were also collected at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit.

a. ***Please clarify why questionnaires were not administered beyond year 1 if patients were still on treatment and progression-free given the maximum treatment duration is approximately 2-years?***

In determining the assessment scheduled the median PFS of the control arm was taken under consideration as a guide to the assessment schedule in addition to stopping administration at a time where completion/compliance rates were expected to be at a level where interpreting results would be acceptable.

b. ***The FAS population were required to have completed at least one EQ-5D-5L questionnaire. Please confirm if this questionnaire is in addition to a questionnaire completed at baseline, or if a baseline questionnaire was considered to be the one questionnaire needed to be completed. If the latter is true, please confirm how many patients were included in the analysis that only had a baseline EQ-5D value***

The FAS population consists of all randomized subjects who have received at least one dose of study medication and have completed at least one PRO assessment during the study follow up for each instrument.

The mixed effects model for the utility analysis was based on the EQ-5D FAS population with baseline questionnaire. Patients were required to complete the baseline questionnaire to be included in the mixed effects model (FAS for EQ-5D with baseline, N=713). 40 patients included in the mixed effects model only had a baseline EQ-5D value.

c. ***Please confirm at what point in time progressed patients that discontinued treatment were told they had progressed in relation to the assessment of HRQoL at the time of discontinuation (i.e., was the***

questionnaire given before or after patients knew they had progressed if that was the reason for discontinuing treatment?).

HRQoL Assessments were administered until the treatment-discontinuation visit (could be for multiple reasons including progression) and at the 30-day safety follow-up visit.

d. Please confirm how many patients died before progression.

Table 10. Summary of Time to Death (ITT population)

	Pembrolizumab + chemotherapy		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	367		360		727	
Death Category						
Died after PD	185	(50.4)	224	(62.2)	409	(56.3)
Died without PD	73	(19.9)	73	(20.3)	146	(20.1)
Alive	109	(29.7)	63	(17.5)	172	(23.7)
(Database Cutoff Date: 02JUL2020)						

B14. Utilities were calculated using two approaches: a time-to-death approach, and a progression-based approach. Both approaches were estimated using linear mixed effects models.

a. Did these models account for baseline utility? If not, please provide revised models which adjust for patients' baseline utility. Please also provide the results of this analysis within an updated cost-effectiveness model and present the cost-effectiveness results using these utility models.

Baseline utility has been accounted for within the mixed linear effects model for both approaches.

b. Please justify why the time points 0-29, 30-89, 90-179, 180-359 and ≥360 days until death were chosen for the time-to-death utility categories.

This approach is consistent with previous HTA's in a metastatic oncology setting (12–14).

c. Please confirm if the 318 utility measures which had an unknown time-to-death category were removed from the analysis.

The unknown time-to-death category was included in the mixed effects model as the records collected in this category can contribute to the AE disutility estimation. Excluding records with

unknown time-to-death category had minimal impact on the results, please see the table below.

Table 11. Comparison of time-to-death utilities with the unknown time-to-death category included and excluded.

Time to death (days)	Pooled treatment arms (unknown included)	Pooled treatment arms (unknown excluded)
unknown	0.829	-
≥360	0.855	0.855
[180, 360)	0.814	0.814
[90, 180)	0.748	0.748
[30, 90)	0.647	0.647
<30	0.499	0.499
Disutility for Grade 3+ AE	-0.036	-0.037
Key: 5-FU, fluorouracil; AE, adverse events. **Source:** KEYNOTE-590 (data cut-off date: July 2, 2020).		

d. Please comment on the face validity of the estimates produced by the time-to-death approach, acknowledging that the value estimated for the state furthest from death suggests a utility in excess of that expected for the age- and sex-adjusted general population (as shown in the company's submitted model)

MSD acknowledge the questionable face validity in suggesting patients with metastatic oesophageal could have higher utility than that of the general population. However, MSD would like to note that this is a phenomenon commonly seen in oncology trials.

MSD have updated the company base case to cap utility with general population

B15. Please provide tables which detail the number of patients and utility observations that were included in the analysis for each of the health state categories (i.e., 0-29, 30-89, 90-179, 180-359 and ≥360 days until death and progression-free/progressive-disease).

Please see the table below.

Table 12. Sample size for utility by time-to-death

Fixed effects parameter	Number of records	Number of patients
T2DTHCAT <30	114	95
T2DTHCAT [30, 90)	483	255
T2DTHCAT [90, 180)	971	355
T2DTHCAT [180, 360)	1488	353
T2DTHCAT >=360	2370	320
Unknown	318	105

Costs and resource use

B16. A blended chemotherapy arm is included in the model and it is assumed that the costs of each of the components within the blended chemotherapy arm are weighted equally (i.e., assumed market share of 12.5% for each of the eight regimens). Please provide justification for this assumption and whether this is reflective of UK clinical practice.

MSD attempted to source market share data and input from clinical experts to inform the comparison versus a blended comparator. However, the market share data lacked face validity when assessed versus the comparators outlined in the NICE Final Scope. MSD also posed the question to clinical experts at an advisory board held on the 29th January. The clinical experts present expressed that although they would not use triplet regimens, they believed that these therapies were still used in the UK. Because of this, they weren't able to provide market share expectations. Therefore, MSD chose to include all therapies listed in the final NICE scope and distribute them evenly with respect to market shares. MSD acknowledges that in practice the market share distribution of comparator therapies is not equal, and a scenario analysis was conducted to investigate the impact that the different regimens included in the blended comparator arm have on the ICER, the results of which showed that there was little difference in the ICER between the results for each of the therapies.

B17. Time on treatment data from KEYNOTE-590 are used to inform how many patients are on treatment per cycle, broken down by each component of the regimen.

a. ***Given the maturity of data, the Kaplan-Meier estimates of ToT are used directly to inform the model. By the data cut off 02 July 2020, please confirm if all patients have discontinued treatment or how many patients are still on treatment in each arm.***

Please see

Table **13**, Table 14 and Table 15 below, which detail the number of events in each treatment of each arm in the ITT population.

Table 13. Estimated Median and Mean Time On Pembrolizumab Treatment (All-Subjects-as-Treated Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC	370	346 (93.5)	24.000	(21.714, 25.286)	33.670	1.659	(30.418, 36.923)

Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method
Time on Treatment is defined as the time from the date of initial dose until the date of last dose
Number of Events is defined as the number of subjects who had discontinued or completed pembrolizumab treatment at the time of the database cutoff date
Database Cutoff Date: 02JUL2020

Table 14. Estimated Median and Mean Time On Cisplatin Treatment (All-Subjects-as-Treated Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC	370	370 (100.0)	15.286	(15.143, 15.571)	13.072	0.314	(12.456, 13.688)
SOC	370	370 (100.0)	15.143	(15.000, 15.286)	12.687	0.316	(12.068, 13.307)

Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method
Time on Treatment is defined as the time from the date of initial dose until the date of last dose
Number of Events is defined as the number of subjects who had discontinued or completed cisplatin treatment at the time of the database cutoff date
Database Cutoff Date: 02JUL2020

Table 15. Estimated Median and Mean Time On 5-Fluorouracil Treatment (All-Subjects-as-Treated Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC	370	362 (97.8)	17.286	(16.714, 18.714)	24.867	1.278	(22.362, 27.372)
SOC	370	367 (99.2)	16.857	(16.143, 17.714)	21.328	0.959	(19.448, 23.207)

Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method
Time on Treatment is defined as the time from the date of initial dose until the date of last dose
Number of Events is defined as the number of subjects who had discontinued or completed 5-FU treatment at the time of the database cutoff date
Database Cutoff Date: 02JUL2020

b. In KEYNOTE-590, some patients received treatment after the "maximum cut-off points" of 6 cycles and 2 years, which may be due to dose delays. Please provide a scenario analysis where the "cut-off points" are disabled.

Please see Appendix C for scenario analysis investigating the removal of cut-off points. MSD would like to note the proportion of patients receiving treatment after the pre-specified stopping rule was very low (<5%).

B18. The model accounts for missed doses and dose reductions using relative dose intensity. For pembrolizumab, the value of 93.4% is taken from the KEYNOTE-590 trial. Please provide more information concerning how this value was estimated. More specifically, please confirm if this value includes dose reductions and if so, please describe the nature of these dose reductions.

Treatment compliance is summarized separately for each component of the protocol regimen.

Treatment compliance of pembrolizumab is expressed as the percentage of actual vs expected number of treatment cycles per subject. More specifically, it is defined as the number of treatment cycles of non-zero dose pembrolizumab a subject received within the protocol regimen, divided by the number of pembrolizumab cycles a subject is expected to receive based on the treatment duration. If it exceeds 100%, it is further investigated whether the treatment duration equals or exceeds the lower bound of the expected treatment duration, which is defined as the actual number of treatment cycles multiplied by 18 days (the lower bound of the visit window (21+/-3days)). If this is the case, then the percentage is remediated to 100%. The treatment duration is defined as the number of days between the date of the first dose until the date of the last dose during the protocol regimen for any treatment component.

Treatment compliance of cisplatin / 5-FU is expressed as the percentage of actual dosage vs expected dosage per subject. More specifically, it is defined as the total dosage of cisplatin or 5-FU a subject received within the protocol regimen, divided by the total dosage of cisplatin or 5-FU a subject is expected to receive based on the treatment duration and the scheduled dose.

B19. On page 112 of the CS, Table 57, the company presents the administration costs associated with each treatment.

a. ***All but one treatment regimen uses the NHS reference cost "SB14Z Deliver complex chemotherapy. Including prolonged in fusional treatment at first attendance". Please confirm why oxaliplatin plus capecitabine uses a different cost code of "SB13Z deliver more complex Parenteral chemotherapy at first attendance".***

The National Tariff Chemotherapy Regimens List was used to ascertain the HRG codes associated with the administration of the each of the regimens included in the cost-effectiveness model (15). Based on the information provided by this source the HRG code for oxaliplatin in combination with capecitabine is SB13Z, whilst the remaining regimens are coded by the HRG code SB14Z (16).

b. ***The unit costs assigned for chemotherapy administrations are based on the expectation that administration would take place in an <u>outpatient</u> setting. Please provide a scenario analysis where costs are instead based on the expectation that administration would take place in a <u>day case</u> setting***

MSD has updated the model and implemented a setting whereby the day case costs can be selected to calculate the ICER, please see Appendix C for cost-effectiveness analyses.

B20. Frequency of resource use for the progression-free health state was based on clinical expert opinion and from a previous NICE appraisal TA378 (ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy) for the progressed state.

a. ***Based on the ERG's understanding of clinical advice provided, in NHS practice patients are currently monitored every three weeks whilst on platinum-based chemotherapy (e.g., cisplatin) then every 3 months while continuing treatment with a fluoropyrimidine (e.g., fluorouracil). If patients are still receiving pembrolizumab after discontinuation of platinum-based chemotherapy, then monitoring would therefore be every 6 weeks, instead of every 3 months (as is currently the case in the company's model). Please revise the frequencies of monitoring in the***

PFS health state to account for the additional monitoring incurred by patients who remain on pembrolizumab treatment after stopping platinum-based chemotherapy.

b. ***The progressed state only considers a consultation visit every 12 weeks; however, this is not reflective of the monitoring patients incur if they go on to receive subsequent therapy. In TA378, monitoring costs for CT scans, full blood count, renal function test, hepatic function test and consultation visits were included whilst patients were on treatment. Please revise the progressed disease state monitoring frequencies to account for monitoring of those patients who have subsequent treatment.***

Disease management costs applied in the model are linked to the progression free survival curve, not to the pembrolizumab time on treatment curve. As such, treatment status does not impact the monitoring costs. For patients in the progression-free health state the frequency of consultation visits, full blood counts, liver function tests, renal function tests and CT scans remain constant irrespective of treatment status.

For progressed disease patients the model has been updated to incorporate a one-off disease management cost for those patients who receive subsequent therapies- this change is reflected within the updated company base case, please see Appendix C.

B21. The model includes subsequent treatment as a one-off cost when a patient progresses. These are based on the distributions observed in KEYNOTE-590 if they were received by ≥5% of patients. Please provide a table which lists all the subsequent treatments received in the KEYNOTE-590 trial with the proportion of patients split by treatment arm. Based on the response to question B13d, about deaths occurring prior to progression, please adjust any estimates used to inform subsequent therapy costs to account for pre-progression deaths versus progression events within the PFS analysis

Please see the full list of subsequent line treatments in Table 16 below.

Table 16. Duration of New Oncologic Therapies in Days Across All Subsequent Lines after Discontinuing from Study Treatment (ITT population)

Treatment duration Across All Lines[a] (days)	Pembrolizumab + SOC (N=370)			SOC (N=370)			Pooled (N=740)		
	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)
With one or more new Oncologic Therapies	[redacted]								
SHP2 protein tyrosine phosphatase inhibitor (unspecified)									
[composition unspecified]									
afatinib									
anlotinib									
anlotinib hydrochloride									
anti-4-1BB/anti-PDL1 bispecific monoclonal antibody									
anti-LAG-3 monoclonal antibody (unspecified)									
anti-PD1 monoclonal antibody (unspecified)									
anti-PDL1 monoclonal antibody TGF-beta fusion protein									
apatinib mesylate									
avelumab									
bavituximab									
bleomycin									
cabozantinib									
calcium folinate									
camrelizumab									
capecitabine									
carboplatin									
cell division cycle 7-related protein kinase inhibitor (unspecified)									
cetuximab									

Treatment duration Across All Lines[a] (days)	Pembrolizumab + SOC (N=370)			SOC (N=370)			Pooled (N=740)		
	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)
cisplatin	[redacted]								
cisplatin (+) irinotecan hydrochloride									
denosumab									
diphenhydramine									
docetaxel									
epirubicin									
eribulin mesylate									
etoposide									
everolimus									
fluorouracil									
folic acid									
folinic acid									
gemcitabine									
gemcitabine hydrochloride									
gimeracil									
gimeracil (+) oteracil potassium (+) tegafur									
ifosfamide									
ipilimumab									
irinotecan hydrochloride									
lenvatinib mesylate									
leucovorin calcium									

Treatment duration Across All Lines[a] (days)	Pembrolizumab + SOC (N=370)			SOC (N=370)			Pooled (N=740)		
	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)
levoleucovorin calcium	[redacted]								
methotrexate	[redacted]								
methotrexate sodium	[redacted]								
mitomycin	[redacted]								
nedaplatin	[redacted]								
nimotuzumab	[redacted]								
nivolumab	[redacted]								
olaparib	[redacted]								
oncolytic recombinant hTERT promotor-expressing virus therapy (adenovirus)	[redacted]								
oteracil	[redacted]								
oteracil potassium	[redacted]								
oxaliplatin	[redacted]								
paclitaxel	[redacted]								
paclitaxel albumin	[redacted]								
pembrolizumab	[redacted]								
raltitrexed	[redacted]								
ramucirumab	[redacted]								
recombinant human endostatin	[redacted]								
recombinant human interleukin-2 (125Ala)	[redacted]								
regorafenib	[redacted]								
rituximab	[redacted]								

Treatment duration Across All Lines[a] (days)	Pembrolizumab + SOC (N=370)			SOC (N=370)			Pooled (N=740)		
	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)
sintilimab	[redacted]								
study drug (unspecified)									
tegafur									
tegafur (+) uracil									
thymosin									
tipiracil hydrochloride (+) trifluridine									
vinorelbine tartrate									
wild turmeric									
yttrium-90									
zoledronic acid									

a: Subsequent therapy duration is defined as the days from start date of the treatment until the stop date of treatment, or until censoring date of overall survival if the stop date is not available, or until the database cutoff date for the treatment initiated after the censoring date of overall survival

b: Every subject is counted a single time for each applicable row and column

c: Each medication is counted a single time for each applicable row and column

NA: Not applicable

Database Cutoff Date: 02JUL2020

In the submitted model, the proportion of patients receiving a specific subsequent line treatment was calculated based on number of patients who received the specific subsequent treatment regardless of treatment lines divided by total number of patients in the as-treated population. Since not all patients had experienced disease progression at the database cut-off date, this simplified approach may slightly underestimate the proportion of patients receiving subsequent line treatments.

The following scenario analysis has been conducted to address the uncertainty in the subsequent line modelling approach.

Subsequent line costs applied at time of progression. At the database cut-off date, 297 (79.6%) patients in the pembrolizumab + SOC arm and 333 (88.6%) patients in the SOC arm had experienced disease progression. The proportion of patients receiving subsequent line treatments were calculated based on the number of patients who received a specific subsequent treatment divided by number of patients who experienced disease progression.

Patients who died before progression were considered as an event in the PFS analysis. They were counted in the denominator when calculating the incidence and when applying the incidence in the model. No additional adjustment is needed.

Table 17. Subsequent therapy distribution scenario analysis

	Pembrolizumab + 5-FU + cisplatin		5-FU + cisplatin	
N experienced a PFS event	297		333	
	n	%	n	%
Cisplatin	32	11.6%	26	8.6%
Docetaxel	36	13.0%	27	8.9%
5-FU	42	15.2%	42	13.9%
Irinotecan hydrochloride	19	6.9%	30	9.9%
Oxaliplatin	23	8.3%	13	4.3%
Paclitaxel	86	31.2%	102	33.7%
Ramucirumab	16	0.0%	20	0.0%

Sensitivity analysis

B22. The ERG has identified a number of errors relating to the parameters included in one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). Please revise the following and provide results of OWSA and PSA after the revisions.

a. ***Normal distributions should be used for cost inputs if they are based on an average for a cohort (e.g., NHS reference costs or PSSRU costs). Please change the Gamma distributions to Normal distributions for these cost inputs.***

b. ***Parameters which have a multi-variate distribution should not be varied individually in OWSA. Please remove these parameters from the OWSA (e.g., survival distribution parameters and utility coefficients)***

c. ***Drug costs derived from eMIT should be included in sensitivity analysis using the uncertainty information provided (i.e., these are not fixed costs, and should be varied within sensitivity analysis using the provided standard errors reported in eMIT). Please include these in OWSA and PSA.***

d. ***Individual elements of costs should be included separately in OWSA and PSA to assess the uncertainty of each parameter (e.g., adverse event rates and unit costs per adverse event instead of total adverse event costs and resource use frequencies and unit costs instead of overall health state costs). Please include all parameters in OWSA and PSA individually before calculating the total costs using the appropriate distributions.***

The economic model has been updated to reflect the changes requested in parts (a), (b) and (c). Please see Appendix C for the updated sensitivity analysis.

The updates requested in part (d) have not been implemented as this would require substantial modification of the model programming, and MSD are confident that the impact on the sensitivity analysis results would be minimal, and unimpactful on the deterministic base case

result. Indeed, this was taken into account in the original model programming, and overall health state costs were accordingly used as the input.

Validation and transparency

B23. The company submission makes several references to clinical expert opinion for various inputs for the model and for validation.

a. ***Please provide details on how this clinical expert opinion was sought, how many clinical advisors were recruited and their relevant experience to oesophageal cancer and/or gastroesophageal junction adenocarcinoma.***

b. ***Please describe information regarding the questions that have been asked and the accompanying responses.***

c. ***Please provide the full reference which details the discussions with clinical experts which have been used throughout the submission document.***

MSD sought clinical expert opinion by conducting informal interviews with four clinical oncologists, separately, working in the treatment of oesophageal cancer. MSD also conducted an advisory board on the 29th January, however due to the proximity to the submission date, the outputs were not used to justify the assumptions made within the company submission.

Due to the informal nature of the interviews with clinical experts, MSD consider that it would not be appropriate to share the outputs of these interviews.

MSD are confident that the information shared by the clinicians interviewed is reflective of UK clinical practice and will be further verified by clinical experts throughout this appraisal.

Section C: Textual clarification and additional points

C1. On page 81, Document B, it is stated that *"For each health state, a specific cost and quality-of-life adjustment weight (i.e., utility) is assigned within each time period for calculating the cumulative costs and cumulative QALYs over the modelled time horizon."* The ERG notes that in the base case utilities are assigned as time-to-death and not to each specific health state of the model structure. Please clarify that this statement refers to the scenario analysis where utilities are based on progression status.

MSD can confirm the ERG's interpretation is correct.

C2. Please can you provide the citation information for the economic evaluations identified in the searches reported in Appendix G (p.165)

The citations for the studies identified in appendix G of the submission are listed below:

Janmaat, V.T., et al., Cost-Effectiveness of Cetuximab for Advanced Oesophageal Squamous Cell Carcinoma. PLoS One, 2016. 11(4): p. e0153943.

Peng-Fei Zhang, D., Qiu Li, Cost–effectiveness analysis of nivolumab in the second-line treatment for advanced oesophageal squamous cell carcinoma. Future Oncology, 2020. 16(17): p. 1189-1198.

Virik, Kiran, and Robert B. Wilson. "The potential drug cost impact of nivolumab (N) in patients with advanced/metastatic gastric cancer (GC) or gastroesophageal junction cancer (GEJC) in Canada." (2019): 101-101.

Yang F, F.Y., Chen M, Cost-Effectiveness Analysis of Camrelizumab As the Second-LINE Therapy for Advanced or Metastatic Esophageal Squamous Cell Carcinoma in Mainland China. ISPOR Europe 2020, Milan, Italy 2020.

Meads, D.M., et al., The Cost Effectiveness of Docetaxel and Active Symptom Control versus Active Symptom Control Alone for Refractory Oesophagogastric Adenocarcinoma: Economic Analysis of the COUGAR-02 Trial. Pharmacoeconomics, 2016. 34(1): p. 33-42.

Webb, A., et al., Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol, 1997. 15(1): p. 261-7.

S., O., C. J.G., and H. C. Cost-efectiveness of immune checkpoint inhibition in metastatic gasric and esophageal tumors. in ASCO. 2018.

Tran, G., et al., PCN95 Pharmacoeconomic Analysis of Direct Medical Costs Associated With the Treatment of Advanced Esophago-Gastric Cancer Therapy With Xeloda or 5-Fluorouracil (5-FU) Regimens: Implications for Health Care Utilisation in Australia. Value in Health, 2012. 15(7): p. A426.

Horgan, A.M., et al., Capecitabine or infusional 5-fluorouracil for gastroesophageal cancer: a cost-consequence analysis. Curr Oncol, 2011. 18(2): p. e64-70.

K, V., Economic evaluation of trifluridine/tipiracil (TT) versus nivolumab (N) in patients with advanced/metastatic gastric cancer (GC) or gastro-esophageal junction cancer (GEJC) in Canada. J Clin Oncol, 2020. 38.

C3. Please can you provide the citation information for Agus et al. (2013) and the 15 non-UK cost and resource use studies identified in the searches reported in Appendix I (p. 203)

The citations for the studies identified in appendix I of the submission are listed below:

Agus, A.M., et al., Description and predictors of hospital costs of oesophageal cancer during the first year following diagnosis in Northern Ireland. Eur J Cancer Care (Engl), 2013. 22(4): p. 450-8.

A list of the citations for the non-UK studies is listed below:

Hsieh CC, Chien CW. A cost and benefit study of esophagectomy for patients with esophageal cancer. Journal of Gastrointestinal Surgery. 2009 Oct 1;13(10):1806-12.

Thein HH, Jembere N, Thavorn K, Chan KK, Coyte PC, de Oliveira C, Hur C, Earle CC. Estimates and predictors of health care costs of esophageal adenocarcinoma: a population-based cohort study. BMC cancer. 2018 Dec;18(1):1-9.

Kaye DR, Min HS, Herrel LA, Dupree JM, Ellimoottil C, Miller DC. Costs of cancer care across the disease continuum. The oncologist. 2018 Jul;23(7):798.

Gordon LG, Eckermann S, Hirst NG, Watson DI, Mayne GC, Fahey P, Whiteman DC, Australian Cancer Study Clinical Follow-Up Study. Healthcare resource use and medical costs for the management of oesophageal cancer. British journal of surgery. 2011 Nov;98(11):1589-98.

Pinto M, Ugá MA. Cost of treating patients with smoking history in a specialized cancer hospital. Revista de saude publica. 2011 Apr 20;45:575-82.

Guo LW, Huang HY, Shi JF, Lv LH, Bai YN, Mao AY, Liao XZ, Liu GX, Ren JS, Sun XJ, Zhu XY. Medical expenditure for esophageal cancer in China: a 10-year multicenter retrospective survey (2002–2011). Cancer Communications. 2017 Dec;36(1):1-2.

Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, Brown ML. Cost of care for elderly cancer patients in the United States. Journal of the National Cancer Institute. 2008 May 7;100(9):630-41.

Yang Z, Zeng H, Xia R, Liu Q, Sun K, Zheng R, Zhang S, Xia C, Li H, Liu S, Zhang Z. Annual cost of illness of stomach and esophageal cancer patients in urban and rural areas in China: A multi-center study. Chinese Journal of Cancer Research. 2018 Aug;30(4):439.

Prithviraj GK, Baksh K, Fulp W, Meredith K, Hoffe S, Shridhar R, Almhanna K. Carboplatin and paclitaxel as first-line treatment of unresectable or metastatic esophageal or gastric cancer. Diseases of the Esophagus. 2015 Dec 1;28(8):782-7.

Ilson DH, Forastiere A, Arquette M, Costa F, Heelan R, Huang Y, Kelsen DP. A phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the esophagus. Cancer journal (Sudbury, Mass.). 2000 Sep 1;6(5):316-23.

Lai WW, Lin CN, Chang CC, Wang JD. Lifetime risks, expected years of life lost, and cost-per-life year of esophageal cancer in Taiwan. Scientific reports. 2020 Feb 28;10(1):1-8.

Jaffe D, DeCongelio M, Dubell A, Stetson J, Gricar J. PCN167 Treatment patterns and healthcare resource utilization (HCRU) in advanced squamous esophageal carcinoma cancer in north america, europe and asia. Value in Health. 2019;22:S87-S8.

Tramontano AC, Chen Y, Watson TR, Eckel A, Hur C, Kong CY. Esophageal cancer treatment costs by phase of care and treatment modality, 2000-2013. Cancer medicine. 2019 Sep;8(11):5158-72.

Abraham P, Wang L, Jiang Z, Gricar J, Tan H, Kelly R. Healthcare resource utilization and total costs of care among patients with esophageal cancer: An administrative claims analysis. Journal of Managed Care and Specialty Pharmacy. 2019;25:S74-S5.Abraham PS, Wang L, Jiang Z, Gricar J, Tan H, Kelly RJ. PCN97 Healthcare resource utilization (hcru) and total costs of care among patients with gastroesophageal junction cancer (gejc): an administrative claims analysis. Value in Health. 2019;22:S74.

C4. Please can you provide the citation information for the list of studies included in the utility review reported in Appendix H (p. 182)

The citations for the studies identified in appendix H of the submission are listed below:

Liu, Q., et al., Health-related quality of life of oesophageal cancer patients in daily life after treatment: A multicentre cross-sectional study in China. Cancer Med, 2018. 7(11): p. 5803-5811.

Zhao, Z.M., et al., Quality of life among patients with oesophageal/cardiac precursor lesion or cancer: A one-year prospective survey. Value in Health, 2014. 17(7): p. A738.

Doherty, M., et al., The relationship between health utility, quality of life, and symptom scores in Canadian patients with oesophageal cancer. Journal of Clinical Oncology, 2015. 33(3).

Doherty, M.K., et al., Health utility scores from EQ-5D and health-related quality of life in patients with oesophageal cancer: a real-world cross-sectional study. Dis Esophagus, 2018. 31(12).

Wildi, S.M., et al., Assessment of health state utilities and quality of life in patients with malignant oesophageal Dysphagia. Am J Gastroenterol, 2004. 99(6): p. 1044-9.

Kato K, C.B., Takahashi M, Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, Phase III trial. Lancet Oncol., 2019. 20(11): p. 1506–1517.

Wang, Y., et al., Health-related quality of life in patients with oesophageal cancer or precancerous lesions assessed by EQ-5D: A multicentre cross-sectional study. Thoracic Cancer, 2020. 11(4): p. 1076-1089.

Janmaat, V.T., et al., Cost-Effectiveness of Cetuximab for Advanced Oesophageal Squamous Cell Carcinoma. PLoS One, 2016. 11(4): p. e0153943.

C5. In Doc B Table 28 the numbers and percentages for Europe have not been inserted for KEYNOTE-590. Please supply these values.

The numbers and percentages of EU participants have been included in Table 18 below. It should be noted that 23 patients from Russia and 25 from Turkey participated in the trial and are not included in the table.

Table 18. Participant Characteristics (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	373		376		749	
Geographic Location: EU						
EU	61	(16.4)	53	(14.1)	114	(15.2)
Database Cutoff Date: 02JUL2020						

References

1. Bang YJ, Kang YK, Catenacci D V., Muro K, Fuchs CS, Geva R, et al. Pembrolizumab alone or in combination with chemotherapy as first-line therapy for patients with advanced gastric or gastroesophageal junction adenocarcinoma: results from the phase II nonrandomized KEYNOTE-059 study. Gastric Cancer [Internet]. 2019;22(4):828–37. Available from: http://dx.doi.org/10.1007/s10120-018-00909-5

2. Antonia SJ, Larkin J, Ascierto PA. Immuno-oncology combinations: A review of clinical experience and future prospects. Clin Cancer Res. 2014;20(24):6258–68.

3. Gabriel SS, Kallies A. Tissue-resident memory T cells keep cancer dormant. Cell Res [Internet]. 2019;29(5):341–2. Available from: http://dx.doi.org/10.1038/s41422-019-0156-5

4. Park SL, Buzzai A, Rautela J, Hor JL, Hochheiser K, Effern M, et al. Tissue-resident memory CD8+ T cells promote melanoma–immune equilibrium in skin. Nature. 2019;565(7739):366–71.

5. Kim PS, Ahmed R. Features of Responding T cells in Cancer and Chronic Infection. Curr Opin Immunol. 2010;22(2):223–30.

6. Pauken KE, Wherry JE. Overcoming T cell exhaustion in infection and cancer. Trends Immunol. 2015;36(4):265–76.

7. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Janis M, Anders RA, et al. Durable Cancer Regression Off-treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody. Clin Cancer Res. 2013;19(2):462–8.

8. Robert C, Ribas A, Schachter J, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol [Internet]. 2019;20(9):1239–51. Available from: http://dx.doi.org/10.1016/S1470-2045(19)30388-2

9. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30(4):582–8.

10. Merck Sharpe & Dohme Corp. Protocol of A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin

and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subj. 2020.

11. Rutherford MJ, Lambert PC, Sweeting MJ, Pennington B, Crowther MJ, Abrams KR, et al. NICE DSU TECHNICAL SUPPORT DOCUMENT 21 : Flexible Methods for Survival Analysis. 2020;(January):1–97.

12. The National Institute for Health and Care Excellence (NICE). Single Technoology Appraisal (STA): Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer [TA600]. 2019;

13. The National Institute for Health and Care Excellence (NICE). Single Technology Appraisal (STA): Pembrolizumab with pemetrexed and platinum chemotherapy for untreated lung cancer [TA557]. 2018;1–765.

14. The National Institute for Health and Care Excellence (NICE). Single Technology Appraisal (STA): Pembrolizumab with axitinib for untreated advanced renal cell carcinoma [TA650]. 2020;101–2.

15. The National Tariff Chemotherapy Regimens List [Internet]. 2018. Available from: https://hscic.kahootz.com/gf2.ti/f/762498/27839109.1/XLSX/-/NatTarChemoRegList1718.xlsx

16. NHS England. National Schedule of NHS Costs - NHS Reference Costs 2018/19 [Internet]. 2019. Available from: https://www.england.nhs.uk/wp-content/uploads/2020/08/2_-_National_schedule_of_NHS_costs_V2.xlsx

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab with platinum-based chemotherapy for untreated, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma [ID3741]

MSD response to Clarification questions

Appendices

February 2021

File name	Version	Contains confidential information	Date
ID3741 Pembro for OC Clarification Letter for ERG v0.1 10.2.2021 APPENDICES ACIC	1	Yes	23-Feb-21

Appendix A

A23. Please provide relevant estimates of PFS across all relevant subgroups using each of the sensitivity analysis censoring rules.

The censoring rules for the primary and sensitivity analyses are summarized in Table 1. The analyses of progression-free survival based on investigator assessment per RECIST 1.1 for the sensitivity censoring rules 1 and 2 are presented in Table 2 and Table 3 for all participants, Table 4 and Table 5 for participants with squamous cell carcinoma, Table 6 and Table 7 for participants with PD-L1 CPS>= 10, Table 8 and Table 9 for participants with adenocarcinoma, Table 10 and Table 11 for participants with adenocarcinoma and PDL1 CPS ≥ 10, Table 12 and Table 13 for participants with squamous cell carcinoma and PD-L1 CPS >= 10. The corresponding KM curves for the sensitivity censoring rules 1 and 2 are presented in Figure 1 to Figure 12.

Table 1 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression after ≥2 consecutive missed disease assessments without further valid non- PD disease assessments, or after new anti-cancer therapy	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
Abbreviations: PD = progressive disease			

Table 2 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months)(95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.Database Cutoff Date: 02JUL2020.

Figure 1 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (ITT Population)

Table 3 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months)(95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC						
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first. Database Cutoff Date: 02JUL2020.

Figure 2 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (ITT Population)

Table 4 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Subjects with Squamous Cell Carcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months)(95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC						
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1). Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: 02JUL2020.

Figure 3 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Subjects with Squamous Cell Carcinoma, ITT Population)

Table 5 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Subjects with Squamous Cell Carcinoma, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months)(95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC						
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1). Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: 02JUL2020.

Figure 4 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Subjects with Squamous Cell Carcinoma, ITT Population)

Table 6 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Subjects with PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months)(95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC						
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.Database Cutoff Date: 02JUL2020.

Figure 5 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Subjects with PD-L1 CPS >= 10, ITT Population)

Table 7 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Subjects with PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months)(95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC						
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and tumor histology (Adenocarcinoma versus Squamous Cell Carcinoma).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first. Database Cutoff Date: 02JUL2020.

Figure 6 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Subjects with PD-L1 CPS >= 10, ITT Population)

Table 8 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Participants with Adenocarcinoma, ITT Population)

				Event Rate/	Median PFS †	PFS Rate at
		Number of	Person-	100 Person-	(Months)	Month 6 in % †
Treatment	N	Events (%)	Months	Months	(95% CI)	(95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: 02JUL2020.

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Figure 7 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Participants with Adenocarcinoma, ITT Population)

Table 9 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Participants with Adenocarcinoma, ITT Population)

				Event Rate/	Median PFS †	PFS Rate at
		Number of	Person-	100 Person-	(Months)	Month 6 in % †
Treatment	N	Events (%)	Months	Months	(95% CI)	(95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: 02JUL2020.

Figure 8 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Participants with Adenocarcinoma, ITT Population)

Table 10 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Participants with Adenocarcinoma and PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: 02JUL2020.

Figure 9 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Participants with Adenocarcinoma and PD-L1 CPS >= 10 , ITT Population)

Table 11 Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Participants with Adenocarcinoma and PD-L1 CPS >= 10, ITT Population)

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months	Median PFS † (Months) (95% CI)	PFS Rate at Month 6 in % † (95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: 02JUL2020.

Figure 10 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Participants with Adenocarcinoma and PD-L1 CPS >= 10 , ITT Population)

Table 12 Analysis of Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Participants with Squamous Cell Carcinoma and PD-L1 CPS >= 10 , ITT Population)

				Event Rate/	Median PFS †	PFS Rate at
		Number of	Person-	100 Person-	(Months)	Month 6 in % †
Treatment	N	Events (%)	Months	Months	(95% CI)	(95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: Database Cutoff Date: 02JUL2020.

Figure 11 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 1) (Participants with Squamous Cell Carcinoma and PD-L1 CPS >= 10 , ITT Population)

Table 13 Analysis of Analysis of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Participants with Squamous Cell Carcinoma and PD-L1 CPS >= 10 , ITT Population)

				Event Rate/	Median PFS †	PFS Rate at
		Number of	Person-	100 Person-	(Months)	Month 6 in % †
Treatment	N	Events (%)	Months	Months	(95% CI)	(95% CI)
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Pembrolizumab + SOC vs. SOC					[redacted]	[redacted]

† From product-limit (Kaplan-Meier) method for censored data.

‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

§ One-sided p-value based on log-rank test stratified by geographic region (Asia versus Rest of the World) and ECOG performance status (0 versus 1).

Progression-free survival is defined as time from randomization to disease progression, or death, whichever occurs first.

Database Cutoff Date: Database Cutoff Date: 02JUL2020.

Figure 12 Kaplan-Meier Estimates of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 (Sensitivity Censoring Rule 2) (Participants with Squamous Cell Carcinoma and PD-L1 CPS >= 10 , ITT Population)

Appendix B

B4. The KEYNOTE-590 study includes 52.5% patients from Asia, versus 47.5% from the rest of the world (ITT population, company submission Table 6). Region has an apparent impact on the hazard ratio (HR) for OS as shown in the Clinical Study Report forest plots (OS HR: [redacted] for Asian patients versus [redacted] for the rest of the world patients). Please provide an analysis using only the rest of the world patients including; a table of baseline patient characteristics (also by treatment arm), Kaplan-Meier plots for OS, PFS and time on treatment (ToT), and cost-effectiveness results.

Rest of World analysis

The analyses analysis using only the rest of the world patients including patient baseline characteristics (by treatment arm), Kaplan-Meier plots for OS, PFS and time on treatment (ToT) are provided in the tables and figures below.

Table 14 Subject Characteristics Subpopulation of Participants from Rest of World (Intention-to-Treat Population)

	Pembrolizumab + SOC		SOC		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	[redacted]					
Gender						
Male	[redacted]					
Female	[redacted]					
Age (Years)						
< 65	[redacted]					
>= 65	[redacted]					

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]		[redacted]		[redacted]	[redacted]
Race						
American Indian Or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
American Indian Or Alaska Native, White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black Or African American, White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity						
Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Hispanic Or Latino	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not Reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary Diagnosis						
Squamous Cell Carcinoma of the Esophagus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma of the Esophagus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma of the Gastroesophageal Junction, Siewert Type I	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic Staging						
M0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
M1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain Metastasis						
Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Current Disease Stage						
IB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
III	[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]
IVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IVB	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IVE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Scale						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histology						
Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous Cell Carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Status						
Metastatic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unresectable - Locally Advanced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 Status						

CPS >= 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CPS < 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(Database Cutoff Date: 02JUL2020).						

Progression Free Survival

Table 15 Estimated Median and Mean Progression-Free Survival Time Based on Investigator Assessment per RECIST 1.1 Subpopulation of Participants from Rest of World (Intention-to-Treat Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated mean and median of Progression-Free Survival Time is from product-limit (Kaplan-Meier) method Database Cutoff Date: 02JUL2020							

Figure 13. Kaplan-Meier Curves of Progression-Free Survival Based on Investigator Assessment per RECIST 1.1 Subpopulation of Participants from Rest of World (Intention-to-Treat Population)

Overall Survival

Table 16. Estimated Median and Mean of Overall Survival Time Subpopulation of Participants from Rest of World (Intention-to-Treat Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC							
SOC							
Estimated mean and median of Overall Survival Time is from product-limit (Kaplan-Meier) method Database Cutoff Date: 02JUL2020							

Figure 14. Kaplan-Meier Curves of Overall Survival Subpopulation of Participants from Rest of World (Intention-to-Treat Population)

Time on Treatment

Table 17. Estimated Median and Mean Time on Pembrolizumab Treatment Subpopulation of Participants from Rest of World (All-Participants-as-Treated Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method

Time on Treatment is defined as the time from the date of initial dose until the date of last dose

Number of Events is defined as the number of subjects who had discontinued or completed pembrolizumab treatment at the time of the database cutoff date

Database Cutoff Date: 02JUL2020

Figure 15. Kaplan-Meier Curves of Time to Pembrolizumab Discontinuation/Completion Subpopulation of Participants from Rest of World (All-Participants-as-Treated Population)

Table 18. Estimated Median and Mean Time On Cisplatin Treatment Subpopulation of Participants from Rest of World (All-Participants-as-Treated Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SOC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method

Time on Treatment is defined as the time from the date of initial dose until the date of last dose

Number of Events is defined as the number of subjects who had discontinued or completed cisplatin treatment at the time of the database cutoff date

Database Cutoff Date: 02JUL2020

Figure 16. Kaplan-Meier Curves of Time to Cisplatin Discontinuation/Completion Subpopulation of Participants from Rest of World (All-Participants-as-Treated Population)

Table 19. Estimated Median and Mean Time On 5-Fluorouracil Treatment Subpopulation of Participants from Rest of World (All-Participants-as-Treated Population)

Treatment	N	Number of Events (%)	Estimated Median Time in Weeks	95% CI of Estimated Median Time in Weeks	Estimated Mean Time in Weeks	SE of Estimated Mean Time in Weeks	95% CI of Estimated Mean Time in Weeks
Pembrolizumab + SOC							
SOC							

Estimated mean and median of Time on Treatment is from product-limit (Kaplan-Meier) method

Time on Treatment is defined as the time from the date of initial dose until the date of last dose

Number of Events is defined as the number of subjects who had discontinued or completed 5-FU treatment at the time of the database cutoff date

Database Cutoff Date: 02JUL2020

Figure 17. Kaplan-Meier Curves of Time to 5-Fluorouracil Discontinuation/Completion Subpopulation of Participants from Rest of World (All-Participants-as-Treated Population)

Appendix C

Updated Cost-effectiveness results

MSD have updated the company base-case with the following revisions:

- Incorporating a 30-year time horizon
- Introducing a utility cap for the time-to-death utility category '≥360 days' according to general population utility
- Including disease management costs for patients who receive subsequent therapy in the progressed disease health state

Base-case incremental cost-effectiveness analysis results

Table 1. Base-case results versus trial comparator SOC (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-
SOC	[redacted]	[redacted]	[redacted]	27,172	0.65	41,688

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 2. Base-case results versus selected non-trial comparator (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus selected comparator (QALYs)
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-
5-FU+cisplatin	[redacted]	[redacted]	[redacted]	27,172	0.65	41,688
5FU + oxaliplatin + leucovorin	[redacted]	[redacted]	[redacted]	25,949	0.65	39,812
Capecitabine + Cisplatin	[redacted]	[redacted]	[redacted]	27,072	0.65	41,535
Capecitabine + oxaliplatin	[redacted]	[redacted]	[redacted]	27,487	0.65	42,172
5-FU + cisplatin + epirubicin	[redacted]	[redacted]	[redacted]	27,115	0.65	41,601
5-FU + oxaliplatin + epirubicin	[redacted]	[redacted]	[redacted]	27,073	0.65	41,536
Capecitabine + cisplatin + epirubicin	[redacted]	[redacted]	[redacted]	27,036	0.65	41,480
Capecitabine + oxaliplatin + epirubicin	[redacted]	[redacted]	[redacted]	26,994	0.65	41,415

Table 3. Base-case results versus non-trial blended comparator (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-
SOC	[redacted]	[redacted]	[redacted]	26,988	0.65	41,405

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Probabilistic sensitivity analysis

Table 4. Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator SOC (discounted price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
SOC	[redacted]	[redacted]	27,253	0.64	42,303

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 1. Scatterplot of PSA results (1,000 simulations) versus trial comparator SOC (discounted price)

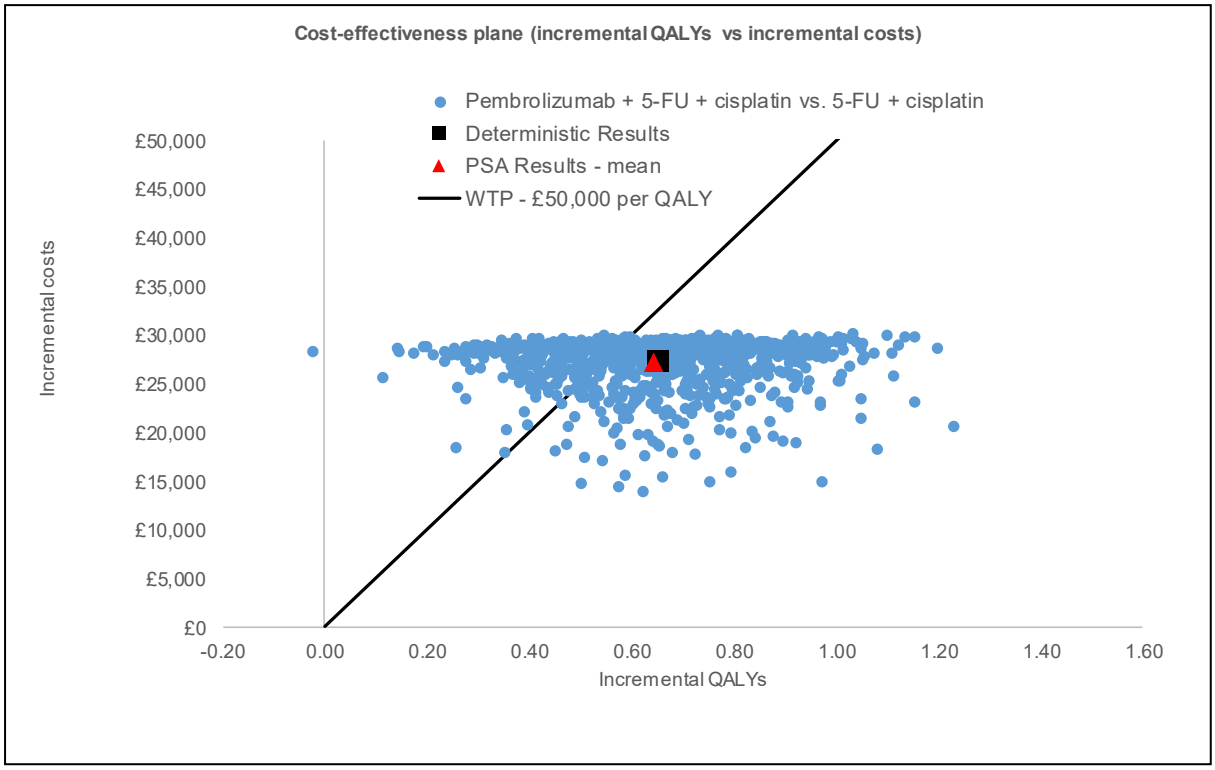
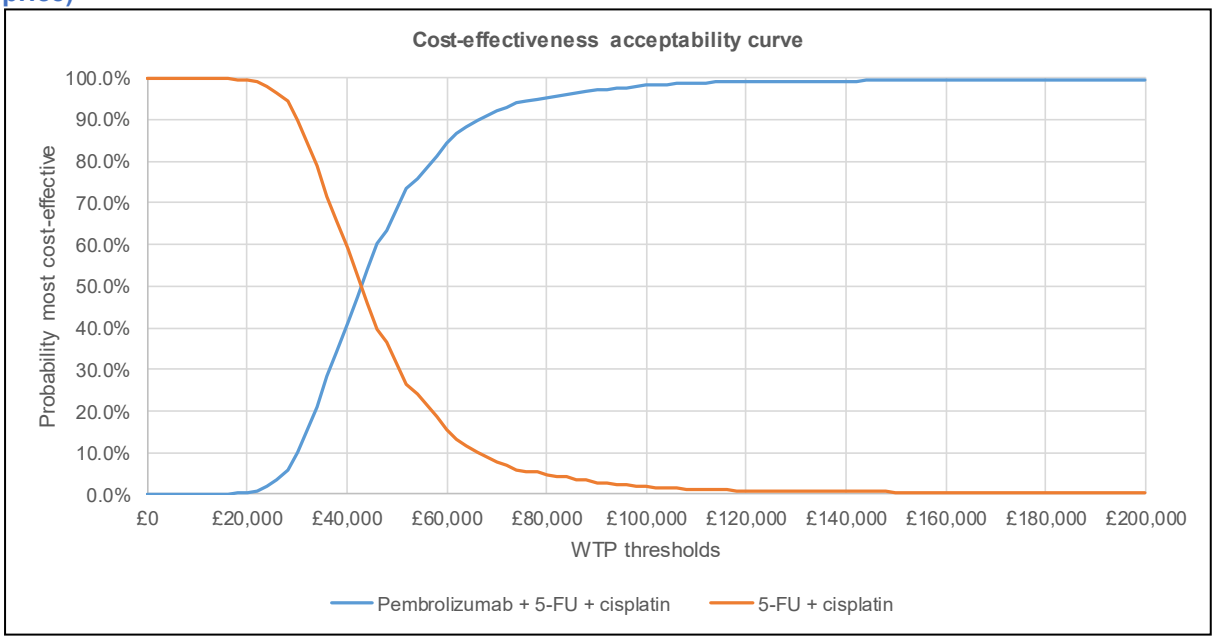
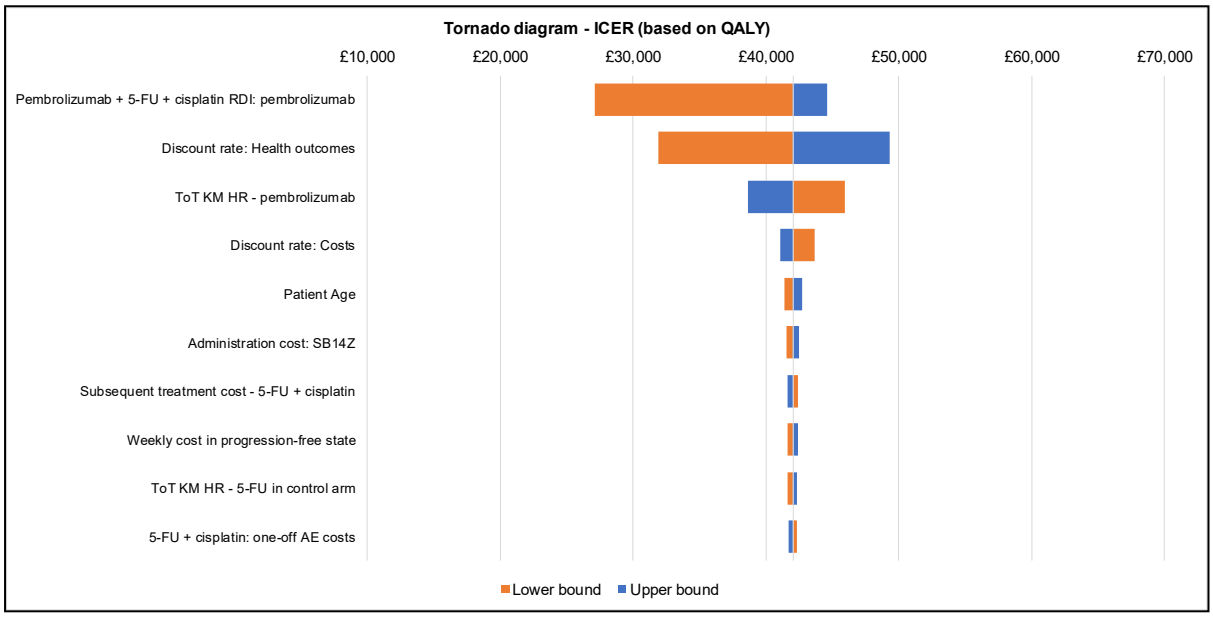


Figure 2. Cost-effectiveness acceptability curve versus trial comparator SOC (discounted price)



Deterministic sensitivity analysis

Figure 3. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensitive variables versus trial comparator SOC (discounted price)



Scenario analysis (updated)

Table 5. Results from the scenario analyses versus trial comparator SoC (discounted price)

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,172	0.65	41,688
Error! Reference source not found.	OS piecewise 40-week cut-off, log-normal distribution	[redacted]	2.29	[redacted]	[redacted]	1.35	[redacted]	27,235	0.74	36,833
Error! Reference source not found.	OS piecewise 40-week cut-off, Weibull distribution	[redacted]	1.57	[redacted]	[redacted]	1.11	[redacted]	26,954	0.38	71,729
Error! Reference source not found.	OS piecewise 32-week cut-off, log-logistic distribution	[redacted]	2.12	[redacted]	[redacted]	1.47	[redacted]	27,074	0.51	52,790
Error! Reference source not found.	OS treatment waning initiated at 5-years, completed at 7-years	[redacted]	2.13	[redacted]	[redacted]	1.39	[redacted]	27,128	0.59	46,331
Error! Reference source not found.	PFS piecewise 10-week cut-off, log-normal distribution	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,129	0.65	41,621

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Error! Reference source not found.	PFS piecewise 37-week cut-off, exponential distribution	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,158	0.65	41,666
Error! Reference source not found.	Alternative TOT approach using fully fitted parametric distributions	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	26,613	0.65	40,831
Error! Reference source not found.	Assuming 100% dose intensity	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	28,928	0.65	44,382
Error! Reference source not found.	Health state based utilities	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,172	0.57	47,661
Error! Reference source not found.	Time horizon 10-years	[redacted]	1.88	[redacted]	[redacted]	1.29	[redacted]	26,780	0.48	55,494
Error! Reference source not found.	Time horizon 20-years	[redacted]	2.13	[redacted]	[redacted]	1.37	[redacted]	27,060	0.61	44,394

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Error! Reference source not found.	Time horizon 40-years	[redacted]	2.22	[redacted]	[redacted]	1.40	[redacted]	27,202	0.66	41,405
Error! Reference source not found.	Assumption of nivolumab monotherapy as subsequent therapy post-SOC	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	5,421	0.65	8,318
Error! Reference source not found.	Removing AE disutility	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,172	0.65	41,680
Error! Reference source not found.	Removing Age-adjusted utility	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,172	0.65	41,597
Error! Reference source not found.	Removing vial sharing assumption	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,173	0.65	41,689
Error! Reference source not found.	Removing Half Cycle Correction	[redacted]	2.22	[redacted]	[redacted]	1.40	[redacted]	27,171	0.65	41,699

Scenario analysis (requested)

Table 6. Results from requested scenario analyses versus trial comparator SoC (discounted price)

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,172	0.65	41,688
Scenario B11b	Fully fitted parametric modelling approach for PFS using log-logistic distribution	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,130	0.65	41,623
Scenario B17c	Removing “cut-off points”	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,396	0.65	42,032
Scenario B19b	Drug administration costs occurring in day-case setting	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,402	0.65	42,041
Scenario 21	Alternative subsequent therapy approach	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,280	0.65	41,854

Table 7. Results from requested scenario analyses versus non-trial comparator Blended SoC (discounted price)

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	26,988	0.65	41,405
Scenario B12a	Yoon 2016	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,834	0.65	43,069
Scenario B12b	Cleary 2019	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,641	0.65	42,688
Scenario B12c	Waddell 2013	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	27,692	0.65	42,797

Sub-population analysis

Table 8. Incremental cost-effectiveness results for pembrolizumab in combination with chemotherapy vs. SOC for patients with CPS≥10 (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	[redacted]	[redacted]	-	-	-
SOC	[redacted]	[redacted]	[redacted]	30,293	0.92	32,995

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal or gastroesophageal cancer [ID3741]

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 manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant	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.

manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	Guts UK has no links at all with the tobacco industry
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. We also asked if anyone had experience of Pembrolizumab in combination with other chemotherapy for oesophageal cancer (cancer between the stomach and gullet.) We have also developed surveys in the past, but these were not successful in getting responses. 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.
Living with the condition	
6. What is it like to live with the condition? What do carers	Oesophageal cancer and cancer between the stomach and gullet are two of six less survivable cancers, for which there are no screening tools to identify them 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

experience when caring for someone with the condition?	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 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 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) 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 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 – pembrolizumab, being immunotherapy is a new type of treatment for these cancers.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Pembrolizumab is a different type of treatment that works in a different way to current treatments. Immunotherapy alone takes time to have an effect so having platinum-based chemotherapy will provide some treatment whilst the immunotherapy has time to be effective. 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?	Immunotherapy may have different side effects to current therapy. 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.	No.

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 and stomach 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 are due to cancer at an early stage. Quality of life vs treatment all depends on the patients functional fitness and nutritional status, ability to eat or if they are using a feeding tube and also family can provide peer pressure too.
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 widely used and they are frequently diagnosed late, when 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 limiting condition it is extremely important that people living with these cancers enjoy time with their family and this treatment could help people to 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.
- Patients 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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Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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New treatments for oesophageal cancer are desperately needed and immunotherapy shows promise for selected patients. As the leading UK charity for Heartburn (oesophageal) cancer we are keen to see evidence-based treatments made widely available in the NHS.

Heartburn Cancer UK

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

A Single Technology Appraisal

Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU

Authors

Dr Maxwell S. Barnish, Research Fellow[1]
Ms Rachael Slater, Associate[1] and Analyst[2]
Mr Justin Matthews, Research Fellow[1]
Dr Linda Long, Research Fellow[1]
Mr Ash Bullement, Associate[1] and Analyst[2]
Ms Naomi Shaw, Information Specialist[1]
Dr Nicole Dorey, Consultant Clinical Oncologist[3]
Dr Stephen Falk, Consultant Clinical Oncologist[4]
Ms Louise Crathorne, Senior Research Fellow[1]
Prof G.J. Melendez-Torres, Professor[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
[2] Delta Hat Limited, Nottingham
[3] Royal Devon and Exeter NHS Foundation Trust, Exeter
[4] Bristol Haematology and Oncology Centre, Bristol

Correspondence to

Dr Maxwell Barnish
3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk

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Author Contributions:

Maxwell S. Barnish	Project managed the ERG team and led the critique of the clinical effectiveness evidence. Contributed towards writing the report.
Rachael Slater	Acted as health economic project lead, critiqued the company's economic evaluation and contributed towards writing the report. Implemented the ERG's preferred settings and exploratory analyses within the company's economic model.
Justin Matthews	Critical appraisal of suitability of indirect treatment comparisons. Contributed towards writing the report.
Linda Long	Critical appraisal of clinical and cost effectiveness evidence. Contributed towards writing the report.
Ash Bullement	Critiqued the company's economic evaluation and contributed towards writing the report.
Naomi Shaw	Critical appraisal of the literature search strategies. Editorial input.
Nicole Dorey	Clinical advisor.
Stephen Falk	Clinical advisor.

Author Contributions:	
Louise Crathorne	Contributed to editing the final report. Editorial input.
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and supervised the final report. Guarantor of the report.

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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

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. Background information on the condition, technology and evidence and information on non-key issues is provided in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1. Overview of the key issues in the clinical effectiveness evidence

Table 1: Key issues in the clinical effectiveness evidence

ID3741	Summary of issues	Report sections
Key Issue 1	The clinical evidence may not be generalizable to the UK population	3.2.2.2, 3.2.3.1
Key Issue 2	Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens	3.3, 3.4, 6.2.4
Key Issue 3	The estimated overall survival projections have a large impact on cost-effectiveness	4.2.6.1, 6.2.1
Key Issue 4	The use of time-to-death utilities may overstate the QALYs accrued by patients	4.2.7.4, 6.2.3
Key Issue 5	The doublet used in the economic model does not reflect clinical practice in the UK	4.2.4, 6.2.5

Abbreviations: QALYs, quality-adjusted life years

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are:

- Method of utility estimation, with the ERG preferring progression-based rather than time-to-death estimation;
- Distributions of subsequent treatments;
- Choice of progression-free survival extrapolation; and
- Implementation of a treatment waning effect.

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) 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 overall survival
- Delaying disease progression

Overall, the technology is modelled to affect costs by:

- Drug acquisition costs for pembrolizumab
- Time on treatment for pembrolizumab

The modelling assumptions that have the greatest effect on the ICER are:

- Assumptions surrounding Overall Survival and the choice of utility method

1.3. The decision problem: summary of the ERG's key issues

The ERG did not identify any key issues with the company's interpretation of the decision problem.

1.4. The clinical effectiveness evidence: summary of the ERG's key issues

Key Issue 1: The clinical evidence may not be generalizable to the UK population

Report sections	3.2.2.2, 3.2.3.1
Description of issue and why the ERG has identified it as important	The pivotal trial, KEYNOTE-590, included a substantial number of patients from East Asian countries, where treatment guidelines for oesophageal cancer are considerably different from those applicable to the UK, and did not reflect the expected population composition of oesophageal squamous cell carcinoma and adenocarcinoma. This limits the ability to generalise findings from the trial to the UK context.
What alternative approach has the ERG suggested?	The ERG noted that the committee may wish to rely on analyses drawing on the 'rest of world' subgroup for decision-making. These are presented where available.
What is the expected effect on the cost-effectiveness estimates?	The impact on the ICER is unclear.
What additional evidence or analyses might help to resolve this key issue?	Greater clarity relating to consistency of estimates between Asian and rest of world populations, and with respect to the type of cancer, would support decision-making.

Abbreviations: ERG, Evidence Review Group

Key Issue 2: Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens

Report sections	3.3, 3.4, 6.2.4
Description of issue and why the ERG has identified it as important	The company's search was carried out without the term 'gastric', and studies were excluded when subgroup results for oesophageal or oesophagogastric junction Siewert type I cancer patients could not be identified. As a consequence, certain evidence was not included such as doublet vs triplet effect estimates from network meta-analyses (NMAs) and the influential REAL-2 study. This led to the company's conclusion that no evidence could be assembled to compare doublet and triplet regimens. There was thus no comparison between pembrolizumab and triplet regimens. Clinical advice received is that systemic treatment is similar for oesophageal and gastric cancers. Including this wider evidence provides estimates

Report sections	3.3, 3.4, 6.2.4
	of doublet vs triplet efficacy in existing UK practice, from existing NMAs or meta-analyses.
What alternative approach has the ERG suggested?	The ERG has identified plausible estimates comparing doublet vs triplet regimens to inform cost-effectiveness analysis.
What is the expected effect on the cost-effectiveness estimates?	The ERG presented scenario analyses integrating this evidence to compare pembrolizumab plus doublet regimens against triplet regimens.
What additional evidence or analyses might help to resolve this key issue?	A precise conclusion could not be reached due to the need to apply effect estimates against summary Kaplan-Meier curves in the economic model. A more direct method of including triplet regimens in cost effectiveness modelling would resolve this uncertainty.

Abbreviations: ERG, Evidence Review Group

1.5. The cost effectiveness evidence: summary of the ERG's key issues

Key Issue 3: The estimated overall survival projections have a large impact on cost-effectiveness

Report sections	4.2.6.1, 6.2.1
Description of issue and why the ERG has identified it as important	The company's overall survival (OS) projections may overestimate the proportion of patients alive in the long term for the pembrolizumab in combination with chemotherapy arm. OS is a key driver of cost-effectiveness results, and projections are currently based on incomplete data from the KEYNOTE-590 study. Clinical advice provided to the ERG suggested that a range of alternative extrapolations appear to be clinically plausible, but each option has a notable impact on the ICER.
What alternative approach has the ERG suggested?	The ERG preferred the company's base case assumptions with a treatment waning effect scenario applied between the year 5-7. This approach made use of the company's base-case approach up until 5 years, after which extrapolations were adjusted such that by 7 years, the curves for both arms project identical hazards of death for the remainder of the modelled time horizon.
What is the expected effect on the cost-effectiveness estimates?	The expected effect on the cost-effectiveness estimates is to increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	More mature KEYNOTE-590 OS data would help resolve the uncertainty inherent within the OS

Report sections	4.2.6.1, 6.2.1
	extrapolations. Clinical expert opinion may also support the selection of appropriate extrapolations, but as highlighted previously, clinical advice provided to the ERG suggested a range of extrapolations appeared plausible, producing a broad range of ICERs.

Abbreviations: ERG, Evidence Review Group

Key Issue 4: The use of time-to-death utilities may overstate the QALYs accrued by patients

Report sections	4.2.7.4, 6.2.3
Description of issue and why the ERG has identified it as important	The company's base case assigned utility values based on time to death, instead of based on progression. This led to markedly different estimates of average utility in each health state, with time-to-death utility generating a mean utility in the pre-progression health state above that of the general population.
What alternative approach has the ERG suggested?	The ERG preferred to use progression-based utility values, which may more appropriate capture expected QALY gains from pembrolizumab.
What is the expected effect on the cost-effectiveness estimates?	The expected effect on the cost-effectiveness estimates is to increase the ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional justification for choice of time-to-death utilities, and evidence as to why the company's two approaches differ so widely in terms of average utilities in each health state, may support decision-making.

Abbreviations: ERG, Evidence Review Group

Key Issue 5: The doublet used in the economic model does not reflect clinical practice in the UK

Report sections	4.2.4, 6.2.5
Description of issue and why the ERG has identified it as important	The pivotal trial, KEYNOTE-590, used a doublet regimen as standard of care, cisplatin with 5-fluorouracil, that is only one of several doublet regimens available. Clinical advice to the ERG was that while doublet regimens are of exchangeable effectiveness (i.e. exhibit a class effect), doublet regimens with 5-fluorouracil are rarely used given the need for lengthy infusion time and only used when patients cannot swallow capecitabine tablets. The company also provided

Report sections	4.2.4, 6.2.5
	different chemotherapy regimens for the comparator arm, but the chemotherapy regimen in combination with pembrolizumab remained as the 5-fluorouracil plus cisplatin. This means that costs may not reflect what would be expected in clinical practice, and lack generalisability to the UK context.
What alternative approach has the ERG suggested?	Following on from the company's scenario results, the ERG has explored alternative costing assumptions for doublet regimens in combination with pembrolizumab and as the comparator, including a blended comparator with more clinically plausible UK market shares.
What is the expected effect on the cost-effectiveness estimates?	Impacts on the ICER vary by type of doublet used in the comparator and in combination with pembrolizumab in addition to varying the mix of treatments based on different market shares.
What additional evidence or analyses might help to resolve this key issue?	Specific market share evidence in the UK for doublet and triplet regimens may generate a more realistic costing assumption. Confirmation of what type of chemotherapies would be used in combination with pembrolizumab in clinical practice.

Abbreviations: ERG, Evidence Review Group

1.6. Other key issues: summary of the ERG's views

The ERG did not identify any other key issues that would be expected to affect decision-making.

1.7. Summary of ERG's preferred assumptions and resulting ICER

The ERG's preferred assumptions for the cost-effectiveness analysis of pembrolizumab in combination with chemotherapy compared to chemotherapy alone are outlined in Table 2.

Table 2: Summary of ERG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case (post clarification questions)	£27,172	0.65	£41,688
ERG corrected company base case (see Section 6.1)	£27,173	0.65	£41,701
Remove half cycle correction	£27,172	0.65	£41,691
Administration costs using a day case setting	£27,402	0.65	£42,044

Scenario	Incremental cost	Incremental QALYs	ICER
Turning off stopping rules for treatments (i.e., just using the ToT KM estimates from KEYNOTE-590)	£27,630	0.65	£42,394
Re-distributing subsequent treatments	£27,439	0.65	£42,100
Progression-based utilities	£27,439	0.57	£48,108
PFS piecewise using 37-week cut-off and log-logistic extrapolation	£28,052	0.59	£47,270
Include treatment waning between 5-7 years	£28,007	0.54	£51,921
ERG's preferred base case (deterministic; see Section 6.3)	**£28,007**	**0.54**	**£51,921**

Abbreviations: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Modelling errors identified and corrected by the ERG are described in Sections 5.3 and 6.1. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

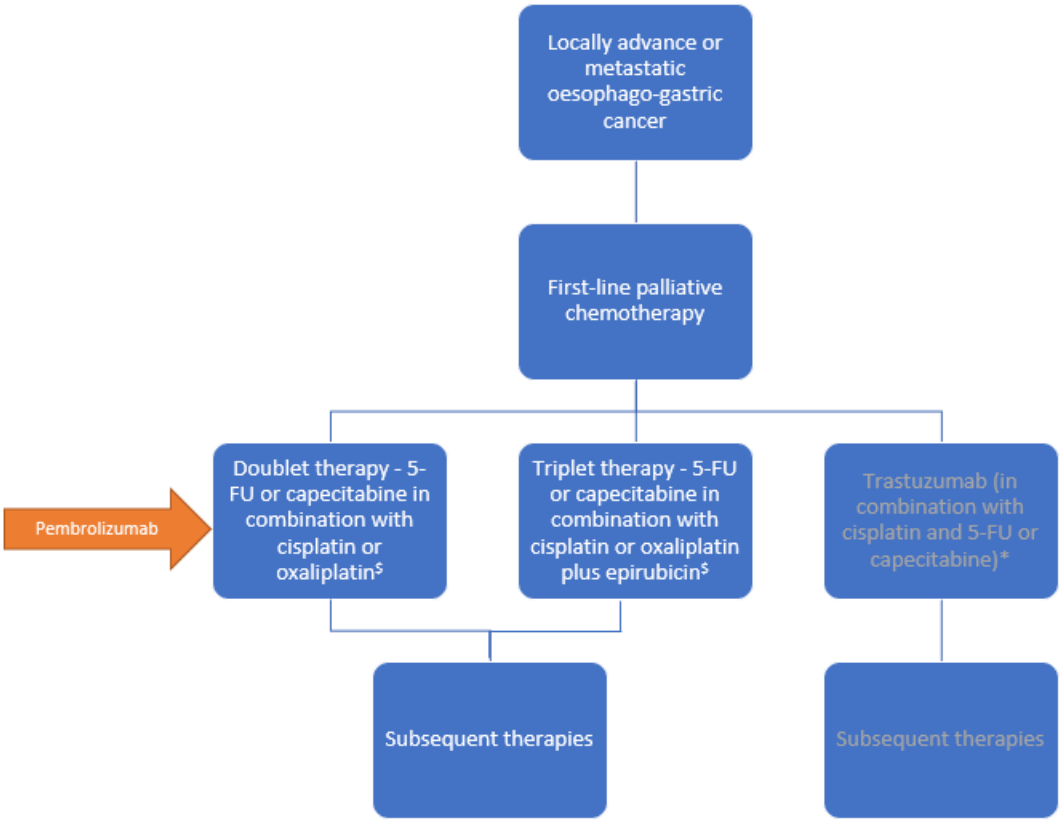
In this report, the ERG provides a review of the evidence submitted by Merck Sharp & Dohme in support of pembrolizumab with platinum-based chemotherapy, for the treatment of adults with untreated advanced oesophageal cancer.

2.2. Background and underlying health problem

Oesophageal cancer is believed to be the eighth most prevalent form of cancer worldwide.[1] The UK has the highest age-standardised incidence of oesophageal cancer in Europe.[2] Four in every five oesophageal cancers occur in adults aged 60 or over[3] with a greater prevalence in males than females.[4] Histologically, oesophageal cancer is subdivided into squamous and adenocarcinoma, the latter representing approximately two-thirds of UK cases and the former one-third.[5] Obesity, smoking and alcohol consumption have been identified as risk factors for oesophageal cancer. Survival prognosis for patients with oesophageal cancer is poor, with most living between three and 12 months after diagnosis and 4% living at least five years.[6] The Evidence Review Group (ERG) considered that the Company Submission (CS) offered an acceptable description of the condition; its pathophysiology, natural course and epidemiology; and the current treatment options available.

NICE Guideline 83[7] was identified in the CS as relevant to this appraisal. The company depicted the treatment pathway in this Guideline, and the proposed positioning of pembrolizumab, in a flowchart (Figure 1). Clinical advisors to the ERG indicated that this flowchart was an accurate depiction of current NHS clinical practice in England and Wales.

Figure 1 NICE pathway on locally advanced or metastatic oesophago-gastric cancer



Source: CS, p.16 – based on NICE Guideline 83. Trastuzumab combinations are used for HER2+ patients.

Pembrolizumab is a monoclonal antibody of the IgG4/Kappa isotope designed to exert dual ligand blockade of the programmed cell death protein 1 (PD-1) pathway by directly blocking the interaction between PD-1 and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), which appear on antigen-presenting or tumour cells. Pembrolizumab is used for a range of other cancer indications in current practice. The ERG considered that the company's intended positioning, as compared to current standard of care, was appropriate and generally well-described.

The company's intended positioning for pembrolizumab occupies the position in the treatment pathway for locally advanced or metastatic oesophageal-gastric cancer currently occupied by palliative care options. These typically take the form of doublet or triplet chemotherapy regimens. Clinical advice to the ERG indicated that while doublet and triplet regimens were the

appropriate comparators, and that class effects could generally be assumed, certain regimens mentioned in the CS would not be currently funded for NHS use:

- Cetuximab + cisplatin + fluorouracil (5-FU)
- Panitumumab + cisplatin + 5-FU
- Cisplatin + 5-FU + recombinant human lymphotoxin-α derivative (rhLTα-DA)
- Mitomycin + cisplatin + 5-FU.

2.3. Critique of company's definition of decision problem

The ERG considered that the company's definition of the decision problem generally matched the decision problem in the NICE scope.[8]

Table 3: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with untreated, unresectable locally advanced or metastatic oesophageal cancer or gastroesophageal junction adenocarcinoma	Adults with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma.	The population described by MSD reflects the anticipated licence indication wording	The ERG considered that the population considered in the company submission was generally well-matched to the NICE scope. However, it was narrower to reflect the anticipated licence indication wording
Intervention	Pembrolizumab with platinum-based chemotherapy	Pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy	The intervention described by MSD reflects the anticipated licence indication wording	The ERG considered that the intervention considered in the company submission was generally well-matched to the NICE scope. However, it was broader, including fluoropyrimidine based chemotherapy, to cover the full breadth of the anticipated licence indication wording
Comparator(s)	Platinum-based chemotherapy without pembrolizumab, such as: • doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin	Platinum-based chemotherapy without pembrolizumab, such as: • doublet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin • triplet treatment with fluorouracil or capecitabine	N/A	As per the scope for this appraisal

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	• triplet treatment with fluorouracil or capecitabine plus cisplatin or oxaliplatin epirubicin	plus cisplatin or oxaliplatin epirubicin		
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life.	N/A	As per the scope for this appraisal
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	N/A	The ERG agreed that the economic analysis presented is aligned with the reference case

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.	Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.		
Subgroups	None specified	Pre-specified efficacy analyses were conducted in KEYNOTE-090 according to: • histology • geographic region • ECOG performance scale • disease status (locally advanced vs metastatic) • age • sex The economic model includes subgroup analysis in the CPS ≥ 10 sub-population	Subgroup analyses were pre-specified in the KEYNOTE-590 study protocol to determine whether the treatment effect was consistent across subgroups The company considered the CPS≥10 sub-population to be of particular clinical significance.	Although no subgroups were specified in the NICE scope, the ERG considered the pre-specified subgroups in KEYNOTE-590 to be generally appropriate

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Special considerations including issues related to equity or equality	Not stated	MSD does not envisage any equality issues with the use of pembrolizumab in combination with platinum-based chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults.	Not applicable	No equity issues were identified

Abbreviations: CPS, combined positive score; ERG, Evidence Review Group; HER-2, human epidermal growth factor receptor 2; MSD, Merck Sharp & Dohme; N/A, not applicable; NICE, National Institute for Health and Care Excellence

3. CLINICAL EFFECTIVENESS

The sections below discuss the evidence submitted by the company in support of the clinical effectiveness of pembrolizumab for adults with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma. The ERG reviewed the details provided on:

- Methods implemented to identify, screen, data extract and assess the risk of bias in relevant evidence
- Clinical efficacy of pembrolizumab
- Safety profile of pembrolizumab
- Assessment of comparative clinical effectiveness of pembrolizumab against relevant comparators

A detailed description of an aspect of the CS is only provided where the ERG disagreed with the company's assessment or proposal, or where the ERG identified a particular area of concern that the ERG considered necessary to highlight for the Committee.

The ERG identified two key issues relating to the clinical effectiveness evidence:

- The clinical evidence may not be generalizable to the UK population
- Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens

3.1. Critique of the methods of review(s)

The company undertook a systematic review to identify relevant publications on the clinical efficacy and safety of pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy, as first line treatment in patients with locally advanced unresectable or metastatic carcinoma of the oesophagous (both squamous and adenosquamous) or HER-2 negative gastroesophageal junction adenocarcinoma in adults. The company considered direct and indirect comparisons between the intervention and comparators, with platinum-based chemotherapy without pembrolizumab, such as a) doublet treatment with fluorouracil or

capecitabine plus cisplatin or oxaliplatin or b) triplet treatment with flourouracil or capecitabine plus cisplatin or oxaliplatin epirubicin considered to be the most relevant comparators.

Table 4: Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix D (page 82)	Broadly appropriate, however, the ERG noted the following limitations: specific searches for adverse effects were not completed; the RCT filter applied to database searches did not include terminology to retrieve single-arm studies; and database searches did not include all variant spellings for gastro-oesophageal junction. The ERG conducted additional searches with search terms for single-arm studies and variant spellings (see section 3.5.1) and did not identify any studies that should have been included with respect to the stated inclusion criteria. The ERG also noted that search terms for the drug S1 were not included, however, clinical advice to the ERG confirmed that this intervention is not relevant to current UK clinical practice.
Inclusion criteria	Appendix D (pages 82-83)	Broadly appropriate. Adults with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ were included. Populations were eligible only if they had not received previous therapy. Subjects with human epidermal growth factor receptor-2 positive tumours were excluded.
Screening	Clarification response	Appropriate. No methodological details were provided in CS. However, appropriate methods were described during clarification (clarification question A10)[a]
Data extraction	Clarification response	Appropriate. No methodological details were provided in CS. However, appropriate methods were described during clarification (clarification question A10) [b]
Tool for quality assessment of included study or studies	Section B.2.5 (page 40)	Broadly appropriate. Study quality was assessed using the new Cochrane ROB2 instrument for included RCTs and the Newcastle Ottawa Scale for single-arm trials. Due to lack of reporting in the CS, it was unclear to the ERG if the ROB quality assessments were conducted rigorously i.e. if they were undertaken by two independent reviewers, and any discrepancies between the two reviewers were resolved by consensus or involvement of a third reviewer. The ERG note

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
		that the company used the Cochrane ROB2 tool to assess the quality of individual RCTs. This deviates from Cochrane's guidance to use the ROB2 tool to assess bias for individual outcome measures.
Evidence synthesis	Appendix D (pages 82 to 109)	Studies were conducted as set out above ('Searches'). The search criteria did not include gastric/stomach cancer: according to the company this 'would have introduced too many non-relevant studies in terms of location of the primary tumour'. Studies were also excluded when 'subgroup outcomes for oesophageal or esophagogastric junction Siewert type I cancer patients' could not be identified. The approach is reasonable, but filters out some relevant evidence, in particular the REAL-2 trial[9] and existing NMAs.[10,11] This led to a sparser evidence network and affected the suitability for NMA.

Abbreviations: CS, Company submission; EGJ, esophago-gastric junction; ERG, Evidence Review Group; NMA, network meta-analysis; RCT, randomised controlled trial; ROB, Risk of Bias

Notes:

[a] Abstracts were dual screened versus pre-defined eligibility criteria. Discrepancies were resolved with a third party. Potential full text articles were retrieved and screened in the same way. A list of excluded studies was provided in Appendix D, Section D1.1.3, Table 6 of the CS together with reasons for exclusion

[b] Data was extracted by a single reviewer using a pre-defined data extraction template, and data was checked by a second reviewer

While appropriate methods for study inclusion were employed by the company, poor reporting meant that the ERG could not evaluate the robustness of the screening and data extraction processes conducted by the company.

The ERG did not identify any studies that should have been included with respect to the stated criteria.

Appropriate tools for trial quality assessment were chosen by the company, but poor reporting meant that the ERG could not evaluate the robustness of the quality assessment process conducted by the company. The ERG did not consider the company's interpretation of the use of the Cochrane Risk of Bias 2 tool to be appropriate as it was used by the company to assess the quality of individual trials rather than individual outcomes (see Section 3.2.2.6 for more details).

In addition to the clinical effectiveness SLR, the company performed a targeted literature review of prognostic factors (see Appendix D) No studies were identified that reported on prognostic

factors in the target population of interest; however, 13 studies reporting multivariate analyses to identify prognostic factors in similar oesophageal-gastric cancer populations were reviewed and included. These publications and the identified prognostic factors are summarized in Section D1.2.6 of Appendix D. Disease stage was the most common prognostic factor identified (n=9), followed by age (n=7), gender (n=5), tumour size/length (n=5), weight loss/BMI (n=4), lymph node involvement (n=4), and grade (n=4). Clinical advisors to the ERG confirmed that these findings were in line with their clinical experience.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described seven studies (Table 5). These comprised one blinded RCT,[12] one RCT with unknown blinding status,[13] four open-label RCTs[14-17] and one open-label single-arm trial.[18] Only one study (KEYNOTE-590[12]) reported evidence for pembrolizumab in combination with chemotherapy – and therefore forms the pivotal trial in the clinical effectiveness evidence. The remaining included studies assessed potentially relevant comparators but not pembrolizumab, and are addressed further in Section 3.3.

Table 5: Clinical evidence included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
KEYNOTE-590[12]	Double-blind placebo-controlled RCT	First-line patients with advanced or metastatic oesophageal carcinoma	Pembrolizumab in combination with cisplatin and 5-fluorouracil	Placebo in combination with cisplatin and 5-fluorouracil	Phase III
Lee 2008[18]	Open-label single-arm trial	First-line patients with advanced oesophageal squamous cell carcinoma	Capecitabine and cisplatin	N/A	Phase II
Lee 2015[14]	Open-label RCT	First-line patients with metastatic esophageal squamous cell carcinoma	Capecitabine in combination with cisplatin	Capecitabine in combination with paclitaxel	Phase II
Lorenzen 2009[17]	Open-label RCT	First-line patients with metastatic squamous cell carcinoma of the oesophagus	Cetuximab plus cisplatin–5-fluorouracil	Cisplatin– 5-fluorouracil	Phase II
POWER[16]	Open-label RCT	Patients with non-resectable, advanced or metastatic oesophageal squamous cell cancer	Cisplatin and 5-fluorouracil with epidermal growth factor receptor inhibition panitumumab	Cisplatin and 5-fluorouracil	Phase III
Ross 2002[13]	RCT (Blinding status N/S)	Patients with advanced oesophagogastric cancer	Mitomycin, cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU)	Epirubicin, cisplatin, and PVI 5-FU	N/S

Study name and acronym	Study design	Population	Intervention	Comparator	Study type
Wang 2017[15]	Open-label RCT	Patients with metastatic oesophageal squamous cell carcinoma	Recombinant human lymphotoxin-a derivative in combination with cisplatin and 5-fluorouracil (at two different doses)	Cisplatin and 5-fluorouracil	Phase IIb

Abbreviations: 5-FU, 5-fluorouracil; CS, company submission; N/A, Not applicable; N/S, Not stated; PVI, protracted venous infusion; RCT, randomized controlled trial

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

The key trial included in the company's SLR, and the only source of directly comparative evidence to inform the economic model, was a Phase III double-blind placebo-controlled RCT (KEYNOTE-590[12]) evaluating pembrolizumab in first-line patients with advanced or metastatic oesophageal carcinoma from 26 countries worldwide. There were 22 participants from three sites in the United Kingdom out of a total of 749 participants worldwide (2.9%). The majority of participants in KEYNOTE-590[12] (N=400, 53.4%) were from Asian sites. The population, intervention, comparator and outcomes in KEYNOTE-590[12] were broadly consistent with the NICE decision problem.

3.2.2.2. Population

The KEYNOTE-590[12] study considered a population of patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the oesophageal-gastric junction. Eligible patients had an ECOG score of 0 or 1, no active central nervous system metastases and/or carcinomatous meningitis, and no active infection or autoimmune disease that required systemic therapy. Detailed inclusion and exclusion criteria are provided in CS Section B.2.3.1, pp.22-24. The population for the pivotal trial was narrower than the NICE scope[8] for this appraisal. However, this was in accordance with the proposed marketing authorisation and was therefore considered appropriate.

3.2.2.3. Intervention

3.2.2.4. The intervention in the KEYNOTE-590[12] study was pembrolizumab 200 mg intravenously every three weeks in combination with cisplatin 80 mg/m^2 intravenously every three weeks and 5-FU 800 mg/m^2/day continuous intravenous infusion (4000 mg/m^2 per three-week cycle). The pembrolizumab dosing regimen was in accordance with the draft SmPC. Clinical advice to the ERG indicated that 5-FU was not the optimal comparator in light of UK clinical practice, where capecitabine-based doublet regimens would be more commonly used. While clinical advice to the ERG was that the choice of comparator regimen would be unlikely to have a substantial impact

upon relative efficacy, the choice of comparator could have cost implications (discussed further in Section 4.2.4). Comparator

The comparator in the KEYNOTE-590[12] study was saline placebo intravenously every three weeks in combination with cisplatin 80 mg/m^2 intravenously every three weeks and 5-FU 800 mg/m^2/day continuous intravenous infusion (4000 mg/m^2 per three-week cycle). Clinical advisers to the ERG indicated that the comparator used in KEYNOTE-590[12] would be considered 'old-fashioned' in the context of routine NHS clinical practice, where oxaliplatin and capecitabine would typically be used in preference (discussed further in Section 4.2.4). Moreover, the method of administration of chemotherapy in the trial, requiring inpatient or PICC line would be considered dated, where typical NHS practice is to provide chemotherapy treatments for oesophageal cancer in a day case setting.

3.2.2.5. Outcomes

The outcomes covered in the KEYNOTE-590[12] study were summarised in the CS (Section B.2.2., Table 3, p.19). Data for the five outcomes specified in the NICE scope[8] were available, and are outlined below. Time to deterioration, duration of response, patient reported outcomes and disease control rate were also available.

Overall survival

Overall survival was defined as the time from randomisation to death by any cause.

Progression-free survival

Progression-free survival was defined as the time from randomisation to the first documented disease progression per RECIST 1.1 criteria,[19] or death due to any cause, whichever occurs first.

Response rate

The measure of response rate used was objective response rate. This was determined per RECIST 1.1 criteria.

Adverse effects of treatment

The safety and tolerability of pembrolizumab was assessed. Total and cause-specific adverse events were profiled.

Health-related quality of life

Health-related quality of life (HRQoL) was assessed using EuroQoL EQ-5D-5L,[20] as well as disease-specific European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30)[21] and the EORTC Quality Of Life Questionnaire Oesophageal Module (QLQ-OES18)[22] measures. EuroQoL EQ-5D-5L[20] was mapped to EQ-5D-3L[23] for use in the economic model following NICE recommendations.

3.2.2.6. Critical appraisal of the design of the studies

The company reported no notable quality issues in relation to the KEYNOTE-590[12] RCT. The complete quality assessment is available in Appendix D of the CS (Section D1.4. Table 3, p.125). The company evaluated KEYNOTE-590[12] using the Cochrane Risk of Bias 2 tool, which the ERG considers an appropriate critical appraisal tool for RCTs. The ERG noted that the company had not followed Cochrane guidance on the correct use of the tool and used the tool to assess individual trial quality rather than the quality of assessment of individual outcomes. However, the ERG did not identify any concerns for risk of bias specifically for the outcomes reported in the CS that informed the decision problem/economic model (primarily overall survival [OS], response (ORR), progression free survival [PFS], HRQoL and also adverse effects [AEs] of treatment).

3.2.3. Description and critique of the results of the studies

3.2.3.1. Baseline characteristics

Baseline characteristics for patients included in the KEYNOTE-590[12] study were reported in the CS (Section 2.3.3, Table 6, p.31) for the ITT population. Considering the ITT population, the ERG agreed with the company's assertion that the pembrolizumab and control arms were generally well balanced for baseline characteristics and reasonably representative of the target population, with an important exception. The ERG noted an important departure from the expected UK clinical practice population with regard to histology. In the CS (Section 1.3, p.15), the company cited evidence[5] that adenocarcinoma accounts for approximately two thirds of UK cases of oesophageal cancer, while squamous cell carcinoma accounting for approximately one third. However, in the KEYNOTE-590[12] ITT population, patients with squamous cell carcinoma accounted for 73.2% of all participants. This substantial overrepresentation of patients with squamous cell carcinoma compared to the UK clinical practice population may have implications for the generalisability of the trial evidence to NHS clinical practice settings in England and

Wales. Moreover, it is important to note that the company used population characteristics from European patients (CS Section B.3.2, Table 41, p.81) in KEYNOTE-590[12] to populate the economic model, although clinical effectiveness inputs were from the global ITT population. The ERG, however, considered that the international population may be more suitable, given the population of Europe as a whole is less ethnically diverse than the UK population.

3.2.3.2. Clinical effectiveness results

Data in the target population were presented for overall survival, progression-free survival, objective response rate, adverse events and health-related quality of life. Statistical analyses were broadly appropriate. The primary efficacy population was the global intention to treat (ITT) population. The primary safety population was the global all subjects as treated (ASaT) population. Efficacy analyses were performed using the July 2020 Interim Analysis dataset, at which the median (range) duration of follow-up was 12.6 (0.1 to 33.6) months in the pembrolizumab arm and 9.8 (0.1 to 33.6) months in the control group, with the exception of patient-reported outcomes, such as HRQoL. These were assessed in the patient reported outcome full analysis set (PRO FAS), which comprised participants who had received at least one dose of study medication and had completed at least one patient-reported outcome assessment.

Overall survival

In the ITT population, the median overall survival was 12.4 months (95% CI 10.5-14.0 months) for the pembrolizumab arm compared to 9.8 months (95% CI 8.8-10.8 months) for the control arm. There was a 27% reduction in the risk of death for people in the pembrolizumab arm compared to the control arm (HR = 0.73, 95% CI 0.62-0.86, p<0.0001).

Progression-free survival

In the ITT population, using the primary PFS censoring rule, the median progression-free survival was 6.3 months (95% CI 6.2-6.9 months) for the pembrolizumab arm compared to 5.8 months (95% CI 5.0-6.0 months) for the control arm. There was a 35% reduction in the risk of progression or death for people in the pembrolizumab arm compared to the control arm (HR = 0.65, 95% CI 0.55-0.76, p<0.001).

The company conducted two sensitivity analyses of PFS using different censoring rules, as outlined in the CS Section B 2.4.1, Table 9, as well as the primary analysis. Results were only

provided in the CS using the primary censoring rule for PFS. Therefore, the ERG asked the company at the Clarification stage for the PFS results using the alternative censoring rules. The HRs for people in the pembrolizumab arm compared to the control arm were [redacted] (95% CI [redacted]) using sensitivity censoring rule 1 and [redacted] (95% CI [redacted]).using sensitivity censoring rule 2. The ERG was satisfied that the choice of PFS censoring rule had little material impact on the PFS results.

Objective response rate

In the ITT population, the objective response rate was 45.0% for the pembrolizumab arm compared to 29.3% for the control arm. This 15.8% difference was considered clinically and statistically ($p<0.0001$) significant.

Health-related quality of life

In the PRO FAS population, there were no clinically meaningful changes in EQ-5D VAS scores from baseline to week 18 for either the pembrolizumab or control arm, and there was no statistically significant difference in change scores from baseline to week 18 between the arms (Baseline mean (SD) pembrolizumab arm 72.59 (18.65); Baseline mean (SD) control arm 74.43 (17.14); week 18 mean (SD) pembrolizumab arm 72.41 (18.55); week 18 mean (SD) control arm 74.04 (16.59)).

Subgroup analyses

Pre-specified subgroup analyses were conducted according to the following stratification factors:

- Histology (adenocarcinoma vs squamous cell carcinoma)
- Geographic region (Asia vs Rest of World)
- ECOG performance status (0 vs 1)
- Disease status (Locally advanced vs metastatic)
- Age category (binary split at 65)
- Sex (male vs female)

The ERG considered histology and geographic region to be particularly important stratification factors, given that the majority of patients were Asian and the balance between adenocarcinoma and squamous cell carcinoma patients was markedly different than would be found in a UK population. Arm-level subgroup results for the two primary efficacy outcomes of overall survival and progression-free survival (CS, Appendix E) were presented solely in terms of numbers of events rather than median survival estimates, which the ERG considered unhelpful in terms of interpreting these results in the context of the headline ITT results. Hazard ratios for overall survival (adenocarcinoma 0.74 (95% CI 0.54, 1.02); squamous cell carcinoma 0.72 (95% CI 0.60, 0.88) and progression-free survival (adenocarcinoma 0.63 (95% CI 0.46, 0.87); squamous cell carcinoma 0.65 (95% CI 0.54, 0.78)) were comparable for adenocarcinoma and squamous cell carcinoma patients, although this comparison must be interpreted with caution due to unequal numbers of patients in the two histological groups. Moreover, the different treatment pathways associated with these two histological groups may have an impact in terms of resource use and costs. However, the relative benefit of pembrolizumab versus control on both overall survival (Asia HR [redacted]); Rest of the World HR [redacted]) and progression-free survival (Asia HR [redacted] Rest of the World HR [redacted]) was stronger for Asian patients than in the Rest of the World. This may mean that the effect estimates in the KEYNOTE-590[12] global ITT population overestimate the clinical effectiveness of pembrolizumab compared to the UK clinical practice setting.

3.2.3.3. Safety results

Adverse effects

Adverse events (AEs) in the KEYNOTE-590[12] study were reported in the CS (Section B.2.10). AEs were considered in the ASaT population, which formed the primary safety analysis population. Overall, the ERG agreed with the company that pembrolizumab had an acceptable safety profile and that AE rates were comparable between the pembrolizumab and control arms. However, the ERG noted that AEs were very common, with all participants in the pembrolizumab arm and 99.5% of participants in the control arm encountering at least one AE. The profile of AE types was comparable between arms, the most common being nausea, anaemia, and decreased appetite. Serious AEs were encountered by the majority of participants, although rates were comparable between arms (55.4% pembrolizumab vs 55.1% control).

Mortality

Death rates were lower overall on pembrolizumab (7.6%) than control (10.3%). However, deaths due to drug-related adverse events were more common on pembrolizumab (2.4%) than control (1.4%). The ERG asked at the clarification stage for information regarding death rates at one month, three months, six months, 12 months, 18 months and two years from randomisation in the pembrolizumab and control arms, and was satisfied that there was no evidence of an elevated risk of early deaths on pembrolizumab.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

3.3.1. Summary

The company search criteria are defined in CS Appendix D Table 1. The search identified '7 studies relevant to the UK context' (CS doc B table 26) including the pivotal trial KEYNOTE-590,[12] and the company sifted further to reach a final total of three studies. Examining these, the company rejected use of a NMA (small, disconnected network) and MAIC (differences between populations and with target population). The ERG notes that a relaxation of the search and exclusion criteria or disease definition increases the available evidence. No further trial comparisons relating specifically to the most typical UK doublet and triplet regimens were found, but some further evidence is available for regimens used previously and believed to have similar efficacy.

3.3.2. Company approach

The company identified seven trials (CS, Appendix D, Figure 1), six of which were in patients with oesophageal cancer only, and these are listed in the CS (Doc B, Table 26). Assessing these for use within a network, the company stated that three trials were excluded for using the comparison (cisplatin + 5FU) 'which is already captured in the population of interest in the index trial, KEYNOTE-590.' (CS, Doc B, p61).

It was unclear to the ERG why network connections to a node representing a common, indeed central node (in this case cisplatin + 5FU) led to exclusion by the company of these studies. On the other hand, clinicians advised the ERG that the interventions used in the three excluded trials (cetuximab, panitumumab and rhLTα-DA) were irrelevant to UK practice, and for this

reason the ERG agreed with their exclusion. A further study was then excluded 'due to a lack of reported patient characteristics for the population of interest'.

The final set of three studies included a trial with IPD (KEYNOTE-590[12]) and two studies with aggregate outcomes.[14,18] Therefore, the company examined them for potential analysis by unanchored MAIC, but this was rejected because of key differences between study populations, including that the comparator studies were limited to South Korean patients with ESCC only.

The company indicated (in response to clarification A6), that the search for evidence excluded the term 'gastric', and the ERG believed that studies covering patients with more general advanced gastric/ stomach cancer (but including relevant information for the decision problem) might have been sifted out. Furthermore (in response to clarification A5) studies were excluded when results specifically for oesophageal or oesophagogastric junction Siewert type I cancer patients could not be identified. The ERG accepted that this was a coherent approach with regard to the decision problem, but noted that:

- relevant patients with junctional/oesophageal cancer that has metastasised to or from the stomach might then be excluded, if the site of the primary tumour is unclear or unreported;
- this rule was not set out in the exclusion criteria (CS Appendix D Table 1);
- Siewart type I is not specified in the scope (CS Doc B Table 1); and,
- the trial by Cunningham (REAL-2 trial)[9] was consequently rejected; yet this influential study provided evidence of the noninferiority of oxalipatin and capecitabine, and the ERG understood that it underpinned the most typical UK clinical practice of substituting these for cisplatin and 5-FU respectively.

3.3.3. Further trials

The ERG was also aware of several existing NMAs and meta-analyses in advanced gastric cancer (ter Veer, 2016; Guo, 2019; Wagner, 2006; Wang, 2017; Okines, 2009; GASTRIC, 2013),[10,11,24-27] albeit often with broader disease definition than the CS. These are termed hereon 'the reviews'. The reviews effectively supply some results of searches for head-to-head trials without excluding the terms 'stomach' or 'gastric'. The ERG focused on further evidence for doublet vs triplet regimens relevant to the UK.

According to clinical advisors to the ERG, the most typical UK treatment/ UK standard of care doublet is (oxaliplatin + capecitabine) and most typical triplet is (oxaliplatin + capecitabine + epirubicin). No further direct comparisons of these were found within the reviews. Ter Veer et al. (2016)[10] remarked in particular that '… although conventional anthracycline-, platinum-, and fluoropyrimidine-based triplets, as defined in the REAL-2 study are used frequently in clinical practice, head-to-head RCTs are missing between these triplets and fluoropyrimidine-based doublets (i.e., fluoropyrimidine/oxaliplatin).'

Some head-to-head trials between relevant UK regimens used more frequently in the past (cisplatin + 5-FU) vs (cisplatin + 5-FU + epirubicin) were found by the reviews but not by the company's search. These were Kim et al. (2001),[28] and KRGCGC (1992).[29] Another relevant doublet vs triplet trial cited is Yun et al. (2010)[30] between (cisplatin + capecitabine + epirubicin) vs (cisplatin + capecitabine). With regard to their omission, the company explained (response to clarification A8) that: 'All of the above studies were conducted in gastric cancer patients and did not include oesophageal or esophagogastric junction Siewert type I patients, therefore are not relevant to the current decision problem'. But, somewhat contrary to this statement, the company also refers to the results of these three studies in CS Doc B Table 43 (comparison number 2 ; these same studies were identified by NG83[7] Section 9.2.2). The ERG reappraised the studies and while it agreed that they were carried out in gastric cancer patients, it was not apparent that oesophageal or oesophagogastric junction cancer patients were not included, as was stated by the company. The ERG further noted that the scope does not specify Siewert type I patients.

There are several further caveats on the use of data from these three trials including:

- The populations are wholly Asian, precluding generalisability to a UK context.
- No support (or rejection) of the constant HR assumption is shown in Kim et al. (2001)[28] or KRGCGC (1992).[29] Indeed, no HRs are given at all, and the HRs adopted in the NMA appear to be based on the reported medians with an assumption of an exponential survival distribution.
- Yun et al. (2010)[30] gives crossing KM curves (conflicting with the constant HR assumption).

3.4. Critique of the indirect comparison and/or multiple treatment comparison

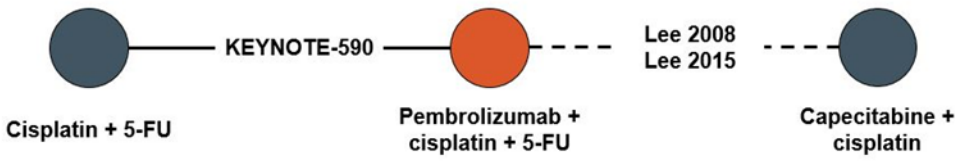
3.4.1. Summary

The company did not carry out an NMA, because the network formed under its search and exclusion criteria was uninformative. The company then considered but rejected a MAIC, primarily because of differences between study populations. While the ERG agreed with these decisions, it considered that the strict exclusion of stomach/gastric cancer, while coherent, limits the available evidence (and in particular excludes an important and influential study, REAL-2 ; Cunningham et al. (2008) [9]). The ERG is aware of several existing meta-analyses/NMAs,[10,11,24-27] and has summarised the most relevant results for UK doublet versus triplet comparisons.

3.4.2. Company approach

The company did not carry out a network meta-analysis, because the network formed under its search criteria (CS Appendix D Table 1 and response to clarification A6) and other exclusion criteria (response to clarification A5) was very minimal. The company's network is reproduced here in Figure 2. Even this small network is disconnected, since two trials shown do not include a common comparator with KEYNOTE-590[12] (improper connection shown by dotted line).

Figure 2. Network diagram of studies identified through SLR



Source: CS Doc B Figure 3

The CS stated that a NMA of (pembrolizumab + chemotherapy) versus competing interventions (including capecitabine plus cisplatin and epirubicin with cisplatin and 5-FU) was not feasible

'*because these interventions have generally only been evaluated in non-comparative studies*.' (CS Doc B Section B.2.9).

The ERG's view differed from this, insofar as there is evidence of existing comparative studies and NMAs, but with a looser definition of the disease and perhaps an assumption of class effects. This is discussed further below.

Having rejected an NMA, the feasibility process was 'adapted to the context of an unanchored MAIC'. The company provided further details of this process in response to clarification A9. The company did not carry out an (unanchored) MAIC on the final three studies because of differences between populations (further details in Section 3.3.2). The ERG agreed with this decision.

3.4.3. Existing indirect comparisons

The ERG is aware of two relevant published NMAs (Section 3.3.3). The disease definition in Wang (2017)[11] on esophagogastric junctional adenocarcinoma overlaps with the decision problem, but its results are presented in terms of broad drug classes that the ERG judged are not suitable for the decision problem (in particular, grouping together first- and second-line drugs: docetaxel, epirubicin and irinotecan). Results obtained from another NMA (ter Veer et al. 2016)[10] are potentially useful because the drug comparisons are apt, but against this, were targeted at less specific disease ('patients with pathologically proven metastatic, unresectable, or recurrent adenocarcinoma of the esophagus, gastroesophageal junction (GEJ), *or stomach'* [ERG italics]).

Clinical experts advised the ERG that advanced oesophageal cancer and gastric cancers are similar in terms of systemic therapy, but also that squamous carcinoma tends to occur in the upper two-thirds of the oesophagus while junctional cancer, like gastric cancer, is predominantly adenocarcinoma.

From the NMA, ter Veer et al. (2016)[10] give results for 'ACF' vs 'CF' (A=anthracycline, C=cisplatin, F= fluoropyrimidine): For OS, HR = 0.86 (95% CI: 0.71 to 1.02; ter Veer et al. Figure 3) and for PFS, HR = 0.85 (95% CI: 0.68 to 1.05; ter Veer et al.[10] Figure. The ERG has briefly critiqued (Section 3.3.3) the three underlying studies in the NMA that provide direct comparative evidence of ACF vs CF (Kim, 2001; KRCGGC, 1992; Yun 2010)[28-30] and some caveats were

noted. On the other hand, individual comparisons are supported by indirect as well as direct evidence in this large NMA (17 regimens and 37 direct comparisons for OS).

The ERG found that several reviews pool direct evidence on the comparison of (cisplatin + 5-FU) vs (cisplatin + 5-FU + anthracyline). For example, NG83 provides an estimate of HR 0.70, 95% CI: 0.43-1.15 (CS Doc B table 43, comparison 2) based on direct evidence alone. The REAL-2 trial (Cunningham et al. 2008)[9] provided evidence that in terms of efficacy, oxaliplatin is noninferior to cisplatin, and capecitabine is noninferior to 5-FU. Taken together these provide direct evidence for the current UK SoC (oxaliplatin + capecitabine) vs (oxaliplatin + capecitabine + epiribucin) on the assumption of exchangeability/class effects, with oxaliplatin substituting for cisplatin and capecitabine substituting for 5-FU. A broader disease definition is adopted when admitting evidence from these trials, but the ERG noted that REAL-2 is likewise premised on a broad disease definition ('carcinoma of the esophagus, gastroesophageal junction, *or stomach* that was locally advanced (inoperable) or metastatic').

3.5. Additional work on clinical effectiveness undertaken by the ERG

3.5.1. Searches

The ERG conducted searches of Ovid MEDLINE (1st March 2021) and Embase (8th March 2021) to confirm that the company's literature searches had identified all relevant studies. These searches used additional free-text search terms for gastro-oesophageal junction adenocarcinoma (and alternate spellings) and single-arm study designs, but did not include search terms for 'gastric' or 'stomach' neoplasms. (Full search strategies are available in Appendix A). The titles and abstracts of search results were screened by one reviewer. The ERG identified two studies[31,32] to review at full-text. The study by Lordick et al. (2013)[31] included patients with HER-2 positive advanced gastric cancer so was excluded on the basis of population. Shah et al. (2017)[32] was excluded as onartazumab was not considered a relevant comparator. The ERG did not identify additional single-arm studies or other relevant trials that should have been included with respect to the stated criteria. However, as described in Section 3.3, the ERG identified further trials from existing NMAs with a broader disease definition of stomach/gastric cancer.[10,11]

3.5.2. Network evidence

The ERG carried out exploratory survival and cost-effectiveness analysis using an effect size estimate on doublet versus triplet treatment, applied to the doublet arm of the KEYNOTE-590[12] trial. The results of applying the NMA-derived hazard ratio from ter Veer et al. (2016)[10] (Section 3.4) within the economic model to the preferred OS and PFS distributions under doublet therapy are described in Section 6.2.4.

3.6. Conclusions of the clinical effectiveness section

The ERG considered that the company had identified all relevant clinical evidence for this appraisal. All key outcomes from the NICE final scope[8] were covered in the CS. Requisite information regarding the methodology and outcomes for clinical effectiveness was available in the CS and clarification responses provided by the company, and was generally reasonably described.

There was one RCT (KEYNOTE-590[12]) comparing pembrolizumab 200 mg intravenously every three weeks in combination with cisplatin 80 mg/m^2 intravenously every three weeks and 5-FU 800 mg/m^2/day continuous intravenous infusion (4,000 mg/m^2 per three-week cycle) to saline placebo intravenously every three weeks in combination with cisplatin 80 mg/m^2 intravenously every three weeks and 5-FU 800 mg/m^2/day continuous intravenous infusion (4,000 mg/m^2 per three-week cycle) that could provide directly comparative evidence for the base case economic model. All other studies included in the company's SLR did not assess pembrolizumab, but rather potentially relevant comparator treatments. The ERG was satisfied that KEYNOTE-590[12] was generally a high quality trial. The ERG's concerns about the trial related to generalisability rather than internal validity. The ERG was satisfied that the trial showed a benefit for pembrolizumab over placebo in terms of OS and PFS. The company considered an NMA or a MAIC analysis given that the comparator regimen in the pivotal trial did not encompass the range of eligible comparators in the NICE final scope.[8] However, the options of conducting an NMA and MAIC were both rejected by the company due to a small, disconnected network and differences between populations and with target population respectively. The ERG identified existing NMAs in gastric cancer and considered, given the similarity of treatment pathways, that data from this broader population could potentially be informative.

The key issues in the clinical effectiveness evidence identified by the ERG were as follows:

- The clinical evidence may not be generalizable to the UK population
- Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens.

4. COST-EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

The company carried out a SLR to identify existing cost-effectiveness evidence, HRQoL evidence, and cost and healthcare resource use evidence in adults with advanced, unresectable or metastatic oesophageal cancer, including carcinoma of the gastro-oesophageal junction. A summary of the ERG's critique of the methods implemented by the company to identify relevant cost-effectiveness evidence is presented in Table 6.

Table 6. Summary of ERG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix G	Appropriate
Inclusion criteria	Appendix G (Table 1, p.160)	Appropriate. Broad criteria were applied. Full economic evaluations of interventions aimed at managing advanced, unresectable or metastatic OC (including carcinoma of the gastro-oesophageal junction) published in English language from data inception to Year 2020 were included as per NICE scope
Screening	Appendix G	Appropriate [a]
Data extraction	Appendix G	No details provided in Appendix G. However, no cost-effectiveness studies relevant to the UK population were identified during screening.
QA of included studies	Appendix G	

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; OC, oesophageal cancer; QA, quality assessment

Notes:

[a] Abstracts were dual screened versus pre-defined PICOS selection criteria. Discrepancies were resolved with a third party. Potential full text articles were retrieved and screened in the same way. A list of excluded studies was provided in Appendix G Table 2, p.165 of the CS together with reasons for exclusion

The ERG was satisfied with the company's review of the cost-effectiveness literature. Ten economic evaluations were identified. The ERG agreed with the company's judgment that none of these ten studies were relevant to the UK population and were hence correctly not summarised in the CS.

Table 7. Summary of ERG's critique of the methods implemented by the company to identify health related quality of life (in terms of utilities)

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix H	Broadly appropriate. The ERG noted that the search strategies used to identify studies reporting HRQoL or utility values did not include terms for specific measures (e.g. EQ-5D), however, the ERG was satisfied that all relevant HRQoL literature was identified.
Inclusion criteria	Appendix H (Table 20, p.179)	Appropriate. Broad criteria were applied. Studies reporting HRQoL or utility values related to advanced, unresectable or metastatic OC, including carcinoma of the gastro-oesophageal junction, published in English language from data inception to Year 2020 were included.
Screening	Appendix H	No detail provided. It was unclear to the ERG if screening was performed independently by two reviewers. Study selection was documented in a PRISMA flow diagram (CS, Appendix H, Figure 4).
Data extraction	Appendix H	No detail provided. The company summarised details for the identified studies (CS, Appendix H, Table 21)
QA of included studies	Appendix H	No detail provided. No formal critical appraisal of the studies was conducted, however the company did provide an assessment of the consistency of each study with the reference case (CS, Appendix H, Table 22)

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; OC, oesophageal cancer; QA, quality assessment

Notes:

[a] Abstracts and full text articles were screened versus pre-defined eligibility criteria (Appendix G, Table 20, p.178) with no further details provided in the CS.

b Data was extracted using a pre-defined data extraction template (Appendix G (Table 22)), with no further details provided in the CS.

The ERG was broadly satisfied with the company's review of the literature reporting health effects (health-related quality of life and utilities). The company identified nine studies[12,33-40] reporting utility estimates in people with OC which are summarised in Appendix H (Table 21 and

Table 22) of the CS. The ERG noted the absence of methodological reporting for screening and data extraction. While no formal critical appraisal of studies was conducted, the company provided an assessment of the consistency of each study with the reference case. The ERG noted that none of the nine studies identified in the review of utilities were used in the model. The ERG was satisfied that the incorporation of utilities data from KEYNOTE-590[12] only into the model was appropriate.

Table 8. Summary of ERG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Searches	Appendix I	Appropriate
Inclusion criteria	Appendix I (Table 40, p.202)	Appropriate. Broad criteria were applied. The company included studies reporting healthcare costs and/or resource use in the treatment and on-going management of advanced unresectable or metastatic oesophageal cancer (including carcinoma of the gastro-oesophageal junction) in order to evaluate the economic burden of oesophageal cancer in the United Kingdom. Studies published in English language from data inception to Year 2020 were included.
Screening	Appendix I	Appropriate [a]
Data extraction	Appendix I	No detail provided. The company summarised details for one study which they judged to meet the criteria of the UK population (Appendix I, Table 41)
QA of included studies	Appendix I	No details provided. No formal critical appraisal was provided.

Abbreviations: CS, Company Submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; QA, quality assessment

Notes:

[a] Abstracts were dual screened versus pre-defined PICOS selection criteria (CS, Appendix I, Table 40).Discrepancies were resolved with a third party. Potential full text articles were retrieved and screened in the same way. A mapping of excluded studies together with reasons for exclusion were provided in a PRISMA flow diagram (CS, Appendix I, Figure 5).

The ERG was broadly satisfied with the company's review of the literature reporting healthcare resource use and costs. The company identified 16 studies which reported cost or resource use

associated with advanced, unresectable or metastatic oesophageal cancer, of which only one study was judged by the company to meet the criteria of the UK population.[41] However, there was no discussion of the applicability of the identified study to the economic model within the CS.

4.2. Summary and critique of company's submitted economic evaluation by the ERG

4.2.1. NICE reference case checklist

Table 9: NICE reference case checklist

Attribute	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓
Perspective on costs	NHS and PSS	✓
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	✓ Pairwise comparison of pembrolizumab in combination with chemotherapy versus trial comparator or non-trial blended comparator
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓ Time horizon of 20 years was originally used. The ERG noted that 3% of patients were still alive in the pembrolizumab + chemotherapy arm. Company amended time horizon to 30 years post clarification questions
Synthesis of evidence on health effects	Based on systematic review	✓ Systematic review undertaken to identify relevant evidence. However none of the findings were used to inform the submission.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	✓ EQ-5D utility values used to inform the model using a time-to-death approach. Sensitivity analysis presented where utility values based on progression status.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	✓ Reported directly by patients in the KEYNOTE-590 trial
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	✓ Based on van Hout et al. (2012)[42] cross walk value set

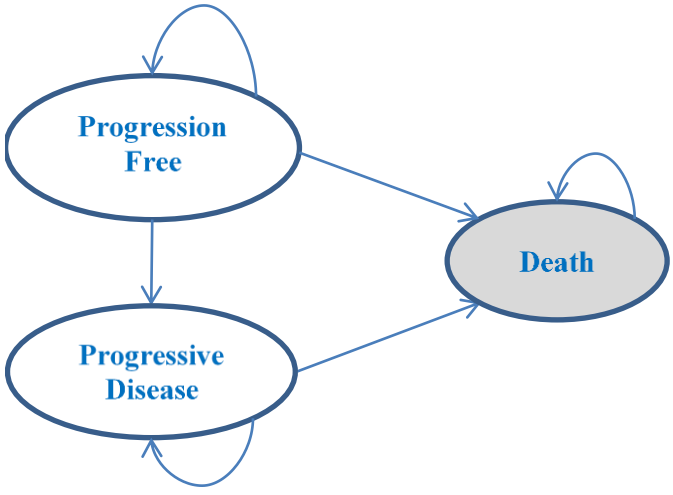
Attribute	Reference case	ERG comment on company's submission
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✓
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	✓

Key: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The company developed a partitioned survival analysis (PartSA) model to estimate health outcomes and costs for pembrolizumab in combination with chemotherapy versus chemotherapy. The company's model schematic is shown in Figure 4.

Figure 4: Company's model schematic



Source(s): CS Figure 10

The three mutually exclusive health states; progression-free, progressive disease and death, are informed by the overall survival (OS) and progression-free survival (PFS) curves. The area under the OS curve is used to estimate the proportion of patients alive over time, and the area

under the PFS curve is used to estimate the proportion of patients who are in the progression-free health state over time. The difference between OS and PFS is used to estimate the proportion of patients in the progressive-disease health state. KEYNOTE-590[12] data were used to generate the PFS and OS curves either by using the Kaplan-Meier estimates or from a parametric distribution.

The company justified its choice of model structure based on its extensive use in previous advanced cancer NICE submissions[43-45] and a recent advanced oesophageal cancer in the second-line setting.[46] The ERG considered the choice of model structure to be appropriate and suitable for decision making in this disease area. Nevertheless, there are several limitations with the PartSA approach which are important to note when interpreting results and model functionality:

- The proportion of patients who progress per model cycle is not explicitly modelled. Thus, there are limitations when needing to assign costs to the exact proportion of patients who progress. Within this context, patients who progress are assigned a one-off subsequent treatment cost which is applied to the proportion of patients who leave the progression-free state and includes those leaving due to death as well as progression. However, it should be noted that post-clarification questions, the company calculated the one-off subsequent treatment cost based on the proportions from the total number of progression events and not just those who progressed and therefore the ERG did not consider this to be of great concern.

- The use of an overarching OS curve impacts the relationship between progressive-disease costs versus efficacy (e.g., subsequent treatment inputs). The company's base case uses the same subsequent treatment distribution as the modelled efficacy, however, should changes to the subsequent treatment distribution be needed to account for a new treatment, this would lead to higher costs with no direct impact on efficacy. At the time of writing, nivolumab monotherapy is not currently available in UK clinical practice, as NICE ID1249 is still under consultation. At clarification stage the company provided further information concerning subsequent treatments, highlighting that a small proportion of patients on both treatment arms went on to receive nivolumab after progression (3.2% for pembrolizumab in combination with chemotherapy versus 4.6% chemotherapy). Therefore, the ERG did not consider this limitation to be of great concern.

In the company's base case, the PFS outcomes only impacted costs associated with resource use and subsequent treatment. Drug costs are calculated separately using a Kaplan-Meier estimates of time-on-treatment (ToT) to estimate the proportion of patients on treatment on either pembrolizumab in combination with chemotherapy or chemotherapy. Quality-adjusted life-years (QALYs) were estimated from utilities using the time-to-death approach and are therefore not impacted by ToT or PFS. Therefore, although the model structure was described as progression-based, progression itself had no impact on quality of life or life-years in the company's base case analysis.

4.2.3. Population

The company stated that the model considered patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma (CS Section B.3.2.2). This population aligned with the anticipated licence and NICE final scope.[8] KEYNOTE-590[12] was used to inform the population and efficacy model parameters, and was reflective of patients with *"locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction"* (CS Section B.2.3.1). The company also included a subgroup population considering patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma who had a combined positive score (CPS) greater than or equal to 10 (CPS≥10). This subgroup was considered by the company to be of clinical significance.

Patient characteristics (age, sex, body weight, and body surface area [BSA]) in the model were based on European patients from KEYNOTE-590.[12] In its submission, the company did not provide an explicit justification for using only the European subgroup to inform its base-case analysis. However, the ERG noted that the full population patient characteristics did not differ greatly from the European patients with the exception of body weight and BSA (see Table 10). Based on the characteristics of the full KEYNOTE-590[12] study population, the ERG expected that the lower average body weight/ BSA in the full ITT population is driven by the inclusion of Asian patients (for whom body weight and BSA are typically lower than a European population). The ERG considered the use of European patient characteristics to inform body weight and BSA in particular to be most appropriate to inform the base-case analysis.

Table 10: Baseline characteristics of patients included in the model (European versus all patients)

Patient characteristic	All patients		CPS ≥ 10	
	European patients	**All patients**	**European patients**	**All patients**
Average age	61.4	62.4	60.8	61.9
Proportion male	80.7%	83.4%	71.9%	81.7%
Average patient weight (kg)	71.2	63.1	68.4	62.6
Body surface area (m^2)	1.84	1.70	1.79	1.70

Abbreviations: CPS, combined positive score

Source(s): CS Table 41; CS Appendix M Table 1; company model (KEYNOTE-590)

The ERG noted some additional important features of the KEYNOTE-590[12] study which have implications concerning the generalisability of the modelled patient population versus those patients that would be treated in UK clinical practice (see Section 3.2.3.1).

Given the inclusion criteria of KEYNOTE-590[12] specifying patients with ECOG status of 0 or 1, it is likely that these patients in the trial are fitter than the UK oesophageal cancer population which includes those with an ECOG score >1. While this is a common feature of many advanced cancer trials, this means that the KEYNOTE-590[12] study does not provide information concerning the safety or efficacy of pembrolizumab in combination with chemotherapy in an ECOG 2+ population.

Over half of the KEYNOTE-590[12] study population comprised of patients from Asia (52.5%, versus 47.5% from the rest of the world [ROW]) (ITT population CS Table 6). Region has an apparent impact on the HR for OS (0.64 [95% CI 0.51-0.81] for Asian patients versus 0.83 [95% CI 0.66-1.05] for the ROW patients).[47] Clinical advice provided to the ERG highlighted that there could be a difference in fitness, screening and treatment approach between Asian and ROW patients (each of which may contribute to differences in outcome). Advice provided to the ERG suggested that patients from Asia tend to be treated more aggressively than their European counterparts, although it is expected that treatment pathways are broadly similar when comparing practices in Asian countries and the UK. Clinical experts also explained that obesity increases the risk of adenocarcinomas which reflects the UK population more than the Asian populations. The ERG considered the high proportion of patients from an Asian region was not reflective of the UK patient population, and noted with concern the impact this appears to have

on OS. The impact of region on OS could have been caused by several reasons, including those highlighted above, as well as which treatments patients receive after progression. The ERG requested that the company provide a scenario analysis removing the Asian region population, however the company did not provide this subgroup in the model stating that *"KEYNOTE-590 was not powered to detect differences by region…and feedback from clinicians MSD has consulted that there is no clinical rationale for the difference"* (see response to clarification question B4). Therefore, the ERG was unable to consider any further analysis for this subgroup.

The ERG also noted the histology in KEYNOTE-590[12] (26.8% adenocarcinoma versus 73.2% squamous cell carcinoma) (ITT population CS Table 6). Clinical advice provided to the ERG confirmed that in UK practice, the proportion of patients by histology would be expected to be approximately two-thirds being adenocarcinoma and one-third being squamous cell carcinoma (i.e., the opposite proportionate split versus the KEYNOTE-590 study). Clinicians also advised that histology is an important factor given the differences in disease and potential treatment (see Section 3.2.3.1).

4.2.4. Interventions and comparators

The company's model considered pembrolizumab in combination with platinum-based chemotherapy in line with the dosing schedule in KEYNOTE-590:

- Pembrolizumab administered intravenously at a fixed dose of 200 mg over 30 minutes every three weeks (Q3W) for up to 35 cycles.
- Cisplatin administered intravenously at a dose of 80 mg/m^2 Q3W for six doses.
- 5-FU administered as a continuous infusion on Days 1 to 5 at a dose of 800 mg/m^2/day (4,000 mg/m^2 in total) Q3W for up to 35 cycles.

The NICE scope identified the relevant platinum-based comparators as doublet treatment (fluorouracil or capecitabine plus cisplatin or oxaliplatin) and triplet treatment (fluorouracil or capecitabine plus cisplatin or oxaliplatin plus epirubicin). The company identified evidence to support the assumption of similar efficacy between doublet treatments and little benefit with the addition of epirubicin supported by data from the NICE Guideline in the assessment and management of oesophago-gastric cancer in adults (NG83)[7] and clinical opinion. This evidence was used to justify the use of the comparator arm from KEYNOTE-590[12] to inform the efficacy of

the chemotherapy arm in the model regardless of treatment regimen selected. The ERG would like to note that the evidence from NG83 presented by the company, reports a HR of 0.7 for the comparison of 5-FU+cisplatin with or without an anthracycline (e.g. epirubicin). Although the confidence intervals cross 1, this should not be used solely as evidence that there is no difference between treatment regimens when the mean is so far from no difference (i.e. 1). Clinician experts advised the ERG that if there is a benefit of triplets versus doublets, it would be small therefore assuming equivalent efficacy is reasonable and that in clinical practice epirubicin is generally dropped as there is concern over the increased toxicity with little benefit. Therefore, the ERG considers the company's assumption to be reasonable, however given the uncertainty, the ERG presented scenarios exploring the efficacy of triplet regimens based on the NMA's discussed in Section 3.5.2. Results of these scenarios are presented in Section 6.2.

The main comparator in the model reflects the KEYNOTE-590[12] trial comparator; cisplatin plus 5-FU with the dosing schedules as per the trial:

- Cisplatin administered intravenously at a dose of 80 mg/m^2 Q3W for six doses
- 5-FU administered as a continuous infusion on Days 1 to 5 at a dose of 800 mg/m^2/day (4,000 mg/m^2 in total) Q3W for up to 35 cycles

Clinical experts advised the ERG that these dosing schedules are slightly different to those commonly used in UK practice, with cisplatin usually given at a dose of 60 mg/m^2 for up to six to eight cycles. The five-day infusion of 5-FU is no longer considered the standard of care in UK clinical practice, and is now mainly replaced by capecitabine (a different fluoropyrimidine that is administered orally, and the body converts to 5-FU) or a two-day infusion of 5-FU (instead of five-day). However, the clinical experts confirmed that the efficacy of 5-FU would not be impacted by these dosing differences. As such, the ERG explored scenarios changing the dose to reflect UK practice (see Section 6.2).

The model also includes other regimens as a pairwise comparison versus pembrolizumab in combination with chemotherapy and as a blended comparison assuming equal market share in scenario analysis (see Table 11).

Table 11: Comparator treatments included in the company's economic model

Type	Platinum	Fluoropyrimidine	Other
Doublets	Cisplatin	5-FU	-
	Cisplatin	Capecitabine	-
	Oxaliplatin	Capecitabine	-
Triplets	Oxaliplatin	5-FU	Leucovorin (folinic acid)*
	Cisplatin	5-FU	Epirubicin (anthracycline)
	Oxaliplatin	5-FU	Epirubicin (anthracycline)
	Cisplatin	Capecitabine	Epirubicin (anthracycline)
	Oxaliplatin	Capecitabine	Epirubicin (anthracycline)

Key: 5-FU, 5-fluorouracil

Note: *The combination of oxaliplatin + 5-FU + leucovorin is also known as FOLFOX and is considered a doublet regimen

At clarification stage, the ERG requested further information from the company to justify the assumption of equal market share. The company claimed that their market share data *"lacked face validity versus the comparators outlined in the NICE Final Scope".* In addition, clinicians were unable to provide market share expectations at their advisory board, as such the company *"chose to include all therapies listed in the final NICE scope and distribute them evenly with respect to market shares"* (see company clarification response B16). The ERG was unable to validate the company's justification as no information on the market share data or clinical input from the advisory board was provided by the company within the submission or in response to clarification questions. The ERG found the company's approach of assuming equal market share inadequate to reflect UK practice. However, the ERG acknowledged that the company ran scenario analysis amending the comparator arm to each of the chemotherapy regimens individually to investigate the impact of comparator therapies. Based on the company's revised base case post clarification questions, the ICER ranged from £39,812 to £42,172.

Clinical advice provided to the ERG noted that not all of these treatments are used in UK practice and certainly do not have equal market shares. Capecitabine (administered orally) is used more than 5-FU as 5-FU is only used in the small number of patients who cannot tolerate tablets or who experience dysphagia. Doublet treatments are more common in UK practice but there is still a small usage of triplet regimens, mainly capecitabine plus oxaliplatin plus epirubicin (a combination also known as EOX). In addition, based on the results on the REAL-2[9] study, oxaliplatin should have largely replaced cisplatin in clinical practice given no decline in efficacy,

reduced toxicity and reduced infusion time, however the decision can also depend on other factors such as comorbidity in patients, histology and capacity of chemotherapy in the day unit. Thus, the ERG considered the trial comparator in KEYNOTE-590[12] was not the most relevant comparator for this decision problem. In addition, some of the other comparators included in the model were considered irrelevant. The ERG ran scenarios using a more clinically plausible distribution of market shares based on clinical expert opinion provided to the ERG. Results of this scenario are presented in Section 6.2.

4.2.5. Perspective, time horizon and discounting

The company discounted costs and outcomes (life-years [LYs] and QALYs) at 3.5% per annum and the model adopted an NHS and PSS perspective. The ERG was satisfied that the perspective and discounting adopted by the company's model are aligned with the NICE reference case.

The model included half cycle correction in their base case; however, the ERG considered this was unnecessary given that the cycle length was only seven days.

A time horizon of 20 years was used to inform the company's base case to reflect a lifetime horizon as specified in the NICE reference case. However, the ERG noted that in the pembrolizumab in combination with chemotherapy arm at 20 years [redacted] of patients were estimated to still be alive using the company's base case survival settings (CS, Doc B, Table 46). The ERG requested justification for this time point at clarification stage. The company stated that their choice of 20 years was *"informed by the current estimates of survival of patients treated within UK clinical practice*", though subsequently amended their time horizon to 30 years in their revised base case "*to fully capture costs and benefits of pembrolizumab in combination with chemotherapy"*. The ERG noted that at this timepoint <1% of patients were estimated to be alive at this timepoint and therefore considered the change appropriate based on the company's base case choice of OS modelling.

4.2.6. Treatment effectiveness and extrapolation

Data from the KEYNOTE-590[12] trial constituted the primary evidence base from which estimates of treatment effectiveness are made to inform the economic model. In terms of treatment effectiveness, two outcomes from the KEYNOTE-590[12] trial are used to inform the model: OS

and PFS. Data from KEYNOTE-590[12] concerning the estimated duration of treatment are discussed separately within Section 4.2.8.3.

For clarity, the descriptions of the time-to-event outcomes used to inform the model are provided below:

- **OS:** the proportion of patients who were alive at each model cycle, regardless of disease progression status. This was calculated as the time from randomisation until the last known date of survival
- **PFS:** the proportion of patients who were alive with non-progressed disease at each model cycle. The proportion of patients with progression-free disease was less than or equal to the proportion of patients alive at each model cycle. Therefore, any extrapolations of PFS were not permitted to "cross" the OS curve

For both OS and PFS, survival modelling methods were used to extrapolate over the lifetime horizon of the model, given that the follow-up period for data collected in the KEYNOTE-590[12] trial was shorter than the time horizon of the economic model (20 years in the company's original base-case analysis, 30 years in the company's revised base-case analysis, and up to a maximum of 33.6 months in the KEYNOTE-590 trial). The CS explained that NICE DSU TSD 14[48] guidance was followed in determining the most suitable survival extrapolations to inform the model.

The model also included the cost and utility implications associated with the occurrence of adverse events. The included adverse events are highlighted in this section, with the impacts on utility and costs discussed later in Sections 4.2.7.3 and 4.2.8, respectively.

4.2.6.1. Overall survival

As described in NICE DSU TSD 14, assuming patient-level data are available for analysis, a comparison of suitable plots should be undertaken to allow initial selection of appropriate models.[48] In the CS however, only cumulative hazard plots and log-cumulative hazard plots (LCHPs) were presented (CS Figures 13 and 14, for the pembrolizumab in combination with chemotherapy versus SoC arms, respectively). These plots allowed for an assessment of whether the proportional hazards (PH) assumption holds, and the potential suitability of PH models, such as the exponential, Gompertz, or Weibull model. However, these plots did not allow for an assessment of whether other types of model are potentially suitable – for example,

a quantile-quantile (Q-Q) plot would allow an assessment of whether a jointly-fitted accelerated failure time (AFT) model would be suitable (such as a lognormal or log-logistic model, with a covariate for treatment arm).

The company concluded in its submission that the PH assumption does not hold (on the basis of non-parallel lines seen in the LCHP, CS Figure 14), and so a joint parametric model fitted within a PH framework (e.g., with a covariate for treatment arm) was deemed inappropriate. In response to a further clarification question concerning the LCHP (clarification question B6), the company provided further justification:

- NICE DSU TSD 14 guidance[48] states: *"Generally, when patient-level data are available, it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach"*. Also mentioned is that when individual-level patient data are available, fewer assumptions are required when fitting separate versus jointly-fitted parametric models. The company explained that both aspects of guidance presented in TSD 14 apply here, suggesting a jointly-fitted model would be less appropriate than separate models.

- The mechanism of action of pembrolizumab (an immune checkpoint inhibitor) given in combination with chemotherapy is purported to differ substantially from that of chemotherapy given alone. Accordingly, the company considered a modelling approach wherein a 'two-dimensional' treatment effect (i.e., an impact on both shape and scale parameters) to be more appropriate when considering alternative modelling approaches.

The ERG agreed that a jointly-fitted, single, PH parametric model is unlikely to provide a good fit to the KEYNOTE-590[12] trial data. However, the ERG disagreed with the company's decision to reject *all* jointly-fitted models on the basis of inspecting only cumulative hazard-based plots. Other types of jointly-fitted models, such as a model that assumes a constant time ratio (i.e., a jointly-fitted AFT model), may be appropriate and this possibility requires further exploration.

At clarification stage, a Q-Q plot was requested, as well as several other plots to further explore the suitability of different parametric models to estimate OS. The Q-Q plot was provided (see company response to clarification question B5), which is re-produced in Figure 5. To justify the use of a jointly-fitted AFT model, the Q-Q plot should show a straight line extending from the origin (shown in Figure 5 as the red dashed line).

Figure 5: Q-Q plot of overall survival from KEYNOTE-590

Key: SOC, standard of care.
Source: Image re-produced from company's response to clarification question B4

In response to clarification question B4, the company states that the Q-Q plot for OS suggests *"that the observed data was bending away from the straight line (slope became smaller over time)"* and that this *"suggests that the hazards of death for the pembrolizumab + chemotherapy arm was decreasing faster than the SOC arm and the trend cannot be captured by an AFT model"*. The ERG acknowledges that the Q-Q plot does not demonstrate an 'perfect' straight line extending from the origin but would not reject the use of a jointly-fitted AFT model on the basis of this Q-Q plot alone, as the plot does not show a clear violation of a constant time ratio (in the view of the ERG). Furthermore, as the number of patients at risk decreases substantially over time, the robustness of the Q-Q plot towards the end of follow-up is especially uncertain.

The CS explained that given the availability of patient-level data from the KEYNOTE-590[12] trial, the assessment of the LCHP (CS Figure 14), and the different mechanistic properties of pembrolizumab in combination with chemotherapy versus chemotherapy, separately-fitted parametric models were preferred over jointly-fitted models. The ERG agreed that separate models required fewer assumptions but noted that these models required additional parameters to be estimated. By specifying separate models, a multi-dimensional effect of pembrolizumab is

implicitly modelled (which is especially important to consider if different model distributions are selected). Nevertheless, considering the visual fit of the independent models (discussed later in this section), the ERG considered it appropriate to exclude jointly-fitted models (both PH and AFT) for the outcome of OS.

Following inspection of KEYNOTE-590[12] trial data, two different modelling approaches were implemented within the economic model for the outcome of OS:

- **Fully-fitted modelling approach (henceforth termed "single parametric model"):** A single parametric model was fitted to the OS data from KEYNOTE-590 (separately for each treatment arm), from $time = 0\ weeks$
  - Six parametric models were considered: exponential, Weibull, Gompertz, lognormal, log-logistic, and generalised gamma
- **Piecewise models:** The Kaplan–Meier estimate of OS was used to directly inform OS within the economic model outcome up until a given cut-off point, after which the remainder of the OS was informed by a parametric model fitted to a reduced set of data from KEYNOTE-590
  - Like the single parametric models, these models were fitted independently by treatment arm, and the same six models were considered per the single model approach
  - Events and censored observations before the cut-off point were not included in the parametric component (i.e., the parametric models were fitted to 're-based' data, where $time_{re-based} = time_{original} - "cut-off"\ point$)

At clarification stage, the ERG asked the company to explain why other alternative modelling approaches were not explored (clarification question B11). In response, the company explained that diagnostic plots for the hazard function (LCHP, smoothed hazard plots, etc.) showed *"a relatively simple trend"*, and that given the maturity of the data from KEYNOTE-590, piecewise models were capable of providing reasonable estimates (company response to clarification question B11). The company went on to explain that other flexible methods require *"additional assumptions"*, highlighting that when fitting spline-based models it is necessary to specify the number and location of knots, which can have an important effect on the resultant extrapolation.

The ERG observed that other possible methods may have also yielded reasonable extrapolations. For example, spline-based models have been used in a range of previous NICE appraisals of immune-checkpoint inhibitor treatments. The ERG noted in particular that while spline-based models require certain assumptions related to the number of knots and their location(s), piecewise models also require similar assumptions (for example, the number and location of cut-off points). Nevertheless, the ERG was satisfied that the range of models provided by the company within its submission was sufficient to inform decision making.

For the piecewise models, it was necessary to specify where the cut-off point should be imposed. To select a cut-off point, the CS explains that Chow tests were conducted to *"identify structural changes"* where *"higher Chow test statistics indicating a higher likelihood of structural change"* (CS Section B.3.3). Plots of the Chow test statistics based on a range of different cut-off points are presented in CS Figure 15 for the pembrolizumab in combination with chemotherapy arm, but a corresponding plot for the chemotherapy arm was not provided, as *"the Chow test statistics for the SOC arm proved inconclusive for determining an appropriate cut-off"* (CS Section B.3.3). At clarification stage, a plot of the Chow test statistics for the chemotherapy arm was requested and provided (see company's response to clarification question B7).

Based on the Chow test statistics for the pembrolizumab in combination with chemotherapy arm, the company selected a base-case cut-off point of Week 40, with an alternative cut-off point of Week 32 explored within scenario analysis. The same cut-off point was selected for both treatment arms. The ERG noted that a Chow test can be used to assess whether a single structural break occurs at a given time point, assuming that the time point is known. For example, the test was illustrated by Chow[49] via an example to explore the demand for automobiles in the United States, and if there was evidence this changed 1922 to 1953 and 1954 to 1957. However, it was the ERG's understanding that the Chow test was not designed to detect the timepoint at which a structural break may occur. In the example presented by Chow, the timepoint was selected based on when data were reported and was not chosen following inspection of Chow test statistics. Accordingly, the ERG did not consider it statistically sound to choose a cut point based on the Chow test statistics alone.

Visual and statistical goodness of fit scores (Akaike's and Bayesian information criterion [AIC and BIC, respectively]), were used by the company to inform its determination of the best-fitting estimate of OS (focusing on fit to the Kaplan-Meier estimate). Based on AIC and BIC scores,

the log-logistic model was highlighted as the best fitting for the pembrolizumab in combination with chemotherapy arm, whereas a lognormal was the best-fitting model for the chemotherapy arm. The company also highlighted that the Gompertz model led to *"clinically-implausible"* outcomes (where the hazard of death after the end of follow-up approached zero, leading to an indefinite plateau in the OS extrapolation, see CS Figure 16).

To aid with model selection, the company undertook a targeted search of the published literature to identify studies that reported longer-term OS estimates in an advanced and metastatic oesophageal cancer population. Three studies were identified, which are summarised below:

- **Gavin et al. (2012):**[50] A European study based on data collected from 66 cancer registries, with patient five-year survival rate of 3.8% for patients with distant stage oesophageal cancer. The ERG highlights that the reported value of 3.8% is an estimate of *relative* survival. In this example, relative survival should be interpreted as the ratio of the proportion of observed survivors in the Gavin et al. (2012) study to the proportion of expected survivors in a relatively healthy population. A five-year relative survival of 3.8% implies that the five-year OS is lower than 3.8% (when taking into account death from other causes), though five-year OS is not reported in the Gavin et al. 2012[50] study)
- **Surveillance, Epidemiology, and End Results (SEER) database:** Several different studies were cited, all based on data collected from the SEER database.

  The American Cancer Society[51] reports a five-year relative survival rate for patients with distant oesophageal cancer of 5%, based on people diagnosed with oesophageal cancer between 2010 and 2016. Again, the ERG highlights that this is an estimate of *relative* survival, and so the true estimate of 5-year OS is expected to be less than 5% based on this study.

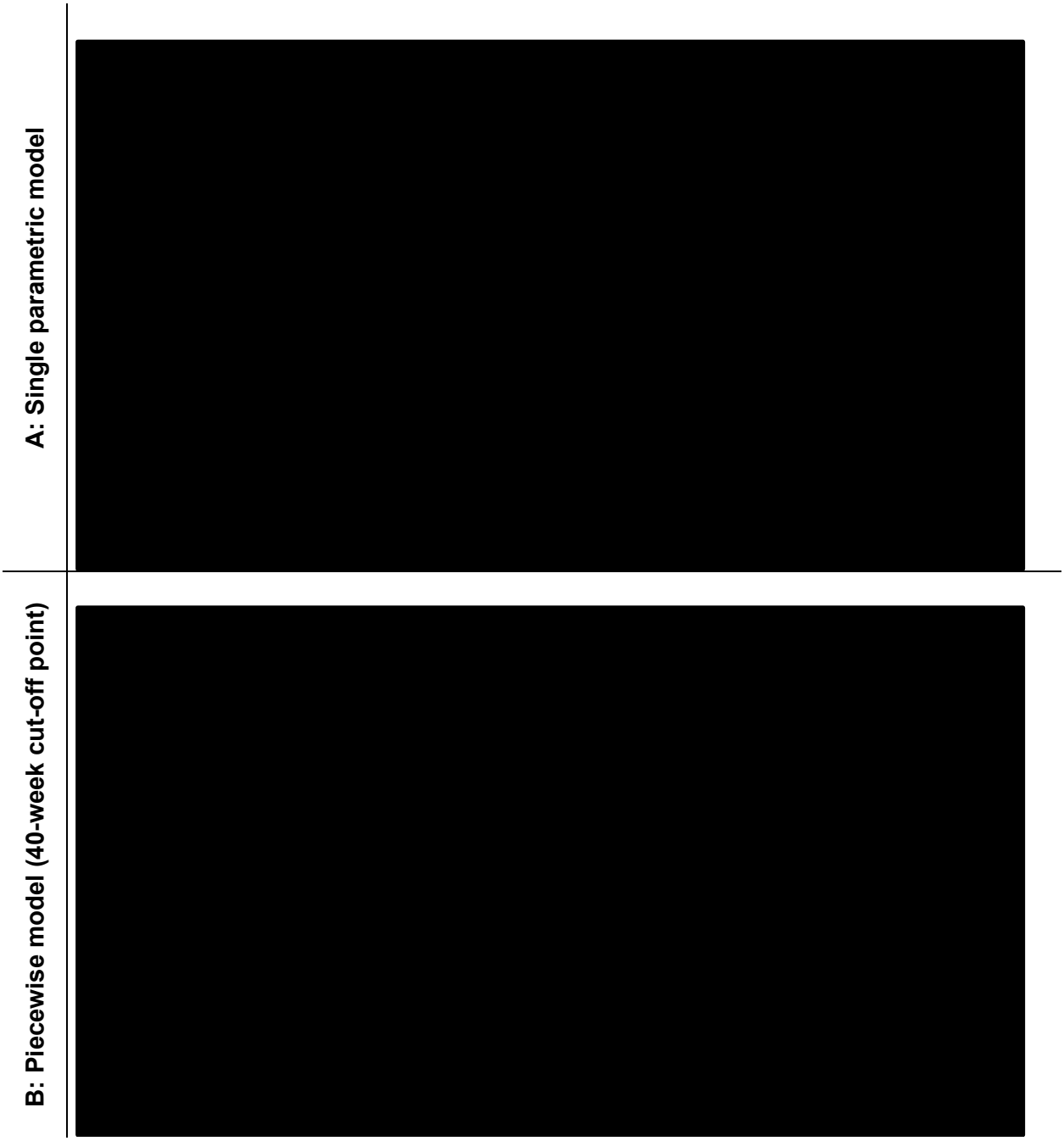
  - In 2016, Wu et al. (2016)[52] reported five- and 10-year OS rates of 5.4% and 3.5%, respectively, for patients with metastatic oesophageal cancer. While not stated in the CS, it should be noted that median OS for this population was 10 months, and that one- and two-year OS rates were 40.5% and 14.6%, respectively. In KEYNOTE-590,[12] median OS for the chemotherapy arm was [redacted] months, with one- and two-year OS rates of [redacted] and [redacted], respectively, demonstrating that the estimates reported by Wu *et al.* [redacted].

  - Another study by Wu et al.[53] published in 2017 demonstrated median OS estimates of between five and six months, depending on whether patients had a single site of distant metastasis, or multiple sites of distant metastasis. However, five-year OS was not possible to robustly estimate from this study. The ERG speculated that median OS is lower in the later study by Wu et al.[53] (published in 2017) versus the earlier study by Wu et al.[52] (published in 2016) due to the latter study likely including more patients with multiple sites of distant metastasis, but this is unclear.

- **Tanaka et al. (2010):**[54] A single-centre, Japanese study of n=80 patients with oesophageal squamous cell cancer and distant organ metastasis. The median OS was 6.4 months, with one- and two-year OS rates of 23.7% and 11.2%, respectively. Five-year OS was not reported, but from the Tanaka *et al.* paper, it can be inferred through inspection of the Kaplan-Meier estimates (Fig 1 in the paper) that five-year OS is likely less than 5% (as the end of the Kaplan-Meier estimate evaluated at approximately five years suggests around 1–2% of patients were still alive, and the OS estimate falls to less than 5% at around three years). The ERG noted, however, that this is a purely squamous cell carcinoma population, from a single centre in Japan. Therefore, this study was unlikely to serve as a useful validation source for the KEYNOTE-590[12] trial (which included adenocarcinoma patients, and patients from outside of Asia)

At clarification stage, the ERG requested that the company provided additional plots to help with selecting a given model for the outcome of OS (clarification question B5 part c). The company provided a range of additional plots, including smoothed hazard plots (company response to clarification question B5 part c). Figures 13 and 14 of the company's response to clarification questions present a comparison of the fitted models to the estimated smoothed hazard functions for the pembrolizumab in combination with chemotherapy arm. These plots are presented together in Figure 6.

Figure 6: Smoothed hazard plots: single versus piecewise models



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

Source: Figures re-produced from company response to clarification question B5.

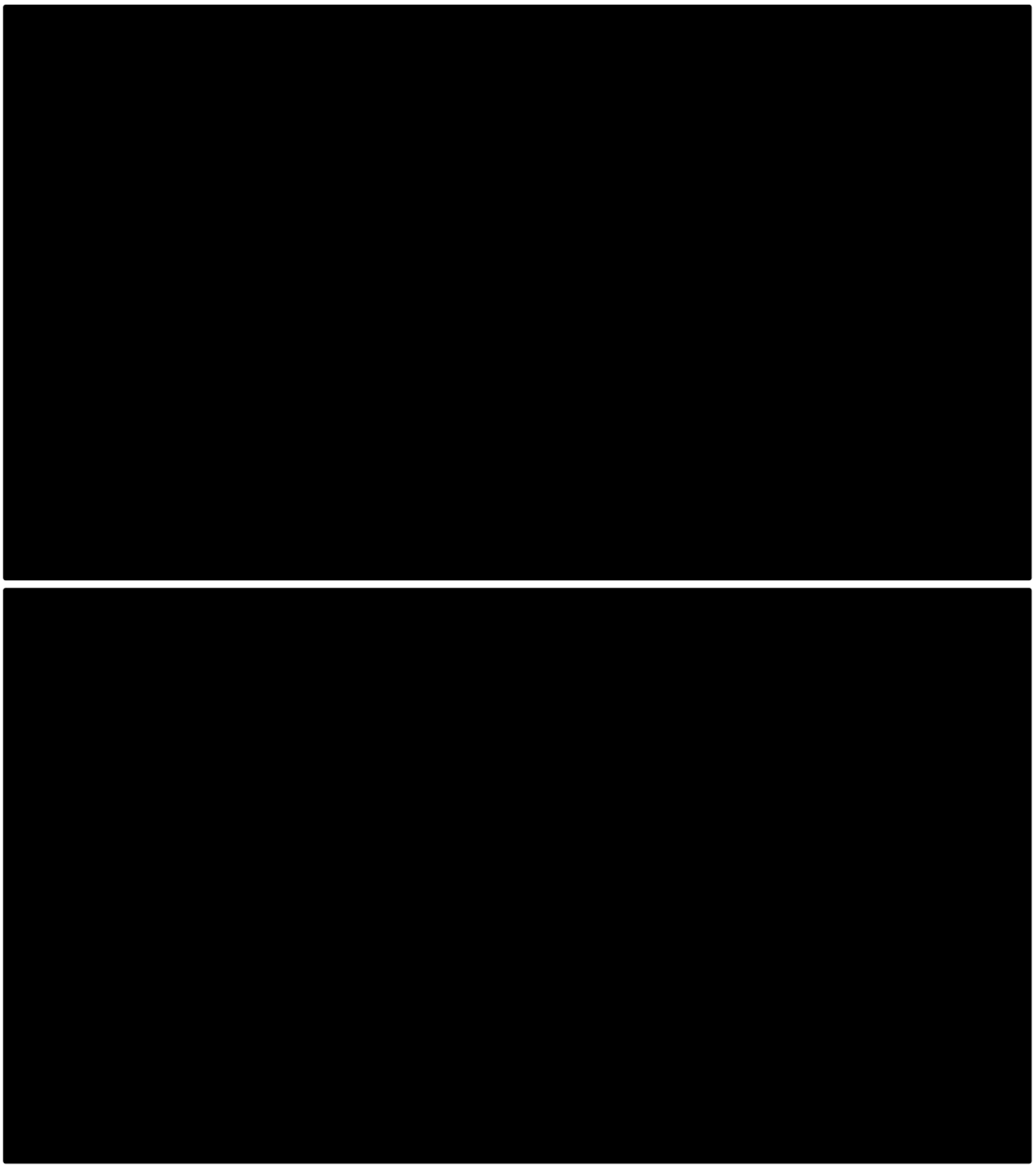
The plots for the single parametric models (Figure 6, panel A) illustrate that none of the seven[1] models were fully capable of reflecting the shape of the hazard function – that is, a gradual increase in the estimated hazard of death until approximately 40 weeks, followed by a consistent decline. As noted by the company, each of the models appear to overestimate the hazard of death from approximately 75 weeks onwards. The plots for the piecewise models with a 40-week cut-off point (Figure 6, panel B) appear to provide estimated hazards that lay closer to the smoothed hazard estimate. However, from these plots, it cannot be readily determined how the estimated hazard of death in the longer-term may differ, and how these may compare to the age- and sex-adjusted general population.

The company selected a piecewise Kaplan-Meier + log-logistic model for the outcome of OS for both treatment arms. These models were selected owing to their statistical goodness-of-fit scores (with the models providing either the best, or second-best fit according to AIC and BIC, see CS Table 44), their visual fit, as well as input from clinical experts concerning the expectation of a percentage of patients deriving a *"long-term survival benefit from treatment with pembrolizumab in combination with chemotherapy"* (CS Section B.3.3). For the chemotherapy arm, the company noted that the log-logistic model produced five- and 10-year OS estimates of [redacted] and [redacted] respectively (CS Table 45); and that these estimates were broadly in keeping with the external studies identified via a targeted review of the literature. However, the CS did not describe the plausibility of using the same model for the chemotherapy arm, given that this regimen does not contain pembrolizumab.

The company's base-case projections of OS for both arms are provided in Figure 7. At the end of the modelled time horizon (20 years), the company's base-case analysis predicts that [redacted] of the chemotherapy arm, and [redacted] of the pembrolizumab in combination with chemotherapy arm, are still alive (CS Tables 45 and 46).

[1] The ERG notes that an additional seventh model is presented in this plot – a 'gamma' model. The ERG understands this to be a two-parameter Gamma model, though this is not presented in the company's submitted economic model and is therefore not discussed further.

Figure 7: Company projections of overall survival (5- and 20-year time horizon)



Key: KM, Kaplan-Meier; SOC, standard of care.

Note(s): This figure is a re-formatted version of CS Figure 19. Figure re-produced for ease of interpretation related to time axis. Company base-case analysis includes cut-off point at week 40 (switch from KM to log-logistic model).

Source(s): Produced based on information provided in the company-submitted economic model.

The ERG considered the company's choice of OS models to inform its preferred base-case analysis to be broadly appropriate – the models provide a reasonable fit to the Kaplan-Meier estimate (helped in part by setting OS to be equal to the Kaplan-Meier estimate until 40 weeks) and appear to provide plausible estimates to inform the cost-effectiveness analysis (see CS Section B.3.3 for company's full rationale).

However, given the uncertainty in the extrapolated tail and the limited information available concerning long-term outcomes in this patient population, a range of alternative extrapolations may be suitable to aid decision making. To provide a range of plausible extrapolation options, the ERG has focused on four scenarios:

1. **Kaplan-Meier + log-logistic tail:** This is the company's base-case estimate of OS, used for both treatment arms. The Kaplan-Meier estimate of OS is applied up until 40 weeks, after which a log-logistic model is used to extrapolate OS for the remainder of the model time horizon
2. **Kaplan-Meier + log-logistic tail + assume treatment waning effect applies linearly between 5 and 7 years:** This approach adjusts the company's base-case estimate of OS by assuming the projection of OS for the pembrolizumab in combination with chemotherapy arm applies up until 5 years, at which point the projected hazard of death gradually approaches that of the chemotherapy arm until 7 years, after which the projected hazards are identical across both arms (equal to the projection for the chemotherapy arm)
    - The ERG highlighted here that while this is termed a "treatment waning effect" within the context of the model, the ERG has used this functionality purely within the interest of exploring how influential the projected tail is on the estimated ICER
3. **Single log-logistic parametric model:** This approach constitutes the best-fitting of the single parametric models, with the second-most optimistic estimate of OS for the pembrolizumab in combination with chemotherapy arm (most optimistic was the lognormal model)
    - The ERG considered this approach important to demonstrate the impact on estimated OS by considering a piecewise approach, per the company's base-case analysis

4. **Kaplan-Meier + generalised gamma tail:** This approach selects a less optimistic/ more pessimistic extrapolation for consideration after 40 weeks versus the company's base-case analysis

    - The generalised gamma model was selected as it represented a mid-range estimate of OS, in consideration of the range presented in the company's model (e.g., five-year OS estimates for the pembrolizumab in combination with chemotherapy arm were [redacted], with the generalised gamma model providing an estimate of [redacted] [see CS Table 46])

The results from these four scenarios are discussed further in Section 6.2.1.

The CS explained that clinical expert opinion was obtained in selecting the base-case approach to modelling OS (CS Section B.3.3). At the clarification stage, the ERG asked for further information to be provided about the process taken to elicit expert opinion (clarification question B23). The company explained that informal interviews were held with four clinical oncologists, separately, working in the treatment of oesophageal cancer. However, additional information was not provided, such as which questions were asked, and if there were any disagreements between experts.

4.2.6.2. Progression-free survival

Unlike OS, for the outcome of PFS diagnostic plots were not provided, and only piecewise models were presented in the original CS. The company explained that PFS data from the KEYNOTE-590[12] trial were relatively complete, with over 90% of patients having reached the PFS endpoint (CS Section B.3.3). The ERG interpreted this statement to be a comment on the proportion of patients still at risk for a PFS event at the end of the Kaplan-Meier estimate, as based on the KEYNOTE-590 CSR, [redacted] of the pembrolizumab in combination with chemotherapy arm, and [redacted] of the chemotherapy arm were recorded with a PFS event by the end of follow up ([redacted]).[47] Nevertheless, the ERG agreed with the statement made by the company that the PFS data are near complete.

The company also described how protocol-scheduled tumour imaging assessment scans had an impact on PFS outcomes. Based on the KEYNOTE-590 trial protocol, the first planned scan was scheduled to take place between Weeks 8 and 10 (at Week 9, ± 1 week either side of this time point). In the Kaplan-Meier estimate of PFS (CS Figure 6), drops in the PFS curve can be

seen at this assessment point, as well as later assessments in nine-weekly intervals. Figure 8 shows an overlay of the Kaplan-Meier estimates of PFS and these nine-weekly scans.

Figure 8: Visualisation of imaging assessments versus drops in PFS curve

Key: KM, Kaplan-Meier; SOC, standard of care.

Note(s): Imaging assessments shown every nine weeks, with a width of two weeks (i.e., ± 1 week either side).

Source(s): Produced based on information provided in the company-submitted economic model.

Based on the ERG's understanding of the KEYNOTE-590[12] study, the Kaplan-Meier estimates shown in Figure 8 may be interpreted as optimistic estimates of PFS for both treatment arms. This is because patients may have progressed prior to a scan, but were only recorded as having progressed at the time the scan was conducted. This feature of the trial is not unique to KEYNOTE-590,[12] but has important implications for the interpretation of the results of the study, and how to most appropriate inform the economic model.

A further consideration of the company's use of PFS to inform its model is the range of censoring rules for PFS within the KEYNOTE-590[12] study (i.e., allocation of individual observations as events or censors). At clarification stage, the company explained the differences between the censoring rules used in the primary analysis, and two sensitivity analyses (company responses to clarification questions A23 and B10). The reasons for the different analyses were related to missed doses and/or initiation of a new anticancer treatment.

The company's model made use of the primary analysis censoring rule. In this analysis, patients were considered to have a PFS event if a progression or death event occurred after either 0 or 1 missed disease assessment, and before new anti-cancer therapy (if applicable). However, patients were censored if either (i) a death or progression event occurred after ≥2 consecutive missed disease assessments without further valid non-PD disease assessments, or after new anti-cancer therapy; (ii) no death or progression event occurred, and new anticancer treatment was not initiated; or (iii) no death or progression event occurred, and new anticancer treatment was initiated.

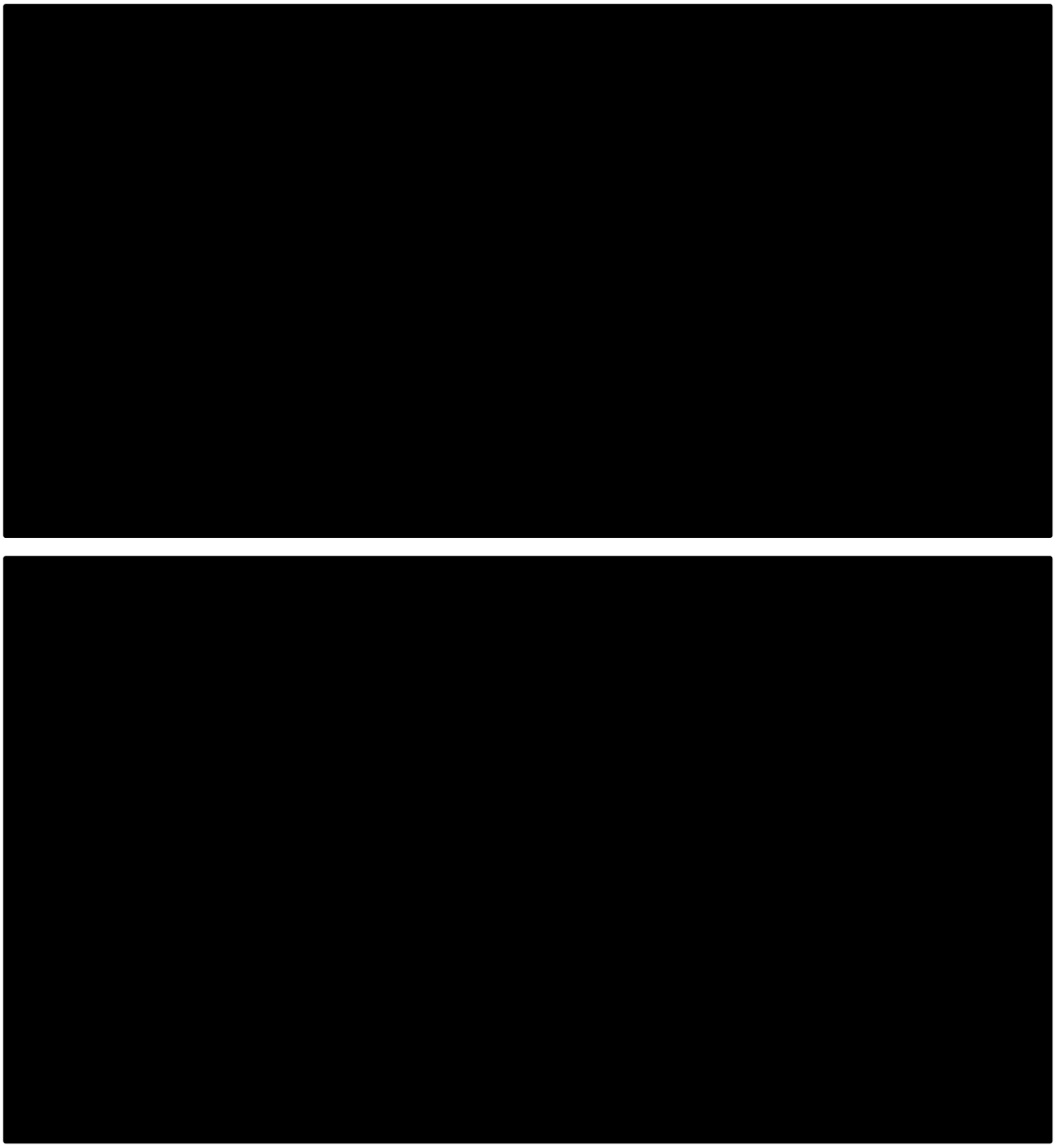
In sensitivity analysis 1, the company considered the first of the three censoring reasons (an event after ≥2 consecutive missed disease assessments without further valid non-PD disease assessments, or after new anti-cancer therapy) to be an event instead of a censored observation. In sensitivity analysis 2, the company considered discontinuation of treatment due to reasons other than complete response or initiation of new anticancer treatment, whichever occurs later, to be an event for subjects without documented PD or death. The analyses provided by the company showed little difference in the estimates of PFS by censoring rule, and so the ERG is satisfied with the use of the primary analysis to inform the model.

The company explained in its submission that through visual inspection of the Kaplan-Meier estimates, a *"steep drop"* is seen at around Week 9 for both arms, which is the time at which the first scan is performed (CS Section B.3.3). The company opted for a piecewise model using a cut-off point of 10 weeks – the time after which all patients are expected to have had their first scan. No explanation is provided in the CS concerning the choice to deviate from a single parametric model, and only consider piecewise models. A scenario analysis is presented in the CS using an alternative cut-off point of 37 weeks, but no explicit rationale for the choice of this alternative cut-off point was provided in the CS.

In choosing a model for PFS, the CS states guidance from NICE DSU TSD 14[48] was followed (CS Section B.3.3). The log-logistic model was determined to provide the best statistical goodness-of-fit (lowest AIC and BIC scores, see CS Table 47 for scores), with the second best-fitting model being the generalised gamma. Owing to PFS being near complete, the company focused mostly on the fit of the models within the observed follow-up period, versus plausibility of long-term extrapolation. Therefore, the piecewise log-logistic model was selected by the company for both arms, given that it provided the best statistical goodness of fit. This is the same modelling approach as used for OS, with the exception that the cut-off point was set at 10

weeks, instead of 40 weeks (as was used for OS). The company's base-case projections of PFS for both arms are provided in Figure 9.

Figure 9: Company projections of progression-free survival (5- and 20-year time horizon)



Key: KM, Kaplan-Meier; SOC, standard of care.

Note(s): This figure is a re-formatted version of CS Figure 22. Figure re-produced for ease of interpretation related to time axis. Company base-case analysis includes cut-off point at week 10 (switch from KM to log-logistic model).

Source(s): Produced based on information provided in the company-submitted economic model.

While the ERG did not consider the company's base-case choice of models for PFS to provide a particularly poor fit to the Kaplan-Meier estimates from the KEYNOTE-590[12] trial, alternative estimates models for PFS were explored for completeness, especially when considering progression-based instead of time-to-death-based utility values (see Section 4.2.7). The ERG highlighted that in the company's base-case analysis, 10-year PFS for the pembrolizumab in combination with chemotherapy arm was <[redacted], yet [redacted] of patients are still projected to be alive at this time. This means that approximately [redacted] of patients alive at 10 years were assumed to have progressed disease, which the ERG considered to have questionable face validity in light of the limited treatment options available for patients that progress following treatment with pembrolizumab in combination with chemotherapy. The results from the PFS scenarios are discussed further in Section 6.2.2.

4.2.6.3. Adverse events

Adverse events were included in the model at Grade 3+ if they occurred in at least 5% of patients on either treatment arm. The observed incidence of AEs in KEYNOTE-590[12] by treatment arm was provided by the company within its submission (see Table 48 of the CS). The most common Grade 3+ AEs (occurring in either treatment arm) were anaemia, neutropenia, hyponatraemia, and decrease neutrophil count. The ERG highlighted that AE rates were similar between arms.

At clarification stage, the company provided scenario analyses exploring the use of alternative AE rates for the blended comparator (clarification question B12). The scenarios led to a small increase in the ICER, driven by fewer AEs resulting in more QALYs at a reduced cost for the comparator arm. The ERG agreed with the company that the published studies suffer from a number of limitations and prefers the use of the KEYNOTE-590[12] derived AE rates to inform the base-case analysis.

4.2.7. Health-related quality of life

4.2.7.1. Summary of data available from KEYNOTE-590

The KEYNOTE-590[12] study collected information concerning patient-reported health-related quality of life (HRQoL) via the EQ-5D-5L questionnaire. The -5L version of the EQ-5D allows respondents to describe each dimension using five different levels: no problems, slight problems, moderate problems, severe problems and extreme problems.[20] However, as of October 2019, NICE no longer recommends the use of utility values generated using published

EQ-5D-5L value sets[55]; instead, NICE recommends use of a mapping function developed by van Hout et al. (2012)[42] for reference-case analyses, to produce corresponding -3L version utility values. The company has used the mapping function by van Hout et al. (2012)[42] to inform its economic model. For brevity, the remainder of this section describes the EQ-5D-5L data collected from the study and the EQ-5D-3L values produced using the van Hout et al. (2012)[42] mapping function, both as EQ-5D.

In KEYNOTE-590, the EQ-5D questionnaire was administered to patients at the following time points:

- Day 1 of each treatment cycle, for Cycle 1 (baseline) to Cycle 9 (Week 24)
- Day 1 of every third treatment cycle, from Cycle 10 (Week 33) to either one year (Week 51) or the end of treatment, whichever was first
- At the time of discontinuation (including time points after one year)
- 30 days after discontinuation of treatment at a follow-up visit.

Per the KEYNOTE-590 trial protocol, a visit window of ±7 days either side of the planned assessment times was permitted for the EQ-5D assessments and factored into the analyses of EQ-5D data. The CS stated that analyses of EQ-5D utilities were based on the Full Analysis Set (FAS) population from KEYNOTE-590 (a total of n=713 participants). In order to be included within the FAS population, patients were required to have been randomised, receive a study treatment, and completed at least one EQ-5D questionnaire. At clarification stage, the ERG asked the company to clarify if the completion of at least one questionnaire was in addition to a baseline measure, or if a baseline measure alone was sufficient for inclusion (clarification question B13). In response, the company confirmed that a total of n=40 patients included within the utility analysis only had a baseline EQ-5D measure reported.

The ERG also asked whether baseline utility was accounted for within the utility analyses conducted (clarification question B14). The company stated in response: *"Baseline utility has been accounted for within the mixed linear effects model for both approaches."*. However, as further information was not provided, it was unclear to the ERG exactly how baseline utility was accounted for. More specifically, the ERG was not able to verify if baseline utilities were

included within the data set analysed, or if post-baseline utility were modelled controlling for baseline utility at the patient level.

The completion rate of the EQ-5D throughout the KEYNOTE-590[12] trial is provided in CS Table 52. At baseline, [redacted] of patients completed the EQ-5D questionnaire, and compliance was consistently greater than [redacted] up until one year after initiation of treatment (range: [redacted]). However, after one year, compliance reduced markedly, and by Week 69 only [redacted] completed the EQ-5D questionnaire out of [redacted] participants that were expected to complete it (equivalent to an overall compliance level of [redacted], CS Table 52).

For each of the utility approaches, mean EQ-5D utility scores by health status were estimated per treatment arm (pembrolizumab in combination with chemotherapy and chemotherapy arms), and pooled for both arms. In addition, 95% CIs were obtained for each estimated EQ-5D utility and the statistical significance of the differences between treatment arms was tested. The level of EQ-5D compliance through time is presented in Table 52.

4.2.7.2. Analysis of data from KEYNOTE-590

Two different approaches to analysing the EQ-5D data from the KEYNOTE-590[12] trial were considered within the company's economic model. The first of these was to calculate utility values for patients according to their progression status, and apply these within the model as health state utility values (a '**progression**' approach). The second was to instead calculate utilities according to the hypothetical time until death associated with each measure of utility, and group these to demonstrate the deterioration in utility expected as patients experience disease progression and get closer to death (a '**time-to-death**' approach). Both approaches are discussed in turn below.

Progression approach

In the progression approach, health states were defined according to disease progression status (i.e., the presence or absence of progression). The company highlighted that a limitation of the progression approach is that due to the distribution and collection of EQ-5D questionnaires within KEYNOTE-590,[12] it is challenging to calculate an average utility value for the progressed disease health state. This is because the utility for patients with newly-progressed disease is expected to be higher than the utility those who progressed earlier,

ceteris paribus. Accordingly, the utility values estimated for the progressed disease state are expected to be greater than the values for the "true" progressed disease state were EQ-5D data collected for progressed patients at time points after the final Day 30 post discontinuation visit (assuming patients discontinued due to progression). For patients who discontinued for reasons other than progression, per the KEYNOTE-590 trial protocol, and did not progress within 30 days following discontinuation, no value for the progressed disease state would be recorded.

To address the concerns highlighted with the progressed disease state, it may be important to consider external data sources. However, as acknowledged by the company, the NICE reference case states a preference for using utility data collected from the relevant clinical trial(s) to inform the model, where available. In addition, use of external data sources requires the availability of relevant sources that would be suitable for consideration within the economic model. From the company's SLR, nine potentially relevant studies were identified (CS Appendix H). However, in its submission, the company explains that *"due to the paucity of data within this disease area, it is not possible to substitute utility values from the literature to alleviate this issue"* (CS Section B.3.4).

A progression approach has often, but not always, been adopted within models for a range of previous evaluations of cancer therapies, particularly those that make use of a three-state PartSA model (as has been used by the company). Therefore, in spite of its limitations, utility values were generated using a progression approach and included as an option within the economic model. Utility observations were separated by progression status using the date of progression recorded in the KEYNOTE-590 trial.[12]

The company used a linear mixed-effects regression model to estimate average utility values for each health state. The model included covariates for progression as well as the presence/ absence of any Grade 3+ AEs. A covariate for treatment arm was not included within the mixed-effects regression model, as utility values were assumed to be the same across all treatment arms.

In the economic model, the utility values by progression status were applied to the proportion of patients expected to reside within each health state over the course of the model time horizon. However, to account for the fact that utility was expected to decrease over time as patients aged, the economic model also includes a multiplier to account for patients aging over the

course of the model time horizon. The age adjustment is based on a study by Ara and Brazier et al. (2010).[56]

The AE-related disutility was used to generate a total QALY loss associated with each treatment arm based on the calculated AE rates and durations over which the disutility was expected to apply. The calculation of AE rates and expected durations over which utility decrements are assumed to apply is described in Section 4.2.7.3. The total QALY loss attributable to AEs was applied within the model as a lump sum in the first model cycle.

Time-to-death approach

In the time-to-death approach, utility values are generated using groupings of utility observations based on how close they were reported versus the patient's OS time. In the CS, a number of applications of a time-to-death approach are cited, including a number of previous NICE technology appraisals of treatments for non-small-cell lung cancer and melanoma.

The CS stated that a time-to-death approach more accurately captures the decrease in HRQoL over time (versus standard progression-based utilities) for patients with advanced oesophageal cancer, but does not provide a source for this justification. A study by Hatswell *et al*. (2014)[57] was highlighted within the CS, which considered an analysis of utility values in melanoma. The authors of this study commented that disease progression alone may not fully capture *"all predictive factors of patient utility"*, and that time-to-death may, as death approaches, be *"as or more important"* than progression status in predicting utility.

In order to consider a time-to-death analysis, patients with a censored OS time which is within the time period of the grouping furthest from death cannot be assigned to a group. In the company's time-to-death analysis, the upper bound was set at 360 days. Therefore, utility values recorded for patients that were censored for the outcome of OS at a time point within 360 days until this censoring time could not be included in the time-to-death analysis. However, in its submission, the company explained that approximately [redacted] of all utility values captured could not be appropriately assigned to a time-to-death category, meaning that [redacted] of recorded values were not affected by this limitation.

In the company's time-to-death analysis, a linear mixed-effects regression model was fitted, with five different groupings. The model included a covariate for the presence/ absence of any Grade

3+ AEs (as was also captured in the progression-based analysis). The groupings used for time-to-death categories were as follows:

- <30 days until death
- 30≤ days until death <90
- 90≤ days until death <180
- 180≤ days until death <360
- ≥360 days until death

The rationale behind the choice of these groupings was not provided within the CS. At clarification stage, the ERG asked for further information concerning these groupings (clarification question B14). The company explained that the groupings were consistent with several previous NICE assessments of pembrolizumab in other indications, including lung and renal cancer. The ERG would have preferred the groupings to have been informed through further inspection of the utility data available from the KEYNOTE-590[12] study.

In addition, it is unclear why these groupings were not aligned with the model cycle length used (seven days). This means that for a practical application of these utility values within the model, each of the time points would need to be rounded to a seven-day model cycle. The application of the utility values within the economic model is shown below, versus the label used to describe utility analysis performed:

- <30 days until death → ≤28 days until death
- 30≤ days until death <90 → 28< days until death ≤84
- 90≤ days until death <180 → 84< days until death ≤175
- 180≤ days until death <360 → 175< days until death ≤357
- ≥360 days until death → >357 days until death

The ERG would have preferred for the categories used to fully align with the model cycle length used, or for a different cycle length to be used such that these categories could be applied as intended (with a preference for the former of these options, given that the remainder of model is aligned with a weekly model cycle length). Nevertheless, the impact of changing these groupings is not expected to have a large impact on the overall utility values produced. In

addition, when the ERG performed a check of the model calculation, an apparent error in the application of the time-to-death utilities was identified (discussed further in Section 5.3, with the impact of resolving this error on results discussed in Section 6.1).

As per the progression-based analysis, age adjustment was applied to account for decreasing utility as patients aged. In addition, the AE-related disutility was used to generate a total QALY loss for each arm, and applied as a lump sum in the first model cycle (also as per the progression-based approach).

4.2.7.3. Impact of adverse events

To include the impact of AEs on utility within the model, the company included covariates within the utility regressions for the presence of a Grade 3+ AE. Then, to estimate the total loss in QALYs due to Grade 3+ AEs, the company extracted the mean duration of the all-cause AEs from the KEYNOTE-590[12] patient-level data and multiplied this by the loss in utility. The duration of AEs was assumed equal between arms, and the average duration was calculated to be 8.24 weeks (see CS Table 49).

4.2.7.4. Utility values used in the model

The utility values generated from both analyses are presented in Table 12. Of note, these values are representative of the utility values used to populate the model in the first cycle only, as future cycles are affected by age-related disutility. The company's preferred base-case analysis made use of the time-to-death derived utility values, with progression-based values explored within sensitivity analysis.

Table 12: Utilities calculated based on KEYNOTE-590 trial data

Health state	Progression approach	Time-to-death approach
Progression-free	[redacted]	-
Progressed disease	[redacted]	-
≥360 days to death	-	[redacted]
180 to 360 days to death	-	[redacted]
90 to 180 days to death	-	[redacted]
30 to 90 days to death	-	[redacted]
0 to 30 days to death	-	[redacted]

Health state	Progression approach	Time-to-death approach
Presence of Grade ≥3 AE	[redacted]	[redacted]

Abbreviations: AE, adverse event.

Source(s): Produced based on CS Tables 50 and 51, as well as information provided in the company-submitted economic model. Time-to-death approach used in base-case analysis, progression approach explored in sensitivity analysis.

Based on the mean age at baseline (61.4 years, for the European population), and the proportion of patients that are male (80.7%, also for the European population), the average utility expected in the general population (based on the study by Ara and Brazier, 2010)[56] is estimated to be 0.829. The average utility value used for the progression-free health state is slightly lower than this value ([redacted]), suggesting that the impact of disease on HRQoL is relatively small (see Table 12). Furthermore, the average utility in the ≥360 days to death grouping ([redacted]) was greater than the equivalent value in the general population (0.829). In response to clarification questions, the company capped the utility values applied within the model to be equal to general population, should the value estimated from KEYNOTE-590 exceed this. Although this addresses the issue of the utility being greater than general population, the capping still assumes that patients with advanced oesophageal cancer over a year away from death have the same quality of life as the general population, most of whom would be expected to have a life expectancy greater than 1 year. As such, these results are misaligned with the expectation of relatively low utility for patients with metastatic cancer undergoing intensive chemotherapy with a relatively poor prognosis (versus 'healthy' individuals in the general population). Therefore, the ERG has concerns with the generalisability of the utility values produced based on analysis of KEYNOTE-590[12] data (regardless of which approach is used), as the outputted values imply that patients have a similar, or potentially better utility than the age- and sex-adjusted UK general population.

To further explore the utility values, the ERG calculated the average utility value for patients on the pembrolizumab in combination with chemotherapy combination arm using both approaches. To do this, the total undiscounted QALYs were divided by the total undiscounted LYs. This crude calculation allows for further exploration of how QALYs are accrued within the company's model.

Using the company's corrected base case model (see Section 6.1), for the progression approach, the average utility was estimated to be [redacted]. Switching to the time-to-death approach,

the average utility was estimated to be [redacted]. Using the ERG's preferred assumptions (see Section 6.3), the average utility values are [redacted] and [redacted], respectively. When setting the utility value for all health states to be 0.829 (average utility expected at baseline for the age- and sex-adjusted general population), and disabling AE-related QALY losses, the equivalent average utility for the general population was estimated to be 0.808. The ERG is concerned that the two utility analysis approaches lead to a substantially different estimation of the "average" utility experienced over the course of the model time horizon. This means that the incremental QALY gain attributable to pembrolizumab in combination with chemotherapy estimated for both utility analyses also varies markedly: The time-to-death approach (company base-case analysis post corrections) yields an incremental QALY gain of 0.652, versus 0.570 for the progression approach. The ERG considers the progression approach to yield a more realistic "average" utility for this patient population, especially given that the time-to-death approach yields an "average" utility that is close to the estimate for the general population.

The ERG has explored several alternative utility values within exploratory analyses, which are described in Section 6.2.3.

In the company's base-case time-to-death analysis, the total QALY loss attributable to Grade 3+ AEs is estimated at [redacted] for the pembrolizumab in combination with chemotherapy combination arm, versus [redacted] for the chemotherapy arm. In the progression approach, the total QALY losses are estimated at [redacted] versus [redacted] (for pembrolizumab in combination with chemotherapy versus chemotherapy). The ERG notes that it is unclear why the estimated QALY loss due to AEs is greater for the progression versus the time-to-death approach. In addition, the ERG questioned the face validity of a near-negligible impact in terms of toxicity for the addition of pembrolizumab to the combination of fluorouracil and cisplatin. Taking these two observations together, the ERG found it strange that the method of analysing the utility data appears to have a notably larger impact on the total estimated loss in QALYs due to AEs versus the introduction of a third treatment.

Further to the concerns raised with the impact of AEs on utility discussed above, the ERG had concerns with the estimated utility decrement associated with a Grade 3+ AE. It was the ERG's understanding that as utility measures are most likely to be taken at the start of each treatment cycle, any AEs resulting in hospitalisation (as implied by only including those at Grade 3 or above) were likely to be recorded after the EQ-5D questionnaire was completed, or that patients currently experiencing a particularly severe AE are likely to have not completed the EQ-5D

questionnaire. Therefore, the magnitude of the estimated decrement associated with all occurrences of Grade 3+ AEs ([redacted] in the company's base-case analysis) may be under-estimated.

4.2.8. Resources and costs

The company's model included costs relating to pembrolizumab, chemotherapy treatments, medial resource use, subsequent treatments, and the resolution of adverse events; each of which are discussed below.

4.2.8.1. Drug acquisition costs

The list price of a 100 mg vial for pembrolizumab is £2,630 resulting in a cost of £5,260 per administration for two 100 mg vials every three weeks, for a maximum of 35 cycles. The cost per administration is [redacted] when the company's patient access scheme (PAS) of [redacted] is applied.

The costs of the chemotherapy treatments were sourced from the NHS drugs and pharmaceutical electronic market information tool (eMIT), and dosing of the regimens were based on the KEYNOTE-590 trial protocol (see Section 4.2.4) or based on the summary of product characteristics (SmPC). The company's base case assumed vial sharing for treatments based on body surface area (BSA) using the minimum cost/mg, therefore costs for wastage are not included. The model included relative dose intensity (RDI) to account for missed doses and dose reductions which the company interprets as *"a proportion of the protocol dose that participants actually received"* (CS Section B.3.5). The RDI from KEYNOTE-590[12] was used assuming that oxaliplatin has the same RDI as cisplatin, and leucovorin, capecitabine and epirubicin has the same RDI as 5-FU. The ERG checked these assumptions with clinical advisors who did not think the assumption of epirubicin being equivalent to 5-FU was appropriate. However, given the triplet regimens are exploratory and epirubicin had a relatively low cost the ERG did not explore this further. In response to clarification questions, the company confirmed that treatment compliance in KEYNOTE-590 is considered different between pembrolizumab and chemotherapy. For pembrolizumab this is defined as the percentage of actual non-zero dose treatment cycles versus the expected number of treatment cycles per subject. For 5-FU or cisplatin, this is defined as total dosage received versus the total dosage expected (company response to clarification questions B18).

The costs and dosing used for each treatment in the company's model are presented in Table 13. As discussed in Section 4.2.4, clinical advice given to the ERG indicated that some of the chemotherapy dosages used in the CS were not reflective of doses currently received by patients in UK clinical practice. As such, the ERG explored alternative doses in scenario analysis (see Section 6.2).

Table 13: Costs and dosing of treatments included in the company's model

Regimen	Drug	Dose per administration	Unit cost	Pack size	RDI	Cost per administration
Pembrolizumab + 5-FU + cisplatin	Pembrolizumab	200 mg Q3W	£2,630	100 mg vial	[redacted]	[redacted]
	5-FU	800 mg days 1-5 Q3W	£2.84	2,500 mg vial	[redacted]	[redacted]
	Cisplatin	80 mg/m^2 Q3W	£6.66	100 mg vial	[redacted]	[redacted]
5-FU + cisplatin	5-FU	800 mg days 1-5 Q3W	£2.84	2,500 mg vial	[redacted]	[redacted]
	Cisplatin	80 mg/m^2 Q3W	£6.66	100 mg vial	[redacted]	[redacted]
5-FU + oxaliplatin + leucovorin	5-FU	2,600 mg/m^2 Q2W	£2.84	2,500 mg vial	[redacted]	[redacted]
	Oxaliplatin	85 mg/m^2 Q2W	£8.67	100 mg vial	[redacted]	[redacted]
	Leucovorin	200 mg/m^2 Q2W	£7.19	500 mg vial	[redacted]	[redacted]
Capecitabine + cisplatin	Capecitabine	2,000 mg/m^2 days 1-14 Q3W	£7.29	60 x 300 mg tablets	[redacted]	[redacted]
	Cisplatin	80mg/m^2 Q3W	£6.66	100 mg vial	[redacted]	[redacted]
Capecitabine + oxaliplatin	Capecitabine	2,000 mg/m^2 days 1-14 Q3W	£7.29	60 x 300 mg tablets	[redacted]	[redacted]
	Oxaliplatin	130 mg/m^2 Q3W	£8.67	100 mg vial	[redacted]	[redacted]
5-FU + cisplatin + epirubicin	5-FU	200 mg/m^2 days 1-21 Q3W	£2.84	2,500 mg vial	[redacted]	[redacted]
	Cisplatin	60 mg/m^2 Q3W	£6.66	100 mg vial	[redacted]	[redacted]
	Epirubicin	50 mg/m^2 Q3W	£19.29	200 mg vial	[redacted]	[redacted]
5-FU + oxaliplatin + epirubicin	5-FU	200 mg/m^2 days 1-21 Q3W	£2.84	2,500 mg vial	[redacted]	[redacted]
	Oxaliplatin	130 mg/m^2 Q3W	£8.67	100 mg vial	[redacted]	[redacted]
	Epirubicin	50 mg/m^2 Q3W	£19.29	200 mg vial	[redacted]	[redacted]
Capecitabine + cisplatin + epirubicin	Capecitabine	625 mg/m^2 days 1-21 Q3W	£7.29	60 x 300 mg tablets	[redacted]	[redacted]
	Cisplatin	60 mg/m^2 Q3W	£6.66	100 mg vial	[redacted]	[redacted]
	Epirubicin	50 mg/m^2 Q3W	£19.29	200 mg vial	[redacted]	[redacted]

Regimen	Drug	Dose per administration	Unit cost	Pack size	RDI	Cost per administration
Capecitabine + oxaliplatin + epirubicin	Capecitabine	625 mg/m^2 days 1-21 Q3W	£7.29	60 x 300 mg tablets	[redacted]	[redacted]
	Oxaliplatin	130mg/m^2 Q3W	£8.67	100 mg vial	[redacted]	[redacted]
	Epirubicin	50mg/m^2 Q3W	£19.29	200 mg vial	[redacted]	[redacted]

Key: 5-FU, fluorouracil; Q2W, every 2 weeks; Q3W, every 3 weeks; RDI, relative dose intensity

Notes: *List price

4.2.8.2. Treatment administration

The majority of treatments included in the company's model are administered via intravenous infusion with the exception of capecitabine which is an oral treatment. The CS stated that administration costs are included in the model based on NHS reference costs 2018-19, however the model inputs actually use NHS reference costs 2018-19 and uplift them to 2019/20 costs using indices from the NHS cost inflation index.[58] All treatment regimens were assigned the cost of £322.88 (uplifted from £317.73 SB14Z, deliver complex chemotherapy, including prolonged infusion treatment at first attendance), except for oxaliplatin plus capecitabine which has the cost of £263.28 assigned (uplifted from £259.08 SB13Z, deliver more complex parenteral chemotherapy at first attendance). At clarification stage, the company confirmed that choice of administration HRG code was based on the National Tariff Chemotherapy Regimens List 2017-18[59] (see company response to clarification questions B19).

The pembrolizumab in combination with chemotherapy does not have a specific code according to the National Tariff Chemotherapy Regimens List. Pembrolizumab would add an additional 30 minutes according to the SmPC, thus it is unclear if another code would be more appropriate. However, given that administration costs have little impact on the ICER, the ERG considered the administration cost codes to be broadly satisfactory.

Clinical advice provided to the ERG was that treatment administration would be given in a day case setting, whereas the company used the outpatient cost code. In addition, clinical experts explained that 5-FU would require more visits to the day case unit and there would be additional charges for pump disconnections and a peripherally inserted central catheter (PICC) line, as such, the administration and monitoring costs of patients receiving 5-FU could have been underestimated. Though the ERG noted that the company's administration code for 5-FU is in line with the National Tariff Chemotherapy Regimens List.

Consequently, the ERG's preferred assumptions for administration costs included costs based on a day case setting. These costs are provided in Table 14 in comparison to the costs used by the company. The ERG's preferred administration costs are factored into the ERG's preferred base case (see Section 6.3).

Table 14: Comparison of company and ERG preferred administration costs

Administration cost	Company	ERG
Deliver more complex parenteral chemotherapy at first attendance	£263.28 (uplifted from £259.08 SB13Z OP)	£319.46 (uplifted from £314.39 SB13Z DCRDN)
Deliver complex chemotherapy, including prolonged infusional treatment, at first attendance	£322.88 (uplifted from £317.73 SB14Z OP)	£391.52 (uplifted from £385.28 SB14Z DCRDN)

Key: OP, outpatient; DCRDN, day case/regular day/night

Source(s): NHS reference costs 2018-19[60]

4.2.8.3. Time on treatment

The company applied maximum treatment durations for pembrolizumab, 5-FU and cisplatin in line with the stopping rules in the KEYNOTE-590 protocol. That is, 35 cycles for both pembrolizumab and 5-FU, and 6 cycles for cisplatin. These stopping rules were applied to the pembrolizumab in combination with chemotherapy arm and the trial-based comparator (5-FU plus cisplatin). No stopping rules were formally applied to the other chemotherapy regimens included in the blended chemotherapy arm.

To estimate the proportion of patients on treatment per cycle, the company used ToT Kaplan-Meier estimates from KEYNOTE-590.[12] Parametric curves were fit to the ToT data separately for each the five component treatments in KEYNOTE-590; pembrolizumab, 5-FU and cisplatin (in the pembrolizumab combination arm), 5-FU and cisplatin (in the chemotherapy control arm), though given the maturity of the ToT data, the Kaplan-Meier estimates were used directly in the base case. At clarification stage, the ERG requested further information on the maturity of the ToT data from the KEYNOTE-590 trial. The company presented the number of events for ToT in each arm by the July 2020 data cut off which showed that [redacted] had discontinued pembrolizumab, [redacted] had discontinued cisplatin (in both arms) with [redacted] and [redacted] having discontinued 5-FU in the pembrolizumab in combination with chemotherapy arm and chemotherapy arm, respectively. The ERG noted that using the Kaplan-Meier curve directly may underestimate treatment costs given not all patients have discontinued treatment (especially in the pembrolizumab arm). However, given the trial stopping rules at 2-years, more mature data is not expected to have a large impact on the ToT Kaplan-Meier data.

These are presented for the full population in the CS Figures 23 and 24, and [redacted]10 and [redacted]11 below. As per the RDI assumptions, for those blended chemotherapy treatments not

included in the trial it is assumed that oxaliplatin had the same ToT as cisplatin, and leucovorin, capecitabine and epirubicin had the same ToT as 5-FU.

The ERG agrees that using the ToT Kaplan-Meier estimates directly is appropriate to account for treatment discontinuations and disruptions for various reasons. However, given that the ToT data from KEYNOTE-590 already incorporate the protocol driven stopping rules, the ERG noted that it was not necessary to apply the maximum treatment durations in addition to using the Kaplan-Meier estimates and RDI. The maximum treatment durations are applied in the model as a hard stop at those time points, whereas the ToT Kaplan-Meier estimates show that some patients were still on treatment after those time points (due to dose interruptions), therefore the model base case does not currently capture these (see [redacted]10 and [redacted]11). At clarification stage, the ERG requested a scenario where the treatment stopping rules are disabled and ToT Kaplan-Meier data is used directly. This resulted in only a slight impact on the ICER (see Section 5.2.3); however, the ERG considered this to be more reflective of clinical practice and therefore, the ERG's preferred base-case analysis removes the maximum treatment durations (see Section 6.3).

[redacted]10

[redacted]

Key: 5-FU, fluorouracil; KM, Kaplan-Meier; ToT, time on treatment

[redacted]11[redacted]

Key: 5-FU, fluorouracil; KM, Kaplan-Meier; ToT, time on treatment

4.2.8.4. Health state unit costs and resource use

Disease management costs associated with the progression-free and progressed health states are included in the model based on resource frequencies derived from clinical expert opinion and a previous NICE appraisal for previously treated advanced gastric cancer or gastro-oesophageal junction adenocarcinoma (TA378),[61] respectively.

Progression-free

The resource frequencies and unit costs were presented in the CS in Table 58. The progression-free health state included a full blood count, a renal function test and a hepatic function test every three weeks, with a consultation visit every four weeks and a CT scan every 12 weeks. Based on clinical advice provided to the ERG, patients are currently monitored every three weeks whilst on platinum-based chemotherapy then every three months whilst continuing treatment with a fluoropyrimidine. If patients are still receiving pembrolizumab after discontinuation of platinum-based chemotherapy, then monitoring would be every six weeks, instead of every three months. At clarification stage, the ERG requested the company to provide revised resource use based on the increased monitoring for those patients remaining on pembrolizumab after discontinuing chemotherapy. In response, the company stated that

*"Disease management costs applied in the model are linked to the progression free survival curve, not to the pembrolizumab time on treatment curve. As such, treatmen*t status does not impact the monitoring costs" (see response to clarification questions B20). As the company did not provide revised estimates post clarification questions, the ERG has explored the impact of increased monitoring within Section 6.2.

Progressed disease

For progressive disease, the only resource use included was a consultation visit every 12 weeks. The ERG registered several concerns with the estimates of progressed resource use frequencies. The progressed disease state resource use appears implausibly reduced compared to progression-free patients. Given this indication is in a first-line setting, some patients will receive subsequent treatment when they progress and are therefore expected to require more than a consultation visit every 12 weeks.

The company states that their progressed disease resource use was based on TA378, however in TA378,[61] patients on (2L+) treatment are assumed to have a full blood count, a renal function test and a hepatic function test every treatment cycle, with a consultation visit every 4 weeks and a CT scan every 12 weeks. Upon progression (or patients off treatment), patients are then assumed to have consultation visits every 12 weeks. This means that the resource use from TA378 has been assumed to apply to an earlier line, but without accounting for resource use needed for patients receiving active therapy in a second-line setting.

In the recent nivolumab appraisal for previously treated advanced oesophageal cancer (ID1249),[46] resource use was determined from a clinical survey for those patients on treatments consisting of consultations, imaging scans, blood tests, liver function tests, kidney function tests, hospitalisations and palliative care specialist nurses. The mean weekly visits were calculated from the possible options of every three months, monthly, biweekly, weekly and never.

The ERG requested more information post clarification questions in which the company revised its base case to include a one-off cost within the subsequent treatment cost to account for extra monitoring for those patients receiving treatment. This includes the monitoring frequencies described in TA378 for those patients on 2L+ treatment. The ERG agreed with the company's revisions on progressed disease monitoring.

PD-L1 testing costs

For the CPS ≥ 10 sub-population PD-L1 testing costs were included to reflect the costs incurred by the NHS when testing for PD-L1 expression. The unit cost per test was based on the cost used in the previous NICE submission TA522[62] (£40.50) uplifted to 2019/20 costs using indices from the NHS cost inflation index.[58] It is assumed that 51.1% of patients tested will be classed as PD-L1 positive based on KEYNOTE-590[12] resulting in a total cost of £85.12.

It is not clear from the company submission or TA522 where the PD-L1 testing cost comes from so the ERG are unable to assess its appropriateness. Clinical experts advised the ERG that PD-L1 will be conducted at the same time at other histologically tests on the biopsy samples, and that the cost of including PD-L1 testing is not expected to be resource intensive. As such the ERG does not envision the PD-L1 test to be expensive and considers the cost used by the company to be appropriate (though not possible to verify).

4.2.8.5. Adverse events unit costs and resource use

The company included management costs associated with each adverse event (discussed in Section 4.2.6.3) based on NHS reference costs 2018-19 uplifted to 2019/20 costs using indices from the NHS cost inflation index.[58] The company justifies its choice of cost codes assigned to each adverse event based on previous pembrolizumab NICE submissions in advanced urothelial cancer and metastatic squamous cell head and neck cancer.[43,63] The ERG did not consider it good practice to refer to previous submissions alone (especially those only conducted by the company itself) in different indications to justify the most appropriate model inputs.

The ERG noted some differences between the cost codes used in the previous submissions cited by the company and the ones used for this submission, mainly due to choosing one cost code over a weighted average as presented in Table 15. There were no justifications for these differences or choices of cost codes for each of the adverse events within the CS.

Table 15: Comparison of adverse event costs used in previous submissions

Adverse event	ID3741 Company submission	TA519	TA661
Anaemia	SA01G - Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+. Non-elective short stay	SA01G-K- Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia. Weighted cost of non-elective long stay, short stay and day case	SA01G-K- Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia. Weighted cost of non-elective long stay, short stay and day case
	£623.25	£1,315.94	£631.88
Decreased Appetite	FD04A - Nutritional Disorders with Interventions, with CC Score 2+. Day case	NR	SPHMSEDSAAPC – Adult Specialist Eating Disorder Services: Admitted patient
	£301.33	-	£461.74
Dysphagia	A13A1 - Speech and Language Therapist, Adult, One to One. Community health services	NR	Assumed to be £0
	£108.24	-	£0.00
Fatigue	SA01G - Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia, with CC Score 8+. Non-elective short stay	WH52A – Follow-Up Examination for Malignant Neoplasm, with Interventions. Non-elective long stay 8-9 days	SA01G-K- Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia. Weighted cost of non-elective long stay, short stay and day case
	£623.25	£2,499.99	£631.88
Hypokalaemia	KC05H - Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4. Non-elective short stay	NR	KC05G-H - Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-5+
	£963.30	-	£1,104.28
Hyponatraemia	KC05H - Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-4. Non-elective short stay	NR	KC05G-H - Fluid or Electrolyte Disorders, with Interventions, with CC Score 0-5+
	£963.30	-	£1,104.28
Nausea	FD10M - Non-Malignant Gastrointestinal Tract Disorders without	NR	FZ91M - Non-Malignant Gastrointestinal Tract Disorders without

Adverse event	ID3741 Company submission	TA519	TA661
	Interventions, with CC Score 0-2. Non-elective short stay		Interventions, with CC Score 0-2: Non elective short stay (two hospital admissions)
	£418.64	-	£894.04
Neutropenia	SA35A - Agranulocytosis with CC Score 13+. Non-elective short stay	WJ11Z – Other disorders of immunity. Weighted average of non-elective long and short stay and day case. (10% require treatment)	WJ11Z – Other disorders of immunity. Weighted average of non-elective long and short stay and day case
	£728.33	£70.80	£78.69
Neutrophil Count Decreased	WJ11Z - Other Disorders of Immunity. Total HRGs	Assumed same as neutropenia	WJ11Z – Other disorders of immunity. Weighted average of non-elective long and short stay and day case
	£474.18	£70.80	£78.69
Platelet count decrease	SA12 - Thrombocytopenia with CC Score 8+. Non-elective short stay	NR	Assumed to be £0
	£620.79	-	£0.00
Pneumonia	DZ11P - Lobar, Atypical or Viral Pneumonia, with Single Intervention, with CC Score 8-12. Total HRGs	DZ11K-V - Lobar, Atypical or Viral Pneumonia. Weighted average of non-elective long and short stay and day case	DZ11K-V - Lobar, Atypical or Viral Pneumonia. Weighted average of non-elective long and short stay and day case
	£3,449.89	£1,751.08	£495.81
Stomatitis	CB02A - Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders, with Interventions, with CC Score 5+. Non-elective short stay	NR	Assumed to be £0
	£669.91	-	£0.00
Vomiting	FD10M - Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2. Non-elective short stay	NR	FZ91M - Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2: Non

Adverse event	ID3741 Company submission	TA519	TA661
			elective short stay (two hospital admissions)
	£418.64	-	£894.04
Weight decrease	N16AF - Specialist Nursing, Enteral Feeding Nursing Services, Adult, Face to face. Community health services	NR	NR
	£108.15	-	-
White blood cell count decrease	WJ11Z - Other Disorders of Immunity. Total HRGs	Assumed to be the same as neutropenia	WJ11Z - Other Disorders of Immunity. Weighted average of non-elective long and short stay and day case
	£474.18	£70.80	£78.69

Key: NR, not reported

Source(s): NHS reference costs 2018-19;[60] TA519;[43], TA661[63]

Some of the choices for adverse events are questionable; for example, the cost code used for dysphagia (A13A1 - Speech and Language Therapist, Adult, One to One. Community health services) does not seem appropriate. Dysphagia affects the patient's ability to swallow foods or liquids and although speech and language therapy could be used to learn new swallowing techniques,[64] this may not be appropriate for a Grade 3 or 4 adverse event, especially for gastro-oesophageal cancer patients. Clinical experts confirmed that these patients are usually treated with a stent or possibly tube fed until fit enough to go onto chemotherapy. Therefore, the ERG thought that a more suitable NHS reference cost could have been utilised (e.g., FE10A-D, Endoscopic Insertion of Luminal Stent into Gastrointestinal Tract).

However, given the similar adverse event profiles of pembrolizumab in combination with chemotherapy and chemotherapy using the KEYNOTE-590[12] data (see CS Table 48 and Section 3.2.3.3), the adverse event rates for dysphagia have a difference of <1%, therefore the resulting total adverse event costs are similar between arms and hence the unit costs have very little impact on cost-effectiveness results. Thus, the ERG did not explore this further.

4.2.8.6. Miscellaneous unit costs and resource use

Subsequent therapy costs

Within the economic model, subsequent treatment costs are applied as a one-off cost when a patient leaves the 'progression-free' health state. The distribution of subsequent treatments and mean durations are based on the KEYNOTE-590[12] data. The company applied an arbitrary cut-off of excluding all subsequent treatments in which less than 5% of patients received. In addition, the distribution was equally re-weighted to exclude ramucirumab as this was not recommended for use in NHS for previously treated advanced gastro-oesophageal junction adenocarcinoma patients.[61] The resulting distributions are presented in the CS (Table 61) with the dosing schedules and costs for each subsequent treatment presented in the CS Table 62. The distributions show a high usage of paclitaxel followed by fluorouracil, whereas the most common treatment in clinical practice is generally docetaxel based on clinical opinion. However, paclitaxel is also commonly used in practice therefore the subsequent treatments included in the model look reflective of UK practice.

Estimates of RDI were not included for subsequent treatments and vial sharing was assumed which the company claims is: *"constituting a conservative approach"* (CS Section B.3.5). The ERG was unclear why this is considered a conservative approach.

At clarification stage, the ERG requested to see the full subsequent treatment list received by patients in the KEYNOTE-590[12] trial before the company applied the arbitrary 5% cut-off. The company provided the full list in addition to exploring an alternative approach to calculate the distribution using the total number of progression events (progression and death) as the denominator instead of the number of patients within the as-treated population.

After reviewing the full subsequent treatment table, the ERG noted with grave concern with the application of the 5% cut-off within the subsequent treatment costing. In KEYNOTE-590, [redacted] and [redacted] patients received subsequent treatments in the pembrolizumab in combination with chemotherapy arm and chemotherapy arm, respectively. Of the [redacted] patients who had subsequent treatments, there was a total of [redacted] subsequent treatments covering multiple treatment lines. When applying the 5% cut-off, the company only includes [redacted] subsequent treatments and excludes the others. This results in an underestimation of subsequent treatment costs and the unnecessary removal of data. In order to account for all subsequent treatments received by patients in KEYNOTE-590, the ERG re-distributed the remaining treatments into the most common treatments received (using the company's 5% threshold). The redistribution and resulting costs are presented in Table 16 compared to the company's estimates. The ERG included this re-distribution within their preferred assumptions (see Section 6.3)

Table 16: Subsequent treatment re-distributions

Subsequent treatment	KEYNOTE-590		Company's re-distribution [a]		ERG's re-distribution [b]	
	Pembrolizumab in combination with chemotherapy	Chemotherapy	Pembrolizumab in combination with chemotherapy	Chemotherapy	Pembrolizumab in combination with chemotherapy	Chemotherapy
N	370	370	370	370	370	370
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irinotecan hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] Remove any below 5% in both treatment arms and re-distribute removing ramucirumab. [b] Remove any below 5% and ramucirumab and re-distribute the remainder between the included treatments. [c] Including multiple subsequent treatment lines. [d] Includes, drug administration and disease monitoring costs.

Terminal care costs

The economic model includes a terminal care cost to reflect the costs associated with death applied as a one-off cost when patients enter the death health state. In the CS (Document B, page 117), the company states the end-of-life cost to be £7,630.19, however the economic model uses £7,795.01 which is the correct value. The terminal care cost was derived from a previous pembrolizumab NICE submission in advanced or metastatic urothelial cancer (TA522)[62] and uplifted to 2019/2020 costs using the indices from the NHS cost inflation index.[58]

The original cost of £7,252.82 used in TA522[62] was derived from a variety of sources based on resource frequencies and unit costs derived from PSSRU 2015. These resources were based on what was previously accepted in TA519 (pembrolizumab for previously treated advanced or metastatic urothelial cancer)[43] which in turn was derived from other previous submissions (TA272, TA374 and TA277).

The ERG noted a few concerns with this cost. Firstly, the ERG considered the use of uplifting the total cost from TA522 to be unnecessary given the breakdown of resources and unit costs are presented and as such the company could have used the latest unit costs per resource to update the costs. Secondly, this cost has been derived from a chain of previous submissions and thus, does not take into consideration the assumptions surrounding the individual resources and whether they are appropriate for gastro-oesophageal cancer patients. For example, in TA519 the company submission states that *"Clinical advice suggested that due to their propensity to bleed, patients with urothelial cancer receive radiotherapy at end of life; therefore, this cost has also been included."*[43] This cost of radiotherapy was included within the terminal care cost used in TA522 and subsequently in this submission. However, the radiotherapy cost may not be appropriate to consider for gastro-oesophageal cancer patients as it was specifically included for patients with urothelial cancer and as such the terminal care costs may be over-estimated. On the other hand, the cost used in the company's model is lower than that used in the recent nivolumab appraisal (ID1249)[46] which used £8,973.61 from the literature (inflated from £7,827.00) estimating the per-patient costs in the last three months of life.[65]

It was not clear from the company's submission or from tracing back through the previous submissions what period of time the terminal care costs covers making it difficult to assess the appropriateness of a one-time cost, but includes resource use associated with 28 hours

community nurse, seven GP home visits, 50 hours of Macmillan nurse time, and terminal care in hospital or a hospice for a proportion of patients per resource.

In conclusion, the company should have provided more information about the origins of this cost and assessment of how reflective these assumptions were to gastro-oesophageal cancer patients, in addition to recalculating the total cost on first principles as rather than inflating the previous total cost. However, the ERG acknowledged that terminal care costs have little influence on cost-effectiveness results given that the model covers almost a lifetime horizon with the majority of patients dead in both arms. Exploring different values (i.e., removing radiotherapy costs or using the same cost as per the ID1249 submission) resulted in minor differences in the ICER (see Section 6.2).

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1.1. Base case results

All patients

The company revised its base case following clarification questions, therefore only the revised results are presented in this section. The changes included:

- Changing the time horizon to 30-years
- Including a utility cap for the time-to-death category '≥360 days' based on general population utility values
- Including disease management costs for those patients who receive subsequent treatment after progression

The revised results reported by the company are shown in Table 17 for the comparison against the trial comparator as per KEYNOTE-590.[12] The deterministic and probabilistic results are consistent with incremental cost-effectiveness ratios (ICERs) of £41,688 and £42,303 per QALY gained respectively. Of note, the company's base case analysis incorporated a PAS discount of [redacted] applied to the list price of pembrolizumab.

Table 17: Company base case results – all patients

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£27,172	0.65	£41,688
Company probabilistic base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£27,253	0.64	£42,303

Key: QALYs, quality adjusted life years

Source(s): Company response to clarification questions, Appendix C Table 1 and Table 4

The results reported by the company for the non-trial comparators are shown in Table 18. As discussed in Section 4.2.4, the company assumed the same efficacy as the trial comparator using the control arm from KEYNOTE-590[12] therefore only the drug costs influenced ICER differences. The CS did not provide fully incremental analysis; however, based on the assumption of equal efficacy and safety, the chemotherapy regimen with the lowest overall costs would be cost-saving versus the other chemotherapy regimens. This means that capecitabine + oxaliplatin is cost-saving versus the other chemotherapy regimens listed in Table 18. The resulting ICER for pembrolizumab in combination with chemotherapy versus capecitabine plus oxaliplatin is £42,172.

Table 18: Company base case results versus the non-trial comparators – all patients

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU+cisplatin	[redacted]	[redacted]	27,172	0.65	41,688
5FU + oxaliplatin + leucovorin	[redacted]	[redacted]	25,949	0.65	39,812
Capecitabine + cisplatin	[redacted]	[redacted]	27,072	0.65	41,535
Capecitabine + oxaliplatin	[redacted]	[redacted]	27,487	0.65	42,172
5-FU + cisplatin + epirubicin	[redacted]	[redacted]	27,115	0.65	41,601
5-FU + oxaliplatin + epirubicin	[redacted]	[redacted]	27,073	0.65	41,536
Capecitabine + cisplatin + epirubicin	[redacted]	[redacted]	27,036	0.65	41,480
Capecitabine + oxaliplatin + epirubicin	[redacted]	[redacted]	26,994	0.65	41,415
Blended comparator*	[redacted]	[redacted]	26,988	0.65	41,405

Key: QALYs, quality adjusted life years; SOC, standard of care

Source(s): Company response to clarification questions, Appendix C Table 2 and Table 3

Notes: *Weighted costs assuming equal market share (~12.5% for each treatment)

CPS ≥10

The results reported by the company for the CPS ≥10 sub-population are shown in Table 19 for the comparison against the trail comparator as per KEYNOTE-590.[12] The deterministic results

gave an ICER of £32,995 per QALY gained. Of note, the company's base case analysis incorporated a PAS discount of [redacted] applied to the list price of pembrolizumab.

Table 19: Company base case results = CPS ≥10

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£30,293	0.92	£32,995

Key: CPS, combined positive score; QALYs, quality adjusted life years

Source(s): Company response to clarification questions, Appendix C Table 8

The results reported by the company for the non-trial comparators are shown in Table 20. As for the full population, the CS did not provide fully incremental analysis; however, based on the assumption of equal efficacy, the chemotherapy regimen with the lowest overall costs would be cost-saving versus the other chemotherapy regimens. Accordingly, capecitabine + oxaliplatin is cost-saving versus the other chemotherapy regimens listed in Table 20. The resulting ICER for pembrolizumab in combination with chemotherapy versus capecitabine plus oxaliplatin was £33,337.

Table 20: Company base case results versus the non-trial comparators – CPS ≥10

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU+cisplatin	[redacted]	[redacted]	£30,293	0.92	£32,995
5FU + oxaliplatin + leucovorin	[redacted]	[redacted]	£29,059	0.92	£31,650
Capecitabine + cisplatin	[redacted]	[redacted]	£30,189	0.92	£32,881
Capecitabine + oxaliplatin	[redacted]	[redacted]	£30,608	0.92	£33,337
5-FU + cisplatin + epirubicin	[redacted]	[redacted]	£30,231	0.92	£32,927
5-FU + oxaliplatin + epirubicin	[redacted]	[redacted]	£30,191	0.92	£32,883
Capecitabine + cisplatin + epirubicin	[redacted]	[redacted]	£30,154	0.92	£32,843

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Capecitabine + oxaliplatin + epirubicin	[redacted]	[redacted]	£30,113	0.92	£32,798
Blended comparator*	[redacted]	[redacted]	£30,105	0.92	£32,789

Key: CPS, combined positive score; QALYs, quality adjusted life years; SOC, standard of care

Source(s): Company model post clarification questions

Notes: *Weighted costs assuming equal market share (~12.5% for each treatment)

5.2. Company's sensitivity analyses

The company reported a number of sensitivity analyses to explore the impact of alternative settings and assumptions, as well as the role of parameter uncertainty within the model results. These analyses are discussed in turn below. Of note, no sensitivity analysis was presented in the CS for the CPS ≥10 sub-population.

5.2.1. One-way sensitivity analysis

The company conducted one-way sensivity analysis (OWSA) on various parameters listed in the CS Section B.3.6. Each variable was varied using the lower and upper bounds of the 95% confidence intervals. The majority of the confidence intervals were calculated from their assigned distributions (see CS Table 64) and assuming the standard error is 10% of the mean. Exceptions to this were the patient characteristics (upper and lower bounds calculated from the data), ToT Kaplan-Meier hazard ratio (upper and lower bounds assumed to be ±10% of the mean), and duration of Grade 3+ adverse events (upper and lower bounds calculated from the data).

A tornado plot was used to present the OWSA results in the CS Figure 27 for pembrolizumab in combination with chemotherapy versus the trial based comparator. The company's results showed that the OS parameters, relative dose intensity and annual discount rate for effectiveness had the greatest influence on the ICER ranging from £27,746 to £60,344.

The ERG identified a number of errors associated with the parameters included in sensivity analysis. Firstly, the company assigned gamma distributions to costs based on an average cohort which should have been assigned normal distrbutions. Secondly, the company included parameters which have a multivariate distribution in the OWSA. As these parameters are linked to other parameters (e.g., survival distribution paramaters shape and scale), they should not be

varied individually. Thirdly, drug costs sourced from eMIT were excluded from sensivity analysis when they should be included using the provided standard errors from eMIT. Finally, the company incorporated total costs into the sensivity analysis instead of the individual components (e.g., Total calculated adverse event cost per treatment are varied instead of adverse event rates and unit costs per adverse event individually varied). The ERG noted that such an approach would mask the individual impact these parameters could have on the results, as they may act in opposite directions or apply only to one treatment arm. In addition, they could be assigned different distributions if done seperately (e.g., adverse event rates assigned the beta distribution and unit costs assigned the normal distribution). Conversely, by grouping these parameters together and assuming a large standrd error, the uncertainty may be substantially over estimated.

The ERG flagged these to the company at clarification stage, and the company subsequently made the following changes:

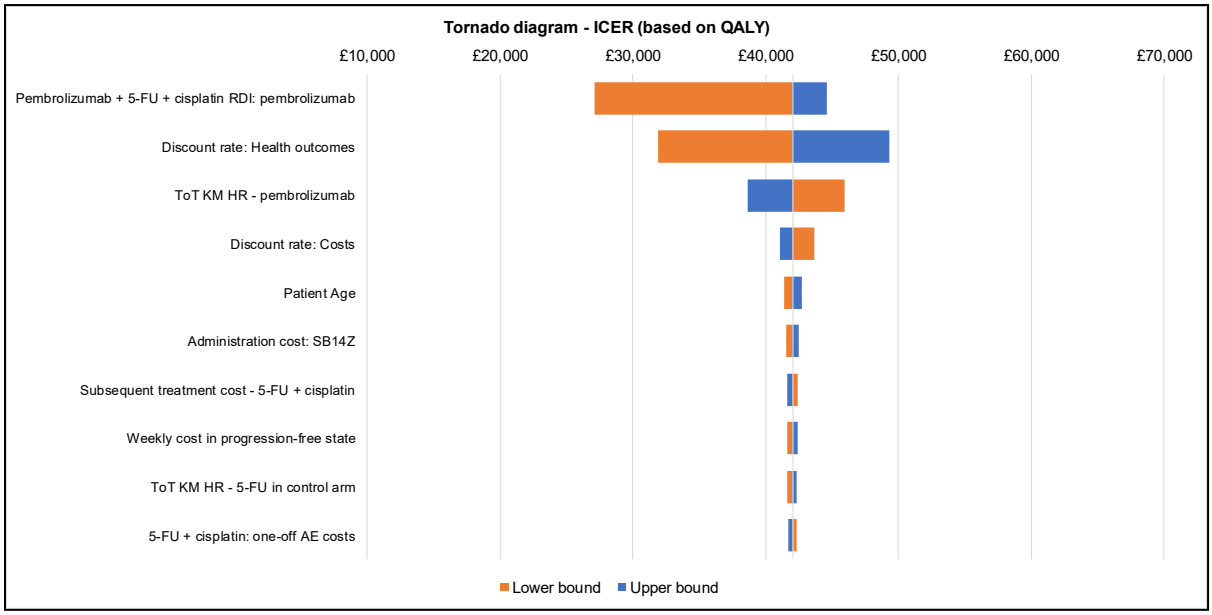
- Removed utility coefficients and survival curve coefficiants from OWSA.
- Revised some cost distributions from Gamma to normal (administration, subsequent treatments, disease management and adverse event costs).
- Included drug costs sourced from eMIT within OWSA and PSA with as assigned Gamma distribution.

The changes made by the company are considered appropriate, however the ERG would like to note that eMIT costs should have been assigned a normal distribution instead of Gamma. In addition, the company did not separate parameters to include them individually stating that *"this would require substantial modification of the model programming, and MSD are confident that the impact on the sensitivity analysis results would be minimal, and unimpactful on the deterministic base case result. Indeed, this was taken into account in the original model programming, and overall health state costs were accordingly used as the input"* (see company's response to clarification questions B22). The ERG believe that this way of incorporating parameters does not meet modelling best practice and as stated previously, grouping paramaters could under or over estimate the uncertainty.

The company's revised OWSA based on the revised base case (see Section 5.1.1.1) and changes described above is presented in Figure 12. This results show that the RDI for

pembrolizumab, annual discount rates and pembrolizumab's duration of treatment had the greatest influence on the ICER ranging from £26,764 to £48,930.

Figure 12: Company's tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensitive variables



Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; QALY, quality-adjusted life-year; RDI, relative dose intensity; ToT, time on treatment

Source: Company response to clarification questions, Appendix C Figure 3

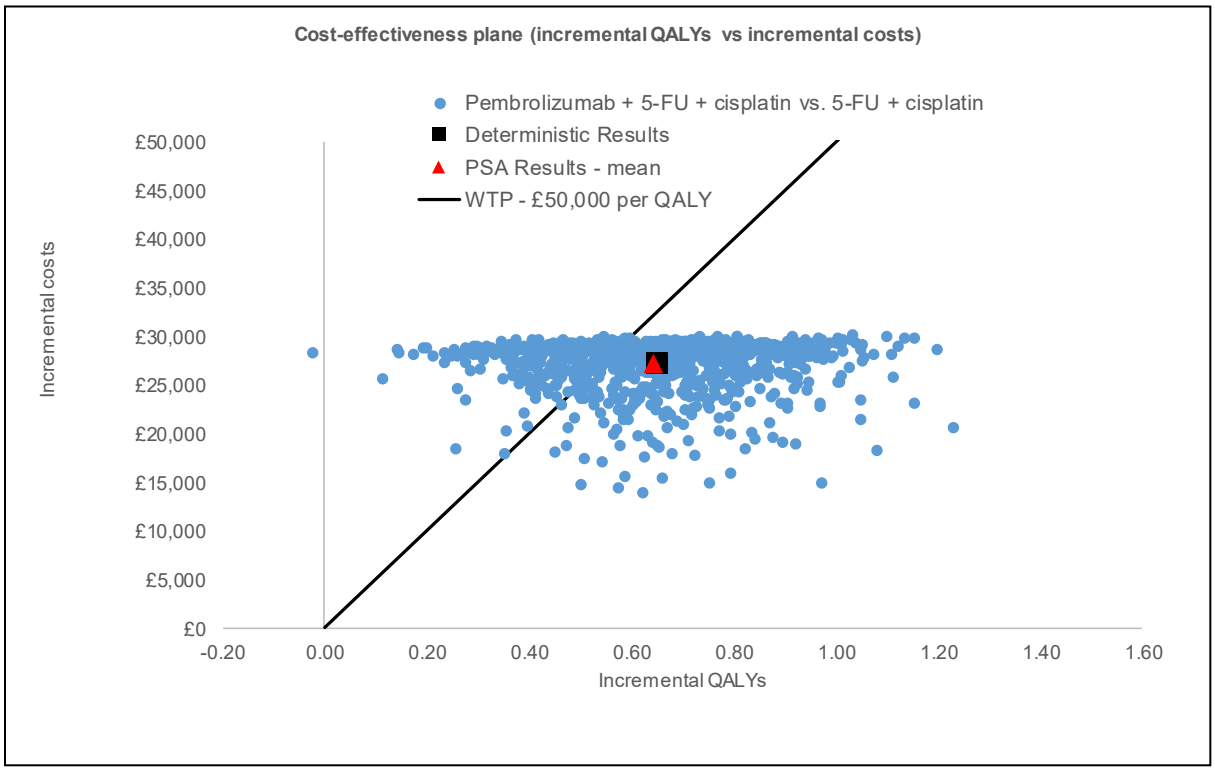
5.2.2. Probabilistic sensitivity analysis

The company conducted probabilstic sensitivity analysis (PSA) to explore the impact of parameter uncertainty. PSA results are presented in the CS Table 69 for pembrolizumab in combination with chemotherapy versus the trial based comparator. This showed consistant results to the detemrinistic ICER and demonstrated a 69.8% chance of pembrolizumab in combination with chemotherapy being cost-effective compared to the trial based comparator at the £50,000 per QALY threshold.

As discussed above in Section 5.2.1, the ERG identified a number of errors associated with the parameters included in sensivity analysis. The ERG requested the company make changes and re-run their analysis. Following clarification questions, the company updated their base case (see Section 5.1.1.1) and made changes to the sensivity analysis as described in Section 5.2.1. The updated PSA results showed consistent results to the deterministic ICER and demonstrated

a 68.5% chance of pembrolizumab in combination with chemotherapy being cost-effective compared to the trial based comparator at the £50,000 per QALY threshold. The revised cost-effectiveness plane and cost-effectiveness acceptability curve are presnted in Figure 13 and Figure 14, respectively.

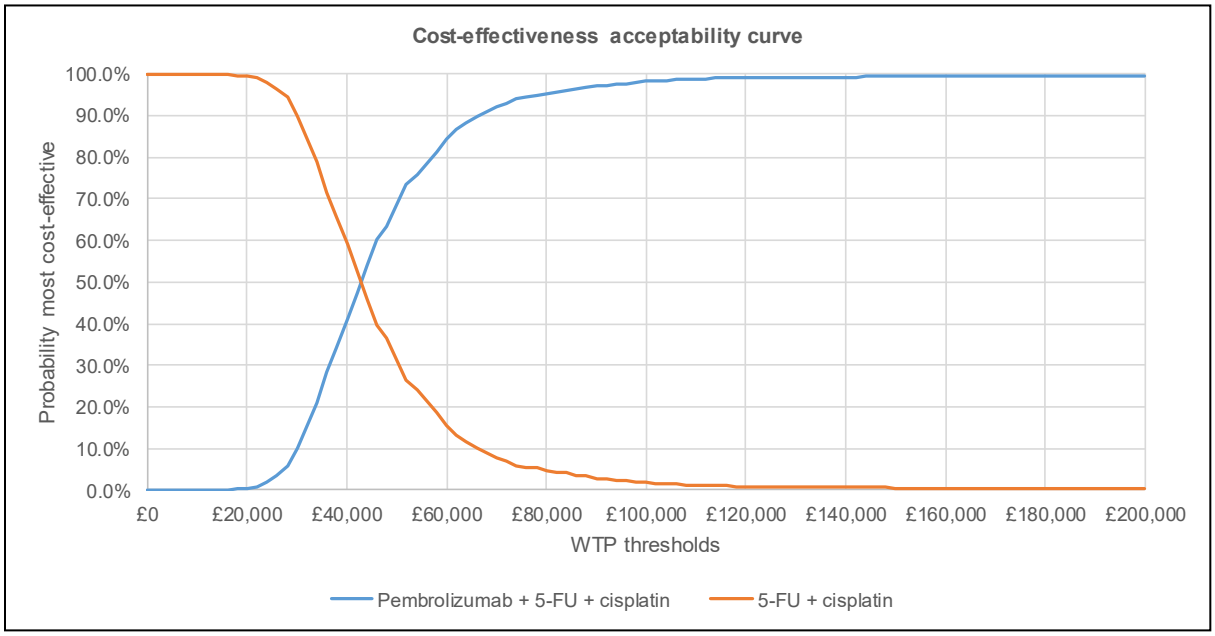
Figure 13: Company's scatter plot of PSA simulations



Key: PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year

Source: Company response to clarification questions, Appendix C Figure 1

Figure 14: Company's cost-effectiveness acceptability curve



Key: 5-FU, five fluoruracil; WTP, willingness to pay

Source: Company response to clarification questions, Appendix C Figure 2

5.2.3. Scenario analyses

The company conducted a number of scenario analyses to assess the impact of structual uncertanties and alternative settings and assumptions on the base ase results versus the trial comparator. These scenarios include:

- Alternative parametric distributions for OS (log-normal and Weibull).
- Alternative cut-off for the OS piece-wise modelling of 32-weeks.
- Exploring a treatment waning effect starting at five years finishing at seven years.
- Alternative parametric distributions for PFS (log-normal).
- Alternative cut-off for the PFS piece-wise modelling of 37-weeks.
- Alternative apporach to model ToT using fully parametric fitted models (generalised gamma for pembrolizumab, Weibull for 5-FU and KM for cisplatin).
- Exploring the removal of relative dose intensity.

- Alternative time horizons (10, 30 and 40 years).
- Assuming all patients go receive nivoumab as subsequent treatment following chemotherapy.
- Disutility scenarios (removing AE related disutity and age-adjusted disutility).
- Exploring the assumption of vial sharing (i.e., no wastage).
- Removing half-cycle correction.

Following clarification questions, the revised results are provided in Table 5 of the company's response to clarifiction questions, Appendix C. Following the requests at the clarification stage, additional scenarios were explored in relation to clarification questions B11, B17, B19 and B21:

- Using a fully parametric model for PFS curves (log-logistic).
- Removing treatment stopping rules.
- Administration costs based on a day case setting.
- Distribution of subsequent treatments based on PFS events.

Based on the company's presented scenarios versus the trial comparator (company's response to clarifiction questions, Appendix C Table 5), the scenario with the largest impact was assuming all patients after chemotherapy receive nivolumab. As this added a large increase in costs to the comparator arm, the ICER was reduced to £8,318. The scenarios which resulted in the highest ICER were due to the alternative OS parametric distribution (Weibull) and alternative OS cut-off point for the piece-wise modelling (32-weeks) resulting in ICERs of £71,729 and £52,790, respectively.

The additional scenarios requested by the ERG at clarification stage are presented in Table 21. All demonstrated minor impacts on the company's base case ICER.

Table 21: Additional scenarios post clarification questions

Scenario	Description	Pembrolizumab in combination with chemotherapy			Chemotherapy			Incremental		
		Total costs	Total LYs	Total QALYs	Total costs	Total LYs	Total QALYs	Costs	QALYs	ICER
Versus trial comparator										
Base Case	-	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,172	0.65	£41,688
B11	Fully fitted parametric modelling approach for PFS using log-logistic distribution	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,130	0.65	£41,623
B17	Removing treatment stopping rules	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,396	0.65	£42,032
B19	Drug administration costs occurring in day-case setting	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,402	0.65	£42,041
B21	Alternative subsequent therapy approach (PFS events)	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,280	0.65	£41,854
Versus blended comparator*										
Base Case	-	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£26,988	0.65	£41,405
B12	AEs based on Yoon 2016	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,834	0.65	£43,069
	AEs based on Cleary 2019	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,641	0.65	£42,688
	AEs based on Waddell 2013	[redacted]	2.21	[redacted]	[redacted]	1.39	[redacted]	£27,692	0.65	£42,797

Key: AEs, adverse events; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years; PFS, progression-free survival

Notes: *Weighted costs assuming equal market share (~12.5% for each treatment)

5.3. Model validation and face validity check

The company internally validated clinical outcomes from the model with what was observed in KEYNOTE-590 (CS Appendix J). The ERG noted some discrepancy between the modelled PFS values compared to the KEYNOTE-590[12] observed data, particularly for the pembrolizumab in combination with chemotherapy arm which appeared to be underestimated in the model. At 6 months, the model predicts PFS to be 56.2% when observed data from KEYNOTE-590[12] is actually 62.4%. At two years, PFS is 8.4% versus 11.8% for the model outcomes versus the KEYNOTE-590.[12] The modelled OS outcomes look reasonable compared to the KEYNOTE-590 trial data.

In additon to internal validation checks, the company stated that the modelling approach was validated by clinical experts, however, no information on how this validation step was conducted was provided in the CS. As such, the ERG reqested information at clarifiation stage. The company confirmed that separate informal interviews were conducted with four clinical oncologists working in the treatment of oesophageal cancer and held an advisory board on the 29th January. However, outputs of the advisory board were not used within the CS due to the close proximity to the submission date. No further information was shared by the company on the questions asked or topics discussed within the informal interviews stating that *"Due to the informal nature of the interviews with clinical experts, MSD consider that it would not be appropriate to share the outputs of these interviews"* (see company's response to clarification questions B23), therefore the ERG was not able to assess whether the clinical opinion sought was fairly executed.

The company also had the model validated through a comprehensive quality check by the economists who developed the model and by an external vendor who the company stated found no implementation errors or bugs.

The results of the model could not be compared to any publications as no studies assessing the cost-effectiveness of pembrolizumab in combination with chemotherapy versus standard of care were identified in the systematic literature review. The ERG replicated the company's model using a simple 'back of the envelope' type model in Excel and pasted values where necessary (e.g., survival curves) and was able to replicate the company's base case results. However, during this exercise, the ERG noted several errors within the model calculations:

- Firstly, when half-cycle correction is not applied in the company's model, the proportion of patients in each health state per cycle is moved to the next cycle (i.e., patients start the model in the progression-free health state at Cycle 1 (seven days) instead of Cycle 0. This misaligns the annual discount rate applied.
- Secondly, the way the company has calculated the life-years in the time-to-death health states is incorrect as they include those patients who die within that cycle. This impacts the QALYs which are accrued over time.

These errors only have minor impact on the results and are corrected in the ERG's base case (see Section 6.1).

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

The ERG identified a number of limitations within the company's base case and explored the impact of parameter values, and assumptions, which the ERG believed were more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the ERG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the ERG. These analyses were conducted within the company corrected base-case analysis.

The scenario analyses presented in Section 6.2 focus on exploring the following issues and uncertainties:

- Exploring progression-based utilities
- Alternative PFS and OS extrapolations
- Exploring efficacy of triplet therapy versus doublet therapy
- Exploring chemotherapy regimens based on UK clinical practice
    - Market share distributions based on clinical exert opinion
    - Alternative doses for some chemotherapies
- Removing half-cycle correction
- Removing treatment stopping rules
- Exploring treatment based monitoring
- Alternative adverse event costs
- Use of all subsequent treatment data from KEYNOTE-590
- Alternative terminal care costs

In Section 6.3, the ERG base-case is presented based on a combination of the exploratory analyses presented in Section 6.2.

6.1. ERG corrections and adjustments to the company's base case model

A small number of errors were identified during the face validity check of the cost-effectiveness model relating to the application of half-cycle correction and time-to-death utilities. These are described in detail within Section 5.3 and below.

- When half-cycle correction is switched-off in the company's model, the proportion of patients in each health state per cycle is moved to the next cycle (i.e., patients start the model in the progression-free health state at Cycle 1 (seven days) instead of Cycle 0. This mis-aligns the annual discount rate applied.
- The way the company has calculated the life-years in the time-to-death health states is incorrect as they include those patients who die within that cycle. Hence these patients are accruing utilities within the death health state. This impacts the QALYs which are accrued over time.

The ERG implemented the corrections within the company's economic model. The correction to the half cycle correction application only applies when half cycle correction is switched off. As such, this correction does not impact the company's base case.

Table 22 and Table 23 present the correct company base case for the full population and CPS ≥10 sub-population, respectively.

Table 22: ERG-corrected company base case results – all patients

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
ERG corrected company deterministic base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£27,173	0.65	£41,701
ERG corrected company probabilistic base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£27,085	0.65	£41,669

Abbreviations: QALYs, quality adjusted life years

Table 23: ERG-corrected company base case results – CPS ≥10

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
ERG corrected company deterministic base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£30,293	0.92	£33,006
ERG corrected company probabilistic base case					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£30,122	0.93	£32,526

Abbreviations: QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a number of additional sensitivity analyses within the company's model, which are described in turn within each section below.

6.2.1. Overall survival

Given the broad range of options available within the model to inform OS, the ERG has focused on four key scenarios to model OS for both treatment arms. These are described in further detail within Section 4.2.6.1. Clinical advice to the ERG was that each of these four scenarios may be considered as broadly clinically-plausible but are not possible to robustly validate given that no long-term data are currently available for the use of pembrolizumab in combination with chemotherapy in this patient population.

Plots demonstrating the difference in projections for each of these models are provided in Table 24, alongside estimates of OS at key time points in the longer-term up until the end of the model time horizon. The corresponding impact of these extrapolations of OS on the ICER is provided within Section 6.2.8.

Table 24: Comparison of four scenarios considered for overall survival

[redacted]

[redacted]

6.2.2. Progression-free survival

Similar to OS, the ERG has considered a number of alternative extrapolations for PFS within the model. The ERG has chosen to focus on four scenarios:

1. The company's base-case analysis.
2. Changing the cut-point to 37 weeks.
3. Changing the extrapolated tail to generalised gamma.
4. Changing both the cut-point to 37 weeks and the extrapolated tail to generalised gamma.

6.2.3. Utilities

Section 4.2.7.4 describes the utility values used within the model, based on two approaches: a progression-based approach, and a time-to-death based approach. The ERG explored additional analyses varying the absolute health state utility values by subtracting 10% of their base values to explore the impact on results. This exploratory scenario was considered because of the utility values appearing relatively high relative to the general population, but is by definition an arbitrary variation of the KEYNOTE-590-derived utility values.

In addition, the ERG sought to identify any utility values identified by the company as part of its SLR that could be applied within the model. Based on the CS (Appendix H, Table 22), the only study that reported values either as a function of the time to death or by progression status was a study by Zhang et al. (2020).[40] While the study by Zhang *et al*. was based on the ATTRACTION-3 study of nivolumab versus chemotherapy for patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy, the utility values themselves were taken from a different study by Saito et al. (2017)[66] – a cost-utility analysis of paclitaxel + ramucirumab for advanced gastric cancer. The study by Saito *et al.* cited utility values of 0.741 for progression-free disease, and 0.581 for progressed disease, but these were taken from two other studies – a study by Al-Batran *et al*. (2016)[67] and NICE TA378[61] of ramucirumab for advanced gastric cancer or gastro-oesophageal junction adenocarcinoma previously treated with chemotherapy. The ERG accepts these values are subject to several important limitations (including, but by no means limited to, the difference in disease area, potential concerns around generalisability, and a lack of reported information concerning the derivation of the utility values themselves). Nevertheless, as these were the only non-

KEYNOTE-590 utility values identified by the company that were possible to consider within the submitted model and acknowledging the ERG's prior comments concerning the magnitude of the utility values derived from KEYNOTE-590,[12] an exploratory analysis was conducted to apply these utility values within the model for both arms.

6.2.4. Efficacy of doublet chemotherapy versus triplet chemotherapy

As discussed in Section 3.5.2 and 4.2.4, the company assumes equivalent efficacy between doublet regimens and triplet regimens based on evidence from the NICE Guideline in the assessment and management of oesophago-gastric cancer in adults (NG83)[7] and clinical opinion. This evidence was used to justify the use of the comparator arm from KEYNOTE-590[12] to inform the efficacy of the chemotherapy arm in the model regardless of treatment regimen selected. In order to explore the sensitivity of this assumption, the ERG looked at scenarios whereby the triplet efficacy was estimated using results from the NMA reported in ter Veer *et al.*[10] which explored the efficacy and safety of first-line chemotherapy in advanced oesophageal cancer using an NMA. The NMA compares 'ACF' vs 'CF' (A=anthracycline, C=cisplatin, F=5FU) and reports a HR for OS and PFS; OS HR = 0.86 (95% CI: 0.71 to 1.02) and for PFS, HR = 0.85 (95% CI: 0.68 to 1.05). The confidence intervals cross 1 showing non- statistical differences and the authors conclude that "anthracycline-containing triplets…were not more effective than F-doublets" but notes they were associated with increased toxicity compared to doublets. As such, the ERG note that these scenarios are limited based on the evidence available and technical application so ICERs should be viewed with caution, however these are deemed necessary to explore the uncertainty associated with efficacy differences between triplet and doublet regimens.

In the ERG's analysis, these HRs were applied to the doublet OS and PFS curves from KEYNOTE-590 and using the blended comparator arm, the resulting OS and PFS curves were weighted based on the proportion of triplets and doublets.

Figure 15 and Figure 16 present the company's base case OS and PFS curves compared to the estimated triplet chemotherapy OS and PFS curves using the NMA HRs, respectively.

Figure 15: Company's base case OS curves with the estimated triplet OS curve

Key: OS, overall survival

Figure 16: Company's base case PFS curves with the estimated triplet PFS curve

Key: OS, overall survival

Using these curves for the triplet regimens, the ERG explored ICERs based on the blended chemotherapy arm with the following assumptions:

- Using the company's estimated market shares (12.5% per regimen resulting in a mix of 37.5% doublets versus 62.5% triplets).
- Using UK estimated market shares (see Section 6.2.5.2, resulting in a mix of 68.8% doublets versus 31.3% triplets).
- Pairwise comparisons versus each triplet therapy individually.

In all scenarios, time on treatment data was assumed to equivalent to the data from KEYNOTE-590[12] due to lack of data to inform otherwise. The resulting ICERs ranged from £46,832 to £68,512 which is an increase of between £5,131 to £26,811 compared to the company's corrected base case.

6.2.5. Chemotherapy regimens

6.2.5.1. UK based chemotherapy regimen

As discussed in Section 4.2.4, the chemotherapy regimen included in KEYNOTE-590[12] and subsequently used to form the company's base case is rarely used in UK clinical practice. Clinical advice provided to the ERG suggested that capecitabine plus oxaliplatin was more commonly used out of the chemotherapy regimens available. The company provided options and scenarios in the model which changed the comparator arm to each individual chemotherapy regimen however, the platinum-based chemotherapy in combination with pembrolizumab remained as 5-FU plus cisplatin. The proposed license states "KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy" (CS Appendix C) which is therefore not specific to 5-FU and cisplatin. However, clinical advice provided to the ERG stated that as the evidence for pembrolizumab is specifically with 5-FU and cisplatin, then there could be a change in practice with more cisplatin and 5-FU use, unless NICE guidance is clear that oxaliplatin can be substituted. Nevertheless, the ERG included additional functionality in the model to change pembrolizumab's combination chemotherapy to oxaliplatin plus capecitabine as per clinical opinion. Amending the chemotherapy regimen to capecitabine plus oxaliplatin (both in combination with pembrolizumab and as the comparator) resulted in an ICER of £42,400 per QALY gained which is a slight increase compared to the company's ICER.

6.2.5.2. UK based market shares for the blended comparator

In the company's comparison to the 'blended chemotherapy arm', the company assumed an equal market share between treatments which was considered by the ERG to be implausible and not reflective of the treatments given in clinical practice (see Section 4.2.4). The ERG requested market shares from clinical experts to explore more clinically plausible options.

Table 25 presents the expected usage in clinical practice versus the usage assumed by the company. Although expected usage varies and can be difficult to estimate, there is a general consensus that capecitabine + oxaliplatin is most commonly used, with a small usage of cisplatin (instead of oxaliplatin) and 5-FU (instead of capecitabine) and still a proportion using triplets instead of doublets.

Table 25: Market shares of chemotherapy regimens

Treatment regimen	Company base case	Expected usage
Capecitabine + oxaliplatin	12.5%	60%
Capecitabine + oxaliplatin + epirubicin	12.5%	15%
Capecitabine + cisplatin	12.5%	5%
Capecitabine + cisplatin + epirubicin	12.5%	5%
5-FU + cisplatin	12.5%	3.75%
5-FU + oxaliplatin + epirubicin	12.5%	3.75%
5-FU + cisplatin + epirubicin	12.5%	3.75%
5-FU + oxaliplatin + leucovorin	12.5%	3.75%

5-FU, five fluorouracil

Using the expected usage increases the ICER to £41,853 per QALY gained (see Table 26).

6.2.5.3. UK based chemotherapy dosing

In addition to including the most appropriate UK based chemotherapies, the ERG explored alternative dosing based on clinical expert opinion. As discussed in Section 4.2.4, clinical experts advised the ERG that some of the chemotherapy dosing schedules are slightly different to those commonly used in UK practice, with cisplatin usually given at a dose of 60 mg/m^2 for up to 6 to 8 cycles. In addition, the two-day infusion of 5-FU is considered the standard of care in UK clinical practice instead of the five-day infusion used in KEYNOTE-590. However, the clinical experts confirmed that the efficacy of 5-FU would not be impacted by these dosing differences. The ERG also considers the administration cost code used in the company base case (SB14Z) to still apply to 5-FU based regimens so no changes are required. The ERG amended the dose

of cisplatin to be 60 mg/m^2 (instead of 80 mg/m^2 used by the company). This change had minimal impact on the results (see Table 26), nevertheless this reflects UK clinical practice more than the company's base case.

6.2.6. Half cycle correction

The company's model cycle length of one week does not warrant the use of half cycle correction, therefore the ERG has explored the impact of removing this. As discussed in Section 5.3 and Section 6.1, the ERG noted an error when half cycle correction is removed which mis-aligns the annual discount rate applied. This error has been fixed in this scenario.

6.2.7. Resources and costs

6.2.7.1. Treatment stopping rules

The company included treatment stopping rules which caps treatment costs at a certain time points in addition to using ToT Kaplan-Meier data estimated directly from KEYNOTE-590.[12] The ERG noted in Section 4.2.8.3 that the ToT data from KEYNOTE-590[12] already incorporates the protocol driven stopping rules, therefore is not necessary to apply the maximum treatment durations in addition to using the Kaplan-Meier estimates and RDI. This is demonstrated in [redacted]10 and [redacted]11. At clarification stage, the ERG requested the company to provide a scenario in which only the ToT Kaplan-Meier estimates were used to inform treatment costs with the removal of treatment stopping rules. The company provided this scenario (see company's response to clarification questions B17), which slightly increases the ICER to £42,045 per QALY gained.

6.2.7.2. Administration costs

The company included administration based on the outpatient setting in their base case; however, as discussed in Section 4.2.8.2, clinical advice provided to the ERG suggested that administration would be given in a day case setting. At clarification stage, the ERG requested the company to provide a scenario in which administration costs were based on the day case setting. The company provided this scenario (see company's response to clarification questions B19), which slightly increases the ICER to £42,054 per QALY gained.

6.2.7.3. Treatment specific monitoring

The CS based the disease monitoring costs on progression status (i.e., progression-free or progressed). Clinical experts stated that monitoring frequency would differ by treatment and whether patients were on treatment or had discontinued (see Section 4.2.8.4). The ERG performed exploratory analysis which amended the progression-free monitoring based on treatment status, i.e., patients are assumed to be monitored every three weeks whilst on platinum-based chemotherapy (e.g., cisplatin) then every three months while continuing treatment with a fluoropyrimidine (e.g., fluorouracil). If patients are still receiving pembrolizumab after discontinuation of platinum-based chemotherapy, then monitoring would be every six weeks. For those patients who discontinued all treatments but remain progression-free, the ERG assumed disease monitoring was the same as the progressed disease state which costs a consultation visit every 12 weeks. The company's progression-based disease monitoring assumes patients are monitored every three with a consultation visit every four weeks which in comparison to the treatment-based monitoring assumes more resource use. Therefore, despite the pembrolizumab in combination with chemotherapy arm having increased frequencies in the treatment-based monitoring compared to chemotherapy, the overall disease monitoring costs are reduced in both arms in this scenario and as such applying the treatment based monitoring reduces the ICER to £41,173.

6.2.7.4. Subsequent treatments

The company applied an arbitrary cut-off of excluding all subsequent treatments received by less than 5% of patients received. As discussed in Section 4.2.8.6, after reviewing the full subsequent treatment table, the ERG noted that applying the 5% cut-off results in an underestimation of subsequent treatment costs and the unnecessary removal of data. In order to account for all subsequent treatments received by patients in KEYNOTE-590,[12] the ERG have re-distributed the remaining treatments into the most common treatments received (using the company's 5% threshold). The redistribution and resulting costs are presented in Table 16 compared to the company's estimates. Re-distributing the subsequent treatments including all incidences reduces the ICER to £41,434.

6.2.7.5. Terminal care costs

The ERG noted that the source of the terminal care cost has been derived from a chain of previous submissions and thus does not take into consideration the assumptions surrounding

the individual resources and whether they are appropriate for gastro-oesophageal cancer patients (see Section 4.2.8.6). The ERG performed some exploratory analysis using different terminal care values.

First, the ERG removed the radiotherapy cost which was included in the previous TA519[43] submission specifically for urothelial cancer and may not be appropriate for gastro-oesophageal cancer patients. The cost used in TA519 for radiotherapy was £3,232.43. The ERG removed this from the company's terminal care cost before this was uplifted to 2020 values, resulting in a cost of £4,320.93. This scenario increased the ICER to £41,864.

Another scenario exploring the cost used in the recent nivolumab appraisal (ID1249)[46] which used £8,973.61 from the literature (inflated from £7,827.00) estimating the per-patient costs in the last three months of life.[65] This scenario reduced the ICER to £41,646.

6.2.8. Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG made the changes described in Sections 6.2.3 to 6.2.7. Each change has been made individually. The results of the ERG's exploratory analyses are provided in Table 26.

The majority of the scenarios when considered in isolation had only a minor impact on the ICER. The key scenarios conducted were the alternative extrapolations to OS (increasing the ICER by between £4,646 to £32,342), exploring efficacy of triplet regimens (increasing the ICER by between £5,908 to £26,811) and different utility options (increasing the ICER by between £3,249 to £12,248).

Table 26: ERG's exploratory analyses

Preferred assumption	Section in ERG report	Pembrolizumab in combination with chemotherapy		Chemotherapy		Incremental		ICER £/QALY	+/- company base case
		Total costs	Total QALYs	Total costs	Total QALYs	Costs	QALYs		
ERG corrected company base-case	*6.1*	[redacted]	[redacted]	[redacted]	[redacted]	£27,173	0.65	£41,701	-
OS: Assume treatment waning effect applies between 5 and 7 years	*6.2.1*	[redacted]	[redacted]	[redacted]	[redacted]	£27,128	0.59	£46,347	+£4,646
OS: Single log-logistic parametric model		[redacted]	[redacted]	[redacted]	[redacted]	£26,970	0.36	£74,043	+£32,342
OS: Change to generalised gamma tail		[redacted]	[redacted]	[redacted]	[redacted]	£27,067	0.50	£54,447	+£12,746
PFS: Change cut-point to 37 weeks	*6.2.2*	[redacted]	[redacted]	[redacted]	[redacted]	£27,792	0.65	£42,653	+£952
PFS: Change to generalised gamma tail		[redacted]	[redacted]	[redacted]	[redacted]	£27,174	0.65	£41,703	+£2
PFS: Change cut-point to 37 weeks and to generalised gamma tail		[redacted]	[redacted]	[redacted]	[redacted]	£27,134	0.65	£41,643	-£58
Utilities: KEYNOTE-590 progression-based utility values	*6.2.3*	[redacted]	[redacted]	[redacted]	[redacted]	£27,172	0.57	£47,661	+£5,960
Utilities: Reduce magnitude of all health state utility values by 10%		[redacted]	[redacted]	[redacted]	[redacted]	£27,172	0.60	£44,950	+£3,249
Utilities: Apply published utility values (by progression status)		[redacted]	[redacted]	[redacted]	[redacted]	£27,172	0.50	£53,949	+£12,248
Triplet efficacy vs doublet efficacy – company market share	*6.2.4*	[redacted]	[redacted]	[redacted]	[redacted]	£26,690	0.52	£51,394	+£9,693
Triplet efficacy vs doublet efficacy – UK expected market share		[redacted]	[redacted]	[redacted]	[redacted]	£27,107	0.58	£46,832	+£5,131

Preferred assumption	Section in ERG report	Pembrolizumab in combination with chemotherapy		Chemotherapy		Incremental		ICER £/QALY	+/- company base case
		Total costs	Total QALYs	Total costs	Total QALYs	Costs	QALYs		
Triplet efficacy vs doublet efficacy – 5-FU + cisplatin + epirubicin		[redacted]	[redacted]	[redacted]	[redacted]	£26,520	0.39	£68,512	+£26,811
Triplet efficacy vs doublet efficacy – 5-FU + oxaliplatin + epirubicin		[redacted]	[redacted]	[redacted]	[redacted]	£26,478	0.39	£68,403	+£26,702
Triplet efficacy vs doublet efficacy – capecitabine + oxaliplatin + epirubicin		[redacted]	[redacted]	[redacted]	[redacted]	£26,398	0.39	£68,198	+£26,497
Triplet efficacy vs doublet efficacy – capecitabine + cisplatin + epirubicin		[redacted]	[redacted]	[redacted]	[redacted]	£26,441	0.39	£68,307	+£26,606
Pembrolizumab in combination with capecitabine plus oxaliplatin versus capecitabine plus oxaliplatin	*6.2.5.1*	[redacted]	[redacted]	[redacted]	[redacted]	£27,628	0.65	£42,400	+£699
Blended comparator based on UK expected market shares	*6.2.5.2*	[redacted]	[redacted]	[redacted]	[redacted]	£27,271	0.65	£41,853	+£152
Cisplatin dosed as 60 mg/m^2	*6.2.5.3*	[redacted]	[redacted]	[redacted]	[redacted]	£27,173	0.65	£41,702	+£1
Remove half-cycle correction	*6.2.6*	[redacted]	[redacted]	[redacted]	[redacted]	£27,172	0.65	£41,691	-£10
Remove treatment stopping rules	*6.2.7.1*	[redacted]	[redacted]	[redacted]	[redacted]	£27,396	0.65	£42,045	+£344
Administration based on the day case setting	*6.2.7.2*	[redacted]	[redacted]	[redacted]	[redacted]	£27,402	0.65	£42,054	+353
Include treatment-based monitoring	*6.2.7.3*	[redacted]	[redacted]	[redacted]	[redacted]	£26,829	0.65	£41,173	-£528
Re-distribute subsequent treatments	*6.2.7.4*	[redacted]	[redacted]	[redacted]	[redacted]	£26,998	0.65	£41,434	-£267
Alternative terminal care costs	*6.2.7.5*								
- Removing radiotherapy		[redacted]	[redacted]	[redacted]	[redacted]	£27,279	0.65	£41,864	+£163
- Based on ID1249						£27,136	0.65	£41,646	-£55

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life year

6.3. ERG's preferred assumptions

The ERG's preferred base case analysis comprises several alternative model settings and assumptions which are discussed in Section 6.2. The cumulative impact of these changes is presented in Table 27 with the final base case presented in

Table 28 compared to the company's base case. The ERG preferred base case ICER is £51,921.

Although the ERG's preferred extrapolation for OS is to use the company's approach with the treatment waning adjustment, the ERG would like to highlight that the other OS extrapolation scenarios listed in Section 4.2.6.1 and Section 6.2.1 are all considered plausible. Therefore, considering all of these the most plausible ICER (incorporating other ERG preferred settings) lies between £47,270 to £77,722.

Table 27: ERG's preferred model assumptions – all patients

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
ERG-corrected company base-case	6.1	£41,701
Remove half cycle correction	6.2.6	£41,691
Administration costs using a day case setting	6.2.7.2	£42,044
Turning off stopping rules for treatments (i.e., just using the ToT KM estimates from KEYNOTE-590)	6.2.7.1	£42,394
Re-distributing subsequent treatments	6.2.7.4	£42,100
Progression-based utilities	6.2.3	£48,108
PFS piecewise using 37-week cut-off and log-logistic extrapolation	6.2.2	£47,270
Include treatment waning between 5-7 years	6.2.1	£51,921

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 28: Comparison of company's and ERG's preferred base case – all patients

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company base case (deterministic)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£27,173	0.65	£41,701
ERG base case (deterministic)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
Chemotherapy	[redacted]	[redacted]	£28,007	0.54	£51,921

Key: QALYs, quality adjusted life years

6.4. Conclusions of the cost-effectiveness section

The company's model is appropriate for decision making

The company's PartSA model is considered appropriate for decision making and consistent with previous NICE submissions in similar disease areas. Overall, the ERG found the company's model to be clear and well-constructed. Where the ERG identified errors, resolving these had little influence on the estimated ICER.

The systematic literature review was satisfactory; however, there was no discussion of the applicability of the identified study to the economic model within the CS.

The ERG was satisfied with the company's review of the cost-effectiveness literature. The ERG agreed with the company's judgment that none of the studies identified were relevant to the UK population. The ERG was broadly satisfied with the company's review of the literature reporting health effects (HRQoL and utilities), health care resource use, and costs. The ERG noted an absence of methodological reporting for screening and data extraction regarding health effects. While no formal critical appraisal of utility studies was conducted, the company provided an assessment of the consistency of each study with the reference case. The ERG noted that none of the studies identified in the review of utilities were used in the model and no discussion of the applicability of the one identified study for health care resource use. However, the ERG was satisfied that the incorporation of utilities data from KEYNOTE-590[12] into the model was

appropriate to inform the base-case analysis and was generally satisfied with the sources used for resource use.

The generalisability of KEYNOTE-590 to UK patients is unclear

Over half of the KEYNOTE-590[12] study population were from Asia (52.5%, versus 47.5% from the ROW), and region was shown to have an apparent impact on the HR for OS. The ERG considered the high proportion of patients from Asia was not reflective of the UK patient population and had concerns with the impact this appears to have on OS. The ERG requested that the company provide a scenario analysis removing Asian patients, however the company declined to provide this subgroup analysis. Therefore, the ERG was unable to consider any further analysis for the ROW population specifically.

The ERG also noted the histology split between adenocarcinoma and squamous cell carcinoma in KEYNOTE-590[12] (26.8% adenocarcinoma versus 73.2% squamous cell carcinoma) was the opposite of the proportionate split expected within the UK population. Histology is an important factor given the differences in disease and potential treatment.

The comparator treatment given in KEYNOTE-590 was not considered the most reflective of current NHS practice

The main comparator considered by the company in its economic model was per the comparator used within the KEYNOTE-590[12] study (5-FU + cisplatin). This was considered by the ERG to not reflect the most common chemotherapy regimen used within NHS practice. In addition, the ERG found the company's approach to reflect NHS practice including multiple chemotherapy doublets and triplets to be inadequate by assuming equal market share for all possible alternatives. However, the ERG acknowledged that the company ran a scenario analysis amending the comparator arm to each of the chemotherapy regimens individually to investigate the impact of comparator therapies.

Clinical advice provided to the ERG noted that of the chemotherapy regimens included within the company's model, not all are used in NHS practice, and by extension do not have equal market shares. Based on advice provided to the ERG, the main chemotherapy used in practice is capecitabine plus oxaliplatin. Thus, the ERG considered the KEYNOTE-590[12] comparator regimen was not the most relevant comparator for this decision problem. The ERG accepted the company's approach of using the KEYNOTE-590[12] efficacy to inform the chemotherapy OS and

PFS within the economic model; however, costs based on the trial comparator do not reflect standard NHS practice.

Estimation of OS is a key driver of cost-effectiveness

Clinical advice to the ERG was that the company's base-case extrapolation was plausible, but that several alternative extrapolations were also plausible. The ERG's base-case used the same extrapolation per the company's base-case analysis with an adjustment for the long-term extrapolation after five years. This adjustment assumes that between five and seven years, the projected hazard of death for the pembrolizumab in combination with chemotherapy arm gradually tends to that of the chemotherapy arm. Hence, from seven years onwards, the projected hazard of death is assumed equal between arms. It was not possible for the ERG to assess with available data the plausibility of a lifetime treatment effect, or a treatment effect that would eventually dissipate by seven years. The choice of OS model remains a key uncertainty of the cost-effectiveness analysis, and considers that a range of scenarios may be informative for decision making.

Concerns were identified concerning the generalisability of the utilities derived from KEYNOTE-590, in particularly using a time-to-death approach

The ERG had concerns with the generalisability of the utility values produced based on analysis of KEYNOTE-590[12] data (regardless of which approach is used), as the outputted values imply that patients have a similar, or potentially better utility than the age- and sex-adjusted UK general population. The ERG was concerned that the two approaches to utility analysis lead to a substantially different estimation of the "average" utility experienced over the course of the model time horizon. This meant that the incremental QALY gain attributable to pembrolizumab in combination with chemotherapy estimated for both utility analyses also varied markedly. The ERG considered the progression approach to yield a more realistic "average" utility for this patient population, especially given that the time-to-death approach yields an "average" utility that is close to the estimate for the general population.

It is inappropriate to justify cost inputs based predominantly on prior company submissions of pembrolizumab in other disease areas

The majority of the company's model cost inputs were justified on the basis of being used in previous company submissions of pembrolizumab in different advanced cancer populations.

Although ultimately no major concerns were identified with the values used, it would be remiss of the ERG not to highlight the shortcomings of this approach to identifying model inputs. The ERG would have preferred that values be identified systematically, including reference where necessary to submissions made by different companies in similar disease areas (i.e., not restricting to those made only by the submitting company for pembrolizumab). Should values be taken from previous company submissions, appropriate clinical validation should be undertaken, and amendments be made as required (with justification presented). The ERG has attempted to correct for some differences in scenario analysis based on expert opinion or flagged the impact on the ICER, however as previously highlighted, no major issues were identified.

The majority of subsequent treatment instances were excluded from the company's calculations

The ERG highlighted concerns with the application of the 5% cut-off within the subsequent treatment costing resulting in [redacted] of subsequent treatments instances being excluded from the model. This results in an underestimation of subsequent treatment costs and the unnecessary removal of data. Consequently, the ERG re-distributed the remaining treatments into the most common treatments received (using the company's 5% threshold) within its preferred assumptions.

The ERG's preferred base case analysis yields an ICER slightly greater than the company's base case ICER and is just over the £50,000 per QALY gained threshold

The ERG's preferred base case analysis includes alternative OS and PFS assumptions, a different utility approach, the removal of half cycle correction and treatment stopping rules, using all subsequent treatment usage and assuming day case setting for administration. When combined, these changes result in larger total costs and fewer QALYs, causing an increase in the ICER from £41,701 to £51,921. The ERG highlights that other OS extrapolation scenarios listed in Section 4.2.6.1 and 6.2.1 are considered plausible. Considering these alternative OS extrapolations, the most plausible ICER (incorporating other ERG preferred settings) lies between £47,270 to £77,722. Accordingly, assuming a willingness-to-pay threshold of £50,000 per QALY gained, there is uncertainty as to whether pembrolizumab in combination with chemotherapy would be a cost-effective use of NHS and PSS resources.

7. END OF LIFE

The company stated that pembrolizumab in combination with chemotherapy meets end of life criteria for this indication, and summarises the basis for this assertion in Table 40 of the CS with respect to the ITT and CPS≥10 populations. The ERG regarded that the company's representations were generally appropriate with respect to the whole trial population, but noted that the strength of evidence was greater for the CPS ≥10 population, and noted that specific evidence for the rest of world subgroup did not substantiate the required increase in life expectancy.

The company noted that in the ITT population, the difference in median OS was 2.6 months, less than the three months required, though the estimated difference in mean months from the economic model was 7.5 months. However, in the rest of world subgroup specifically, the difference in median OS was approximately [redacted] (clarification response appendices, Table 3). For the CPS≥10 population, both the difference in median OS (4.1 months) and the difference in model-estimated means (10.6 months) were above the requisite threshold, but these were not presented for the rest of world subgroup.

Moreover, in the KEYNOTE-590[12] trial, the ITT population that received standard of care had median survival of 9.8 months, whereas the CPS≥10 population that received standard of care had median survival of 9.4 months. This suggests that with respect to the entire trial population, the short life expectancy criterion was met. In the rest of world subgroup, the median OS for the standard of care arm was 44.2 weeks for the ITT population; specific rest of world estimates for the CPS≥10 population and this subgroup were not provided.

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Appendix A: Search strategies for Ovid MEDLINE and Embase

Search strategies for additional work completed by the ERG reported in Section 3.5.1.

Search strategy for Ovid MEDLINE

1 exp Esophageal Neoplasms/ (51854)
2 exp esophagus cancer/ (51854)
3 (Cancer of the esophagus or esophageal adenocarcinoma or esophageal squamous cell carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (15585)
4 ((Esophageal or esophagus) and (cancer or carcinom? or tumour? or tumor? or neoplasm?)).mp. (76667)
5 (("adenocarcinoma of the esophagus" or "squamous cell carcinoma of the esophagus" or "Siewert type 1 adenocarcinoma of the esophageal junction") and (stage 3 or stage III or stage 3b or stage IIIb or stage 4 or stage IV or metasta? or advanced)).mp. (425)
6 or/1-5 (77194)
7 (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. (5154)
8 exp Nivolumab/ (2975)
9 (nivolumab or ONO-4538 or ONO 4538 or BMS-936558 or BMS 936558 or MDX-1106 or MDX 1106 or MDX1106 or opdivo).mp. (6205)
10 exp ipilimumab/ (2071)
11 ("Anti-CTLA-4 MAb" or "Anti CTLA 4 MAb Ipilimumab" or "Ipilimumab, Anti-CTLA-4 Mab" or Yervoy or "MDX 010" or "MDX010" or "MDX-010" or "MDX-CTLA-4" or "MDX CTLA 4").mp. (197)
12 exp epirubicin/ (5260)
13 (epirubicin or epiadriamycin or epidoxorubicin).mp. (7561)
14 exp trastuzumab/ (7251)
15 exp paclitaxel/ (27506)
16 (paclitaxel or nab-paclitaxel or "abi 007" or "abi007" or abraxane or anzatax or asotax or "bms 181339" or "bms181339" or britaxol or coroxane or "mbt 0206" or "mbt0206 or nab paclitaxel or nsc 125973 or nsc125973" or pacitaxel or praxel or paxene or taxol).mp. (41285)
17 (ramucirumab or cyramza or "imc 1121 b" or "imc 1121b" or "imc1121 b" or "imc1121b" or "ly3009806" or "ly 3009806").mp. (903)
18 exp docetaxel/ (10907)
19 (docetaxel or docetaxol accord or daxotel or dexotel or "lit 976" or "lit976" or "nsc 628503" or "nsc628503" or "rp 56976" or "rp56976" or taxoter or taxotere).mp. (17519)
20 exp irinotecan/ (7199)
21 (irinotecan or camptosar or campto or "cpt 11" or "cpt11" or irinotecan hydrochloride or irinotel).mp. (11863)
22 exp capecitabine/ (4738)
23 (capecitabine or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or xeloda).mp. (7570)
24 exp carboplatin/ (11915)
25 (carboplatin or paraplatin).mp. (18281)
26 exp leucovorin/ (10289)

27 exp folinic acid/ (10289)
28 (leucovorin or folinic acid or Wellcovorin or Citrovorum Factor or leucovorin or leucovoran or leukovorin).mp. (13829)
29 exp 5-FU/ (47430)
30 exp fluorouracil/ (47430)
31 (5-fluorouracil or "5 fluorouracil" or adrucil or "5-FU" or "5 FU" or fluoroblastin or fluorolex or "fluorouracil 5" or "nsc 18913" or "nsc18913" or "nsc 19893" or "nsc19893").mp. (39372)
32 exp cisplatin/ (53179)
33 (cisplatin or cisplatinum or cis-platinum or cis platinum or platamin or neoplatin or cismaplat or cis-maplat or "mpi 5010" or "mpi5010" or "nk 801" or platinol or platinex or platamine).mp. (79657)
34 exp oxaliplatin/ (6803)
35 (Oxaliplatin or eloxatin).mp. (12612)
36 (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. (811)
37 (FOLFOX* or FOLFOX6 or FOLFOX-6 or "folfox regimen").mp. (3553)
38 (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. (1529)
39 (CAPOX or XELOX or capecitabine-oxaliplatin).mp. (1165)
40 capecitabine-carboplatin.mp. (4)
41 or/7-40 (211467)
42 Randomized Controlled Trials as Topic/ (141253)
43 randomized controlled trial/ (524786)
44 Random Allocation/ (104805)
45 Double Blind Method/ (162861)
46 Single Blind Method/ (29846)
47 clinical trial/ (527778)
48 clinical trial, phase i.pt. (21375)
49 clinical trial, phase ii.pt. (34350)
50 clinical trial, phase iii.pt. (18066)
51 clinical trial, phase iv.pt. (2060)
52 controlled clinical trial.pt. (94093)
53 randomized controlled trial.pt. (524786)
54 multicenter study.pt. (289732)
55 clinical trial.pt. (527778)
56 exp Clinical Trials as topic/ (353660)
57 or/42-56 (1413298)
58 (clinical adj trial$).tw. (391486)
59 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (178444)
60 PLACEBOS/ (35369)
61 placebo$.tw. (222942)
62 randomly allocated.tw. (30522)
63 (allocated adj2 random$).tw. (33923)
64 or/58-63 (668871)
65 57 or 64 (1699891)
66 6 and 41 and 65 (1558)
67 limit 66 to english language (1422)
68 limit 67 to yr=2000-current (1171) [original search reported in CS]
69 exp Esophageal Neoplasms/ (51854)
70 exp esophagus cancer/ (51854)

71 (Cancer of the esophagus or esophageal adenocarcinoma or esophageal squamous cell carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (15585)
72 ((Esophag* or oesophag* or gastroesophag* or gastrooesophag* or gastro-esophag* or gastro-oesophag* or siewert*) and (adenocarcinoma* or cancer or carcinom? or tumour? or tumor? or neoplasm? or metastas* or metastatic)).mp. (87890)
73 (("adenocarcinoma of the esophagus" or "squamous cell carcinoma of the esophagus" or "Siewert type 1 adenocarcinoma of the esophageal junction") and (stage 3 or stage III or stage 3b or stage IIIb or stage 4 or stage IV or metasta? or advanced)).mp. (425)
74 or/69-73 (87890)
75 (pembrolizumab or MK-3475 or MK3475 or lambrolizumab or keytruda).mp. (5154)
76 exp Nivolumab/ (2975)
77 (nivolumab or ONO-4538 or ONO 4538 or BMS-936558 or BMS 936558 or MDX-1106 or MDX 1106 or MDX1106 or opdivo).mp. (6205)
78 exp ipilimumab/ (2071)
79 ("Anti-CTLA-4 MAb" or "Anti CTLA 4 MAb Ipilimumab" or "Ipilimumab, Anti-CTLA-4 Mab" or Yervoy or "MDX 010" or "MDX010" or "MDX-010" or "MDX-CTLA-4" or "MDX CTLA 4").mp. (197)
80 exp epirubicin/ (5260)
81 (epirubicin or epiadriamycin or epidoxorubicin).mp. (7561)
82 exp trastuzumab/ (7251)
83 exp paclitaxel/ (27506)
84 (paclitaxel or nab-paclitaxel or "abi 007" or "abi007" or abraxane or anzatax or asotax or "bms 181339" or "bms181339" or britaxol or coroxane or "mbt 0206" or "mbt0206 or nab paclitaxel or nsc 125973 or nsc125973" or pacitaxel or praxel or paxene or taxol).mp. (41285)
85 (ramucirumab or cyramza or "imc 1121 b" or "imc 1121b" or "imc1121 b" or "imc1121b" or "ly3009806" or "ly 3009806").mp. (903)
86 exp docetaxel/ (10907)
87 (docetaxel or docetaxol accord or daxotel or dexotel or "lit 976" or "lit976" or "nsc 628503" or "nsc628503" or "rp 56976" or "rp56976" or taxoter or taxotere).mp. (17519)
88 exp irinotecan/ (7199)
89 (irinotecan or camptosar or campto or "cpt 11" or "cpt11" or irinotecan hydrochloride or irinotel).mp. (11863)
90 exp capecitabine/ (4738)
91 (capecitabine or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or xeloda).mp. (7570)
92 exp carboplatin/ (11915)
93 (carboplatin or paraplatin).mp. (18281)
94 exp leucovorin/ (10289)
95 exp folinic acid/ (10289)
96 (leucovorin or folinic acid or Wellcovorin or Citrovorum Factor or leucovorin or leucovoran or leukovorin).mp. (13829)
97 exp 5-FU/ (47430)
98 exp fluorouracil/ (47430)
99 (5-fluorouracil or "5 fluorouracil" or adrucil or "5-FU" or "5 FU" or fluoroblastin or fluorolex or "fluorouracil 5" or "nsc 18913" or "nsc18913" or "nsc 19893" or "nsc19893").mp. (39372)
100 exp cisplatin/ (53179)

101 (cisplatin or cisplatinum or cis-platinum or cis platinum or platamin or neoplatin or cismaplat or cis-maplat or "mpi 5010" or "mpi5010" or "nk 801" or platinol or platinex or platamine).mp. (79657)
102 exp oxaliplatin/ (6803)
103 (Oxaliplatin or eloxatin).mp. (12612)
104 (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. (811)
105 (FOLFOX* or FOLFOX6 or FOLFOX-6 or "folfox regimen").mp. (3553)
106 (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. (1529)
107 (CAPOX or XELOX or capecitabine-oxaliplatin).mp. (1165)
108 capecitabine-carboplatin.mp. (4)
109 or/75-108 (211467)
110 Randomized Controlled Trials as Topic/ (141253)
111 randomized controlled trial/ (524786)
112 Random Allocation/ (104805)
113 Double Blind Method/ (162861)
114 Single Blind Method/ (29846)
115 clinical trial/ (527778)
116 clinical trial, phase i.pt. (21375)
117 clinical trial, phase ii.pt. (34350)
118 clinical trial, phase iii.pt. (18066)
119 clinical trial, phase iv.pt. (2060)
120 controlled clinical trial.pt. (94093)
121 randomized controlled trial.pt. (524786)
122 multicenter study.pt. (289732)
123 clinical trial.pt. (527778)
124 exp Clinical Trials as topic/ (353660)
125 or/110-124 (1413298)
126 (clinical adj trial$).tw. (391486)
127 ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (178444)
128 PLACEBOS/ (35369)
129 placebo$.tw. (222942)
130 randomly allocated.tw. (30522)
131 (allocated adj2 random$).tw. (33923)
132 (single arm or "single arm").ti,ab. (8516)
133 or/126-132 (675347)
134 125 or 133 (1703120)
135 74 and 109 and 134 (2209)
136 limit 135 to english language (2044)
137 limit 136 to yr=2000-current (1673) [search strategy amended by ERG]
138 137 not 68 (502) [additional studies identified by ERG search strategy]

Search strategy for Ovid Embase

1 exp Esophageal Neoplasms/ (86939)
2 exp esophagus cancer/ (73510)
3 exp esophagus carcinoma/ (40124)
4 exp esophagus metastasis/ (552)
5 exp esophagus tumor/ (86939)
6 exp esophageal adenocarcinoma/ (11913)

7 exp esophageal squamous cell carcinoma/ (14800)
8 (Cancer of the esophagus or esophageal adenocarcinoma or esophageal squamous cell carcinoma).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (31062)
9 ((Esophageal or esophagus) and (cancer or carcinom? or tumour? or tumor? or neoplasm?)).mp. (122919)
10 (("adenocarcinoma of the esophagus" or "squamous cell carcinoma of the esophagus" or "Siewert type 1 adenocarcinoma of the esophageal junction") and (stage 3 or stage III or stage 3b or stage IIIb or stage 4 or stage IV or metasta? or advanced)).mp. (682)
11 or/1-10 (124826)
12 exp pembrolizumab/ (18704)
13 (pembrolizumab or "mk-3475" or "mk3475" or "mk 3475" or lambrolizumab or keytruda).mp. (19814)
14 exp Nivolumab/ (20909)
15 (nivolumab or ONO-4538 or ONO 4538 or BMS-936558 or BMS 936558 or MDX-1106 or MDX 1106 or MDX1106 or opdivo).mp. (22048)
16 exp ipilimumab/ (15724)
17 ("Anti-CTLA-4 MAb" or "Anti CTLA 4 MAb Ipilimumab" or "Ipilimumab, Anti-CTLA-4 Mab" or Yervoy or "MDX 010" or "MDX010" or "MDX-010" or "MDX-CTLA-4" or "MDX CTLA 4").mp. (1334)
18 exp epirubicin/ (29473)
19 (epirubicin or epiadriamycin or epidoxorubicin).mp. (30167)
20 exp trastuzumab/ (40894)
21 exp paclitaxel/ (111046)
22 (paclitaxel or nab-paclitaxel or "abi 007" or "abi007" or abraxane or anzatax or asotax or "bms 181339" or "bms181339" or britaxol or coroxane or "mbt 0206" or "mbt0206 or nab paclitaxel or nsc 125973 or nsc125973" or pacitaxel or praxel or paxene or taxol).mp. (117528)
23 exp ramucirumab/ (3030)
24 (ramucirumab or cyramza or "imc 1121 b" or "imc 1121b" or "imc1121 b" or "imc1121b" or "ly3009806" or "ly 3009806").mp. (3307)
25 exp docetaxel/ (61159)
26 (docetaxel or docetaxol accord or daxotel or dexotel or "lit 976" or "lit976" or "nsc 628503" or "nsc628503" or "rp 56976" or "rp56976" or taxoter or taxotere).mp. (63326)
27 exp irinotecan/ (39113)
28 (irinotecan or camptosar or campto or "cpt 11" or "cpt11" or irinotecan hydrochloride or irinotel).mp. (41110)
29 exp capecitabine/ (30495)
30 (capecitabine or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or xeloda).mp. (32522)
31 exp carboplatin/ (72037)
32 (carboplatin or paraplatin).mp. (74583)
33 exp leucovorin/ (37701)
34 exp folinic acid/ (37701)
35 (leucovorin or folinic acid or Wellcovorin or Citrovorum Factor or leucovorin or leucovoran or leukovorin).mp. (39615)
36 exp 5-FU/ (141803)
37 exp fluorouracil/ (141803)
38 (5-fluorouracil or "5 fluorouracil" or adrucil or "5-FU" or "5 FU" or fluoroblastin or fluorolex or "fluorouracil 5" or "nsc 18913" or "nsc18913" or "nsc 19893" or "nsc19893").mp. (54115)

39 exp cisplatin/ (189824)
40 (cisplatin or cisplatinum or cis-platinum or cis platinum or platamin or neoplatin or cismaplat or cis-maplat or "mpi 5010" or "mpi5010" or "nk 801" or platinol or platinex or platamine).mp. (199050)
41 exp oxaliplatin/ (41594)
42 (Oxaliplatin or eloxatin).mp. (43970)
43 (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. (1585)
44 (FOLFOX* or FOLFOX6 or FOLFOX-6 or "folfox regimen").mp. (6761)
45 (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. (3823)
46 (CAPOX or XELOX or capecitabine-oxaliplatin).mp. (2640)
47 capecitabine-carboplatin.mp. (8)
48 or/12-47 (517617)
49 clinical trial/ (1004398)
50 Randomized controlled trial/ (650791)
51 controlled clinical trial/ (466124)
52 multicenter study/ (282811)
53 Phase 3 clinical trial/ (52263)
54 Phase 4 clinical trial/ (4248)
55 exp RANDOMIZATION/ (90715)
56 Single Blind Procedure/ (42240)
57 Double Blind Procedure/ (182483)
58 Crossover Procedure/ (66463)
59 PLACEBO/ (364703)
60 randomi?ed controlled trial$.tw. (253069)
61 rct.tw. (41261)
62 (random$ adj2 allocat$).tw. (46065)
63 Single blind$.tw. (26659)
64 Double blind$.tw. (218829)
65 ((treble or triple) adj blind$).tw. (1315)
66 Placebo$.tw. (323746)
67 Prospective study/ (671266)
68 or/49-67 (2477180)
69 11 and 48 and 68 (4143)
70 limit 69 to english language (3880)
71 limit 70 to yr=2000-current (3573) [original search reported in CS]
72 exp Esophageal Neoplasms/ (86939)
73 exp esophagus cancer/ (73510)
74 exp esophagus carcinoma/ (40124)
75 exp esophagus metastasis/ (552)
76 exp esophagus tumor/ (86939)
77 exp esophageal adenocarcinoma/ (11913)
78 exp esophageal squamous cell carcinoma/ (14800)
79 (Cancer of the esophagus or esophageal adenocarcinoma or esophageal squamous cell carcinoma).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (31062)
80 ((Esophageal or esophagus) and (cancer or carcinom? or tumour? or tumor? or neoplasm?)).mp. (122919)

81 (("adenocarcinoma of the esophagus" or "squamous cell carcinoma of the esophagus" or "Siewert type 1 adenocarcinoma of the esophageal junction") and (stage 3 or stage III or stage 3b or stage IIIb or stage 4 or stage IV or metasta? or advanced)).mp. (682)
82 ((Esophageal or esophagus or esophagogastric* or oesophageal or esophagus or esophagogastric* or gastroesophag* or gastrooesophag* or gastro-esophag* or gastro-oesophag* or siewert*) and (adenocarcinoma* or cancer or carcinom? or tumour? or tumor? or neoplasm? or metastas* or metastatic)).mp. (134020)
83 or/72-82 (134189)
84 exp pembrolizumab/ (18704)
85 (pembrolizumab or "mk-3475" or "mk3475" or "mk 3475" or lambrolizumab or keytruda).mp. (19814)
86 exp Nivolumab/ (20909)
87 (nivolumab or ONO-4538 or ONO 4538 or BMS-936558 or BMS 936558 or MDX-1106 or MDX 1106 or MDX1106 or opdivo).mp. (22048)
88 exp ipilimumab/ (15724)
89 ("Anti-CTLA-4 MAb" or "Anti CTLA 4 MAb Ipilimumab" or "Ipilimumab, Anti-CTLA-4 Mab" or Yervoy or "MDX 010" or "MDX010" or "MDX-010" or "MDX-CTLA-4" or "MDX CTLA 4").mp. (1334)
90 exp epirubicin/ (29473)
91 (epirubicin or epiadriamycin or epidoxorubicin).mp. (30167)
92 exp trastuzumab/ (40894)
93 exp paclitaxel/ (111046)
94 (paclitaxel or nab-paclitaxel or "abi 007" or "abi007" or abraxane or anzatax or asotax or "bms 181339" or "bms181339" or britaxol or coroxane or "mbt 0206" or "mbt0206 or nab paclitaxel or nsc 125973 or nsc125973" or pacitaxel or praxel or paxene or taxol).mp. (117528)
95 exp ramucirumab/ (3030)
96 (ramucirumab or cyramza or "imc 1121 b" or "imc 1121b" or "imc1121 b" or "imc1121b" or "ly3009806" or "ly 3009806").mp. (3307)
97 exp docetaxel/ (61159)
98 (docetaxel or docetaxol accord or daxotel or dexotel or "lit 976" or "lit976" or "nsc 628503" or "nsc628503" or "rp 56976" or "rp56976" or taxoter or taxotere).mp. (63326)
99 exp irinotecan/ (39113)
100 (irinotecan or camptosar or campto or "cpt 11" or "cpt11" or irinotecan hydrochloride or irinotel).mp. (41110)
101 exp capecitabine/ (30495)
102 (capecitabine or apecitab or ecansya or "ro 09 1978" or "ro 091978" or "ro091978" or "ro09 1978" or xeloda).mp. (32522)
103 exp carboplatin/ (72037)
104 (carboplatin or paraplatin).mp. (74583)
105 exp leucovorin/ (37701)
106 exp folinic acid/ (37701)
107 (leucovorin or folinic acid or Wellcovorin or Citrovorum Factor or leucovorin or leucovoran or leukovorin).mp. (39615)
108 exp 5-FU/ (141803)
109 exp fluorouracil/ (141803)
110 (5-fluorouracil or "5 fluorouracil" or adrucil or "5-FU" or "5 FU" or fluoroblastin or fluorolex or "fluorouracil 5" or "nsc 18913" or "nsc18913" or "nsc 19893" or "nsc19893").mp. (54115)
111 exp cisplatin/ (189824)

112 (cisplatin or cisplatinum or cis-platinum or cis platinum or platamin or neoplatin or cismaplat or cis-maplat or "mpi 5010" or "mpi5010" or "nk 801" or platinol or platinex or platamine).mp. (199050)
113 exp oxaliplatin/ (41594)
114 (Oxaliplatin or eloxatin).mp. (43970)
115 (mFOLFOX6 or mFOLFOX-6 or m-FOLFOX6 or m-FOLFOX-6 or modified FOLFOX6 or modified FOLFOX-6).mp. (1585)
116 (FOLFOX* or FOLFOX6 or FOLFOX-6 or "folfox regimen").mp. (6761)
117 (FOLFIRI or FOLinic acid-Fluorouracil-IRInotecan).mp. (3823)
118 (CAPOX or XELOX or capecitabine-oxaliplatin).mp. (2640)
119 capecitabine-carboplatin.mp. (8)
120 or/84-119 (517617)
121 clinical trial/ (1004398)
122 Randomized controlled trial/ (650791)
123 controlled clinical trial/ (466124)
124 multicenter study/ (282811)
125 Phase 3 clinical trial/ (52263)
126 Phase 4 clinical trial/ (4248)
127 exp RANDOMIZATION/ (90715)
128 Single Blind Procedure/ (42240)
129 Double Blind Procedure/ (182483)
130 Crossover Procedure/ (66463)
131 PLACEBO/ (364703)
132 randomi?ed controlled trial$.tw. (253069)
133 rct.tw. (41261)
134 (random$ adj2 allocat$).tw. (46065)
135 Single blind$.tw. (26659)
136 Double blind$.tw. (218829)
137 ((treble or triple) adj blind$).tw. (1315)
138 Placebo$.tw. (323746)
139 Prospective study/ (671266)
140 "single arm".mp. (18467)
141 or/121-140 (2484235)
142 83 and 120 and 141 (4856)
143 limit 142 to english language (4583)
144 limit 143 to yr=2000-current (4266) [search strategy amended by ERG]
145 144 not 71 (693) [additional studies identified by ERG search strategy]

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 30 April 2021** 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 Overview of key model outcomes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1, page 11 of the ERG report states, ***"The modelling assumptions that have the greatest effect on the ICER are:*** *Acquisition and administration costs for standard of care chemotherapy regimens*"	***"The modelling assumptions that have the greatest effect on the ICER are:*** *Assumptions surrounding Overall Survival and the choice of utility method*"	This appears to be a typographical error. MSD do not consider the acquisition and administration costs for standard of care chemotherapy regimens to be a key driver of the ICER.	The ERG made the suggested amendment (p.11).

Issue 2 Grammatical errors and mistypes

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2, page 18 of the ERG report Figure 1 in the rightmost box it states: "*Trastuzumab (in combination with cisplatin and 5-FU or capecitabine)**"	In the source footnote, an explanation should be added for "*" to make it clear that trastuzumab combinations are used for HER2+ patients, as per page 16 of the company submission.	Figure 1 of the ERG report could mislead readers to think that trastuzumab is a relevant comparator within this appraisal. The recommended footnote would clarify this.	The ERG did not consider this to be a factual inaccuracy, but has added the suggested footnote for additional clarity (Figure 1, p.18)
Section 4, page 46 of the ERG report Table 8 states: "*The company included studies reporting healthcare costs and/or resource use in the treatment and on-going management of advance unresectable or metastatic oesophageal cancer (including*	"*The company included studies reporting healthcare costs and/or resource use in the treatment and on-going management of* ***advanced*** *unresectable or metastatic oesophageal cancer (including carcinoma of the gastro-oesophageal junction) in order to evaluate the economic burden of oesophageal cancer in the United Kingdom.*"	Amended for accuracy.	Typographical error corrected (Table 8, p.46)

carcinoma of the gastro-oesophageal junction) in order to evaluate the economic burden of oesophageal cancer in the United Kingdom."			
Section 4, page 53 of the ERG report states, "*The ERG would like to note that the evidence from NG38 presented by the company"*	"*The ERG would like to note that the evidence from **NG83** presented by the company"*	Amended for accuracy.	Typographical error corrected (p.53)

Issue 3 Treatment effectiveness and extrapolation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4, page 61 of the ERG report states: *"In KEYNOTE-590,12 median OS for the chemotherapy arm was 9.8 months, with one- and two-year OS rates of 39.9% and 16.3%, respectively, demonstrating that the estimates reported by Wu et al. are similar to those obtained from the KEYNOTE-590 trial."*	*"In KEYNOTE-590,12 median OS for the chemotherapy arm was 9.8 months, with one- and two-year OS rates of **39.4%** and 16.3%, respectively, demonstrating that the estimates reported by Wu et al. are similar to those obtained from the KEYNOTE-590 trial."*	The number reported is slightly incorrect.	The ERG corrected this typographical error (p.61).

Issue 4 Health-related quality of life

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4, page 74 of the ERG report states *"A progression approach is considered the standard for models for a range of previous evaluations of cancer therapies, particularly those that make use of a three-state PartSA model (as has been used by the company)."*	*"A progression approach **has often, but not always, been adopted within** models for a range of previous evaluations of cancer therapies, particularly those that make use of a three-state PartSA model (as has been used by the company)."*	MSD note that although a progression-based approach is often used this is not always the case. The use of the terminology "*standard approach*" implies that the alternative is not standard, which could be misleading for the reader. MSD request a slight change in language to acknowledge that other utilities approaches have often been considered plausible by NICE committees.	The ERG agreed with the company's justification and made the suggested amendment (p.74).
Section 4, page 78 of the ERG report states "*Furthermore, the average utility in the ≥360 days to death grouping ([redacted]) was greater than the equivalent value in the general population (0.829), most of whom would be expected to have a life expectancy greater than 1 year. As such, these results are misaligned with the expectation of relatively low utility for patients with metastatic cancer undergoing intensive chemotherapy with a relatively poor prognosis (versus 'healthy' individuals in the general*	"*Furthermore, the average utility in the ≥360 days to death grouping ([redacted]) was greater than the equivalent value in the general population (0.829), most of whom would be expected to have a life expectancy greater than 1 year. **After clarification questions, the utility within this group has been capped to that of the general population.** As such, these results are misaligned with the expectation of relatively low utility for patients with metastatic cancer undergoing intensive chemotherapy with a relatively poor prognosis (versus 'healthy' individuals in the general population)."*	After clarification questions, the model caps utility at that of general population. This should be reflected within the text.	The ERG agreed with the company's justification and has made the following change: "*Furthermore, the average utility in the ≥360 days to death grouping ([redacted]) was greater than the equivalent value in the general population (0.829). **In response to clarification questions, the company capped the utility values applied within the model to be equal to general population, should the value estimated from KEYNOTE-590 exceed this. Although this addresses the issue of*

population).”			***utility being greater than general population, the capping still assumes that patients with advanced oesophageal cancer over a year away from death have the same quality of life as the general population,*** *most of whom would be expected to have a life expectancy greater than 1 year. As such, these results are misaligned with the expectation of relatively low utility for patients with metastatic cancer undergoing intensive chemotherapy with a relatively poor prognosis (versus ‘healthy’ individuals in the general population).” (p.78)*
Section 4, page 78 of the ERG report states “*For the progression approach, the average utility was estimated to be [redacted]. Switching to the time-to-death approach, the average utility was estimated to be [redacted].”*	“**Using the companies preferred assumptions, f***or the progression approach, the average utility was estimated to be [redacted]. Switching to the time-to-death approach, the average utility was estimated to be [redacted]. **Using the ERG’s preferred assumptions, the respective numbers are [redacted] and [redacted]”***	MSD were unable to replicate the quoted numbers using either the ERG or company models.	The values reported by the ERG were correct using the company’s original submitted model which was used when writing this section. The ERG agreed, that results using the updated models should be reported and so the following change was made: *“**Using the company’s corrected base case model (see Section 6.1),** for the progression approach, the average utility was estimated to be [redacted]. Switching to the time-*

			to-death approach, the average utility was estimated to be [redacted]. ***Using the ERG's preferred assumptions (see Section 6.3), the average utility values are*** [redacted] ***and*** [redacted]***, respectively."*** (p.78)
Section 4, page 78 of the ERG report states "*The time-to-death approach (company base-case analysis) yields an incremental QALY gain of 0.628, versus 0.535 for the progression approach."*	"*The time-to-death approach (company base-case analysis) yields an incremental QALY gain of 0.**652**, versus 0.**570** for the progression approach."*	MSD believe the incremental QALY gain cited is incorrect.	The values used to draft this text were also based on the company's original submitted model (see response to comment above). The ERG corrected these in line with the correct (updated) company's base case: *"The time-to-death approach (company base-case analysis **post corrections**) yields an incremental QALY gain of **0.652**, versus **0.570** for the progression approach."* (p.78)

Issue 5 Health related quality of life associated with adverse events

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4, page 79 of the ERG report states "*The ERG notes that it is unclear why the estimated QALY loss due to AEs is greater for the*	Please remove this sentence.	QALY loss due to AEs are different between the two approaches because Grade 3+ AE disutility estimates are different between the two approaches, -0.036 vs. -0.050 for time-to-death and progression-	The ERG did not consider this to be a factual accuracy. No change made.

progression versus the time-to-death approach."		based approaches. MSD recommend removing this sentence.	
Section 4, page 79 of the ERG report states "*In addition, the ERG questioned the face validity of a near-negligible impact in terms of toxicity for the addition of pembrolizumab to the combination of fluorouracil and cisplatin."*	Please remove this sentence.	Pembrolizumab is recognised as a tolerable therapy, and its' addition to platinum-based chemotherapy has shown to have a minimal impact on the toxicity profile. This is seen in the overall Grade 3+ AE rates between the two arms in KN590. Based on the ERG's model, the total Grade 3+ AE rates are 138% and 135.7% for the intervention and trial comparator arms. With the same disutility and AE duration assumed across modelled arms, the overall AE rates determine that the AE QALY losses for each arm. MSD recommend removing this sentence.	The ERG did not consider this to be a factual accuracy. No change made.
Section 4, page 79 of the ERG report states *"Taking these two observations together, the ERG found it strange that the method of analysing the utility data appears to have a notably larger impact on the total estimated loss in QALYs due to AEs versus the introduction of a third treatment."*	Please remove this sentence.	Following on from the above two queries, MSD recommend that this conclusion should be removed.	The ERG does not consider this to be a factual accuracy. No change made.

Issue 6 Efficacy of doublet chemotherapy versus triplet chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 5, page 100 of the ERG report states "*The majority of the confidence intervals were calcuated from their assigned distributions (see CS Table 64) and assuming the standard error is 20% of the mean. Exceptions to this were the patient characteristics"*	"*The majority of the confidence intervals were **calculated** from their assigned distributions (see CS Table 64) and assuming the standard error is **10**% of the mean. Exceptions to this were the patient characteristics"*	The reported standard error is incorrect, as well as 'calculated' being misspelt.	The ERG made these corrections. (p.100)

Issue 7 Efficacy of doublet chemotherapy versus triplet chemotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6, page 114 of the ERG report states "*The ERG explored scenarios whereby the triplet efficacy was estimated using results from the NMA reported in ter Veer et al.10 comparing 'ACF' vs 'CF' (A=anthracycline, C=cisplatin, F=5FU). The NMA reports a HR for OS and PFS; OS HR = 0.86 (95% CI: 0.71 to 1.02) and for PFS, HR = 0.85 (95% CI: 0.68 to 1.05)."*	"*The ERG explored scenarios whereby the triplet efficacy was estimated using results from the NMA reported in ter Veer et al.10 comparing 'ACF' vs 'CF' (A=anthracycline, C=cisplatin, F=5FU). The NMA reports a HR for OS and PFS; OS HR = 0.86 (95% CI: 0.71 to 1.02) and for PFS, HR = 0.85 (95% CI: 0.68 to 1.05).* ***However, the study by Veer er al concluded that,"anthracyclin-containing triplets … were not more effective than F-doublets".***	Incomplete interpretation. As the ter Veer et al paper is used to inform analyses whereby triplet therapies have greater efficacy than doublet therapies, MSD would consider it more appropriate that the conclusion of that paper is also included within the text to ensure the reader is aware of the limitations of the approach used.	The ERG agreed that relevant limitations highlighted by the original study authors should be noted and made the following changes: ***"In order to explore the sensitivity of this assumption****, the ERG looked at scenarios whereby the triplet efficacy was estimated using results from the NMA reported in ter Veer et al.[10]* ***which explored the efficacy and safety of first-line chemotherapy in advanced oesophageal cancer using an NMA.*** *The NMA compares 'ACF' vs 'CF' (A=anthracycline, C=cisplatin, F=5FU) and reports a HR for OS and PFS; OS HR = 0.86 (95% CI: 0.71 to 1.02) and for PFS, HR = 0.85 (95% CI: 0.68 to 1.05).* ***The confidence intervals cross 1 showing non- statistical differences and the authors conclude that "anthracycline-containing triplets…were not more effective than F-***

			doublets" but notes they were associated with increased toxicity compared to doublets. As such, the ERG note that these scenarios are limited based on the evidence available and technical application so ICERs should be viewed with caution, however these are deemed necessary to explore the uncertainty associated with efficacy differences between triplet and doublet regimens." (p.114)
Section 6, page 114 of the ERG report states "*In the ERG's analysis, these HRs were applied to the doublet OS and PFS curves from KEYNOTE-590 and using the blended comparator arm, the resulting OS and PFS curves were weighted based on the proportion of triplets and doublets."*	"*In the ERG's analysis, these HRs were applied to the doublet OS and PFS curves from KEYNOTE-590 and using the blended comparator arm, the resulting OS and PFS curves were weighted based on the proportion of triplets and doublets.* ***The comparison created has severe limitations and can only be considered a crude analysis with limited use in decision making. The ICERs generated from this approach should be viewed with caution****"*	For completeness limitations of the ERG approach should be included.	See above
Section 6.2.8 Page 122 Table 26 of the ERG report presents ICERs for *"Triplet efficacy vs doublet efficacy – 5-FU + oxaliplatin + leucovorin"*	Removal of scenario analysis.	The triplet combination of 5-Fu + oxaliplatin + leucovorin does not contain an anthracycline (i.e. epirubicin), with the addition of leucovorin/folinic acid in order to improve the safety profile of the 5-	The ERG removed this scenario and amended the *"Triplet efficacy vs doublet efficacy – company market share"* and *"Triplet efficacy vs doublet efficacy – UK*

		Fu component. Clinicians consulted by MSD consider this combination to be a doublet therapy, hence this scenario should be removed.	*expected market share"* scenarios. (p.122)

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Technical engagement response form

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **Thursday 10 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- 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.
- Do not use abbreviations.

- Do not include attachments such as journal articles, letters or leaflets. 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.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**MSD**
Disclosure 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

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
On the 20 May 2021 Committee for Medicinal Products for Human Use (CHMP) granted a positive opinion for pembrolizumab (Keytruda). The final licence wording is: Pembrolizumab (Keytruda), in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 (1). Focus of this response is the PD-L1 CPS≥10 population.		
Key issue 1: The clinical evidence may not be generalisable to the UK population	Yes	The KEYNOTE 590 trial is well balanced and generalisable to UK patients with advanced metastatic oesophageal cancer. The trial baseline demographic characteristics are comparable to those of UK patients with advanced metastatic oesophageal cancer. The mean age of KEYNOTE 590 participants is 62.4, most people in the UK are diagnosed with oesophageal cancer at the age of 60 (2). The proportion of male patients in KEYNOTE 590 is 83.4% and in the UK oesophageal cancer is more prevalent in males than females (3). The majority of characteristics that dive and determine prescribing decisions for this patient population in the UK and the KEYNOTE 590 trial population are similar. Asian and Rest of world participants The ERG report mentions differences in patient characteristics based on ethnicity between the trial and the relevant UK patient population. A higher proportion of Asian patients was included in the KEYNOTE 590

		trial to ensure that efficacy results from the trial were relevant to the Asian population which has higher oesophageal cancer prevalence in the world. The KEYNOTE 590 trial recruited patients from 26 countries, including 6 countries in Europe namely UK (3.1%), Germany (1.8%), Denmark (0.8%), Spain (3.7%), France (4.4%), Romania (1.3%) and 6 countries in Asia namely Japan (21.9%), China (16.6%), Korea (7.8%), Taiwan (6.5%), Thailand (3.1%) and Malaysia (1%). The proportion of patients above is referring to KEYNOTE 590 participants with PD-L1 CPS≥10 sub-population. In the ITT population of KEYNOTE 590 trial there were 52.2% participants from Asian region and 47.5% of participants from the rest of world. The PD-L1 CPS≥10 sub-population of KEYNOTE 590 trial included 54.8% participants from Asian region and 45.2% from the rest of world. In discussion with UK clinicians, one clinician suggested that Asian countries treat early stage cancers of the oesophagus more aggressively than is typical in Europe. However, China, Japan, Malaysia, Korea and Taiwan apply pan-Asian adaptation of ESMO guidelines in their clinical practice (4). According to the pan-Asian guideline, patients with advanced metastatic oesophageal cancer are treated with 5FU, cisplatin and nedaplatin which is a cisplatin analogue. This indicates that patients in the Asian region receive similar chemotherapy regimens as the European patients. Both adenocarcinoma and squamous cell carcinoma oesophageal cancer histologies follow identical treatment pathways. In a recent NICE technology appraisal 'Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer' (5) the appraisal committee concluded that the Attraction 3 trial (6), which recruited 96% of Asian patients, was generalisable to the UK population. Therefore, MSD considers that the results seen in Asian sub-population of Keynote 590 trial are generalisable to the UK clinical practice. The European Medicines Agency granted a positive CHMP opinion to pembrolizumab with platinum and fluoropyrimidine based chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD L1 with a CPS ≥ 10 in Europe based on the

		KEYNOTE 590 trial data. The indication has been narrowed to patients with PD-L1 CPS ≥10 but was not restricted based on any other factors such as ethnicity, geography, or histology. **Europe versus non-Europe results in PD-L1 CPS≥10 sub-population** MSD conducted an ad-hoc analysis comparing the overall survival hazard ratios in European versus non-European region participants with PD-L1 CPS≥10. The HR in European region was [redacted] compared to the non-European region [redacted]. The confidence intervals of the hazard ratios within the European region (n=57) are a bit wider than those for the non-European population (n=326) because of smaller sample size, however the treatment effect on OS across Europe versus non-Europe is homogeneous and consistent with the overall treatment effect. **Histology** KEYNOTE 590 results show a positive trend in the overall survival in patients with advanced metastatic oesophageal cancer regardless of the tumour histology (7). There is a variation in the histology of oesophageal cancer both globally and across Europe (8, 9). In the KEYNOTE 590 trial the PD-L1 CPS≥10 population consisted of 43.9% adenocarcinoma participants and 56.1% of patients were squamous cell carcinoma patients. The clinical experts explained that squamous cell carcinoma and adenocarcinoma of oesophagus occur in different parts of oesophagus and present in different types of patients. Squamous cell carcinoma is located in the upper part of oesophagus and is more common in patients with a history of tobacco, alcohol abuse or both. Squamous cell oesophageal cancer is more prevalent in patients from the lower socioeconomic background. Adenocarcinoma of oesophagus is located in lower part of oesophagus and GEJ. Adenocarcinoma is more prevalent in overweight patients from the middle to upper socioeconomic class. At the time the KEYNOTE 590 trial was designed, little was known about the differences between adenocarcinoma and squamous cell carcinoma patients' response to treatments. Currently there is still lack of robust evidence about the differences between the adenocarcinoma and squamous cell carcinoma oesophageal cancer patient response to different treatment options, particularly immune-oncology agents (8). The NICE clinical guideline NG83 (10) and ESMO guidelines (11) do not recommend different treatment

		regimens according to histology. The clinical experts confirmed that in the UK patients receive the same treatment regimens regardless of the histology type. The clinical experts noted that the unmet need in both histology types in the UK is equally high. Therefore, MSD concludes that patients in the UK will benefit from pembrolizumab regardless of histology.
Key issue 2: Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens	**No**	MSD noted additional literature searches and analyses conducted by the ERG. As it was outlined in our response to the clarification questions, MSD considers inappropriate to use gastric cancer studies for the purpose of the indirect treatment comparison in advanced, metastatic oesophageal cancer. Although the treatment options of oesophageal and gastric cancers are similar, the disease epidemiology, prevalence, survival are different. The clinical experts consulted by MSD confirm that it is inappropriate to use gastric data for indirect treatment comparison in oesophageal cancer. Therefore, MSD considers that all relevant clinical effectiveness evidence was provided in the company submission and the response to the clarification questions. Also, MSD noted that the ERG's changes made to the economic model make a minor difference in the overall cost effectiveness results, please see the response to issue 5 below.
Key issue 3: The estimated overall survival projections have a large impact on cost-effectiveness	**No**	In line with most oncology submissions, MSD recognise the large impact of overall survival modelling assumptions on the cost-effectiveness of pembrolizumab in combination with chemotherapy in this indication. MSD's approach to modelling OS within this appraisal is outlined below (please see Section B.3.3, pages 86-94, of the company submission for all details and note this is in respect to the all-comer population): • On reflection of the multiple Chow test statistic plot for OS in the pembrolizumab in combination with chemotherapy arm, the smoothed hazard plots denoting a peak at week 40, and the visual fit of parametric fittings at different time points, a piecewise modelling approach with a 40-week cut-off point was deemed most appropriate.

		• The AIC/BIC statistics suggested that for pembrolizumab in combination with chemotherapy the best fitting distribution is the log-logistic function. For the SOC arm the best fitting distribution is the log-normal function, with the log-logistic function being the second best with a difference of <1. • The log-logistic curve with a cut-off at 40 weeks provides the most clinically plausible prediction for a survival rate of 4.8% and 2.0% at 5-years and 10-years for the SOC arm compared with available external data (see Table 45 of the company submission). • The long-term extrapolation for the pembrolizumab in combination with chemotherapy arm (5-year OS of 11.4% see Table 46 of the company submission) was also considered as clinically plausible by clinical experts, based on the mechanism of action for immunotherapy; where a subgroup of patients are expected to receive long-term survival benefit. • Taking all of these factors into consideration; visual fit, statistical fit, clinical plausibility of long-term OS estimates, the piecewise log-logistic model with a cut-off at week 40 was used to model OS for both the intervention and comparator arms. MSD also outlined the modelling approach for the CPS≥10 population within Appendix M of the company submission: • As per the all-comer approach, on reflection of the multiple Chow test statistic plot for OS in the pembrolizumab in combination with chemotherapy arm, the smoothed hazard plot detecting a peak at ~40 weeks, and the visual fit of parametric fittings at different time points, a piecewise modelling approach with a 40-week cut-off point was deemed most appropriate. Although the Chow test for the CPS≥10 sub-population suggested a peak at around week 60, an earlier peak at week 40 was also detected. However, to retain more data for extrapolation and to be consistent with the overall population, the earlier cut-off at Week 40 was used as the preferred cut-off. • The AIC/BIC statistics suggested that for pembrolizumab in combination with chemotherapy the best fitting distribution is the log-normal function, with the log-logistic function being the second best with a difference of <1. For the SOC arm the best fitting distribution is the exponential function, with the log-normal and log-logistic functions being the second and third best with minimal difference in AIC/BIC statistics. • Clinical expert opinion suggested that PD-L1 expression was not a prognostic factor for patients treated with SOC. This was further exemplified by the minimal difference in median OS between

		the all-comer and CPS≥10 populations (CPS≥10 median OS 9.4 months [8.0,10.7] all-comer median OS 9.8 months [8.8,10.8]). The log-logistic curve produced similar estimates in both the all-comer and CPS≥10 populations for the SOC arm at both 5 and 10 years (4.8% and 2.0%, respectively)— as PD-L1 expression was not a prognostic factor for patients treated with SOC, these estimates are in line with available external data as per the all-comer population. • The log-logistic function was selected for the base case to maintain consistency with the overall population, good statistical fit based on AIC/BIC and OS estimates in line with clinical expectations. The OS estimates were more conservative than the best fitting log-normal function in the pembrolizumab in combination with chemotherapy arm. The ERG did not comment on their preferred modelling assumptions for the CPS≥10 sub-population. In the all-comer population, the ERG outlined four scenarios for consideration: 1) Company base case— piecewise modelling approach using KM data up to a 40-week cut-off with a log-logistic distribution to extrapolate. 2) ERG base case— as per the company base case, assuming a gradual treatment waning effect applied linearly between five and seven years. This is equivalent to Scenario analysis 4 from the company submission. 3) Using a fully-fitted parametric approach with a log-logistic curve to extrapolate. 4) Using a piecewise modelling approach with KM data up to a 40-week cut-off with a generalised gamma distribution to extrapolate. MSD acknowledge the importance of exploring different scenarios when investigating modelling assumptions that are associated with high levels of uncertainty and have a large impact on cost-effectiveness estimates. However, it is important to note the limitations of the ERGs scenario analyses: • ERG base case— the ERG have adopted a gradual/linear treatment waning effect, beginning at 5 years and completing at 7 years, as per company Scenario Analysis 4. MSD's preference is for no treatment waning effect to be implemented, due to a lack of any evidence suggesting treatment waning occurs, however, NICE have regularly preferred a treatment waning effect to be implemented.

		The ERG have not provided a rationale for the inclusion of a gradual treatment waning effect applied linearly from 5 to 7 years in their base case. MSD provided further justification to a sustained treatment benefit and the rationale behind the choice of 5 and 7 years within Scenario Analysis 4 in response to Clarification Question B9. As per that response, it is the company's assertion that the biological mode of action, clinical plausibility and longer-term data from other KEYNOTE trials suggest a sustained treatment benefit. It is MSD's assertion that the longer-term KEYNOTE trial data provided shows evidence of up to a 5-year treatment effect, and therefore a scenario whereby the treatment effect wanes after this point would be conservative. • The fully fitted log-logistic distribution is less appropriate — when comparing the visual fit of fully fitted parametric curves against a piecewise modelling approach with a KM cut-off at either 32 or 40 weeks, the piecewise approach has much better visual fit to the observed data. When observing different diagnostic plots, in particular the multiple Chow test statistic (see Figure 15 of the company submission), structural change is evident at ~40 weeks. Figures 13 and 14 submitted within MSD's response to clarification B5c provide further evidence that the hazards produced by the piecewise modelling approach better reflects the smoothed hazard seen within the observed data than a fully parametric approach. The limitation of a fully fitted parametric approach is that structural changes are unlikely to be appropriately captured by the fitted distributions, hence the poor visual fit. Further to the poor visual fit, comparison of the estimated overall survival versus the observed KM provides further support to the piecewise approach, please see Table 1 below. At the 1 year, 1.5 year and 2 year timepoints, the piecewise approach using either the Log-Logistic or Generalized Gamma functions produce OS estimates that are much closer to the observed trial data than that of the fully parametric approach, regardless of treatment arm. Whilst the differences appear minor, if the distribution has poor validity within the observed period, this is likely to be exacerbated when extrapolated beyond the trial data. MSD consider the fully parametric approach to be an inappropriate extrapolation of overall survival within this appraisal.

Table 1. Overall Survival estimates for both arms, comparing modelling approaches

Pembrolizumab + chemotherapy				
Timepoint	KM	Piecewise approach, 40-week cut-off, Log-logistic	Piecewise approach, 40-week cut-off, Generalized Gamma	Fully-parametric approach, Log-logistic
3 month	93.8%	93.8%	93.8%	91.9%
6 month	79.5%	79.5%	79.5%	78.0%
1 year	50.6%	50.6%	50.4%	52.8%
1.5 year	35.3%	35.2%	35.6%	36.2%
2 year	27.7%	27.3%	27.3%	26.0%
5 year		11.4%	9.7%	7.1%
10 year		5.8%	3.3%	2.3%
SOC				
Timepoint	KM	Piecewise approach, 40-week cut-off, Log-logistic	Piecewise approach, 40-week cut-off, Generalized Gamma	Fully-parametric approach, Log-logistic
3 month	90.1%	90.1%	90.1%	89.5%
6 month	73.1%	73.1%	73.1%	70.9%
1 year	39.9%	40.3%	39.9%	41.2%
1.5 year	24.0%	23.7%	23.9%	25.2%
2 year	16.3%	16.1%	16.3%	16.7%
5 year		4.8%	4.0%	3.7%
10 year		2.0%	1.0%	1.1%

		• Piecewise modelling approach with 40-week cut-off and generalised gamma distribution— MSD note the ERG's justification for using a generalised gamma function is attributed to the mid-range estimates for OS at 5-years. However, the generalised-gamma function has poor statistical fit according to the AIC/BIC criteria; being the 5th best fitting curve for pembrolizumab in combination with chemotherapy and the 4th best fitting curve for SOC. MSD consider statistical fit to be of particular importance due to the maturity of the observed OS data from KEYNOTE-590 and hence the generalised gamma is not the optimal curve for estimating overall survival. MSD maintain the base case selections outlined within the company submission and appendices for overall survival are clinically plausible and reflective of the observed KM data from KEYNOTE-590.
Key issue 4: The use of time-to-death utilities may overstate the QALYs accrued by patients	**Yes**	MSD acknowledge that the utility approach has a large impact on cost-effectiveness estimates. MSD's preference for using time-to-death utilities for modelling is outlined below (please see Section B.3.4, pages 99-104, of the company submission for further details): • Oesophageal cancer has a large impact on patients' quality of life due to the debilitating nature of the disease. Often patients have difficulty eating, and swallowing can also become difficult- leading to weight loss[12]. Furthermore, as the cancer grows it can block or partially block the oesophagus, preventing food entry through the gut and hence the absorption of nutrients and calories. If patients are not able to eat and drink, they become more susceptible to other problems such as infection. Patients can also often feel fatigued and lacking in energy, with the emotional and physical changes affecting patients' relationships. These factors exacerbate as a patient comes closer to death, alongside other physical changes such as being semi-conscious, loss of bladder and bowel control, restlessness, changes in breathing and confusion[13,14]. • A time-to-death approach more accurately captures the decrease in health-related quality of life over time (versus standard progression-based utilities) for patients with advanced oesophageal cancer. Hatswell et al[15] noted that disease progression may not fully capture all predictive factors of patient utility and time-to-death provides a good fit to patient data.

		The ERG's main concern surrounding the time-to-death utility approach relates to the average utility derived when compared to general population utility and the average utility using the progression-based approach. MSD addresses the ERGs concerns below. In addition, MSD have updated the economic model to include additional analyses whereby utility is derived using a progression-based, time-to-death interaction utility model; please see the New Evidence submission for further details of this approach. We consider this to be an appropriate methodology given that it maintains the primary intent of the company submission: to accurately describe the patients' experience and quality of life associated with such an aggressive disease whilst addressing the ERG's concern relating to an over-estimation of quality of life. The ERG report states: *"To further explore the utility values, the ERG calculated the average utility value for patients on the pembrolizumab in combination with chemotherapy combination arm using both approaches. To do this, the total undiscounted QALYs were divided by the total undiscounted LYs. This crude calculation allows for further exploration of how QALYs are accrued within the company's model.* *Using the company's corrected base case model (see Section 6.1), for the progression approach, the average utility was estimated to be [redacted]. Switching to the time-to-death approach, the average utility was estimated to be [redacted]. Using the ERG's preferred assumptions (see Section 6.3), the average utility values are [redacted] and [redacted], respectively. When setting the utility value for all health states to be 0.829 (average utility expected at baseline for the age- and sex-adjusted general population), and disabling AE-related QALY losses, the equivalent average utility for the general population was estimated to be 0.808. The ERG is concerned that the two utility analysis approaches lead to a substantially different estimation of the "average" utility experienced over the course of the model time horizon. This means that the incremental QALY gain attributable to pembrolizumab in combination with chemotherapy estimated for both utility analyses also varies markedly: The time-to-death approach (company base-case analysis post corrections) yields an incremental QALY gain of 0.652, versus 0.570 for the progression approach. The ERG considers the progression approach to yield a more realistic "average" utility for this patient*

		population, especially given that the time-to-death approach yields an "average" utility that is close to the estimate for the general population." The ERG notes this is a crude calculation, as such, MSD suggests it should be interpreted with caution. As would be expected, the time-to-death approach awards the highest utility to patients who are furthest away from death; who are living with, and managing, their disease. Pembrolizumab in combination with chemotherapy is a life-extending treatment for patients within this indication, and therefore keeps patients in a better health state for longer than SOC. The corresponding figure using the progression-based, time-to-death interaction approach (and the company base-case assumptions) is [redacted] which could alleviate the uncertainty surrounding Key Issue 3. The ERG's interpretation of the utility approach penalises a therapy that is extending patients' lives. The calculation adopted by the ERG is informative, albeit crude, however using this calculation over the entire horizon is misrepresenting the average utility observed by the majority of patients, from the start of treatment, whilst they are alive. Using the same approach, but shortening the time horizon of the model to consider only the first year, draws very different results. Note that after 1 year 59.7% of patients in the comparator arm and 49.4% of patients in the intervention arm have died. Conducting the calculation, using MSD's preferred (and corrected) assumptions, for the progression-based approach the average utility was [redacted] and [redacted] for the time-to-death approach. When using the interaction model, the corresponding figure using company preferred assumptions is [redacted], below that of the progression-based approach. Using the ERG's preferred assumptions the corresponding figures were [redacted] and [redacted] for the progression-based and time-to-death approaches, respectively. This means that looking solely at the first year within the model there is a much smaller difference between the two approaches, hence considering the average utility of patients over the course of the entire time horizon is in essence penalising a life-extending therapy. When considering a longer time horizon, the model estimates a small percentage of patients who are part of a long tail which is why the average utility using the time-to-death approach looks to be substantially higher than that of the progression-based approach.

		Having examined the ERG report, the discussion on average utility and introducing a novel approach, MSD asserts that the most appropriate utility approach is that of TTD based utility. Adopting the 'average utility calculation' for a more appropriate timeframe supports this. As an alternative the progression-based, time-to-death integration approach could be considered. MSD does not think the progression-based approach is the most appropriate as it unduly penalises a life extending therapy.
Key issue 5: The doublet used in the economic model does not reflect clinical practice in the UK	**No**	MSD agree with the ERG approach of exploring additional scenarios. MSD note the impact of type of chemotherapy in combination with pembrolizumab and changing the market shares of the blended comparator to better reflect UK clinical practice both have a negligible effect on cost-effectiveness estimates.

Additional key issue: The appraisal committee can accept analysis which explores an additional QALY weighting for life-extending treatments at the end of life, if the following criteria have been met: • the treatment is for patients with a short life expectancy, normally less than 24 months • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. The company stated that pembrolizumab with platinum-based chemotherapy meets the criteria to be a life-extending treatment at the end of life.	**No**	MSD maintain, as per Table 40 of the company submission, that end-of-life criteria are met within this indication. Median OS is lower than 24 months: • Patients with untreated, unresectable locally advanced or metastatic oesophageal cancer or HER-2 negative gastroesophageal junction adenocarcinoma, have a short life expectancy with median survival measured to be less than 10 months[10]. • Median OS in KEYNOTE-590, for patients in the CPS≥10 analysis treated with SOC, was 9.4 months. Clinical experts confirmed this is in line with UK clinical practice. Pembrolizumab in combination with chemotherapy offers an extension to life of at least 3 months compared to SOC: • The median OS difference is greater than 3 months in the CPS≥10 sub-population. The median OS for pembrolizumab in combination with chemotherapy was 13.5 months (95% CI, 11.1, 15.6) compared to 9.4 months (95% CI 8.0, 10.7) for SOC. This demonstrates an increase in OS of 4.1 months. • The estimated mean months gained in the economic model, in the CPS≥10 population, with pembrolizumab in combination with chemotherapy is 23.0 months compared to 12.4 months with SOC. This is an expected increase in mean OS of 10.6 months.

Please refer to page 131 of the ERG report for further information on this issue.		

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer (ID1249)	N/A	Yes	NICE released a Final Appraisal Document on the 17th May for the technology appraisal "Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer (ID1249)". The recommendation reads: *"Nivolumab is recommended, within its marketing authorisation, for treating unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma in adults after fluoropyrimidine and platinum-based therapy. It is recommended only if the company provides nivolumab according to the commercial arrangement"* MSD consider this change in the treatment landscape to be pertinent to this appraisal. Scenario Analysis 13 within the company submission investigated the impact of assuming all patients who received subsequent therapy within KEYNOTE-590 being costed with receiving Nivolumab. The main limitation of this approach is that not all patients who received subsequent therapy within KEYNOTE-590 received Nivolumab (or any anti-PD1/PDL1 therapy). Hence MSD have produced further analyses exploring the impact of Nivolumab's recommendation in previously treated oesophageal cancer in order to align closest with clinical practice in England and Wales. On review of the distribution of subsequent therapies within KEYNOTE-590, within the CPS≥10 sub-population, [redacted] of patients in the pembrolizumab in combination with chemotherapy arm and [redacted] of patients in the SOC arm received an anti-PD1 therapy after discontinuing from study treatment. It was assumed these patients would receive subsequent therapy for 44 weeks as per the ATTRACTION-3 study[16]. The updated company base case includes this new analysis.

Additional issue 2: Marketing authorisation restriction (please see submitted New Evidence)	N/A	**Yes**	The European label for KEYTRUDA within this indication has been restricted, with a positive CHMP opinion within the following indication statement: *"KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10"* MSD previously outlined within Appendix M of the company submission the preferred assumptions for the CPS≥10 sub-population. Please see below these assumptions: • Overall Survival extrapolation: piecewise modelling approach, using KM data up to 40-weeks, after which extrapolating with the log-logistic distribution • Progression-free Survival extrapolation: piecewise modelling approach, using KM data up to 10-weeks, after which extrapolating with the log-logistic distribution • Time on Treatment: utilising the mature KM data to accurately reflect drug acquisitions costs from KEYNOTE-590 • Utilities: using the time-to-death approach • Subsequent treatment distribution: MSD were unable to replicate the ERG's redistribution of subsequent therapies. Subsequent therapy distribution is representative of the specific sub-population. Please see the cost-effectiveness analyses submitted within the New Evidence document.

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Summary of changes to the company's cost-effectiveness estimate(s)

For company only: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report 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 ICER
Additional Key issues 1 and 2	Prior to technical engagement, MSD's base-case analysis was within the all-comer population and did not cost anti-PD1 subsequent therapies (as this was reflective of UK clinical practice at this point).	In line with the EMA granted marketing authorisation alongside with NICE's decision to recommend nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer, MSD have changed the base case analysis.	Updated Company base-case ICER: £28,651 Original Company base-case ICER (after ERG corrections): £41,688
Company's preferred base case following technical engagement	Incremental QALYs: 0.9178	Incremental costs: 26,296	Updated Company base-case ICER: £28,651

References:

1. European medicines agency positive CHMP opinion: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-3
2. Cancer Research UK. Risks and causes | Oesophageal cancer | Cancer Research UK [Internet]. [cited 2021 Feb 5]. Available from: https://www.cancerresearchuk.org/about-cancer/oesophageal-cancer/causes-risks
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4. Muro et al Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with metastatic oesophageal cancer: a JSMO–ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. Annals of Oncology 30: 34–43, 2019
5. NICE Final Appraisal Document 'Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer', published on 15 May 2021.
6. Kato et al Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019; 20: 1506–17
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9. C. Castro, C. Bosetti, M. Malvezzi, P. Bertuccio, F. Levi, E. Negri, C. La Vecchia, N. Lunet, Patterns and trends in esophageal cancer mortality and incidence in Europe (1980–2011) and predictions to 2015, Annals of Oncology, Volume 25, Issue 1, 2014, Pages 283-290
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13. Cancer Research UK. Changes to eating and drinking | Dying with cancer | Cancer Research UK [Internet]. 2019 [cited 2021 Feb 5]. Available from: https://www.cancerresearchuk.org/about-cancer/coping/dying-with-cancer/last-few-weeks-and-days/changes-to-eating-drinking
14. Cancer Research UK. What happens in the final days of life | Dying with cancer | Cancer Research UK [Internet]. 2019 [cited 2021 Feb 5]. Available from: https://www.cancerresearchuk.org/about-cancer/coping/dying-with-cancer/last-few-weeks-and-days/final-days

15. Hatswell AJ, Pennington B, Pericleous L, Rowen D, Lebmeier M, Lee D. Patient-reported utilities in advanced or metastatic melanoma, including analysis of utilities by time to death. Health Qual Life Outcomes. 2014;12(1):1–9.
16. NICE Committee Papers 'Nivolumab for previously treated unresectable advanced oesophageal cancer' Published on 04 November 2020.

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Technical engagement proposed new evidence form (company only)

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

As the company for this appraisal, you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses will be used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting. As part of your response, you may intend to provide new evidence to address some or all of the key issues identified in the executive summary of the ERG report (that is, evidence that has not already been provided during the appraisal).

We would like to understand the extent of new evidence that you propose to provide in your response to technical engagement. This will help the ERG to plan its critique of your response. You do not have to provide new evidence in response to every issue. However, in general, any new evidence provided should have the purpose of addressing a key issue identified in the executive summary of the ERG report. Decisions about whether NICE will accept new evidence will be made on a case by case basis. Please note that NICE may need to extend timelines and reschedule the appraisal committee meeting to allow new evidence to be considered. Therefore, it is important that you notify NICE about new evidence in advance by completing this form as comprehensively as possible. Please be aware that NICE will not routinely accept new evidence provided after the deadline for technical engagement responses.

Deadline for returning this form: **Thursday 10 June 2021**

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses.
- Please ensure your response clearly identifies which key issue from the executive summary of the ERG report your proposed new evidence is intended to address. Please use the same issue numbers that have been used in the executive summary of the ERG report.
- If you intend to provide new evidence to address issues in the ERG report that have not been identified as key issues, please make this clear.
- 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.

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Summary of proposed new evidence

Please use the table below to provide details of any proposed new evidence that you intend to submit in response to technical engagement.

Please be as comprehensive as possible.

Key issue(s) that the new evidence will address	Summary of the proposed new evidence (short title)	How will the new evidence address the key issue(s)?	Is the new evidence expected to alter the company's base-case ICER?	Additional details about the proposed new evidence (if available)
Key Issue 1	**Efficacy analyses in participants with PD-L1 CPS ≥ 10**	**Efficacy analyses in participants with PD-L1 CPS ≥ 10 in European versus non-European region will provide additional data which could reduce the uncertainty associated with trial result generalisability to UK patients with advanced metastatic oesophageal cancer.**	**NO**	**Please see the main response document for further details.**
Key Issue 4	**Time-to-death, progression-based interaction utility approach**	**The new approach combines both the time-to-death and progression-based utility approaches within an interaction model. This approach helps to alleviate the ERG's concerns that the pure time-to-death utility method may overstate the QALYs accrued by patients.**	**NO**	**A progression-based, time-to-death interaction model is presented within the new evidence. Please see the main response document and additional details about the approach, below.**
Additional Issue 1 (not highlighted	**Subsequent therapy distribution for the**	**The new evidence is necessary for the ERG to critique MSD's approach of costing subsequent anti-PD1 therapy observed within KEYNOTE-590**	**YES**	**N/A**

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within ERG report)	**CPS≥10 sub-population**	**in line with the recent NICE determination of nivolumab in previously treated oesophageal cancer. MSD consider this analysis to best reflect UK clinical practice.**		
Additional Issue 2 (not highlighted within ERG report)	**Full cost-effectiveness analyses of updated base-case within CPS≥10 sub-population.**	**With confirmation of the EMA's final indication wording:** **"*Keytruda, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10*"** **MSD have provided the full cost-effectiveness analyses for the CPS≥10 sub-population, incorporating the ERG corrections to the company model.**	**YES**	**Please see the main response document for further details.**

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Key Issue 4: The use of time-to-death utilities may overstate the QALYs accrued by patients

The economic model has been updated with the progression-based, time-to-death interaction utility approach. The approach calculates progression-based and time-to-death life year categories (for example progression free and >=360) by splitting the existing life years based on the percentage of progression-free vs progressed-disease in each model cycle. The utility values in Table 1 below are used within the economic model. Table 2 presents the results of the interaction regression analysis.

Table 1. EQ-5D health utility scores by time-to-death, progression-based interaction approach

	Progression Free	Progressed Diseased
	Estimate	Estimate
≥360 days	[redacted]	[redacted]
180 to 360 days	[redacted]	[redacted]
90 to 180 days	[redacted]	[redacted]
30 to 90 days	[redacted]	[redacted]
0 to 30 days	[redacted]	[redacted]

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Table 2. Time-to-death, progression-based interaction approach regression model results

	Estimate	Std. Error	df	t value	Pr(>|t|)
(Intercept)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[180, 360)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[30, 90)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[90, 180)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT<30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT>=360	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFINVFLNo_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFINVFLW_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[180, 360):PFINVFLNo_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[30, 90):PFINVFLNo_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[90, 180):PFINVFLNo_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT<30:PFINVFLNo_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT>=360:PFINVFLNo_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[180, 360):PFINVFLW_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[30, 90):PFINVFLW_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT[90, 180):PFINVFLW_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT<30:PFINVFLW_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
T2DTHCAT>=360:PFINVFLW_PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Additional Issue 1

Table 3. Duration and distribution of New Oncologic Therapies in Days Across All Subsequent Lines after Discontinuing from Study Treatment (CPS≥10 sub-population)

Treatment duration Across All Lines[a] (days)	Pembrolizumab + SOC (N=185)			SOC (N=193)			Pooled (N=378)		
	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)
With one or more new Oncologic Therapies	[redacted]								
afatinib									
anlotinib									
anlotinib hydrochloride									
anti-LAG-3 monoclonal antibody (unspecified)									
anti-PD1 monoclonal antibody (unspecified)									
apatinib mesylate									
avelumab									
bavituximab									
bleomycin									
capecitabine									
carboplatin									
cell division cycle 7-related protein kinase inhibitor (unspecified)									
cisplatin									
diphenhydramine									
docetaxel									
eribulin mesylate									
etoposide									
fluorouracil									
folic acid									
folinic acid									

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Treatment duration Across All Lines[a] (days)	Pembrolizumab + SOC (N=185)			SOC (N=193)			Pooled (N=378)		
	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)
gemcitabine	[redacted]								
gemcitabine hydrochloride	[redacted]								
gimeracil	[redacted]								
gimeracil (+) oteracil potassium (+) tegafur	[redacted]								
ifosfamide	[redacted]								
ipilimumab	[redacted]								
irinotecan hydrochloride	[redacted]								
lenvatinib mesylate	[redacted]								
leucovorin calcium	[redacted]								
levoleucovorin calcium	[redacted]								
methotrexate	[redacted]								
methotrexate sodium	[redacted]								
nedaplatin	[redacted]								
nimotuzumab	[redacted]								
nivolumab	[redacted]								
oteracil	[redacted]								
oteracil potassium	[redacted]								
oxaliplatin	[redacted]								
paclitaxel	[redacted]								
paclitaxel albumin	[redacted]								
pembrolizumab	[redacted]								

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Treatment duration Across All Lines[a] (days)	Pembrolizumab + SOC (N=185)			SOC (N=193)			Pooled (N=378)		
	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)	n (%)[b]	m[c]	Mean (SD)
ramucirumab	[redacted]								
recombinant human endostatin	[redacted]								
recombinant human interleukin-2 (125Ala)	[redacted]								
regorafenib	[redacted]								
rituximab	[redacted]								
sintilimab	[redacted]								
tegafur	[redacted]								
tipiracil hydrochloride (+) trifluridine	[redacted]								
vinorelbine tartrate	[redacted]								

a: Subsequent therapy duration is defined as the days from start date of the treatment until the stop date of treatment, or until censoring date of overall survival if the stop date is not available, or until the database cutoff date for the treatment initiated after the censoring data of overall survival

b: Every subject is counted a single time for each applicable row and column

c: Each medication is counted a single time for each applicable row and column

NA: Not applicable

Database Cutoff Date: 02JUL2020

Please note the proportion of patients treated with anti-PDL1 therapy (considered anti-PD1 monoclonal antibody (unspecified), avelumab, nivolumab, pembrolizumab and sintilimab) for the intervention arm is [redacted], and for the comparator arm is [redacted]

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Additional Issue 2: CPS≥10 sub-population

The results of the cost-effectiveness analysis of the CPS≥10 population are presented below, in line with the final licence wording. MSD consider this population to meet end-of-life criteria, according to both current life expectancy and expected overall survival gain. When assessed against a willingness to pay threshold of £50,000 per QALY gained, pembrolizumab in combination with chemotherapy is a cost-effective use of NHS resources. When using MSD preferred assumptions, the probabilistic sensitivity analyses results showed a 92.7% probability that pembrolizumab in combination with chemotherapy is the most cost-effective therapy. Figure 1 also shows the PSA indicates a stable model. Deterministic sensitivity analyses and scenario analyses show that the ICER is consistently below the threshold when considering variations in parameters and alternative, plausible, scenarios.

In the base-case analysis vs SOC, the estimated mean overall survival was [redacted] years with pembrolizumab in combination with chemotherapy, and [redacted] years with SOC. Patients treated with pembrolizumab in combination with chemotherapy accrued [redacted] QALYs compared to [redacted] among patients in the SOC cohort. This gives an incremental life year gain of 1.16 years and an incremental QALY gain of 0.92 QALYs. MSD considers this to be a substantial and clinically meaningful improvement in both LYs gained, and QALYs gained, considering the vast unmet need within this patient population.

Please note the ICERs presented below include the list-price of Nivolumab monotherapy, which is now available in the subsequent line for squamous cell carcinoma patients, after platinum-based therapy.

Table 4. Deterministic base-case analysis versus trial comparator SOC in CPS≥10 sub-population (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	2.52	[redacted]	-	-	-
SOC	[redacted]	1.36	[redacted]	26,296	0.9178	28,651

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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Table 5. Deterministic analysis versus blended chemotherapy in CPS≥10 sub-population (using ERG market shares assuming equivalent efficacy) (discounted price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Pembrolizumab + chemotherapy	[redacted]	2.52	[redacted]	-	-	-
UK blended comparator	[redacted]	1.36	[redacted]	26,393	0.9178	28,757

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 6. Incremental cost-effectiveness results based on probabilistic sensitivity analysis versus trial comparator SOC in CPS≥10 sub-population (discounted price)

Intervention	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
SOC	[redacted]	[redacted]	26,213	0.92	28,564

ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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Figure 1. Scatterplot of PSA results (1,000 simulations) versus trial comparator SOC in CPS≥10 sub-population (discounted price)

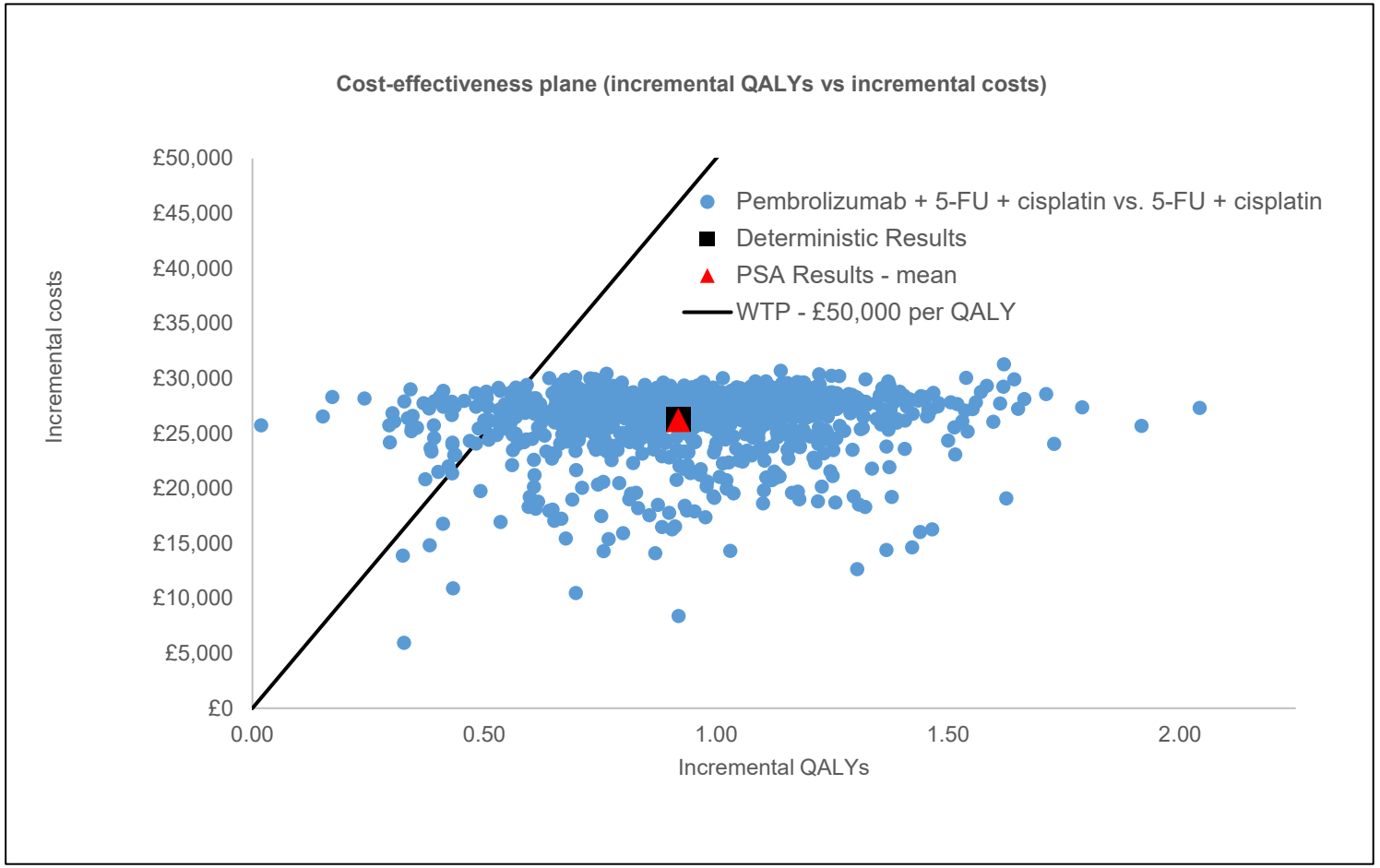

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Figure 2. Cost-effectiveness acceptability curve versus trial comparator SOC in CPS≥10 sub-population (discounted price)

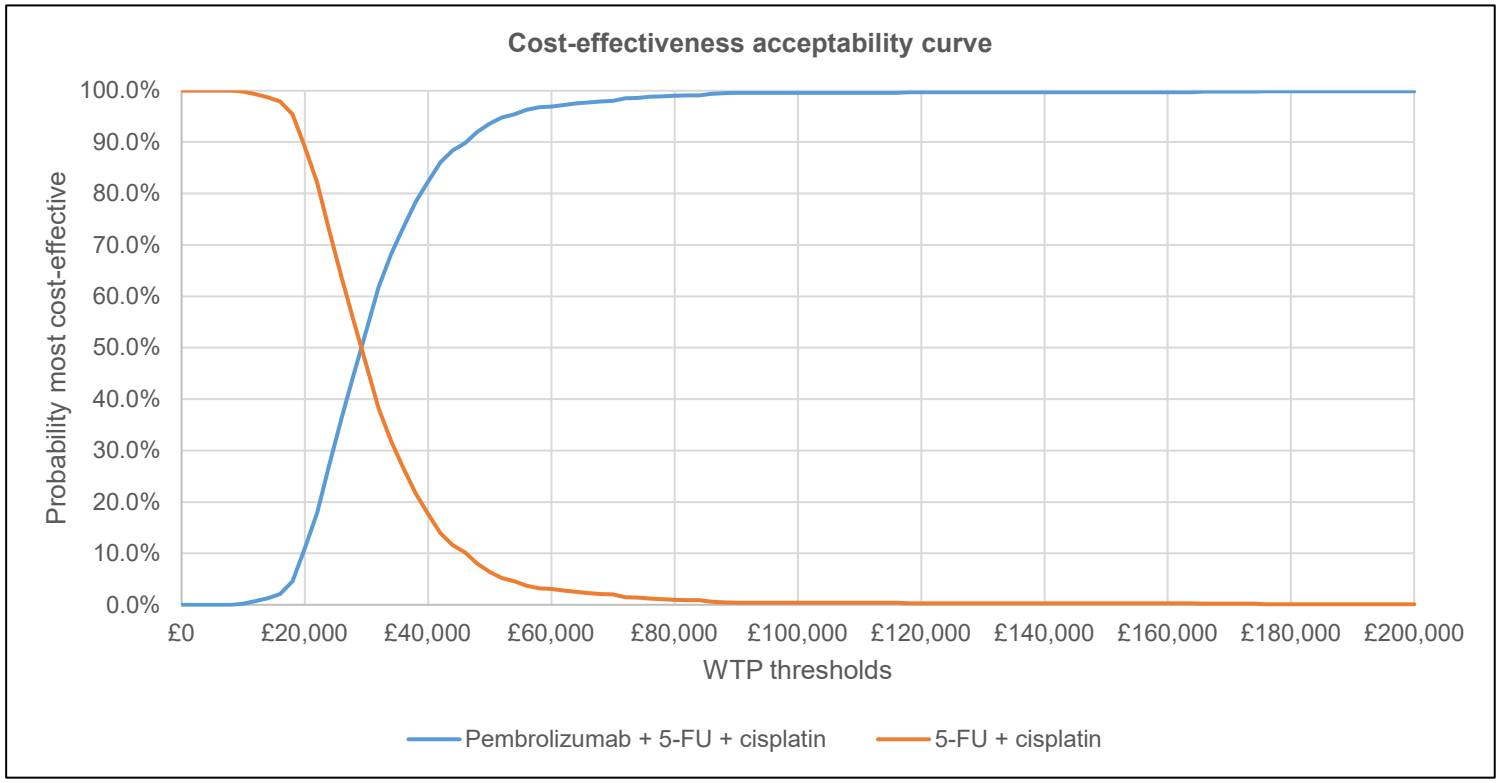

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Figure 3. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensitive variables versus trial comparator SOC in CPS≥10 sub-population (discounted price)

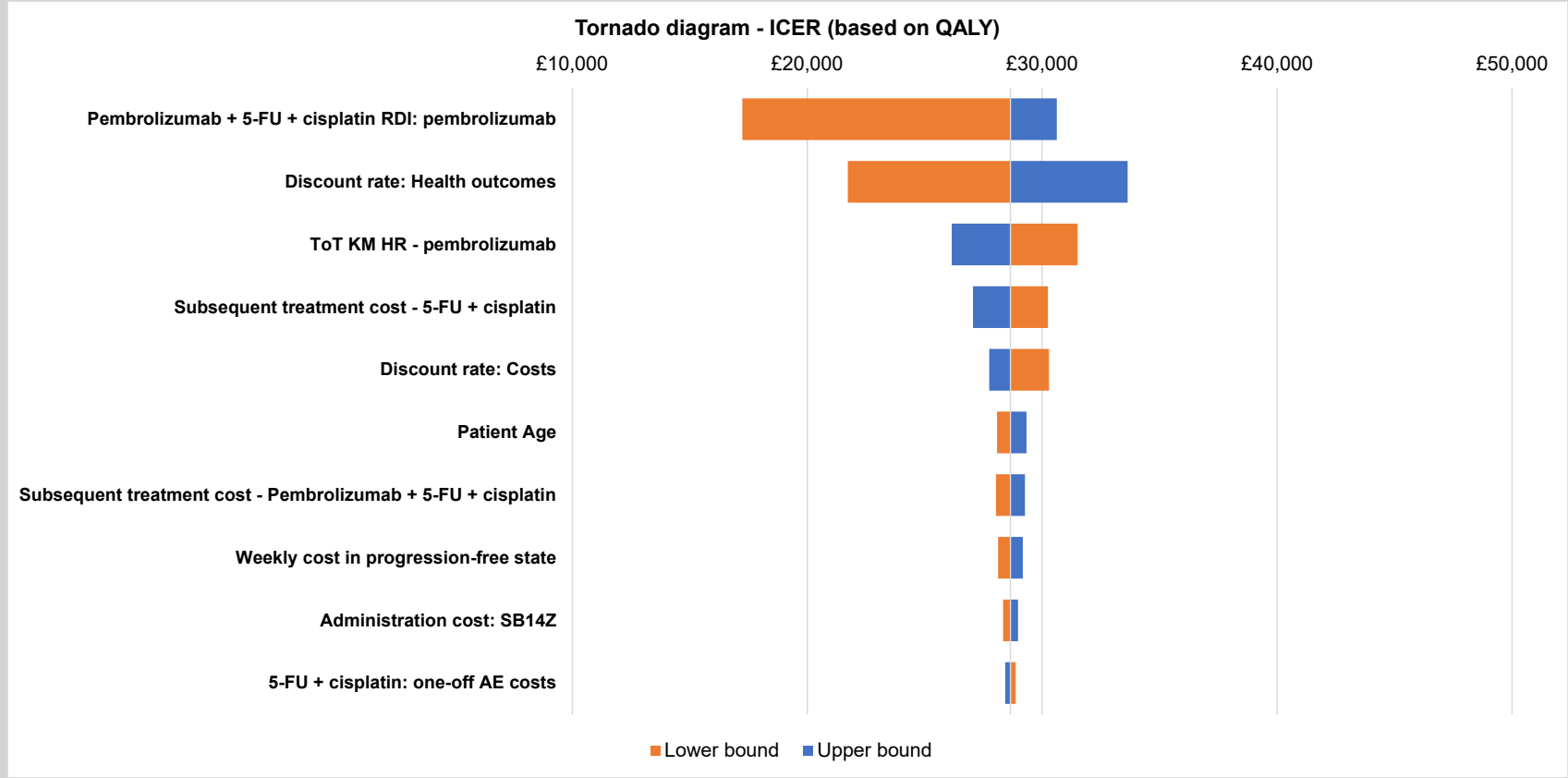

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Table 7. Results from the scenario analyses versus trial comparator SoC in CPS≥10 sub-population (discounted price)

Scenario No.	Description	Pembrolizumab + chemotherapy			SOC			Pembrolizumab + chemotherapy vs SoC		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	[redacted]	2.52	[redacted]	[redacted]	1.36	[redacted]	26,296	0.92	28,651
Error! Reference source not found.	OS piecewise 40-week cut-off, log-normal distribution	[redacted]	2.61	[redacted]	[redacted]	1.33	[redacted]	26,368	1.02	25,865
Error! Reference source not found.	OS piecewise 40-week cut-off, generalised gamma distribution	[redacted]	2.52	[redacted]	[redacted]	1.17	[redacted]	26,404	1.07	24,767
Error! Reference source not found.	OS treatment waning initiated at 5-years, completed at 7-years	[redacted]	2.40	[redacted]	[redacted]	1.36	[redacted]	26,234	0.82	31,839
Error! Reference source not found.	PFS piecewise 37-week cut-off, log-logistic distribution	[redacted]	2.52	[redacted]	[redacted]	1.36	[redacted]	26,744	0.92	29,140
Error! Reference source not found.	Time-to-death, progression based interaction approach for utilities	[redacted]	2.52	[redacted]	[redacted]	1.36	[redacted]	26,296	0.89	29,539
Error! Reference source not found.	Progression-based approach	[redacted]	2.52	[redacted]	[redacted]	1.36	[redacted]	26,296	0.82	31,963
Error! Reference source not found.	Turning off stopping rules for treatments	[redacted]	2.52	[redacted]	[redacted]	1.36	[redacted]	26,732	0.92	29,127

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Scenario 8	Administration costs using a day case setting	[redacted]	2.52	[redacted]	[redacted]	1.36	[redacted]	26,431	0.92	28,798

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Technical engagement response form

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **Friday 11 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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.

About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Dr Elizabeth Smyth on behalf of the Royal College of Physicians**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No funding from the tobacco industry**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: The clinical evidence may not be generalisable to the UK population	No	The ERG notes **“** The pivotal trial, KEYNOTE-590, included a substantial number of patients from East Asian countries, where treatment guidelines for oesophageal cancer are considerably different from those applicable to the UK” I disagree with this statement – treatment paradigms for advanced squamous and oesophageal adenocarcinoma are similar in Europe, the US and Asia. The standard treatment is a platinum and fluoropyrimidine chemotherapy. This is highlighted by the fact that there are combined international ESMO-JSMO guidelines (2019) of which I am a co-author. These guidelines were developed with European Society of Medical Oncology representatives and delegates from many Asian countries (Japan, Korea, China, Malaysia and Singapore) using a Delphi consensus approach. Furthermore, one cannot argue that oesophageal cancer has a different biology in Asia vs non-Asia. As squamous cancers are usually caused by smoking and alcohol this is independent of country of origin. The composition of the population vis a vis SCC/adeno breakdown is not relevant to the efficacy of the drug if the population is biomarker selected using PD-L1 CPS 10. This overrides the underlying histology as a predictor of benefit. To clarify further, the benefit for the combination is only for PD-L1 CPS 10 or greater patients, as supported by the recent EMA CHMP opinion. The oncology

		community believes that this is the optimal population to treat and that patients with lower PD-L1 scores do not benefit.
Key issue 2: Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens	**No**	The ERG raises concerns as why triplet regimens are not considered compared to chemotherapy plus pembrolizumab. Triplet regimens are not recommended by international guidelines. The NICE guidelines in this case are outdated and hospitals in the UK should not be using triplet therapy. If they are, this would be historical based on anthracycline use in UK trials. This year at ASCO, definitive evidence of the lack of efficacy of adding a third anthracycline drug to platinum and 5FU was demonstrated (**https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.4014**) Doublet is the standard of care and is the correct comparator. Either cisplatin or oxaliplatin could be used, and there could be widespread clinical variation in practice, eg FOLFOX, XELOX (14 day or 21 day), CF or CX would all be reasonable choices.
Key issue 3: The estimated overall survival projections have a large impact on cost-effectiveness	NO	We believe that chemotherapy + pembrolizumab patients are likely to have a long term benefit. This is the "tail of the curve" effect of immunotherapy. As such, if a patient is alive at 2 years, then it may be that their disease is in remission and may not progress in future. I draw the ERGs attention to the long term follow up of the ATTRACTION-2 study which was anti-PD-1 monotherapy in chemorefractory gastric cancer https://link.springer.com/article/10.1007/s10120-019-01034-7 In responding patients median overall survival was almost two years. These benefits are likely to be more pronounced when chemotherapy is used in conjunction with PD-1 inhibition.
Key issue 4: The use of time-to-death utilities may overstate the QALYs accrued by patients	*No*	Agree with the ERG that time to progression utility values are more likely to capture QoL as progression will lead to increased symptom burden. However, a counter argument could be that if response is deeper on pembrolizumab plus chemotherapy than on chemotherapy alone, that symptom burden might always be

		always be reduced compared to what it would have been otherwise. I defer to the expertise of the ERG on what is standard in this area.
Key issue 5: The doublet used in the economic model does not reflect clinical practice in the UK	No	As per the answer above, although oxaliplatin is slowly replacing cisplatin as standard of care, both regimens are still used and may be appropriate for different patients. Regarding the fluoropyrimidine, ome patients can swallow and are suitable for capecitabine, some require infused 5FU. There is significant variability in practice and models to consider this might be appropriate. The efficacy outcomes for all regimens are similar.
Additional key issue: The appraisal committee can accept analysis which explores an additional QALY weighting for life-extending treatments at the end of life, if the following criteria have been met: • the treatment is for patients with a short life expectancy, normally less than 24 months • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.	*No*	The population has a survival of < 1 year in general. In the trial, if only the PD-L1 CPS 10 or greater population is considered, the addition of pembrolizumab surpasses what is required (i.e. more than three months benefit). As this is the population for which there is a clear benefit, I would not advocate for treatment of a non-biomarker selected population with a lesser benefit.

The company stated that pembrolizumab with platinum-based chemotherapy meets the criteria to be a life-extending treatment at the end of life. Please refer to page 131 of the ERG report for further information on this issue.		

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

For company only: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report 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 ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

Thank you for agreeing to comment on the ERG report for this appraisal, 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 ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal 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 you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having 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.

NICE National Institute for Health and Care Excellence

Please return this form by **5pm** on **Friday 11 June 2021**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- 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 want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- 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.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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PART 1 – Treating a patient with previously untreated advanced oesophageal cancer and current treatment options	
About you	
1. Your name	**Wasat Mansoor**
2. Name of organisation	**Christie Hospital NHS FT**
3. Job title or position	**Professor / Medical oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ a specialist in the treatment of people with oesophageal cancer? **x**☐ a specialist in the clinical evidence base for oesophageal cancer 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)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't 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**
The aim of treatment for previously untreated advanced oesophageal cancer	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve survival. Within this condition improvement in survival is the main unmet need. This is especially true for the squamous histology cancer where median survival if often less than 10 months and treatments options are even more limited than for adenocarcinoma histology.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	An improvement in median overall survival of 3 or more months with improvement or no deterioration in QOL compared to the control arm.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in treating previously untreated advanced oesophageal cancer?	Yes, as stated previously, there is an unmet need for both adenocarcinoma (AC) and squamous cancer (SCC). The standard of care first line treatment for both types of cancer is Platinum and Fluroprymidine. Most commonly in the UK, this tends to be oxaliplatin and capecitabine (based on the REAL-2 trial). The response rate for squamous cancer is less than that for adenocarcinoma. The improvement in median overall survival is modest for both cancers with survival, with or without therapy, currently being less than 12 months (terminal). Improvement in survival is worse for squamous cancer.
What is the expected place of the technology in current practice?	
11. How is the condition currently treated in the NHS?	As above, the standard of care first line treatment for both types of cancer is Platinum and Fluroprymidine. Most commonly in the UK, this tends to be oxaliplatin and capecitabine - based on the REAL-2 trial. Although the REAL-2 Trial advocated triplet therapy with the addition of epirubicin, the use of epirubicin has been phased out in the UK due to finding in meta-analysis and prospective studies such as GO-2 tria l(Seymour et al, JAMA 2021). Doublet chemotherapy is widely felt to be standard of care. Beyond 1st line therapy, there is only one further line of therapy for AC and SCC in the UK. However, globally, there are further lines of therapy available for AC BUT NOT for SCC (even in SE Asia). This is relevant information when looking at the primary endpoint (median OS) for KN 590 trial which included 76% of patients with SCC and 26% of patients with AC. The median OS for this study is representative of the UK population as it is representative mainly of the SCC majority which are treated similarly globally.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, ESMO and NICE
• Is the pathway of care well defined? Does it vary or are	The pathway of care is well defined, however, as explained previously – most centres have modified their approach to first line therapy in the palliative setting to only offering doublet chemotherapy (oxaliplatin/ capecitbine). Some

there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	centres (minority) may still be offering triplet chemotherapy with the addition of epirubicin. Otherwise, there is very little variation in practice for stage IV or non resectable cancer.
• What impact would the technology have on the current pathway of care?	Depending on the type of approval, diagnostics maybe altered by the requirement of PD-L1/ CPS testing. Realistically, this would have to be reflex testing The management pathway will alter: for patients with CPS >10: cis/ 5FU + pembro at 1st line, and then chemo at 2nd line For patients with CPS<10: chemo at 1st line and then nivolumab at 2nd line. At 3rd line, challenged with taxane
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, as an out patient service. No alteration in the timing of CT scans. More scans will be required for the extra cycles given to the patients doing well.
• How does healthcare resource use differ between the technology and current care?	As above
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training/ staffing of pathology labs to do the CPS testing.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the KN590 trial demonstrated clear and meaning median survival data which was most pronounced in the SSC cohort with CPS>10, followed by all patients with CPS>10. This demonstrates the importance of the CPS which drives the meaningful responses regardless of histology. So regardless of the fact that the SCC: AC ratio in the trial did not match the UK ratio, it is CPS that drives the meaningful results.
• Do you expect the technology to increase length of life more than current care?	Yes, as per the Keynote 590 results
• Do you expect the technology to increase health-related quality of life more than current care?	As per Keynote 590 results, the HR QoL should not deteriorate
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As stated previously, this technology is especially beneficial to those patients with a SPS score>10. Although all patients benefited with a clinically meaningful improvement in mOS, the best results are obtained in those patients with a high CPS regardless of histology.
The use of the technology	

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.)	There will be little difference in ease of use of the new regimen compared to current therapies. Apart from the need for initial testing for CPS (assuming CPS selection), there will be little other clinical requirements. The toxicity profile for immune therapies is different from standard chemotherapy. Whereas these toxicities do not require any special investigations prior to starting pembrolizumab, diagnostics tests maybe required during treatment if toxicities ensue.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	As per trial, pembrolizumab and 5FU were given up to week 35 and then stopped. CT scans demonstrating progression of disease, intolerable toxicity or patients withdrawing consent.
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	As previously discussed in section 11, the treatment pathway will alter with respect to how long patients remain on 1st line therapy due to the efficacy of pembrolizumab. Patients will, therefore, maintain their HR QOL levels for longer than with current treatments.

the quality-adjusted life year (QALY) calculation?	
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?	Yes – we have not observed this magnitude of improvement in survival for oesophageal cancer previously!
• Does the use of the technology address any particular unmet need of the patient population?	Yes, it significantly improves survival
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?	As per the KN 590 trial, there were no safety concerns for chemotherapy + pembrolizumab compared to chemotherapy alone. No new safety signals were identified in the trial or are expected in real world practice.

Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	Although the trial included 73% of the patients with SCC and 27% with adenocarcinoma and this is not representative of the presenting patients in UK where patients with AC is more common, the driver for response was the high CPS score mainly rather than histology. Based on this observation and to the best of my knowledge, the incidence of high CPS scores does not vary depending on geography. Therefore, the important driver for efficacy in this clinical trial is representative of the UK population. Regarding the backbone chemotherapy used, the SOC platinum/ fluoropyrimidine combination used in the UK is oxaliplatin and capecitabine (and most people use doublet rather than triplet chemotherapy) and NOT cisplatin/5FU as per trial. It would be easier to give the pemborlizumab in combination with oxaliplatin/ capecitabine as this regimen is easier to administer, does not require central venous catheterisation and is already in use in the UK. Learning from the past: when trastuzumab was introduced into the UK in 2012, the trial had tested cisplatin/ 5FU +trastuzumab. Clinicians continued to use this regimen rather than trastuzumab with oxaliplatin and capecitabine – even though oxaliplatin/ capecitabine was the SOC in 2012. Unless NICE guidance states that oxaliplatin / capecitabine can be used with pemborlizumab – we must assume people will continue to use the trial regimen.
• If not, how could the results be extrapolated to the UK setting?	See above
• What, in your view, are the most important outcomes, and were they measured in the trials?	Median OS for the **All** patients with CPS>=10. This was measured in this trial

• 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?	No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	As evidenced by audits done of our practice where we have used trial data as a comparator, the data is very comparable
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	NA

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the issues below, but you do not have to respond to every issue. If you think an issue that is important to clinicians or patients has been missed in the ERG report, 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 appraisal committee meeting. For information: the professional organisation that nominated you has 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 ERG report, these will also be considered by the committee.	
Key issue 1: The clinical evidence may not be generalisable to the UK population	50% of the population in the trial was SE Asian: 1. For oesophageal cancer, there is no biological difference based on ethnicity. The Aetiology of these cancers are based on alcohol, smoking and obesity (GOJ tumours) 2. The Asian practice uses the same number of lines of treatment for oesophageal cancer as the Western population, so, survival data is comparable 3. Although the trial included 73% of the patients with SCC and 27% with adenocarcinoma and this is not representative of the presenting patients in UK where patients with AC is more common, the driver for response was the high CPS score mainly rather than histology. Based on this observation and to the best of my knowledge, the incidence of high CPS scores does not vary depending on geography. Therefore, the important driver for efficacy in this clinical trial is representative of the UK population. 4. A different backbone chemotherapy (cisplat/ 5FU) was used rather than the SOC treatment in the UK (oxaliplatin/capecitabine): the two regimens are equivalent in efficacy as observed in REAL-2

Key issue 2: Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens	• The current treatment for stage IV oesophageal cancer is similar to stomach cancer in first line treatment. • Clinical equivalence of doublet vs triplet regimens is a reasonable assumption to make • From my own observations taken from the 2nd opinions I get and talking to other clinicians around the country, most people are now using doublet therapy (this is supported by trials such as the GO-2 study)
Key issue 3: The estimated overall survival projections have a large impact on cost-effectiveness	•
Key issue 4: The use of time-to-death utilities may overstate the QALYs accrued by patients	• **For patients living with stage 4 cancer who have not progressed**, these patients can be of 2 types: 1. Not on treatment: their QOL tends to be very good and better than those on treatment and those who have progressed. 2. On treatment: QOL can be affected by treatment but is generally better than those patients who have progressed. • **For patients who have progressed**: in general their QOL deteriorates over a period of 2-5 months and it is worse than those patients who have not progressed

Key issue 5: The doublet used in the economic model does not reflect clinical practice in the UK	As stated previously, when trastuzumab was introduced for the treatment of gastric cancer, it had been trialled alongside cisplatin and 5FU. When NICE approved trastuzumab/ cisplatin/5 FU, clinicians continued to use this regimen and did not switch the chemotherapy to oxaliplatin/capecitabine – even though oxaliplatin and capecitabine was the SOC regimen in 2012. Clinicians may well adhere to whatever NICE state in their approval. That said, oxaliplatinc/ capecitabine is a safer and more user friendly regimen
Additional key issue: The appraisal committee can accept analysis which explores an additional QALY weighting for life-extending treatments at the end of life, if the following criteria have been met: • the treatment is for patients with a short life expectancy, normally less than 24 months • there is sufficient evidence to indicate that the treatment has the	The criteria described for a life-extending treatment at the end of life are met for this technology Patients with this condition are regarded as terminal (less than 12 months survival) with or without current treatments. The data demonstrates significant improvements in life especially for those patients with CPS>=10

prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. The company stated that pembrolizumab with platinum-based chemotherapy meets the criteria to be a life-extending treatment at the end of life. Please refer to page 131 of the ERG report for further information on this issue. In your view, are the criteria described above for a life-extending treatment at the end	

of life met? Please explain if this differs for particular subgroups (for example CPS ≥10 population).	
Are there any important issues that have been missed in ERG report?	No

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- the trial demonstrates meaningful improvements in survival; especially for those patients with CPS>=10
- HR QOL does not deteriorate with the addition of pembrolizumab
- The trial is representative of the UK population because efficacy is driven mainly by CPS and not histology or ethinicty
- Most clinicians are now using doublet first line therapy rather than triplet. This has been supported by organisations such as AUGIS
- CPS scoring / PDL-1 testing is an important part of the appraisal to factor into an approval

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments: **Friday 11 June 2021**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report 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 appraisal, 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.
- 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.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. 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.

- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- 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 replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NCRI-ACP-RCP-RCR**
Disclosure 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

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses?**	Response
Key issue 1: The clinical evidence may not be generalisable to the UK population	No	The ERG notes **'**The pivotal trial, KEYNOTE-590, included a substantial number of patients from East Asian countries, where treatment guidelines for oesophageal cancer are considerably different from those applicable to the UK' Our experts disagreed with this statement – treatment paradigms for advanced squamous and oesophageal adenocarcinoma are similar in Europe, the US and Asia. The standard treatment is a platinum and fluoropyrimidine chemotherapy. This is highlighted by the fact that there are combined international ESMO-JSMO guidelines (2019) which one of our experts is a co-author. These guidelines were developed with European Society of Medical Oncology representatives and delegates from many Asian countries (Japan, Korea, China, Malaysia and Singapore) using a Delphi consensus approach. Furthermore, one cannot argue that oesophageal cancer has a different biology in Asia vs non-Asia. As squamous cancers are usually caused by smoking and alcohol this is independent of country of origin. The composition of the population vis a vis SCC/adeno breakdown is not relevant to the efficacy of the drug if the population is biomarker selected using PD-L1 CPS 10. This overrides the underlying histology as a predictor of benefit. To clarify further, the benefit for the combination is only for PD-L1 CPS 10 or greater patients, as supported by the recent EMA CHMP opinion. The oncology

		community believes that this is the optimal population to treat and that patients with lower PD-L1 scores do not benefit.
Key issue 2: Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens	No	The ERG raises concerns as why triplet regimens are not considered compared to chemotherapy plus pembrolizumab. Triplet regimens are not recommended by international guidelines. The NICE guidelines in this case are outdated and hospitals in the UK should not be using triplet therapy. If they are, this would be historical based on anthracycline use in UK trials. This year at ASCO, definitive evidence of the lack of efficacy of adding a third anthracycline drug to platinum and 5FU was demonstrated (**https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.4014**) Doublet is the standard of care and is the correct comparator. Either cisplatin or oxaliplatin could be used, and there could be widespread clinical variation in practice, eg FOLFOX, XELOX (14 day or 21 day), CF or CX would all be reasonable choices.
Key issue 3: The estimated overall survival projections have a large impact on cost-effectiveness	No	We believe that chemotherapy + pembrolizumab patients are likely to have a long-term benefit. This is the 'tail of the curve' effect of immunotherapy. As such, if a patient is alive at 2 years, then it may be that their disease is in remission and may not progress in future. Our experts note the long term follow up of the ATTRACTION-2 study which was anti-PD-1 monotherapy in chemorefractory gastric cancer https://link.springer.com/article/10.1007/s10120-019-01034-7 In responding patients' median overall survival was almost two years. These benefits are likely to be more pronounced when chemotherapy is used in conjunction with PD-1 inhibition.
Key issue 4: The use of time-to-death utilities may overstate the QALYs accrued by patients	No	Agree with the ERG that time to progression utility values are more likely to capture QoL as progression will lead to increased symptom burden. However, a counter argument could be that if response is deeper on pembrolizumab plus chemotherapy than on chemotherapy alone, that symptom burden might always be

		always be reduced compared to what it would have been otherwise. Our experts defer to the expertise of the ERG on what is standard in this area.
Key issue 5: The doublet used in the economic model does not reflect clinical practice in the UK	No	As per the answer above, although oxaliplatin is slowly replacing cisplatin as standard of care, both regimens are still used and may be appropriate for different patients. Regarding the fluoropyrimidine, ome patients can swallow and are suitable for capecitabine, some require infused 5FU. There is significant variability in practice and models to consider this might be appropriate. The efficacy outcomes for all regimens are similar.
Additional key issue: The appraisal committee can accept analysis which explores an additional QALY weighting for life-extending treatments at the end of life, if the following criteria have been met: • the treatment is for patients with a short life expectancy, normally less than 24 months • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.	No	The population has a survival of < 1 year in general. In the trial, if only the PD-L1 CPS 10 or greater population is considered, the addition of pembrolizumab surpasses what is required (i.e. more than three months benefit). As this is the population for which there is a clear benefit, our experts would not advocate for treatment of a non-biomarker selected population with a lesser benefit.

The company stated that pembrolizumab with platinum-based chemotherapy meets the criteria to be a life-extending treatment at the end of life. Please refer to page 131 of the ERG report for further information on this issue.		

Additional issues

Please use the table below to respond to additional issues in the ERG report 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 appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

For company only: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report 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 ICER
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]

A Single Technology Appraisal

ERG Review of Company's Response to Technical Engagement Response

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Produced by

Peninsula Technology Assessment Group (PenTAG)
University of Exeter Medical School
South Cloisters
St Luke's Campus
Heavitree Road
Exeter
EX1 2LU

Authors

Dr Maxwell S. Barnish, Research Fellow[1]
Ms Rachael Slater, Associate[1] and Analyst[2]
Mr Justin Matthews, Research Fellow[1]
Dr Linda Long, Research Fellow[1]
Mr Ash Bullement, Associate[1] and Analyst[2]
Ms Naomi Shaw, Information Specialist[1]
Dr Nicole Dorey, Consultant Clinical Oncologist[3]
Dr Stephen Falk, Consultant Clinical Oncologist[4]
Ms Louise Crathorne, Senior Research Fellow[1]
Prof G.J. Melendez-Torres, Professor[1]

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter Medical School, Exeter
[2] Delta Hat Limited, Nottingham
[3] Royal Devon and Exeter NHS Foundation Trust, Exeter
[4] Bristol Haematology and Oncology Centre, Bristol

Correspondence to Dr Maxwell Barnish
3.09 South Cloisters, St Luke's Campus, Heavitree Road, Exeter, EX1 2LU; m.s.barnish@exeter.ac.uk

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This TE response is linked to ERG report Barnish MS, Slater R, Matthews J, Long L, Bullement A, Shaw N, Dorey N, Falk S, Crathorne L, Melendez-Torres GJ. Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]. Peninsula Technology Assessment Group (PenTAG), 2021.

1. INTRODUCTION

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of Pembrolizumab with platinum-based chemotherapy for untreated advanced oesophageal cancer [ID3741]. Due to a change in the indication, the ERG consider the company's new base case in Section 2. (Updated versions of the ERG's analyses reflecting the change in indication are presented in the Appendix.) Each of the issues outlined in the technical report is discussed in further detail in Section 3.

The company have also provided changes to the economic model. The ERG critique of additional evidence is presented in Section 4.

2. UPDATED COMPANY ALTERNATIVE ERG BASE CASE ANALYSES

In response to the technical engagement report, the company presented updated base case analyses using the CPS ≥10 subpopulation. This is in accordance with the European label for pembrolizumab within this indication which has been restricted:

"KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10"

Model inputs are included based on this subpopulation from the KEYNOTE-590 trial. The base case for this population was presented in the original company submission Appendix M. All model settings remain consistent with the overall population base case including the choice of base case curves and piece-wise time points.

In addition to the base case patient population changing, the company have also made changes to their subsequent treatments to include nivolumab. Nivolumab was recommended for routine commissioning in May 2021 by NICE for previously treated unresectable advanced or recurrent oesophageal cancer and therefore now part of the patient treatment pathway.

For the comparison to the blended comparator of relevant doublet and triplet regimens, the company have used the ERG's suggested UK based market share. Aside from the above changes, the company have not taken any of the ERG's preferred assumptions forward in their new base case. Table 1 presents the company's revised base case.

Table 1: Company revised base case results - CPS ≥10

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company revised deterministic base case versus 5-FU + cisplatin					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£26,296	0.92	£28,651
Company revised deterministic base case versus the blended comparator					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Blended chemotherapy	[redacted]	[redacted]	£26,393	0.92	£28,757

Key: CPS, combined positive score; QALYs, quality adjusted life years

Source(s): Company response to technical engagement new evidence form, Table 4 and Table 5

3. ERG REVIEW OF KEY ISSUES

Issue 1: The clinical evidence may not be generalisable to the UK population

The Evidence Review Group (ERG) considered it to be a key issue in its report that the clinical evidence may not be generalizable to the UK population. This related to the high proportion of patients from Asian countries, where treatment guidelines are considerably different from those applicable in the UK. Moreover, the trial population did not reflect the expected population composition of oesophageal squamous cell carcinoma and adenocarcinoma. This limits the ability to generalise findings from the trial to the UK context. Accordingly, the ERG suggested that the committee may wish to rely on analyses drawing on the 'rest of the world' subgroup for decision making. In response to technical engagement, the company have submitted additional clinical effectiveness evidence relating to European vs non-European participants with PD-L1 CPS ≥ 10. However, the company indicated that this new information is not expected to alter the company's base case ICER. The company seeks to provide a justification that the overall trial population irrespective of geographical location is generalizable to a UK clinical practice setting. The ERG remain concerned about this claim of generalizability. Two important issues highlighted in clinical advice to the ERG underscored that i) the trial population contained around two thirds squamous patients while in a UK clinical setting squamous patients would be expected to be around one third of the total; and that ii) there may be aetiological reasons and reasons related to differences in treatment pathways why evidence from Asian patient populations does not generalize well to UK settings. Therefore, the ERG consider that this remains a key issue.

Issue 2: Clinical effectiveness evidence excluded probative estimates of effectiveness between standard of care regimens

The ERG considered it to be a key issue in its report that company's search was carried out without the term 'gastric', and studies were excluded when subgroup results for oesophageal or oesophagogastric junction Siewert type I cancer patients could not be identified. As a consequence, certain evidence was not included such as doublet vs triplet effect estimates from network meta-analyses (NMAs) and the influential REAL-2 study. This led to the company's conclusion that no evidence could be meaningfully assembled to compare doublet and triplet regimens. There was thus no comparison between the pembrolizumab triplet and other triplet regimens. Clinical advice received is that systemic treatment is similar for oesophageal and

gastric cancers. Including this wider evidence provides estimates of doublet vs triplet efficacy in existing UK practice, from existing NMAs or meta-analyses.

The ERG note but are not persuaded by the company's response that it would be inappropriate to consider evidence from a wider gastric cancer population to inform an NMA, and that therefore all relevant clinical effectiveness evidence was included. The company state that:

> *"Although the treatment options of oesophageal and gastric cancers are similar, the disease epidemiology, prevalence, survival are different"*

but do not supply any supporting evidence. Furthermore, the ERG note that no arguments were given by the company to counter the preparedness of a number of research teams to group gastric with oesophagogastric junction and oesophageal cancers. These include Cunningham et al (REAL2 trial), ter Veer et al. 2016 (network meta analysis), and NG83.

The company agreed with the additional scenarios provided by the ERG but noted the "negligible effect on cost-effectiveness results" (see company response to technical engagement Issue 5, and also to Issue 2). The ERG would like to highlight that the scenario analysis exploring the efficacy of triplet regimens versus doublet regimens can have a large impact depending which treatment is considered. Using the UK based market share increases the ICER by £2,796 and using individual triplet regimens as the comparator increases the ICER by up to £10,889. However, the ERG would also like to note that the ICER remains below £40,000 for all these scenarios (see Table 8).

Issue 3: The estimated overall survival projections have a large impact on cost-effectiveness

The ERG agree with the company's statement that as with most oncology submissions, overall survival (OS) modelling assumptions have a large impact on estimated cost-effectiveness results. Within the response to the TE report, the company re-iterate their approach to determine the most suitable OS models to inform its base-case analysis, and clarify the approach taken specifically to inform the base-case analysis of the CPS≥10 population (which was not the focus of the original CS, or the ERG report).

The ERG first address the commentary raised by the company concerning the ERG's approach taken to inform its base-case analysis. For context:

- The company's base-case analysis includes the specification of a piecewise log-logistic model, wherein the Kaplan-Meier curve is used to inform OS up until 40 weeks, after which a log-logistic model was fitted to the re-based survival data to inform the remainder of the modelled time horizon (with separate models used for each arm)

- The ERG's base-case analysis makes use of the same base survival models, with an additional component to reflect a 'treatment waning effect', wherein at 5 years the estimated hazard of death for the pembrolizumab in combination with chemotherapy arm gradually becomes that of the chemotherapy arm over the course of the next 2 years, such that by 7 years the hazard of death used to inform the remainder of the model time horizon is identical between treatment arms

The ERG previously explained that while their preferred extrapolation for OS is to use the company's approach with the treatment waning adjustment, the other OS extrapolation scenarios considered within exploratory and sensitivity analyses were also potentially plausible (please refer to Sections 6.2 and Section 6.3 of the ERG report for further details).

In its response to the TE report, the company state: *"The ERG have not provided a rationale for the inclusion of a gradual treatment waning effect applied linearly from 5 to 7 years in their base case."* (Company response to Key Issue 3, p.8). The company later acknowledges its response to clarification question B9, wherein evidence from previous KEYNOTE-001 and KEYNOTE-006 studies was provided to justify the expectation of a minimum treatment effect duration of 5 years, though no commentary was provided by the company with respect to the choice of an upper limit of 7 years.

The ERG highlight that the treatment waning effect was explored as part of a range of different estimates which were considered potentially plausible. The plausibility of these models was determined on the basis of clinical advice to the ERG which was that each of these four scenarios considered in the ERG's exploratory and sensitivity analyses may be considered as broadly clinically plausible; however, these scenarios are not possible to robustly validate (given that no long-term data are currently available for the use of pembrolizumab in combination with chemotherapy in this patient population).

The ERG did not provide specific justification for its choice to use the treatment waning effect to inform its base-case analysis within its report. However, the choice to apply the treatment waning effect was made based on the effect providing mid-range estimates when considering

the four scenarios presented by the ERG, all of which were considered potentially clinically plausible. For example, of the four scenarios considered by the ERG (including the company's base-case analysis), the range of estimates for 10-year survival (for the full ITT population, per the ERG report) was [redacted] with the ERG's base-case estimate being [redacted] (and the company's base-case estimate the upper bound of this range).

In addition to the face validity of the estimates as noted above, the choice of 5 and 7 years was made for two reasons. First, this specific scenario was provided within the CS. Secondly, the ERG acknowledged that treatment effect could plausibly be maintained until 5 years (though this is uncertain); however, the ERG expect that the duration of treatment effect is unlikely to be indefinite. An upper bound of 7 years allows for the estimated hazard of death for the pembrolizumab in combination with chemotherapy arm to gradually approach that of the SOC arm over the course of 2 years, starting at 5 years. On balance, the ERG considered this to be a more realistic estimation of survival, and thus applied this approach to inform its base-case analysis. Again, however, the ERG highlight that other modelling approaches also yield potentially plausible estimates and should not be discounted entirely.

The company are correct to note a lack of evidence in support of a particular treatment waning effect application, though the same argument also holds for a lack of evidence to reject inclusion of a treatment waning effect in the longer term. The ERG consider that, in light of the available evidence, applying a treatment waning effect earlier than 2.5 years would seem inappropriate, as the Kaplan-Meier estimates of OS extend to this time. However, applying a treatment waning effect beyond this time may be plausible. On balance, an application between 5 and 7 years was considered a plausible scenario, but the ERG agree that the overall estimation of OS to inform the model is uncertain.

Referring further to the four scenarios considered, the ERG have regard to the company's comment that a fully-parametric modelling approach is an *"inappropriate extrapolation of overall survival within this appraisal"* (Company response to Key Issue 3, p.9). The ERG acknowledge that the fully-parametric models do not appear to provide as good a fit as the piecewise models, but disagree with the assertion that a fully-parametric modelling approach is wholly inappropriate for this appraisal. When considering the choice between a fully-parametric or piecewise modelling approach, a number of trade-offs need to be contemplated, including visual fit, long-term plausibility, potential over-fitting to limited data towards the end of follow-up, and the plausibility of the underlying hazard function associated with each choice of parametric

model. Therefore, while the ERG continue to prefer a piecewise modeling approach to inform its base-case analysis, the ERG also acknowledge that other approaches (including a fully-parametric approach) may be helpful for decision making.

Next, the ERG consider the company's base-case analysis for the CPS≥10 population. The approach taken to inform the model is provided within the company's TE response, which in summary is the same overall choice of model fits per the original CS for the ITT population – that is, a piecewise log-logistic model with a cut point at 40 weeks. The estimated outcomes for the chemotherapy arm are nearly identical to those produced for the full ITT population, and so the ERG has limited its commentary below to the extrapolations produced for the pembrolizumab in combination with chemotherapy arm.

For the base case, the company use a piece-wise approach using a 40-week cut-off and log-logistic distribution. Justification for the 40-week cut-off appeared to be based on the choice of cut-off used for the ITT population. The Chow test output presented in Figure 1 (and CS Appendix M, page 251) shows peaks at approximately 60 weeks and 75 weeks and lower peaks at around 45 weeks and 85 weeks. The company acknowledge this but choose a 40-week cut-off as this *"retains more data for extrapolation and to be consistent with the overall population"* (Company response to Key Issue 3, p.7). Previously, the ERG stated that it did not consider Chow tests to be statistically sound to choose a cut point (ERG report, page 60). The company have opted to disregard the Chow test outputs and instead choose a 40-week cut point, which further vindicates the ERG's aversion to using these tests to inform the selection of a cut point in a piecewise modelling exercise. However, the ERG also consider that choice of cut point should not be based solely on findings from a different population (even if there is substantial overlap between these groups). Therefore, it is the ERG's view that the choice of the 40-week cut point does not seem to be appropriately justified in the company's new population base case.

Figure 1: Chow test statistics for OS in KEYNOTE-590: pembrolizumab plus chemotherapy CPS ≥10.

Looking at the extrapolations from the 40-week cut point, the ERG observe that the log-logistic, generalised gamma, and log-normal models provide very similar projections of OS, with the log-normal providing slightly more optimistic estimates compared to the log-logistic model (see Figure 2). Gompertz, exponential and Weibull models provide different estimates, however the Gompertz model provides implausible extrapolations suggesting a plateau in survival from around 50 months. In addition, it is implausible to consider that the exponential and Weibull models would be appropriate to estimate the hazard profile of the pembrolizumab plus chemotherapy trajectory. As such, these curves leave relatively few options to explore within sensitivity analysis. The ERG reiterate that the curves produced from the fully-parametric models are deemed suitable to be considered in sensitivity analysis.

Figure 2: OS KM curve with fitted piecewise model, 40-week cut-off, for pembrolizumab plus chemotherapy based on KEYNOTE-590 (CPS≥10)

The ERG encourage a focus on the most plausible long-term survival estimates, for both treatment arms, and have prepared Table 2 to demonstrate the assumptions made in both the company's and ERG's base-case analysis, both for the ITT and CPS≥10 populations. For the chemotherapy group in the CPS population, while partially an artefact of censoring, the Kaplan-Meier estimate of OS for the comparator arm hits 0% at approximately 2.5 years. Therefore, the ERG considers an important question to be: What proportion of patients are expected to survive until 10 or 20 years, if treated with pembrolizumab in combination with chemotherapy? In the company's base-case analysis, [redacted] of patients are expected to still be alive at 10 years, of whom over [redacted] are expected to survive an additional 10 years.

Table 2: Overall survival proportions based on modelling approach taken (pembrolizumab in combination with chemotherapy arm)

Population	ITT		CPS≥10	
Apply waning effect?	No	Yes	No	Yes
5 years	[redacted]	[redacted]	[redacted]	[redacted]

Population	ITT		CPS≥10	
10 years	[redacted]	[redacted]	[redacted]	[redacted]
20 years	[redacted]	[redacted]	[redacted]	[redacted]
30 years	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CPS, combined positive score; ITT, intention to treat.

Issue 4: The use of time-to-death utilities may overstate the QALYs accrued by patients

The company state that "*The ERG's main concern surrounding the time-to-death utility approach relates to the average utility derived when compared to general population utility and the average utility using the progression-based approach."* (Company response to Key Issue 4, p.11). However, the ERG would like to clarify its concern was regarding the face validity of the estimates. This face validity arises from three issues.

1. The time to death estimates from KEYNOTE-590 predicted that patients with more than 1 year to death had a higher utility than that of the age- and sex-adjusted general population. The company rectify this issue by capping the utilities to equal the general population if they are greater. The ERG acknowledged the amendment but the capping still assumes that patients with advanced oesophageal cancer over a year away from death have the same quality of life as the general population, most of whom would be expected to have a life expectancy greater than 1 year.
2. The results of the time to death and progression-based analyses yielded substantially different estimates of overall 'average' utility. By considering the health state occupancy of patients over time, and ultaimtely calculating the 'mean' utility (taken as a ratio of the total, undiscoutned QALYs and LYs), a notably higher utility was estimated for the time to death analysis versus the progression analysis (see ERG report, Section 4.2.7.4).
3. The results of the utility analysis are misaligned with the expectation of relatively low utility for patients with metastatic cancer undergoing intensive chemotherapy with a relatively poor prognosis (versus 'healthy' individuals in the general population). Hence, the ERG has concerns with the generalisability of the utility values produced based on analysis of KEYNOTE-590 data (regardless of which approach is used), as the outputted values imply that patients have a similar, or potentially better utility than the age- and sex-adjusted UK general population. Given the lack of alternative values from identified from the literature, the ERG chose the least optimistic utility estimates within its preferred base case.

The company state that the ERG's crude calculations averaging the utility over the lifetime of the patients is *"misrepresenting the average utility observed by the majority of patients from the start of treatment, whilst they are alive"* (Company response to Key Issue 4, p.11) and proceed to produce average utilities using 1 year time horizon due to the fact that 59.7% and 49.4% have died in the comparator and intervention arm, respectively by this time point. The ERG raise several issues with the company's arguments. Firstly, the average utilities provided by the company are based on the ITT population which is no longer within scope of the appraisal. Re-calculating the average utilities using the CPS ≥10 population gives [redacted], [redacted], and [redacted] using the company's base case for time-to-death, progression based, and interaction model, respectively. For the ERG's base case, the average utilities are [redacted], and [redacted] for time-to-death, progression based, and interaction model, respectively. The company's point was that using just a 1-year time horizon shows a smaller difference in average utilities between the different approaches, however the ERG notes that both time-to-death approaches still show greater utility averages than the progression-based approach.

Secondly, using the 1-year timepoint fails to provide all the information for a useful comparison of the true 'average' utilities over the modelled time horizon. Table 3 presents the proportion of patients at the start of each year in each health state for the pembrolizumab in combination with chemotherapy arm (aligned to company's base-case analysis). As shown, there are more people predicted to live for at least an additional year than there are progression-free (PF) patients from year 2 to year 10 of the model. For example, OS at 2 years is [redacted] at 4 years is [redacted] and PFS at 2 years is [redacted] This means that over the next model cycle (i.e., from 2 to 3 years), if we take a time-to-death approach, at least [redacted] of patients will be assigned a utility equivalent to the state furthest from death, which exceeds both the PF and progressed disease (PD) utilities. However, if we take a progression-based approach, [redacted] of patients are assigned a PF utility, with the remainder assigned a PD utility. It is therefore clear why the *"average"* utility over the model time horizon seems higher for the time-to-death versus the progression-based utility approach, because there are a substantial number of people who have progressed disease but have a life expectancy greater than 1 year.

Table 3: Proportion of patients in each health state over time for pembrolizumab plus chemotherapy

Time (years)	A OS	B PFS	C = A-B PD	D = A[i] – A[i+2] TTD>1 year	E Is B > D?
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: OS, overall survival; PD, progressed disease; PFS, progression-free survival

In its response to the TE report, the company provided a third analysis of utility data – combining both progression status and time-to-death categories such that both impact the estimation of utility within the model. The company explain that this approach *"maintains the primary intent of the company submission: to accurately describe the patients' experience and quality of life associated with such an aggressive disease whilst addressing the ERG's concern relating to an over-estimation of quality of life"* (Company response to Key Issue 4, p.12). However, later in its response, the company states that *"the most appropriate utility approach is that of TTD based utility"* (Company response to Key Issue 4, p.13), which the ERG has interpreted to be a continued preference for the time-to-death based utility estimates (excluding progression status), aligned with the company's revised base-case analysis provided alongside its response.

The ERG accept the company's attempt to resolve this issue by providing a hybrid approach as an alternative option to its previous base-case analysis. However, the ERG cannot appropriately critique the combined analysis owing to the limited information available to assess its suitability to inform the model. The ERG would ideally want to consider the following key aspects of any utility analysis:

- How many observations were available to inform each combination of progression status and time-to-death category?

- What was the relative goodness-of-fit between the models?
- Was the utility analysis considered based on the full ITT population, or was this restricted to the CPS≥10 population?

In addition, this interaction model analysis still suffers from the same issue previously identified with the company's original time-to-death analysis – that the utility for the state furthest from death exceeds general population utility estimates:

- Time-to-death analysis: >= 360 days: [redacted] (ERG report, Table 12)
- Interactive time-to-death/progression analysis: >= 360 days (PF): [redacted] (New evidence form, Table 1)
- General population estimate: 0.829 (ERG report, Section 4.2.7.4)

The ERG strongly disagree with the company's assertion that the ERG's interpretation of the utility approach *"penalises a therapy that is extending patients' lives"* (Company response to Key Issue 4, p.13). Regardless of approach taken, the model assigns utility values to patients that survive in the longer term, though depending on the approach taken the utility value applied can vary substantially, hence the ERG's exploratory, albeit crude, analysis to estimate the 'average' utility over the model time horizon to determine the most appropriate option for decision making. Based on the above, the ERG's preferred analysis remains as the progression approach to inform the model's utilities.

Issue 5: The doublet used in the economic model does not reflect clinical practice in the UK

The ERG acknowledge the points raised by the company within its response but have no further comments at this time.

4. ERG CRITIQUE OF ADDITIONAL EVIDENCE

Additional Issue 1: Nivolumab for previously treated unresectable advanced or recurrent oesophageal cancer (ID1249)

Nivolumab is now recommended for patients with previously treated unresectable advanced or recurrent oesophageal cancer and is therefore part of the patient's treatment pathway. In order to incorporate nivolumab within the economic analysis, the company have costed for nivolumab as a subsequent treatment as per the KEYNOTE-590 trial. Within KEYNOTE-590 CPS ≥10 population, [redacted] and [redacted] of patients received an anti-PD1/PDL1 after pembrolizumab in combination with chemotherapy and chemotherapy, respectively (Table 4). In the model, these are costed as nivolumab assuming 44 weeks duration and included within the subsequent treatment costs.

Table 4: Anti-PD1/PDL1 subsequent treatments in KEYNOTE-590

Subsequent anti-PD1/PDL1	Pembrolizumab plus chemotherapy (n=185)	Chemotherapy (n=193)
Nivolumab	[redacted]	[redacted]
Unspecified anti-PD1	[redacted]	[redacted]
Sintilimab	[redacted]	[redacted]
Avelumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Total	[redacted]	[redacted]

The ERG agree that the company's approach is the most sensible method to include nivolumab within the treatment pathway without needing to make any assumptions on the efficacy implications, given that the costs are still consistent with the efficacy based on KEYNOTE-590. However, the trial data shows that some patients are re-treated with an anti-PD1/PDL1 after pembrolizumab plus chemotherapy which is not generalisable to UK clinical practice. In addition, with the availability of nivolumab as a second-line treatment, there may be an expectation that a higher proportion of patients receive nivolumab after chemotherapy than those in the trial.

In the original company submission, the company attempted to include nivolumab as a subsequent treatment by assuming all patients who had a subsequent treatment after

chemotherapy received nivolumab. This was a limited scenario as only the costs were amended without considering the impact nivolumab would have on the control arm's OS estimates.

Based on the above, the ERG have provided a sensitivity analysis, attempting to incorporate nivolumab within the patient pathway as would be used in clinical practice whilst also adjusting the efficacy. In KEYNOTE-590 CPS≥10 population, [redacted] of patients had at least one subsequent therapy after chemotherapy with [redacted] subsequent therapies in total including patients receiving multiple lines of subsequent therapy. In the ERG's sensitivity analysis, it is assumed that all [redacted] patients received nivolumab. The remaining [redacted] subsequent treatments are then proportionally distributed across the other therapies as per the distributions observed in KEYNOTE-590. For the pembrolizumab plus chemotherapy arm, it is assumed that no patient receives subsequent anti-PD1/PDL1, and these incidences are proportionally re-distributed to the other treatments observed in KEYNOTE-590 (see Table 5). As per the ERG preferred base case, the 'other' subsequent treatments are proportionally distributed to the costed treatments (see ERG report, Section 6.2.7.4 for details).

Table 5: ERG scenario including nivolumab in the treatment pathway

Subsequent treatment	KEYNOTE-590		ERG scenario	
	Pembrolizumab plus chemotherapy (N=185)	Chemotherapy (n=197)	Pembrolizumab plus chemotherapy (N=185)	Chemotherapy (n=197)
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
5-FU	[redacted]	[redacted]	[redacted]	[redacted]
Irinotecan hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]
Oxaliplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1/PDL1 (costed as nivolumab)	[redacted]	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

In order to account for the efficacy impact including nivolumab would have, the ERG have used the same concept as 'treatment waning' but reversed the effect to adjust the comparator arm instead of the intervention arm. At a specified time-point, it is assumed that the proportion of patients who have nivolumab after chemotherapy ([redacted] follow the same hazard of death as per the patients in the pembrolizumab plus chemotherapy arm representing the immunotherapy effect these patients may incur. The proportion of patients who do not have subsequent nivolumab follow the same hazard of death projected by the chemotherapy OS curve. In the ERG's exploratory analysis, the time point this hazard adjustment occurs has been assumed equal to the mean PFS of the chemotherapy arm (6.3 months) to represent the average time patients would be receiving subsequent treatment. Figure 3 presents the chemotherapy OS used in the base case versus the ERG's scenario after adjustment.

Figure 3: Chemotherapy OS with and without the hazard adjustment

The results show a marginal improvement on chemotherapies overall survival and a large increase in subsequent treatment costs in comparison to pembrolizumab resulting in a largely decreased ICER of £7,528 (see Table 8).

The ERG would like to clarify that this exploratory analysis has many limitations and should be interpreted with caution. Firstly, the scenario analysis tries to demonstrate the impact of including nivolumab as subsequent therapy for both costs and efficacy however the ERG are limited by the partitioned survival model framework. Thus, the adjustments made to the survival curves are unconventional and are incompatible with the ERG's base case assuming a treatment waning effect on the pembrolizumab plus chemotherapy arm. Moreover, this analysis assumes a lifetime 'immuno-oncology' effect for both the pembrolizumab plus chemotherapy arm and those patients who received nivolumab as subsequent therapy, which as stated previously there is no evidence to support. Secondly, the time point where the hazards are adjusted can be considered arbitrary given that patients progress and receive subsequent treatments at various times over the model time horizon therefore applying one time point is not reflective of clinical practice. Thirdly, the actual impact nivolumab would have on overall survival is uncertain with this patient group and therefore, this analysis only provides some method of being able to adjust the chemotherapy survival. Finally, the proportion of patients who would receive nivolumab following chemotherapy is unknown at this stage, therefore the estimates were restricted to the observed subsequent treatment rates from KEYNOTE-590.

The ERG would also like to clarify that this analysis differs from the original scenario that was presented by the company (see CS, page 117). The company's scenario assumed all subsequent treatments following chemotherapy was nivolumab. As the company's base case only included subsequent treatments which met the arbitrary 5% threshold and left the remaining subsequent treatments out of the economic model, this meant that 80% of patients were assumed to have nivolumab. This is greater than the number of patients who actually had at least one subsequent therapy therefore assuming that patients would receive multiple lines of nivolumab. In addition, the company did not attempt to adjust the survival to supplement the cost increase.

Additional Issue 2: Market authorisation restriction

The company noted that the approved European label for pembrolizumab within the indication relevant to this appraisal has been restricted compared to the company's proposal. The approved indication states:

"KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic

carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD L1 with a CPS ≥ 10".

Clinical analyses for patients with a CPS ≥ 10 were included as a sub-group analysis in the initial company submission, with the company's preferred analytical assumptions for this sub-group outlined in Appendix M.

The company reports in its TE response having conducted additional clinical effectiveness analyses comparing European and non-European patients with a CPS≥ 10. It reports that the hazard ratio for OS was slightly lower in the European sub-population than in the non-European sub-population ([redacted]However, absolute values for e.g. mean and median overall survival, as opposed to relative effect estimates in the form of hazard ratios, for the two geographical subgroups were not provided. Moreover, this comparison was not presented for other outcomes. This presents challenges in terms of using this information to inform discussions regarding generalizability.

5. REFERENCES

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6. APPENDIX: ERG BASE CASE AND SCENARIOS

6.1. ERG's preferred assumptions

The ERG's preferred base case analyses for the CPS≥10 population are consistent with those used for the overall population. The cumulative impact of these changes are presented in Table 6 with the final base case presented in

Table 7.

Table 6: ERG's preferred model assumptions – CPS ≥ 10

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company revised base-case post TE	NA	£28,651
Remove half cycle correction	6.2.6	£28,624
Administration costs using a day case setting	6.2.7.2	£28,769
Turning off stopping rules for treatments (i.e., just using the ToT KM estimates from KEYNOTE-590)	6.2.7.1	£29,255
Re-distributing subsequent treatments	6.2.7.4	£28,116
Progression-based utilities	6.2.3	£31,360
PFS piecewise using 37-week cut-off and log-logistic extrapolation	6.2.2	£31,285
Include treatment waning between 5-7 years	6.2.1	£34,330

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Table 7: Comparison of company's and ERG's preferred base case – CPS ≥ 10

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company base case (deterministic)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
5-FU + cisplatin	[redacted]	[redacted]	£26,296	0.92	£28,651
ERG base case (deterministic)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-
Chemotherapy	[redacted]	[redacted]	£26,192	0.76	£34,330
ERG base case (probabilistic)					
Pembrolizumab + chemotherapy	[redacted]	[redacted]	-	-	-

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Chemotherapy	[redacted]	[redacted]	£26,271	0.76	£34,607

Key: QALYs, quality adjusted life years

6.2. ERG scenarios

Results of the ERG's exploratory analyses for the CPS ≥10 population are provided in Table 8. These are consistent with the scenarios done for the all comers population (see ERG report) with the addition of the subsequent nivolumab scenario (explained in Additional Issue 1).

Table 8: ERG's exploratory analysis – CPS ≥10

Preferred assumption	Pembrolizumab in combination with chemotherapy		Chemotherapy		Incremental		ICER £/QALY	+/- company base case
	Total costs	Total QALYs	Total costs	Total QALYs	Costs	QALYs		
ERG corrected company base-case	[redacted]	[redacted]	[redacted]	[redacted]	26,296	0.92	28,651	-
OS: Assume treatment waning effect applies between 5 and 7 years	[redacted]	[redacted]	[redacted]	[redacted]	26,234	0.82	31,839	+3,187
OS: Single log-logistic parametric model	[redacted]	[redacted]	[redacted]	[redacted]	26,001	0.50	52,238	+23,587
OS: Change to generalised gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	26,404	1.07	24,767	-3,884
PFS: Change cut-point to 37 weeks	[redacted]	[redacted]	[redacted]	[redacted]	26,744	0.92	29,140	+488
PFS: Change to generalised gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	25,885	0.92	28,203	-448
PFS: Change cut-point to 37 weeks and to generalised gamma tail	[redacted]	[redacted]	[redacted]	[redacted]	25,696	0.92	27,997	-654
Utilities: KEYNOTE-590 progression-based utility values	[redacted]	[redacted]	[redacted]	[redacted]	26,296	0.82	31,963	+3,312
Utilities: KEYNOTE-590 time-to-death/ progression-based utility values	[redacted]	[redacted]	[redacted]	[redacted]	26,296	0.89	29,539	+888
Utilities: Reduce magnitude of all health state utility values by 10%	[redacted]	[redacted]	[redacted]	[redacted]	26,296	0.85	30,978	+2,327
Utilities: Apply published utility values (by progression status)	[redacted]	[redacted]	[redacted]	[redacted]	26,296	0.74	35,772	+7,121

Preferred assumption	Pembrolizumab in combination with chemotherapy		Chemotherapy		Incremental		ICER £/QALY	+/- company base case
	Total costs	Total QALYs	Total costs	Total QALYs	Costs	QALYs		
Triplet efficacy vs doublet efficacy – UK expected market share	[redacted]	[redacted]	[redacted]	[redacted]	26,243	0.83	31,447	+2,796
Triplet efficacy vs doublet efficacy – 5-FU + cisplatin + epirubicin	[redacted]	[redacted]	[redacted]	[redacted]	25,712	0.65	39,478	+10,827
Triplet efficacy vs doublet efficacy – 5-FU + oxaliplatin + epirubicin	[redacted]	[redacted]	[redacted]	[redacted]	25,752	0.65	39,540	+10,889
Triplet efficacy vs doublet efficacy – capecitabine + oxaliplatin + epirubicin	[redacted]	[redacted]	[redacted]	[redacted]	25,634	0.65	39,359	+10,708
Triplet efficacy vs doublet efficacy – capecitabine + cisplatin + epirubicin	[redacted]	[redacted]	[redacted]	[redacted]	25,675	0.65	39,421	+10,770
Pembrolizumab in combination with capecitabine plus oxaliplatin versus capecitabine plus oxaliplatin	[redacted]	[redacted]	[redacted]	[redacted]	26,756	0.92	29,152	+501
Cisplatin dosed as 60 mg/m^2	[redacted]	[redacted]	[redacted]	[redacted]	26,297	0.92	28,652	+1
Remove half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]	26,277	0.92	28,624	-27
Remove treatment stopping rules	[redacted]	[redacted]	[redacted]	[redacted]	26,732	0.92	29,127	+476
Administration based on the day case setting	[redacted]	[redacted]	[redacted]	[redacted]	26,431	0.92	28,798	+147
Include treatment-based monitoring	[redacted]	[redacted]	[redacted]	[redacted]	25,075	0.92	27,321	-1,330
Re-distribute subsequent treatments	[redacted]	[redacted]	[redacted]	[redacted]	25,291	0.92	27,556	-1,095
Alternative terminal care costs	[redacted]	[redacted]	[redacted]	[redacted]				
- Removing radiotherapy					26,447	0.92	28,816	+165
- Based on ID1249					26,245	0.92	28,595	-56
Additional scenario: include nivolumab post chemotherapy for all patients	[redacted]	[redacted]	[redacted]	[redacted]	4,980	0.66	7,528	-21,123