NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Contents:

The following documents are made available to consultees and commentators:

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

1. **Company submission** from Merck Sharp & Dohme

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. The Swallows

4. **Expert personal perspectives** from:
   a. Dr Robert Metcalfe – clinical expert, nominated by NCRI-ACP-RCP
   b. Dr Shanmugasundaram Ramkumar – clinical expert, nominated by Royal College of Radiologists

5. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group

6. **Evidence Review Group – factual accuracy check**

7. **Technical engagement response** from Merck Sharp & Dohme

8. **Technical engagement responses from experts:**
   a. Dr Shanmugasundaram Ramkumar – clinical expert, nominated by Royal College of Radiologists

9. **Technical engagement response from consultees and commentators:**
   a. NCRI-ACP-RCP-RCR

10. **Evidence Review Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group

11. **Final Technical Report**

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 for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Document B

Company evidence submission

June 2019

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Pembrolizumab HNSCC ID1140 Document B Final	1.0	Yes	03-JUN-2019

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

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation. This submission is limited to patients with programmed cell death ligand 1 expression defined as ≥1 combined positive score as defined by a central laboratory immunohistochemistry assay (PD-L1 CPS≥1) for pembrolizumab monotherapy and pembrolizumab + chemotherapy combination therapy. The proposed population reflects where pembrolizumab provides the most clinical benefit.

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 recurrent or metastatic squamous cell carcinoma of the head and neck previously untreated in the recurrent or metastatic setting.	Adults with recurrent or metastatic squamous cell carcinoma of the head and neck previously untreated in the recurrent or metastatic setting, with programmed cell death ligand 1 expression defined as ≥1 combined positive score as defined by a central laboratory immunohistochemistry assay.	In line with expected licence wording and reflects population where pembrolizumab provides the most clinical benefit.
Intervention	Pembrolizumab alone or in combination with platinum-based chemotherapy	Pembrolizumab alone or in combination with platinum-based chemotherapy	N/A
Comparator(s)	• Platinum-based chemotherapy regimens • Cetuximab in combination with platinum-based chemotherapy (only if the cancer started in the oral cavity)	• Platinum-based chemotherapy regimens • Cetuximab in combination with platinum-based chemotherapy	The KEYNOTE-048 trial was not pre-specified to conduct subgroup analysis in the oral cavity subgroup. Consideration of the relative efficacy versus cetuximab in combination with platinum-based chemotherapy was not restricted specifically to the subgroup of patients whose cancer started in the oral cavity to maintain randomisation and powering.
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Duration of response • Adverse effects of treatment • Health-related quality of life	We have also included 'duration of response' as an additional outcome measure. It is known that the response to immunotherapies (immuno-oncology drugs) may be delayed, but once triggered, is likely to be durable, bringing long-term survival benefit for a subset of patients; this benefit is not

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			captured by the proposed outcome measures, but would be captured in the duration of response outcome.

B.1.2 Description of the technology being appraised

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 a dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its associated ligands, PD-L1 and PD-L2 which appear on the 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 inactivity.
Marketing authorisation/CE mark status	The technology does not currently have a UK marketing authorisation/CE marking for the indication in this submission. The expected date of the opinion from the Committee for Human Medicinal Products is 25 July 2019.

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated indications in the UK: • [redacted] Current indications in the UK: • 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-L1with 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-L1with 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 is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)in adults whose tumours express PD-L1 with a ≥50%TPS and progressing on or after platinum-containing chemotherapy.
Method of administration and dosage	• Pembrolizumab monotherapy: 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (Q6W) • Pembrolizumab in combination with platinum-based chemotherapy 200mg every 3 weeks (Q3W)
Additional tests or investigations	PD-L1 tumour expression level is measured by the combined proportion score (CPS) which consists of the percentage of PD-L1–positive tumour cells (TCs) and infiltrating immune cells relative to the total number of TCs as measured using the PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay on samples collected by core needle or excisional biopsies or in resected tissue.
List price and average cost of a course of treatment	£2,630 per 100mg vial.
Patient access scheme (if applicable)	A Commercial Access Agreement has been arranged with NHS England.

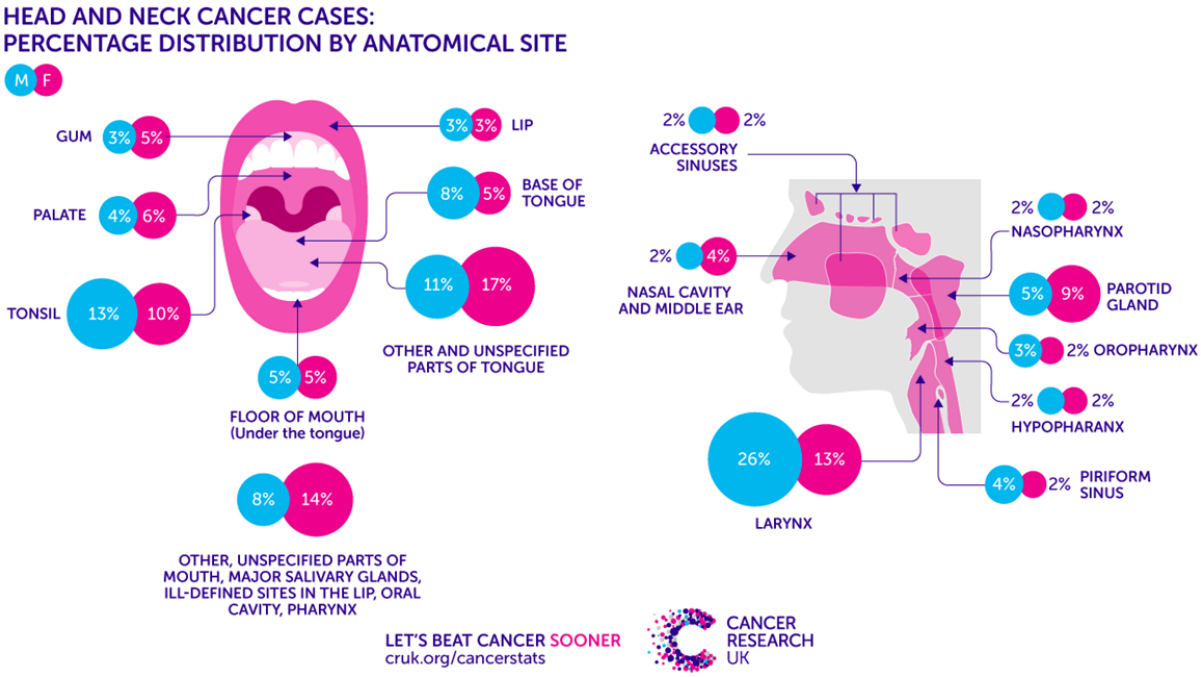
B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Brief overview of the disease or condition for which the technology is indicated

Head and neck cancers describe an anatomically heterogeneous group of cancers that arise most often from the oral cavity, oropharynx, hypopharynx, and larynx (1). More than 90% of head and neck cancers are squamous cell carcinomas (HNSCC), originating from the epithelium of the mucosal lining of the upper aerodigestive tract (2). These neoplasms are aggressive in their biologic behaviour, resulting in significant destructive disease above the clavicle, with the development of local (cervical) lymph node metastases and distant metastases even after effective local therapy (2). This submission will focus on malignancies of the oral cavity, oropharynx, hypopharynx and larynx, excluding other primary tumour sites. Figure 1 outlines these tumour sites and their distribution of occurrence (3).

Worldwide, head and neck cancer is the eighth most common malignancy, with 834,860 new cases diagnosed in 2018, corresponding to age-standardised incidence rates of 15.0 and 4.3 per 100,000 in males and females, respectively (4, 5). In the EU, head and neck cancer accounts for 139,000 new cases per year (6). Head and neck cancer was the eighth most common cancer in the UK, with 12,061 new cases of head and neck cancer reported in 2015 accounting for 3% of all new cancer cases, HNSCC is more prevalent in a male population, occurring at approximately a 2:1 male:female ratio (7).

Figure 1 Incidence of HNSCC by anatomical site (7).



Historically, major risk factors for head and neck cancers include alcohol and tobacco use; however, in recent years human papillomavirus (HPV) has been shown to be a causative agent in the majority of oropharyngeal cancers (1, 8). Tobacco-related HNSCC disease has declined, whereas HPV-positive disease has increased (8). HPV-positive and HPV-negative HNSCC represent two distinct biologies with different clinical presentations and prognosis (8).

Classical presentation of HNSCC includes pain, dysphagia, odynophagia, dysphonia, otalgia, hoarseness, and citrus intolerance (8). HPV-positive oropharyngeal disease is characterised with early cervical lymph node metastases (8). Presentation is, therefore, usually with a painless neck mass, typically treated with antibiotics initially, due to the presentation (8). Sites of metastases include lymph nodes, bone and lung (8).

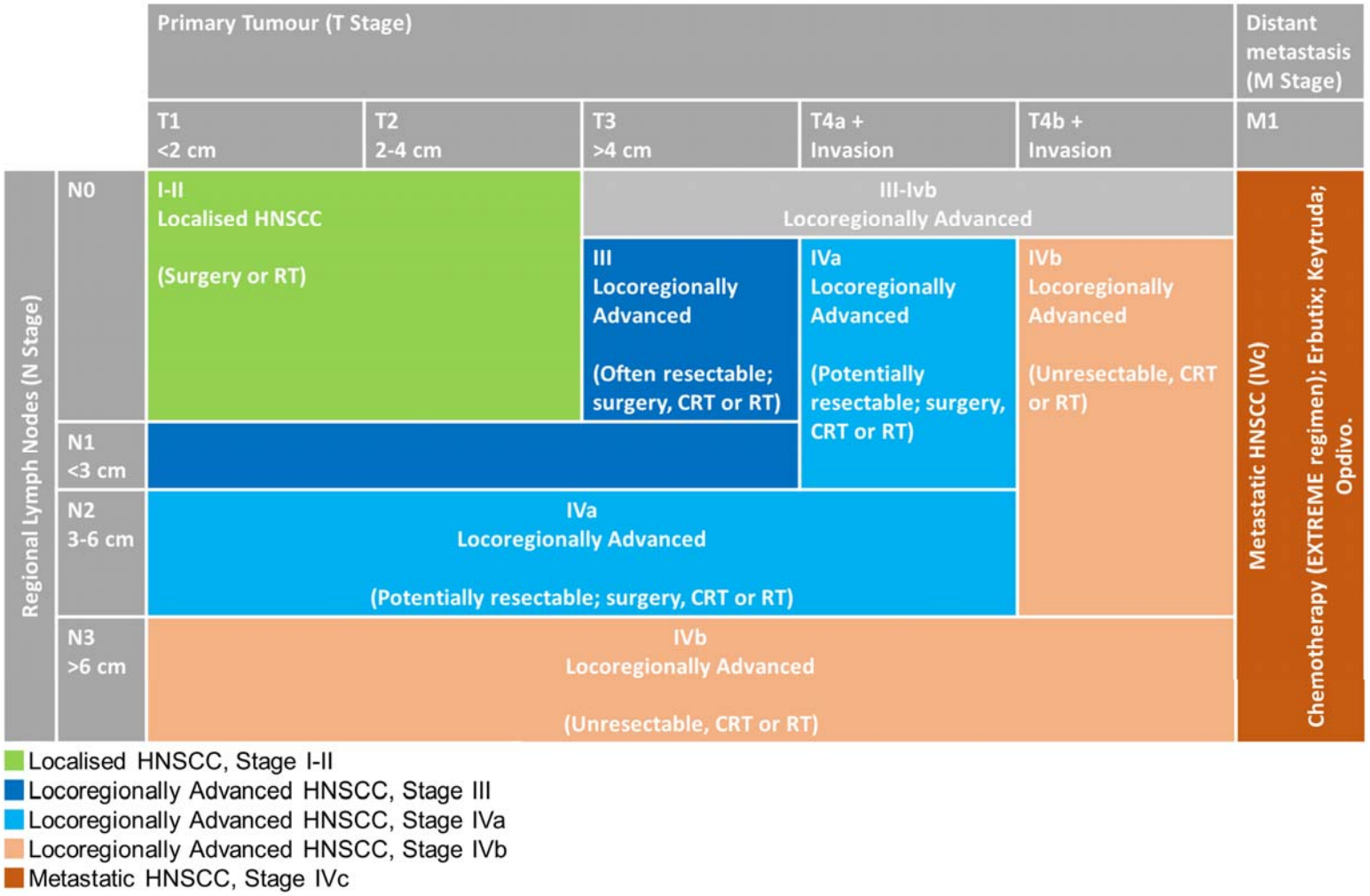
Head and neck cancer is staged according to the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) tumour, node, and metastasis (TNM) staging classification system (Figure 2) (9). HNSCC tumour staging is complex and based on the location of tumour, nodal involvement, and the degree of structural involvement at subsites. Classification considers local, regional, and distant

characteristics of the disease; local disease includes the primary tumour (T 1-4); regional disease indicates the involvement of cervical lymph nodes (N 0-3); and distant metastasis (M 0-1) assesses spread of the primary tumour to sites beyond the cervical lymphatic system.

Approximately 3% to 4% of all HNSCC have distant metastases at diagnosis (10). In the literature, reported recurrence rates vary widely depending on tumour localisation, primary tumour stage, and treatment modality. Significantly, 10% to 30% of patients with cancer of the lip or oral cavity subsequently develop second primary neoplasms of the upper aerodigestive tract (2). Studies generally report recurrence rates of approximately 40%-50% for head and neck carcinomas.

The challenges of recurrent/metastatic (R/M) HNSCC include pain, altered speech, and difficulties with swallowing, breathing, and social function (11). Patients with R/M disease have a poor prognosis, with a median survival time of 6 to 9 months (1). In summary, R/M HNSCC is a devastating disease that severely impacts the daily life of patients (12-14).

Figure 2 TNM staging of HNSCC.



CRT: chemoradiotherapy; EXTREME regimen: cetuximab plus platinum-based chemotherapy; HNSCC: head and neck squamous cell carcinoma; RT: radiotherapy

Adapted from the AJCC cancer staging manual (9).

B.1.3.2 Summary of the clinical pathway including context and proposed placement of the technology within the pathway

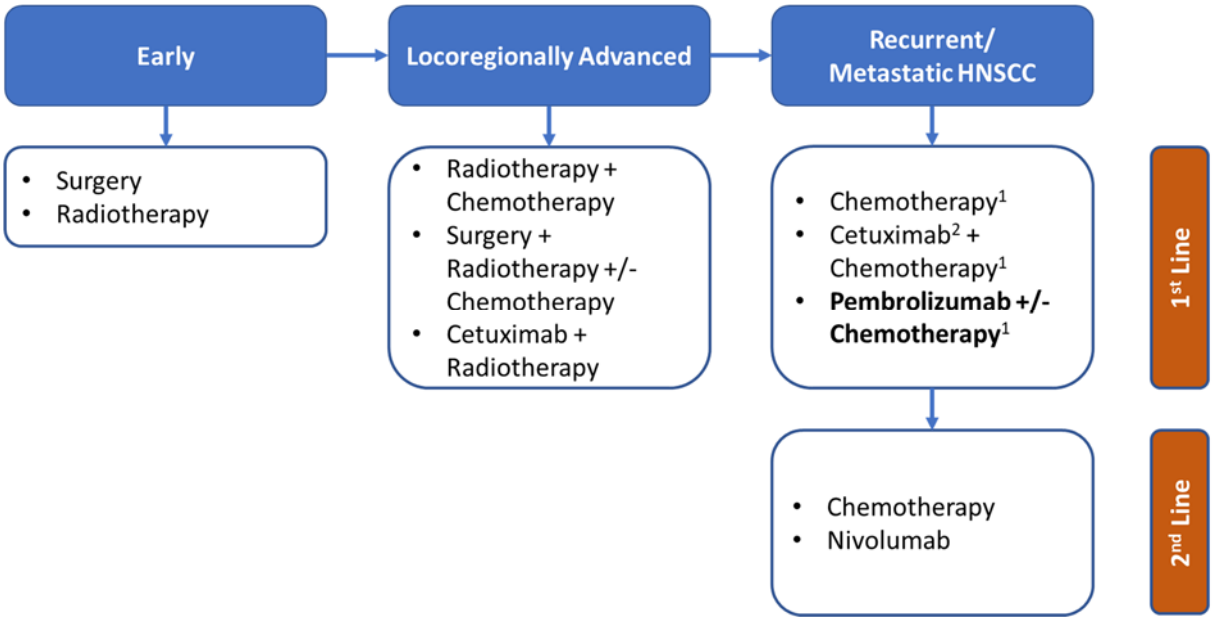
Treatment for HNSCC vary according to the specific tumour sites and typically treatment involves surgery and/or radiotherapy with curative intent, with systemic therapy in cases of locoregionally advanced disease. For R/M disease, patients typically receive chemotherapy after resection. Guidelines for the treatment of HNSCC have been published by several organisations, however recommendations for the first-line treatment of R/M HNSCC are not consistent (summarised in Table 3). In the UK, combination chemotherapy is the mainstay of treatment for R/M HNSCC in the first-line setting, although cetuximab in combination with cisplatin/carboplatin plus 5-fluorouracil (the EXTREME regimen) is also recommended as an option but only if the cancer started in the oral cavity (15-17). The EXTREME regimen is also recommended for this population by the European Head & Neck Society (EHNS), European Society for Medical Oncology (ESMO), and European Society for Radiotherapy & Oncology (ESTRO) joint clinical practice guidelines (6). The US National Comprehensive Cancer Network (NCCN) guidelines provide a comprehensive list of systemic therapy options for HNSCC and also includes the EXTREME regimen as one of only two Category 1 evidence supported combination regimens they recommend as first-line treatment for patients with R/M HNSCC.

The current clinical pathway of care for HNSCC in the UK is summarised in Figure 3 (17), with the proposed place of pembrolizumab in this pathway indicated. This is the proposed place for both pembrolizumab monotherapy and pembrolizumab + chemotherapy combination therapy, with the decision on which one to use to be based on the judgement of the treating physician and patient wishes.

Table 3 Treatment guidelines for HNSCC

Organisation	Guideline	Recommendations for chemotherapy for R/M HNSCC in the first-line setting
National Institute for Health and Care Excellence (NICE)	Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over – NG36 (2018) (17)	None given
	Cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (2017) NICE technology appraisal 473 (16)	Cetuximab in combination with platinum-based chemotherapy is recommended as an option for treating recurrent or metastatic squamous cell cancer of the head and neck in adults only if the cancer started in the oral cavity
British Association of Head and Neck Oncologists (BAHNO)	Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines - Chemotherapy: United Kingdom National Multidisciplinary Guidelines (2016) (15)	Chemotherapy or targeted biological agents, such as cetuximab, may be indicated for patients with recurrent and/or metastatic disease
European Head & Neck Society (EHNS), European Society for Medical Oncology (ESMO), European Society for Radiotherapy & Oncology (ESTRO)	Squamous cell carcinoma of the head and neck: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2010) (6)	For local, regional, and metastatic recurrence, first-line option for fit patients should include the combination of cetuximab with cisplatin or carboplatin plus 5-fluorouracil
National Comprehensive Cancer Network (NCCN)	Head and Neck Cancers (2018) (18)	For recurrent, unresectable, or metastatic HNSCC, combination therapy and single-agent systemic therapy options are recommended at first-line

Figure 3 Proposed position of pembrolizumab in the clinical treatment pathway for HNSCC (16, 17, 19)



HNSCC: head and neck squamous cell carcinoma.
[1]Platinum-based chemotherapy regimens.
[2]If the cancer started in the oral cavity

B.1.4 Equality considerations

We do not anticipate any equity or equality considerations.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

To identify and select relevant studies, a systematic literature review (SLR) search was carried out in accordance with NICE guidance, according to a previously prepared protocol to identify relevant studies to inform indirect comparisons between pembrolizumab and placebo. Please refer to Appendix D for full details of the process and methods undertaken.

B.2.2 List of relevant clinical effectiveness evidence

A SLR was performed to identify all relevant published and unpublished randomised controlled trials (RCTs) and non-randomised clinical trials (non-RCTs) relating to pembrolizumab as per the final scope in Table 4.

A single trial was identified from the SLR that provided clinical effectiveness information on pembrolizumab in the patient population of relevance to this submission (first-line treatment of R/M HNSCC). At the time of the SLR search, unpublished evidence from KEYNOTE-048 was available.

KEYNOTE-048 is a Phase 3 randomised, active-controlled, multi-site open-label study that compared pembrolizumab monotherapy or pembrolizumab plus platinum plus 5-fluorouracil chemotherapies versus cetuximab plus platinum plus 5-fluorouracil in patients with first line R/M HNSCC.

Table 4 Clinical effectiveness evidence

Study	A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (MK-3475-048/ KEYNOTE-048).
Study design	Randomised, active-controlled, multi-site, open-label study
Population	Male and female patients of at least 18 years of age with histologically or cytologically confirmed recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) considered incurable by local therapies. Patients did not have had prior systemic therapy administered in the recurrent or metastatic setting.
Intervention(s)	• Pembrolizumab monotherapy • Pembrolizumab + Platinum + 5-fluorouracil
Comparator(s)	• Cetuximab + Platinum + 5-Fluorouracil

Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale for use/non-use in the model	KEYNOTE-048 is the only available trial with data for pembrolizumab in this indication				
Reported outcomes specified in the decision problem	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life				
All other reported outcomes	• Duration of response				

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

B.2.3.1 Summary of the methodology of KEYNOTE-048

Trial design

KEYNOTE-048 is a randomised, active-controlled, multi-site, open-label study of pembrolizumab monotherapy or pembrolizumab plus chemotherapy (platinum plus 5-fluorouracil) versus cetuximab plus chemotherapy (standard treatment) in patients with advanced head and neck cancer. Patients with first line R/M HNSCC were enrolled for examination of the efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy versus standard treatment. Patients were randomised 1:1:1 between the three arms of the trial. A diagram of the trial design is shown in Figure 4.

Randomisation occurred centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). Randomisation and allocation in the three treatment arms were stratified according to the following factors:

1. PD-L1 tumour expression as determined by PD-L1 immunohistochemistry (strongly positive vs not strongly positive)

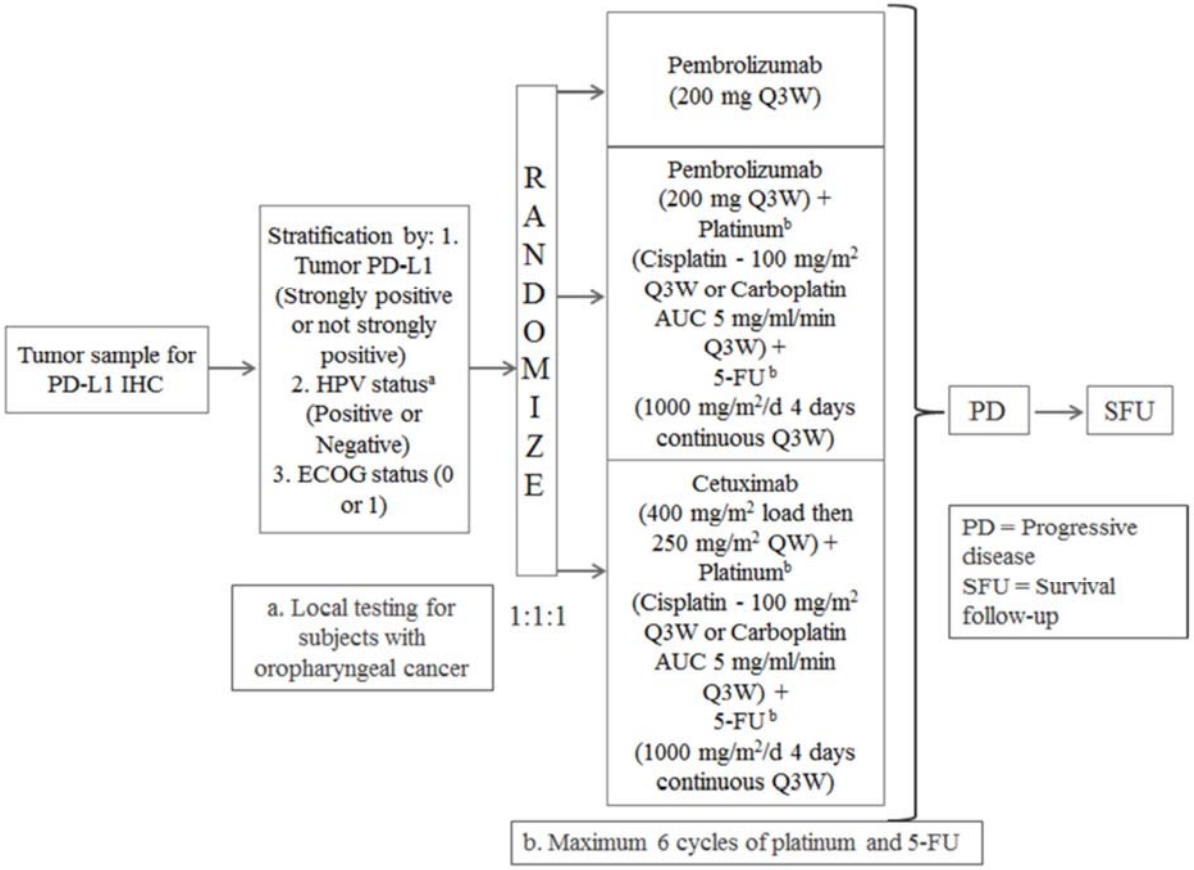
   Note: Strongly positive includes those patients whose tumour expression levels are TPS≥50%. Not strongly positive includes those patients whose

tumour expression levels are TPS<50%, or are not able to be determined for any reason.

2. HPV status for oropharynx cancer as determined by p16 immunohistochemistry (IHC) tested at a local laboratory (positive vs negative); HPV status for patients without oropharynx cancer (e.g. cancers of the oral cavity, hypopharynx and larynx) were considered HPV negative.

3. Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1)

Figure 4 Trial design of the KEYNOTE-048 study



Eligibility criteria

Male and female patients of at least 18 years of age with histologically or cytologically confirmed R/M HNSCC considered incurable by local therapies were included in the study. Patients were not to have had prior systemic therapy administered in the recurrent or metastatic setting. The full details of the eligibility criteria of the KEYNOTE-048 study are provided in Appendix L.

Setting and locations where the data were collected

This was a global study undertaken in 229 centres in 37 countries (listed in Table 7)

Trial drugs and concomitant medications

Patients were randomised to three treatment groups as described in Table 5. The details of interventions in each treatment regimen are shown in Table 6.

Table 5 Treatment arms and trial drugs of the KEYNOTE-048 study

Treatment group	Treatment regimen
Pembrolizumab plus chemotherapy group	Pembrolizumab + platinum[a] + 5-FU group
Pembrolizumab monotherapy group	Pembrolizumab
Standard treatment group	Cetuximab + platinum[a] + 5-FU group

5-FU=5-fluorouracil; HNSCC=Head and neck squamous cell carcinoma; QW=Every week; Q3W=Every 3 weeks; R/M=Recurrent or metastatic. [a]Platinum: platinum-containing chemotherapy (carboplatin or cisplatin)

Table 6 Study interventions in the KEYNOTE-048 study

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles)	Experimental
Cisplatin	100 mg/m^2	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
Carboplatin	AUC 5	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
5-FU	1000 mg/m^2/day Days 1-4 of each cycle	Every 3 weeks	Intravenous	Days 1-4 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen	Use
Cetuximab	Initial dose on Day 1 is 400 mg/m^2 followed by weekly doses of 250 mg/m^2	Every week	Intravenous	Days 1, 8, and 15 of each cycle (3 week cycles)	Comparator regimen

Trial outcomes

The outcomes assessed and reported in the KEYNOTE-048 trial are those that were prespecified in the trial protocol.

The primary efficacy endpoints of the KEYNOTE-048 trial were:

- Progression-free survival - Progression-free-survival (PFS) was defined as the time from randomisation to the first documented disease progression per response evaluation in solid tumours (RECIST) 1.1 based on central radiologists' review or death due to any cause, whichever occurs first.

- Overall survival - Overall Survival (OS) was defined as the time from randomisation to death due to any cause. Patients without documented death at the time of the final analysis were censored at the date of the last follow-up.

The secondary efficacy endpoints of the KEYNOTE-048 trial were:

- Proportion progression free at 6 months and 12 months - The proportion progression free at 6 months and at 12 months was defined as the Kaplan-Meier estimate of the survival function for PFS at 6 months and 12 months, respectively. The progression-free status was based upon blinded central radiologists' review per RECIST 1.1.

- Objective response rate - Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon blinded central radiologists' review per RECIST 1.1.

The exploratory efficacy endpoints assessed in the KEYNOTE-048 trial were:

- Duration of response - For patients who demonstrated CR or PR, response duration was defined as the time from first documented evidence of CR or PR until disease progression or death. Response duration for patients who had not progressed or died at the time of analysis were censored at the date of their last tumour assessment. Response duration was calculated per RECIST 1.1 based on central radiologists' review.

The patient-reported outcomes (PRO) endpoints assessed in the KEYNOTE-048 trial were:

- Global health status/quality of life assessment based on the global health status/quality of life scales of the QLQ-C30 (items 29 and 30).
- Pain based on the pain multi-item scales of the EORTC QLQ-H&N35 (items 31-34).
- Time-to-deterioration (TTD) in swallowing based on the swallowing multi-item scales of the EORTC QLQ-H&N35 (items 35-38).

  TTD was defined as the time from baseline to first onset of PRO deterioration with confirmation (true deterioration). True deterioration in the global health status/quality of life, pain, and swallowing endpoints was defined as a 10 points or greater worsening from baseline for each multi-item scale and confirmed by a second adjacent 10 or more deterioration from baseline under a right-censoring rule.
- Utilities using the EuroQol EQ-5D.

Safety outcomes including adverse events and discontinuations were also measured (further details provided in section B.2.4).

B.2.3.2 Tabulated summary of the methodology of KEYNOTE-048

Table 7 Comparative summary of trial methodology

Trial number (acronym)	**KEYNOTE-048**
Location	Multinational
Trial design	Randomised, active-controlled, multi-site, open-label study
Eligibility criteria for participants	Male and female subjects of at least 18 years of age with histologically or cytologically confirmed recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) considered incurable by local therapies. Subjects should not have had prior systemic therapy administered in the recurrent or metastatic setting.
Settings and locations where the data were collected	229 centres in 37 countries: Argentina, Australia, Austria, Brazil, Canada, Chile, Colombia, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Hong Kong, Hungary, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Peru, Philippines, Poland, Russian Federation, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, United States
Trial drugs **Permitted and disallowed concomitant medication**	**Trial drugs:** • Pembrolizumab arm (n=301) - Participants receive pembrolizumab 200 mg, intravenously (IV) on Day 1 of each week in 3-week cycles for up to 24 months • Pembrolizumab + Platinum + 5-FU arm (n=281) - Participants receive pembrolizumab 200 mg, intravenously (IV) on Day 1 of each week in 3-week cycles for up to 24 months; plus cisplatin 100 mg/m2 IV or carboplatin AUC 5 IV (Investigator's choice) on Day 1 of each week in 3-week cycles (6 cycle maximum); plus 5-FU 1000 mg/m2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum) • Cetuximab + Platinum + 5-FU arm (n=300) - Participants receive cetuximab on Day 1 at a dose of 400 mg/m2 IV, and then 250 mg/m^2 IV on Day 1 of each week until disease progression or unacceptable toxicity; plus cisplatin 100 mg/m2 IV or carboplatin AUC 5 IV (Investigator's choice) on Day 1 of each week in 3-week cycles (6 cycle maximum for platinum-based therapy); plus 5-FU 1000 mg/m2/day IV continuous from Day 1-4 of each 3-week cycle (6 cycle maximum)

Trial number (acronym)	KEYNOTE-048
	Concomitant medication: All treatments that the investigator considered necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Patients were prohibited from receiving the following therapies during the Screening and Treatment Phase of the trial: • 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[1] • Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial[2] • Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic aetiology[3] [1]Note: Radiation therapy to a symptomatic solitary lesion or to the brain was considered on an exceptional case by case basis. The patient must have had clear measurable disease outside the radiated field. Administration of palliative radiation therapy was considered clinical progression for the purposes of determining PFS. [2]Note: It was acceptable for patients receiving the cetuximab + platinum + 5-FY therapy to receive live vaccines while participating in the trial. [3]Note: For patients randomised to the standard treatment arm (cetuximab plus chemotherapy) the use of systemic glucocorticoids on trial treatment was acceptable and may be required for premedication. Inhaled steroids were allowed for management of asthma. Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) was permitted.
Primary outcomes (including scoring methods and timings of assessments)	• Progression-free survival • Overall survival
Other outcomes used in the economic model/specified in the scope	**Efficacy secondary outcomes:** • Proportion progression free at 6 months and 12 months

Trial number (acronym)	KEYNOTE-048
	• Objective response rate **Efficacy exploratory outcomes:** • Duration of response **PRO outcomes:** • Global health status/quality of life (EORTC QLQ-C30 items 29 and 30). • Pain (EORTC QLQ-H&N35 items 31-34). • Swallowing (EORTC QLQ-H&N35 items 35-38). • Utilities using the EuroQol EQ-5D. **Safety outcomes:** • Adverse events and discontinuations
Pre-planned subgroups	To determine whether the treatment effect was consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint were estimated and plotted by treatment group within each category of the following classification variables: • Stratification factors o HPV status (HPV positive vs. HPV negative) o ECOG status (0 vs. 1) • PD-L1 expression level defined by CPS (≥ 20 vs. not ≥ 20; and ≥ 1 vs. not ≥ 1) • Age category (<65 vs. ≥65 years) • Sex (female vs. male) • Race (white vs. non-white) • Region (North America [NA] vs European Union [EU] vs Rest of the World [ROW]) • Smoking status (never vs. former vs. current) • Disease status (recurrent vs. metastatic)

B.2.3.3 Characteristics of the participants at baseline for each of the trials

Patient characteristics, pembrolizumab monotherapy vs. control, CPS≥1 subgroup

Intervention groups were generally balanced for all baseline characteristics (Table 8), for the population of participants with PD-L1 ≥1. The demographics and disease characteristics observed in the study are consistent with those of the 1L R/M HNSCC population. The majority of participants were male with a median age of 61 years, White, not Hispanic, and former smokers. With regard to baseline disease characteristics, the majority of participants had an ECOG performance status of 1, metastases (M1), and were overall disease stage IVc. Most had a negative HPV status. Overall disease burden was similar in the two treatment groups, and the median number of days since the last platinum therapy and from prior systemic therapy was less for participants randomised to the pembrolizumab monotherapy group.

Table 8 KEYNOTE-048 study patient characteristics, pembrolizumab monotherapy vs. control, intention-to-treat (ITT) population, CPS≥1 subgroup

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	257		255		512	
Gender						
Male	209	(81.3)	220	(86.3)	429	(83.8)
Female	48	(18.7)	35	(13.7)	83	(16.2)
Age (Years)						
<65	163	(63.4)	166	(65.1)	329	(64.3)
>=65	94	(36.6)	89	(34.9)	183	(35.7)
Mean	60.8		60.8		60.8	
SD	9.7		10.2		10.0	

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Median	62.0		61.0		61.0	
Range	22 to 94		24 to 84		22 to 94	
Race						
American Indian Or Alaska Native	4	(1.6)	6	(2.4)	10	(2.0)
Asian	50	(19.5)	47	(18.4)	97	(18.9)
Black Or African American	3	(1.2)	3	(1.2)	6	(1.2)
Multi-Racial	10	(3.9)	9	(3.5)	19	(3.7)
White	188	(73.2)	189	(74.1)	377	(73.6)
Missing	2	(0.8)	1	(0.4)	3	(0.6)
Ethnicity						
Hispanic Or Latino	35	(13.6)	34	(13.3)	69	(13.5)
Not Hispanic Or Latino	204	(79.4)	199	(78.0)	403	(78.7)
Not Reported	16	(6.2)	15	(5.9)	31	(6.1)
Unknown	2	(0.8)	7	(2.7)	9	(1.8)
Region Group						
NA	68	(26.5)	54	(21.2)	122	(23.8)
EU	74	(28.8)	92	(36.1)	166	(32.4)
ROW	115	(44.7)	109	(42.7)	224	(43.8)
Smoking Status						
Never Smoker	59	(23.0)	61	(23.9)	120	(23.4)
Ex Smoker	154	(59.9)	156	(61.2)	310	(60.5)
Current Smoker	44	(17.1)	36	(14.1)	80	(15.6)
Missing	0	(0.0)	2	(0.8)	2	(0.4)
ECOG						
0	104	(40.5)	101	(39.6)	205	(40.0)

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
1	153	(59.5)	154	(60.4)	307	(60.0)
HPV Status						
Positive	54	(21.0)	55	(21.6)	109	(21.3)
Negative	203	(79.0)	200	(78.4)	403	(78.7)
PD-L1 TPS Status						
Strongly Positive	67	(26.1)	66	(25.9)	133	(26.0)
Not Strongly Positive	190	(73.9)	189	(74.1)	379	(74.0)
PD-L1 CPS Status (CPS>=20)						
CPS >=20	133	(51.8)	122	(47.8)	255	(49.8)
CPS <20	123	(47.9)	131	(51.4)	254	(49.6)
Missing	1	(0.4)	2	(0.8)	3	(0.6)
Baseline Tumour Size (mm) (Grouping by ITT Median)						
>=Median	102	(39.7)	111	(43.5)	213	(41.6)
<Median	133	(51.8)	125	(49.0)	258	(50.4)
Missing	22	(8.6)	19	(7.5)	41	(8.0)
Subjects with data	235		236		471	
Mean	74.3		73.2		73.7	
SD	60.4		58.2		59.3	
Median	52.7		56.0		53.6	
Range	10 to 338		10 to 419		10 to 419	
Disease Status						
Metastatic	179	(69.6)	168	(65.9)	347	(67.8)
Recurrent	75	(29.2)	84	(32.9)	159	(31.1)
Neither	3	(1.2)	3	(1.2)	6	(1.2)
T0	23	(8.9)	37	(14.5)	60	(11.7)

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
T1	11	(4.3)	11	(4.3)	22	(4.3)
T2	33	(12.8)	47	(18.4)	80	(15.6)
T3	41	(16.0)	32	(12.5)	73	(14.3)
T3A	1	(0.4)	0	(0.0)	1	(0.2)
T3B	0	(0.0)	1	(0.4)	1	(0.2)
T4	51	(19.8)	43	(16.9)	94	(18.4)
T4A	55	(21.4)	40	(15.7)	95	(18.6)
T4B	13	(5.1)	23	(9.0)	36	(7.0)
TX	29	(11.3)	21	(8.2)	50	(9.8)
Regional Lymph Nodes Staging						
N0	71	(27.6)	67	(26.3)	138	(27.0)
N1	37	(14.4)	42	(16.5)	79	(15.4)
N2	119	(46.3)	113	(44.3)	232	(45.3)
N3	18	(7.0)	25	(9.8)	43	(8.4)
NX	12	(4.7)	8	(3.1)	20	(3.9)
Metastatic Staging						
M0	78	(30.4)	87	(34.1)	165	(32.2)
M1	179	(69.6)	168	(65.9)	347	(67.8)
Overall Cancer Staging						
II	1	(0.4)	1	(0.4)	2	(0.4)
III	10	(3.9)	11	(4.3)	21	(4.1)
IVA	56	(21.8)	57	(22.4)	113	(22.1)
IVB	11	(4.3)	18	(7.1)	29	(5.7)
IVC	179	(69.6)	168	(65.9)	347	(67.8)
Primary Tumour Location-Oral Cavity						

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Yes	75	(29.2)	80	(31.4)	155	(30.3)
No	182	(70.8)	175	(68.6)	357	(69.7)
Primary Tumour Location-Larynx						
Yes	57	(22.2)	53	(20.8)	110	(21.5)
No	200	(77.8)	202	(79.2)	402	(78.5)
Primary Tumour Location-Hypopharynx						
Yes	34	(13.2)	32	(12.5)	66	(12.9)
No	223	(86.8)	223	(87.5)	446	(87.1)
Primary Tumour Location-Oropharynx						
Yes	97	(37.7)	94	(36.9)	191	(37.3)
No	160	(62.3)	161	(63.1)	321	(62.7)
Time from Latest Platinum Therapy (days)						
Subjects with data	112		120		232	
Mean	754.6		860.9		809.6	
SD	676.3		864.3		779.4	
Median	510.0		585.5		539.0	
Range	193 to 4620		201 to 6817		193 to 6817	
Time from Prior Systemic Therapy (days)						
Subjects with data	130		125		255	
Mean	810.8		847.0		828.5	
SD	1029.7		846.5		942.7	
Median	507.5		627.0		530.0	
Range	35 to 9264		201 to 6817		35 to 9264	

Patient characteristics, pembrolizumab combination therapy vs. control, CPS≥1 subgroup

The pembrolizumab plus chemotherapy and standard treatment groups were generally balanced for all baseline characteristics (Table 9), for the population of participants with PD-L1 CPS≥1. The demographics and disease characteristics observed in the study are consistent with those of the R/M HNSCC population. The majority of participants were male with a median age of 61 years, White, not Hispanic, and former smokers. With regard to baseline disease characteristics, the majority of participants had an ECOG performance status of 1, metastases (M1), and were overall disease stage IVc. Most had a negative HPV status. In the pembrolizumab plus chemotherapy group versus standard treatment, there were fewer male participants, overall disease burden was greater with a median baseline tumour size of 68.1 mm versus 56.0 mm, respectively, and the median number of days since last platinum therapy and from prior systemic therapy was less.

It should be noted that enrolment in the pembrolizumab plus chemotherapy group was paused on 13-AUG-2015 and reopened on 02-OCT-2015 due to an external data monitoring committee (DMC) recommendation. After the DMC completed their safety assessment, the DMC recommended lifting the enrolment pause for this treatment group. As a result, randomisation between the pembrolizumab plus chemotherapy versus standard treatment was not concurrent between 13-AUG-2015 and 02-OCT-2015, and all participants (n=22) randomised to standard treatment during the pause were excluded for the comparison between pembrolizumab plus chemotherapy group versus the standard treatment group, according to the intention-to-treat (ITT) principle. As a result, the number of participants in the standard treatment group in demographic and efficacy comparisons versus pembrolizumab plus chemotherapy is 278 in the overall population and (235 in the CPS≥1 subgroup), while the number of participants in the standard treatment group in efficacy comparisons versus pembrolizumab monotherapy is 300 in the overall population (255 in the CPS≥1 subgroup). All participants are included in the safety analyses.

Table 9 KEYNOTE-048 study patient characteristics, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	242		235		477	
Gender						
Male	188	(77.7)	203	(86.4)	391	(82.0)
Female	54	(22.3)	32	(13.6)	86	(18.0)
Age (Years)						
<65	153	(63.2)	152	(64.7)	305	(63.9)
>=65	89	(36.8)	83	(35.3)	172	(36.1)
Mean	60.6		60.8		60.7	
SD	9.9		10.3		10.1	
Median	61.0		61.0		61.0	
Range	20 to 85		24 to 84		20 to 85	
Race						
American Indian Or Alaska Native	2	(0.8)	6	(2.6)	8	(1.7)
Asian	48	(19.8)	43	(18.3)	91	(19.1)
Black Or African American	10	(4.1)	3	(1.3)	13	(2.7)
Multi-Racial	4	(1.7)	9	(3.8)	13	(2.7)
White	178	(73.6)	173	(73.6)	351	(73.6)
Missing	0	(0.0)	1	(0.4)	1	(0.2)
Ethnicity						
Hispanic Or Latino	39	(16.1)	34	(14.5)	73	(15.3)
Not Hispanic Or Latino	185	(76.4)	181	(77.0)	366	(76.7)
Not Reported	14	(5.8)	13	(5.5)	27	(5.7)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Unknown	4	(1.7)	7	(3.0)	11	(2.3)
Region Group						
NA	53	(21.9)	51	(21.7)	104	(21.8)
EU	76	(31.4)	82	(34.9)	158	(33.1)
ROW	113	(46.7)	102	(43.4)	215	(45.1)
Smoking Status						
Never Smoker	50	(20.7)	58	(24.7)	108	(22.6)
Ex Smoker	143	(59.1)	142	(60.4)	285	(59.7)
Current Smoker	49	(20.2)	33	(14.0)	82	(17.2)
Missing	0	(0.0)	2	(0.9)	2	(0.4)
ECOG						
0	92	(38.0)	94	(40.0)	186	(39.0)
1	150	(62.0)	141	(60.0)	291	(61.0)
HPV Status						
Positive	53	(21.9)	50	(21.3)	103	(21.6)
Negative	189	(78.1)	185	(78.7)	374	(78.4)
PD-L1 TPS Status						
Strongly Positive	66	(27.3)	62	(26.4)	128	(26.8)
Not Strongly Positive	176	(72.7)	173	(73.6)	349	(73.2)
PD-L1 CPS Status (CPS>=20)						
CPS >=20	126	(52.1)	110	(46.8)	236	(49.5)
CPS <20	115	(47.5)	123	(52.3)	238	(49.9)
Missing	1	(0.4)	2	(0.9)	3	(0.6)
Baseline Tumour Size (mm) (Grouping by ITT Median)						

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
>=Median	128	(52.9)	102	(43.4)	230	(48.2)
<Median	95	(39.3)	116	(49.4)	211	(44.2)
Missing	19	(7.9)	17	(7.2)	36	(7.5)
Subjects with data	223		218		441	
Mean	82.7		73.0		77.9	
SD	59.8		58.6		59.3	
Median	68.1		56.0		63.6	
Range	12 to 385		10 to 419		10 to 419	
Disease Status						
Metastatic	173	(71.5)	154	(65.5)	327	(68.6)
Recurrent	65	(26.9)	78	(33.2)	143	(30.0)
Neither	4	(1.7)	3	(1.3)	7	(1.5)
Primary Tumour Staging						
T0	33	(13.6)	33	(14.0)	66	(13.8)
T1	18	(7.4)	9	(3.8)	27	(5.7)
T1A	1	(0.4)	0	(0.0)	1	(0.2)
T2	38	(15.7)	42	(17.9)	80	(16.8)
T3	33	(13.6)	31	(13.2)	64	(13.4)
T3B	0	(0.0)	1	(0.4)	1	(0.2)
T4	31	(12.8)	43	(18.3)	74	(15.5)
T4A	48	(19.8)	39	(16.6)	87	(18.2)
T4B	11	(4.5)	20	(8.5)	31	(6.5)
TX	29	(12.0)	17	(7.2)	46	(9.6)
Regional Lymph Nodes Staging						
N0	64	(26.4)	63	(26.8)	127	(26.6)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
N1	33	(13.6)	41	(17.4)	74	(15.5)
N2	114	(47.1)	102	(43.4)	216	(45.3)
N3	20	(8.3)	23	(9.8)	43	(9.0)
NX	11	(4.5)	6	(2.6)	17	(3.6)
Metastatic Staging						
M0	69	(28.5)	81	(34.5)	150	(31.4)
M1	173	(71.5)	154	(65.5)	327	(68.6)
Overall Cancer Staging						
III	14	(5.8)	10	(4.3)	24	(5.0)
IVA	42	(17.4)	54	(23.0)	96	(20.1)
IVB	13	(5.4)	17	(7.2)	30	(6.3)
IVC	173	(71.5)	154	(65.5)	327	(68.6)
Primary Tumour Location-Oral Cavity						
Yes	77	(31.8)	73	(31.1)	150	(31.4)
No	165	(68.2)	162	(68.9)	327	(68.6)
Primary Tumour Location-Larynx						
Yes	37	(15.3)	48	(20.4)	85	(17.8)
No	205	(84.7)	187	(79.6)	392	(82.2)
Primary Tumour Location-Hypopharynx						
Yes	33	(13.6)	30	(12.8)	63	(13.2)
No	209	(86.4)	205	(87.2)	414	(86.8)
Primary Tumour Location-Oropharynx						

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Yes	98	(40.5)	88	(37.4)	186	(39.0)
No	144	(59.5)	147	(62.6)	291	(61.0)
Time from Latest Platinum Therapy (days)						
Subjects with data	109		113		222	
Mean	734.4		866.8		801.8	
SD	939.9		883.0		911.7	
Median	441.0		575.0		503.5	
Range	146 to 6278		201 to 6817		146 to 6817	
Time from Prior Systemic Therapy (days)						
Subjects with data	118		118		236	
Mean	705.3		851.8		778.5	
SD	905.8		863.8		886.2	
Median	440.0		601.0		498.0	
Range	146 to 6278		201 to 6817		146 to 6817	

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

Primary hypotheses

Objectives and hypotheses

The primary objectives and hypotheses of the KEYNOTE-048 trial that are under consideration for this submission were:

- Objective: To compare PFS per RECIST 1.1 as assessed by BICR in 1L R/M HNSCC participants, treated with pembrolizumab monotherapy versus standard treatment.
    - Hypothesis (H1): Pembrolizumab monotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of 1L R/M HNSCC participants with PD-L1 ≥20 CPS compared to standard treatment.
    - Hypothesis (H2): Pembrolizumab monotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of 1L R/M HNSCC participants with PD-L1 ≥1 CPS compared to standard treatment.
    - Hypothesis (H3): Pembrolizumab monotherapy prolongs PFS by RECIST 1.1 (BICR) in all 1L R/M HNSCC participants compared to standard treatment.
- Objective: To compare PFS per RECIST 1.1 as assessed by BICR in 1L R/M HNSCC participants, treated with pembrolizumab in combination with chemotherapy versus standard treatment.
    - Hypothesis (H4): Pembrolizumab in combination with chemotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of 1L R/M HNSCC participants with PD-L1 ≥20 CPS compared to standard treatment.
    - Hypothesis (H5): Pembrolizumab in combination with chemotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of 1L R/M HNSCC participants with PD-L1 ≥1 CPS compared to standard treatment.

- Hypothesis (H6): Pembrolizumab in combination with chemotherapy prolongs PFS by RECIST 1.1 (BICR) in all 1L R/M HNSCC participants compared to standard treatment.

- Objective: To evaluate the OS in 1L R/M HNSCC participants, treated with pembrolizumab monotherapy versus standard treatment.
  - Hypothesis (H7): Pembrolizumab monotherapy prolongs OS in 1L R/M HNSCC participants with PD-L1 ≥20 CPS compared to standard treatment.
  - Hypothesis (H8): Pembrolizumab monotherapy prolongs OS in 1L R/M HNSCC participants with PD-L1 ≥1 CPS compared to standard treatment.
  - Hypothesis (H9): Pembrolizumab monotherapy is non-inferior to standard treatment in terms of OS in all 1L R/M HNSCC participants.
  - Hypothesis (H10): Pembrolizumab monotherapy prolongs OS in all 1L R/M HNSCC participants compared to standard treatment.

- Objective: To evaluate OS in 1L R/M HNSCC participants, treated with pembrolizumab in combination with chemotherapy versus standard treatment.
  - Hypothesis (H11): Pembrolizumab in combination with chemotherapy prolongs OS in 1L R/M HNSCC participants with PD-L1 ≥20 CPS compared to standard treatment.
  - Hypothesis (H12): Pembrolizumab in combination with chemotherapy prolongs OS in 1L R/M HNSCC participants with PD-L1 ≥1 CPS compared to standard treatment.
  - Hypothesis (H13): Pembrolizumab in combination with chemotherapy is non-inferior to standard treatment in terms of OS in all 1L R/M HNSCC participant.

- Hypothesis (H14): Pembrolizumab in combination with chemotherapy prolongs OS in all 1L R/M HNSCC participants compared to standard treatment.

Sample size

The study was planned to randomise approximately 825 subjects with 1:1:1 ratio into the treatment groups of pembrolizumab monotherapy, a combination of pembrolizumab with chemotherapy and standard treatment, stratified by PD-L1 expression (strongly positive vs. not strongly positive as defined by TPS 50% cut-point), HPV status (HPV+ vs. HPV-), and ECOG performance status (0 vs. 1). The prevalence of the PD-L1 positive sub-population was projected to be 50% for the PD-L1 CPS 20 and 80% for the PD-L1 CPS ≥1 subpopulation. Two interim efficacy analyses were planned in this study. A Hwang-Shih-DeCani alpha-spending function with gamma parameter (-4) was constructed to implement group sequential efficacy boundaries to control the Type I error for each PFS and each OS hypothesis.

PFS

Two PFS analyses are planned at interim analyses 1 and 2. The PFS hypotheses were tested at interim analysis 1, and a second test of PFS, which will be the final PFS analyses, will occur at interim analysis 2 only if superior PFS is not declared at interim analysis 1. At the time of final PFS analysis:

- H1, H4: for patients with PD-L1 CPS 20, it was expected that approximately 237 PFS events will have been observed between one experimental treatment and standard treatment. The study has 90% power with each experimental treatment (pembrolizumab monotherapy [H1] or pembrolizumab in combination with chemotherapy [H4]) to detect a hazard ratio of 0.58 vs. standard treatment at alpha = 0.19% (one-sided).

- H2, H5: for patients with PD-L1 CPS ≥1, it was expected that approximately 378 PFS events will have been observed between one experimental treatment and standard treatment. The study has 98.6% power with each experimental treatment (pembrolizumab monotherapy [H2] or pembrolizumab in combination with chemotherapy [H5]) to detect a hazard ratio of 0.59 vs. standard treatment

at alpha = 0.19% (one-sided). (Note that H2 will be tested only if H1 is rejected and H5 will be tested only if H4 is rejected)

- H3: for all patients, it is expected that approximately 474 PFS events will have been observed between pembrolizumab monotherapy and standard treatment. The study has 99.6% power with pembrolizumab monotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.19% (one-sided). (Note that H3 will be tested only if H1 and H2 are rejected under the multiplicity strategy.)

- H6: for all patients, it is expected that approximately 474 PFS events will have been observed between pembrolizumab in combination with chemotherapy and standard treatment. The study has 97.7% power with pembrolizumab in combination with chemotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.02% (one-sided).

The PFS sample size calculation was based on the following assumptions: 1) PFS follows an exponential distribution with a median of 6 months in the standard treatment arm; 2) hazard ratios are 0.58 for patients with PD-L1 CPS 20, 0.59 for patients with PD-L1 CPS ≥1 and 0.6 for all patients; 3) an enrolment period of 21 months; 4) at least 9 months follow-up at interim analysis 1, and 17 months follow-up at interim analysis 2; and 5) a yearly dropout rate of 5%.

OS

Three OS analyses are planned at interim analyses 1, 2 and the final analysis. At the time of the final analysis:

- H7, H11: for patients with PD-L1 CPS 20, it was expected that approximately 222 deaths will have been observed between one experimental treatment and standard treatment. The study has 90.5% power with each experimental treatment (pembrolizumab monotherapy [H7] or pembrolizumab in combination with chemotherapy [H11]) to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.7% (one-sided).

- H8, H12: for patients with PD-L1 CPS ≥1, it was expected that approximately 359 deaths will have been observed between one experimental treatment and standard treatment. The study has 94.3% power with each experimental treatment (pembrolizumab monotherapy [H8] or pembrolizumab in combination with chemotherapy [H12]) to detect a hazard ratio of 0.65 vs. standard treatment at alpha = 0.7% (one-sided). (Note that H8 will be tested only if H7 is rejected and H12 will be tested only if H11 is rejected.)

- H9, H13: for all patients, it was expected that approximately 455 deaths will have been observed between one experimental treatment and standard treatment. The study has 87.85% power with a hazard ratio of 0.85 to establish non-inferiority (NI margin = 1.2) for each experimental treatment (pembrolizumab monotherapy [H9] or pembrolizumab in combination with chemotherapy [H13]) vs. standard treatment at alpha = 0.7% (one-sided). (Note that H9 will be tested only if H7 and H8 are rejected under the multiplicity strategy.)

- H10, H14: for all subjects, it was expected that approximately 455 deaths will have been observed between one experimental treatment and standard treatment. The study has 90.4% power with each experimental treatment (pembrolizumab monotherapy [H10] or pembrolizumab in combination with chemotherapy [H14]) to detect a hazard ratio of 0.7 vs. standard treatment at alpha = 0.7% (one-sided). (Note that H10 will be tested only if H7 through H9 are rejected under the multiplicity strategy and H14 will be tested only if non-inferiority is established for H13.)

The OS sample size calculation is based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 10 months in the standard treatment arm; 2) the hazard ratios are 0.6 for patients with PD-L1 CPS 20, 0.65 for subjects with PD-L1 CPS ≥1, 0.7 for all subjects for the superiority hypotheses, and 0.85 for all subjects for the non-inferiority hypotheses; 3) an enrolment period of 21 months; 4) at least 23 months follow-up; and 5) a yearly dropout rate of 2%.

The assumptions for median PFS of 6 months and median OS of 10 months in the standard treatment arm is based on the median PFS and median OS estimates from the EXTREME trial. The assumptions do not take into account potential prognostic implications in a biomarker selected population. As such, the median of the standard treatment arm for the PD-L1 positive subgroups may be more or less than 6 months for PFS and more or less than 10 months for OS.

Analysis population

The analysis of primary efficacy endpoints were based on the intention-to-treat (ITT) population, i.e., patients were included in the treatment group to which they are randomised.

Statistical methods used to compare groups

Progression-free survival

The non-parametric Kaplan-Meier method was used to estimate the PFS curve in each treatment group. The treatment difference in PFS were assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate were reported. The same stratification factors used for randomisation were as the stratification factors in both the stratified log-rank test and the stratified Cox model for the analyses in all patients. For analyses in the PD-L1 strongly positive subgroup, HPV status and ECOG status were used as the stratification factors.

Since disease progression was assessed periodically, progressive disease (PD) could occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the patients who had PD, the true date of disease progression was approximated by the date of the first assessment at which PD was objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Death was always considered as a confirmed PD event. In order to evaluate the robustness of the PFS

endpoint, two sensitivity analyses with different sets of censoring rules were performed as shown in Table 10.

Table 10 Censoring rules for primary and sensitivity analyses of PFS in the KEYNOTE-048 study

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

Overall survival

The Kaplan-Meier method was used to estimate the survival curves. The treatment difference in survival was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate was reported. The same stratification factors used for randomisation were used as the stratification factors in both the stratified log-rank test and the stratified Cox model for the analyses in all subjects. For analyses in the PD-L1 strongly positive subgroup, HPV status and ECOG status were used as the stratification factors.

Overall survival - Adjustment for the post-study treatment switch-over of control arm subjects to another anti-PD-1 treatment

Since subjects in the standard therapy arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arms, they may switch to another immune checkpoint inhibitor following confirmation of progressive disease. Another anti PD-1 treatment (nivolumab) is currently approved and widely used as a treatment for HNSCC after platinum-base chemotherapy (TA490) (20). However, NICE have issued a position paper which outlines that drugs recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals (21). Therefore, the use of PD-1 targeted treatments following disease progression in KEYNOTE-048 has been adjusted for using treatment switching adjustment methods for subsequent treatment with immune checkpoint inhibitors, to reflect the actual benefit of patients receiving the regimens in the control arm in the absence of treatment switching to alternative therapies.

Three statistical methods were applied to adjust for treatment switching:

- Simplified 2-stage method
- Rank preserving structural failure (RPSFT)
- Inverse probability of censoring method (IPCW)

The details of these methods are described in Appendix L.

Interim analyses

Two interim analyses (IA1 and IA2) for efficacy were planned, followed by the final analyses (FA). The details of these are provided in Appendix L. The results of the IA2 analyses are used in this submission.

Secondary efficacy analyses

Statistical methods used to compare groups

Objective response rate

Stratified Miettinen and Nurminen's method was used for comparison of the objective response rates between the treatment groups (22). A 95% confidence interval for the difference in response rates between the experimental arms and the standard therapy arm was calculated. The same stratification factors used for randomisation were used as the stratification factors in the analysis of all patients. For analyses in the PD-L1 strongly positive subgroup, HPV status and ECOG status were used as the stratification factors. Sensitivity analyses were performed for comparison of ORR based on investigator's assessment. Patients with missing data were considered non-responders.

Response duration

Response duration was summarised descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who showed a complete response or partial response were included in this analysis. Response duration was assessed using RECIST 1.1 separately by central radiologists' review and by investigator assessment.

Safety analyses

Analysis population

All safety analyses were conducted using data from the all subjects as treated (ASaT) population, which included all randomised participants who received at least 1 dose of study treatment. Participants were included in the treatment group corresponding to the study treatment they actually received.

Statistical methods used to compare groups

The analysis of safety results followed a tiered approach (see Table 11). No Tier 1 safety parameters were pre-specified in the protocol. The between-treatment differences were planned to be analysed using the Miettinen and Nurminen method (22). Continuous measures such as changes from baseline in laboratory test values

were considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values were provided by treatment group.

Table 11 Safety analyses in the KEYNOTE-048 study

Safety tier	Safety endpoint	95% CI for treatment comparison	Descriptive statistics
Tier 2	Any AE	X	X
	Any Grade 3-5 AE	X	X
	Any Serious AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death	X	X
Tier 3	Specific AEs, SOCs		X
	Change from Baseline Results (Labs)		X

X represents analyses that were conducted.

Subgroup analyses

The between-group treatment effect for OS, PFS, and ORR (with a nominal 95% CI) was estimated and plotted within each category of the following classification variables:

- Stratification factors
    - HPV status (HPV positive vs. HPV negative)
    - ECOG status (0 vs. 1)
- PD-L1 expression level defined by CPS (≥ 20 vs. not ≥ 20; and ≥ 1 vs. not ≥ 1)
- Age category (<65 vs. ≥65 years)
- Sex (female vs. male)
- Race (white vs. all others)

- Region (North America vs. Europe vs. rest of the world)
- Smoking status (never vs. former vs. current)
- Disease status (recurrent vs. metastatic)

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of the KEYNOTE-048 trial is described in Appendix D section D1.3.

Consideration of how closely the trial reflects routine clinical practice in England

Treatments established as routine clinical practice for the first-line treatment of R/M HNSCC in the NHS are platinum-based chemotherapy regimens and cetuximab in combination with platinum-based chemotherapy (only if the cancer started in the oral cavity) (16, 17). The chemotherapy regimens used in the standard treatment and pembrolizumab plus chemotherapy arms of the KEYNOTE-048 study are comparable to the platinum-based chemotherapy regimens currently used in this indication in the NHS. The comparator of the KEYNOTE-048 study, cetuximab in combination with platinum-based chemotherapy, is only recommended for use in the UK in a the subset of patients with R/M HNSCC, therefore network meta-analyses (NMAs) have been conducted using the results of the KEYNOTE-048 study as well as other relevant studies identified via a systematic literature review (described in Appendix D) in order to compare pembrolizumab (monotherapy and in combination therapy with platinum-based chemotherapy regimens) with the platinum-based chemotherapy regimens used in UK clinical practice in this indication. It should be noted that cetuximab in combination with platinum-based chemotherapy regimens can be considered at least equal in efficacy to the platinum-based chemotherapy regimens used in routine clinical practice in the UK (as suggested in the NMA results in section B.2.9), and so any data from the KEYNOTE-048 study that shows that treatment with pembrolizumab has superior efficacy to treatment with cetuximab in combination with platinum-based chemotherapy regimens (as shown in section B.2.6) would suggest that

pembrolizumab could offer a significant step-change in benefit for patients with R/M HNSCC in the UK.

R/M HNSCC is an aggressive and devastating disease that is symptomatic, significantly destructive, and severely impactful on the daily life of patients. To capture how pembrolizumab has on quality of life, in absolute terms and in comparison to cetuximab in combination with platinum-based chemotherapy, health-related quality of life assessed using the EORTC QLQ-C30, EORTC QLQ-H&N35, and EuroQol EQ-5D instruments.

While the KEYNOTE-048 study was a global study that included patients from 229 centres in 37 countries, 35% of the total study population (34.2% of the study population in CPS≥1 subgroup) were patients in Europe and two of the centres were in the UK, the baseline characteristics of the study population are likely to be similar to and representative of those typically seen in UK clinical practice.

B.2.6 Clinical effectiveness results of the relevant trials

Please note that all clinical effectiveness results shown in section B.2.6 are from the KEYNOTE-048 second interim analysis (IA2)

B.2.6.1 Pembrolizumab monotherapy in patients with CPS≥1

Extent of exposure

The median duration of exposure was [redacted] days for pembrolizumab monotherapy, and 148 days for standard treatment (Table 12). The mean number of cycles was [redacted] (range: [redacted] to [redacted]) for patients treated with pembrolizumab monotherapy, and 8.46 cycles (range: 1.00 to 48.0) for patients treated with standard treatment (Table 12). More participants in the pembrolizumab monotherapy group received treatment for ≥12 months than those in the standard treatment group (Table 13).

Table 12 Extent of Exposure, pembrolizumab monotherapy versus control, ASaT population, CPS≥1 population

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	256		245	
Number of administrations[†]				
1 Cycle	[redacted]	[redacted]	20	(8.2)
2 Cycles	[redacted]	[redacted]	9	(3.7)
3 Cycles	[redacted]	[redacted]	30	(12.2)
4 Cycles	[redacted]	[redacted]	18	(7.3)
5 Cycles	[redacted]	[redacted]	18	(7.3)
6 Cycles	[redacted]	[redacted]	22	(9.0)
>=7 Cycles	[redacted]	[redacted]	128	(52.2)
Mean	[redacted]		8.46	
Median	[redacted]		7.00	
SD	[redacted]		7.75	
Range	[redacted] to [redacted]		1.00 to 48.0	
Number of days on therapy (days)				
Mean	[redacted]		178.97	
Median	[redacted]		148.00	
SD	[redacted]		170.60	
Range	[redacted] to [redacted]		1.00 to 1073.0	

[†] For Control arm, if any drug was administered during a cycle, it is counted as one administration.

For subjects who received second course treatment, doses administered in second course are excluded.

Table 13 Exposure by duration, pembrolizumab monotherapy versus control, ASaT population, CPS≥1 population

	Pembrolizumab (N=256)		Cetuximab + Chemotherapy (N=245)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	[redacted]	[redacted]	245	120
≥ 1 m	[redacted]	[redacted]	221	119
≥ 3 m	[redacted]	[redacted]	173	111
≥ 6 m	[redacted]	[redacted]	90	80
≥ 12 m	[redacted]	[redacted]	17	32

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.
For subjects who received second course treatment, doses administered in second course are excluded.

Overall survival

Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

Comparing pembrolizumab monotherapy with standard treatment in participants whose tumours express PD-L1 CPS ≥1 at the second interim analysis (IA2), pembrolizumab monotherapy demonstrated a statistically significant and clinically meaningful OS benefit compared with standard treatment (HR 0.78 [0.64, 0.96], p=0.00855) (Table 14). Median OS was 12.3 months (95% CI: 10.8, 14.9 months) versus 10.3 months (95% CI: 9.0, 11.5 months) (Table 14). By Kaplan-Meier (KM) estimation, OS rate at 12 months was 51.0% versus 43.6%, and at 18 months was 39.5% versus 26.3% (Table 15), the extended tail of the KM curve suggests long-term survival benefits from pembrolizumab monotherapy treatment (Figure 5).

Table 14 OS, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS† (Months) (95% CI)	OS Rate at Months 12 in %† (95% CI)
Pembrolizumab	257	177 (68.9)	3519.3	5.0	12.3 (10.8, 14.9)	51.0 (44.7, 57.0)
Cetuximab + Chemotherapy	255	206 (80.8)	3112.4	6.6	10.3 (9.0, 11.5)	43.6 (37.4, 49.6)
Pairwise Comparisons					**Hazard Ratio‡ (95% CI)‡**	**p-Value**
Pembrolizumab vs. Cetuximab + Chemotherapy					0.78 (0.64, 0.96)	0.00855§

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

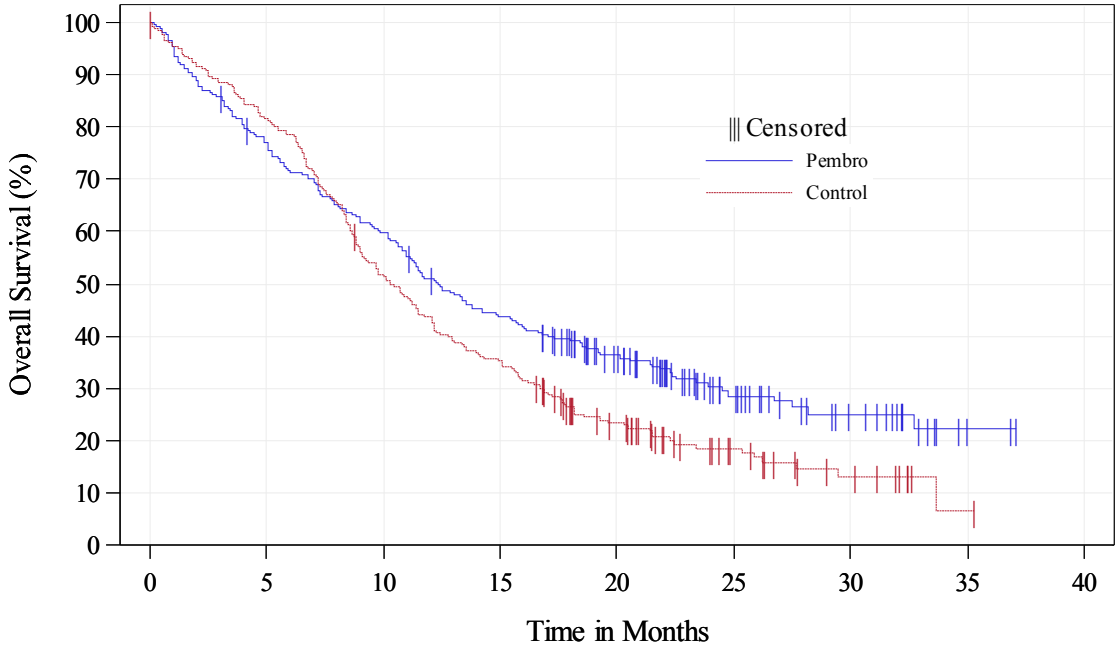
§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

Table 15 OS rate, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
OS rate at 9 Months in (95% CI)†	62.5 (56.2, 68.1)	56.7 (50.3, 62.5)
OS rate at 12 Months in (95% CI)†	51.0 (44.7, 57.0)	43.6 (37.4, 49.6)
OS rate at 18 Months in (95% CI)†	39.5 (33.4, 45.4)	26.3 (21.0, 31.9)

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

Figure 5 Kaplan-Meier estimates of OS, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup



At Risk

Pembro	257	196	152	110	74	34	17	2	0
Control	255	207	131	89	47	21	9	1	0

Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

Table 16 and Figure 6 present the results of the analysis of OS adjusting for treatment post-study switch from control arm to immune checkpoint inhibitors including Kaplan-Meier estimates of OS and estimation of treatment effect (without re-censoring procedure applied). The number of events in control arm is the same in the adjusted analysis as in the unadjusted ITT analysis (206 events). The adjusted HR for OS is 0.74 (95% CI: 0.58; 0.95) with a two-sided p-value of 0.0171 in the pembrolizumab monotherapy arm versus the control arm. Details of the 2-stage methodology for this analysis are provided in Appendix L.

Table 16 Analysis of overall survival, without recensoring, pembrolizumab vs, cetuximab + chemotherapy, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population with CPS≥1

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)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶¶]	p-Value[‖]
Cetuximab + Chemotherapy	255	206 (80.8)	3112.4	6.6	10.3 (9.0, 11.5)	43.6 (37.4, 49.6)	---	---	---
Cetuximab + Chemotherapy, 2-stage adjusted[¶]	255	206 (80.8)	2950.6	7.0	10.1 (9.0, 11.5)	42.7 (36.6, 48.7)	---	---	---
Pembrolizumab	257	177 (68.9)	3519.3	5.0	12.3 (10.8, 14.9)	51.0 (44.7, 57.0)	0.74 (0.58, 0.95)	0.0172	0.0171
Stage 1 model[††]							**Acceleration factor[‡‡]**		
[§] Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching							1.646 (1.199, 2.26)		

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)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio‡ (95% CI)‡	p-Value¶¶	p-Value‖

¶ Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5. The 95% CI is derived by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

¶¶ Two sided p-value based on stratified Cox model, ITT population, analysis not adjusted for treatment switch.

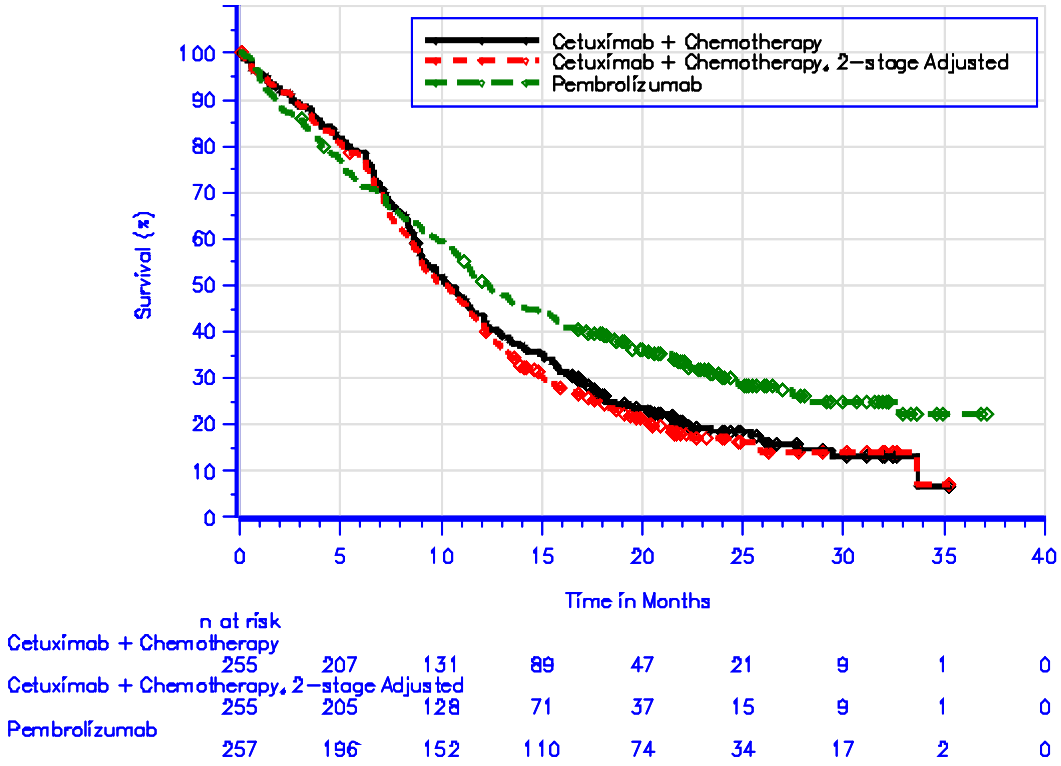
‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for treatment switch.

†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS <20 vs. CPS ≥20), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), hemoglobin at secondary baseline and tumour size at secondary baseline.

§ Patients were eligible to switch if they had documented progression.

‡‡ Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

Figure 6 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, without recensoring, pembrolizumab vs. cetuximab + chemotherapy, ITT population with CPS≥1



Database Cutoff Date: 13JUN2018

Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the rank preserving structural failure (RPSFT) method

Table 17 and Figure 7 present the results of the OS analysis adjusting for receiving subsequent immune checkpoint inhibitors after discontinuation of protocol treatment for the control arm using the RPSFT model without re-censoring. A total of 67/255 (26.3%) of control patients switched to an immune checkpoint inhibitor after discontinuation of the protocol treatment. The RPSFT-adjusted HR for OS is 0.76 (95% CI: 0.60; 0.95) with a two-sided ITT log-rank p-value of 0.0171 for the comparison between pembrolizumab monotherapy versus cetuximab plus chemotherapy.

Table 17 Analysis of overall survival, without recensoring, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, ITT population with CPS≥1, pembrolizumab monotherapy vs. cetuximab + chemotherapy

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS[†] (Months) (95% CI)	Survival Rate at Month 12[†] (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[§]	p-Value[‖]	p-Value[¶]
Cetuximab + Chemotherapy	255	206 (80.8)	3112.4	6.6	10.3 (9.0, 11.5)	43.6 (37.4, 49.6)			
Cetuximab + Chemotherapy, RPSFT adjusted	255	206 (80.8)	3002.5	6.9	10.1 (9.0, 11.5)	43.1 (37.0, 49.1)			
Pembrolizumab	257	177 (68.9)	3519.3	5.0	12.3 (10.8, 14.9)	51.0 (44.7, 57.0)	0.76 (0.60, 0.95)	0.0172	0.0171

Rank-preserving structural failure time (RPSFT) model is used to adjust for the effect in overall survival analysis for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors.

[†] From product-limit (Kaplan-Meier) method.

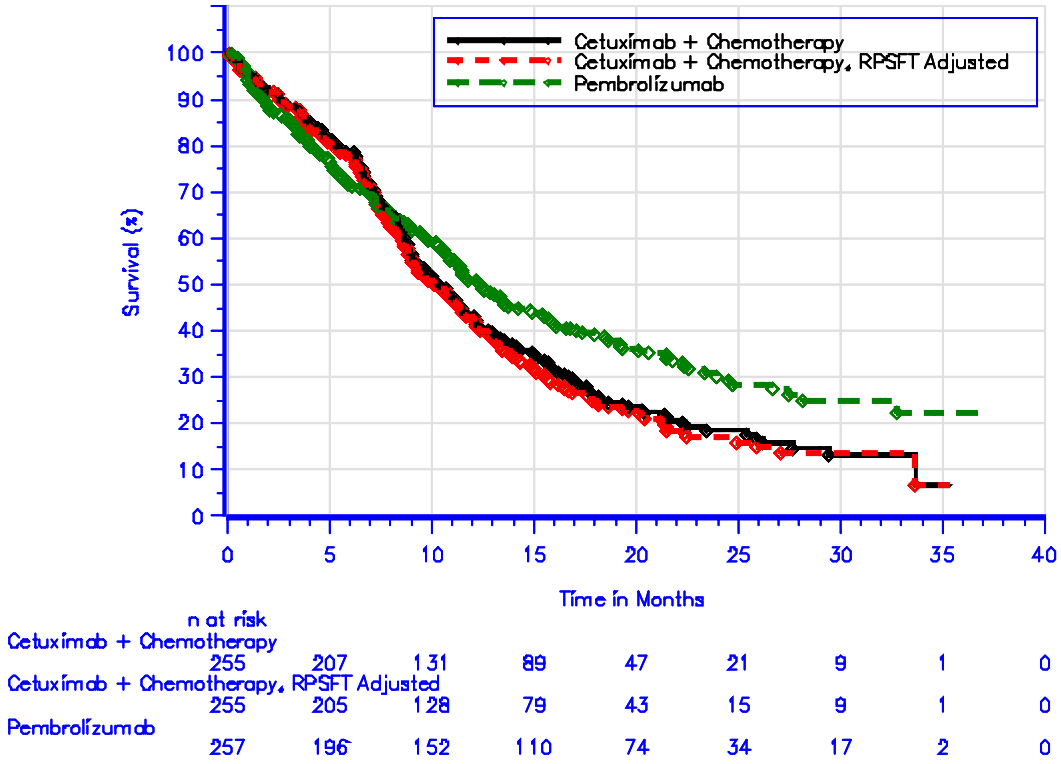
[‡] Based on Cox regression model with Efron′s method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

[§] Obtained by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[‖] Two sided p-value based on stratified Cox model, analysis not adjusted for treatment switch.

[¶] Two-sided p-value based on stratified log-rank test, analysis not adjusted for treatment switch.

Figure 7 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, without recensoring, ITT population with CPS≥1, pembrolizumab vs. cetuximab + chemotherapy



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Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the inverse probability censored weighting (IPCW) method

Of those who switched in the SOC arm, 48/67 (71.6%) subjects died after switching, and therefore 48/206 (23.3%) observed events in the SOC arm were lost due to censoring at the time of switch. Among those who did not switch in the SOC arm, 158/188 (84.0%) deaths were observed, and included in the analysis. Table 18 summarises the results from the weighted Cox proportional hazard regression. The IPCW-adjusted hazard ratio of pembrolizumab versus control is 0.85, with 95% bootstrap percentile confidence interval of 0.69 to 1.06 (bootstrap p-value = 0.1650).

Figure 8 shows the survival curves for the ITT-unadjusted and the IPCW-adjusted control arm compared to the pembrolizumab arm.

Table 18 Analysis of overall survival adjusting for treatment switch to immune checkpoint inhibitors in standard treatment arm using IPCW model comparison pembrolizumab versus cetuximab + chemotherapy, intention-to-treat population with CPS≥1

Treatment	N	Number of Events (%)	Person-Month	Event Rate/100 Person-Month (%)	Median OS† (Month) (95% CI)	Pembrolizumab vs. Cetuximab + Chemotherapy		
						Hazard Ratio†† (95% CI)	p-Value§	p-Value§§
Cetuximab + Chemotherapy	255	206 (80.8)	3112.4	6.6	10.3 (9.0, 11.5)			
Cetuximab + Chemotherapy, IPCW Adjusted	255	158 (62.0)	2646.6	6.0	10.8 (9.7, 12.1)			
Pembrolizumab	257	177 (68.9)	3519.3	5.0	12.3 (10.8, 14.9)	0.85 (0.69, 1.06)	0.1454	0.1650

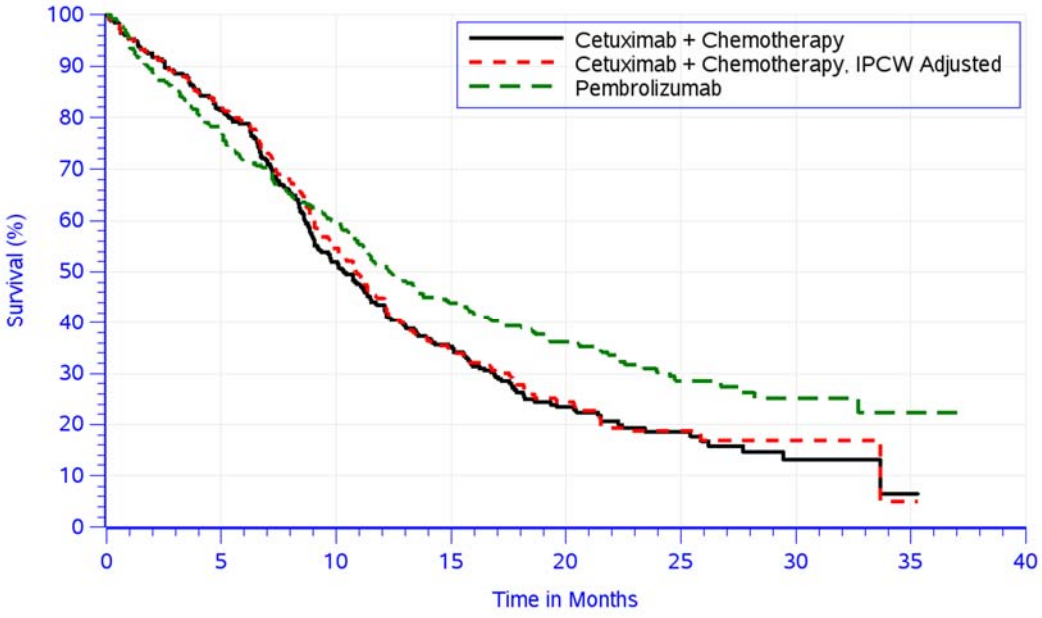
† From product-limit (Kaplan-Meier) method for censored data, if the median OS is reached

†† HR based on Cox regression model with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status, and bootstrap 95% CI. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ Two-sided p-value based on the IPCW log-rank test

§§ Two-sided p-value based on bootstrap percentiles

Figure 8 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received immune checkpoint inhibitors using IPCW comparison pembrolizumab versus cetuximab + Chemotherapy, intention-to-treat population with CPS≥1



n at risk

Cetuximab + Chemotherapy	255	207	131	89	47	21	9	1	0
Cetuximab + Chemotherapy, IPCW Adjusted	255	195	110	64	33	14	9	1	0
Pembrolizumab	257	196	152	110	74	34	17	2	0

Database Cutoff Date: 13JUN2018

Progression-free survival (based on BICR assessment per RECIST 1.1)

No alpha was initially allocated to the PFS PD-L1 CPS≥1 hypothesis. The PFS CPS≥1 hypothesis could only be tested if alpha was passed from a successful CPS≥20 hypothesis as per the multiplicity analysis strategy (as described in section B.2.4). Since the PFS hypothesis for CPS ≥20 was not statistically significant at IA2, the CPS≥1 hypothesis could not be tested statistically at this time.

Comparing the populations of participants with PD-L1 CPS ≥1 in the pembrolizumab monotherapy group with the standard treatment group, median PFS was 3.2 months (95% CI: 2.2, 3.4) versus 5.0 months (95% CI: 4.8, 5.8) (Table 19). By KM estimation,

PFS rates were higher at 12 months (19.6% vs 11.9%) (Table 20 and **Error! Reference source not found.**).

Table 19 PFS based on BICR assessment per RECIST 1.1, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median PFS† (Months) (95% CI)	PFS Rate at Months 6 in %† (95% CI)
Pembrolizumab	257	226 (87.9)	1659.9	13.6	3.2 (2.2, 3.4)	28.1 (22.7, 33.7)
Cetuximab + Chemotherapy	255	231 (90.6)	1634.4	14.1	5.0 (4.8, 5.8)	43.0 (36.8, 49.1)
Pairwise Comparisons					**Hazard Ratio‡ (95% CI)‡**	**p-Value**
Pembrolizumab vs. Cetuximab + Chemotherapy					1.16 (0.96, 1.39)	0.93303§

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

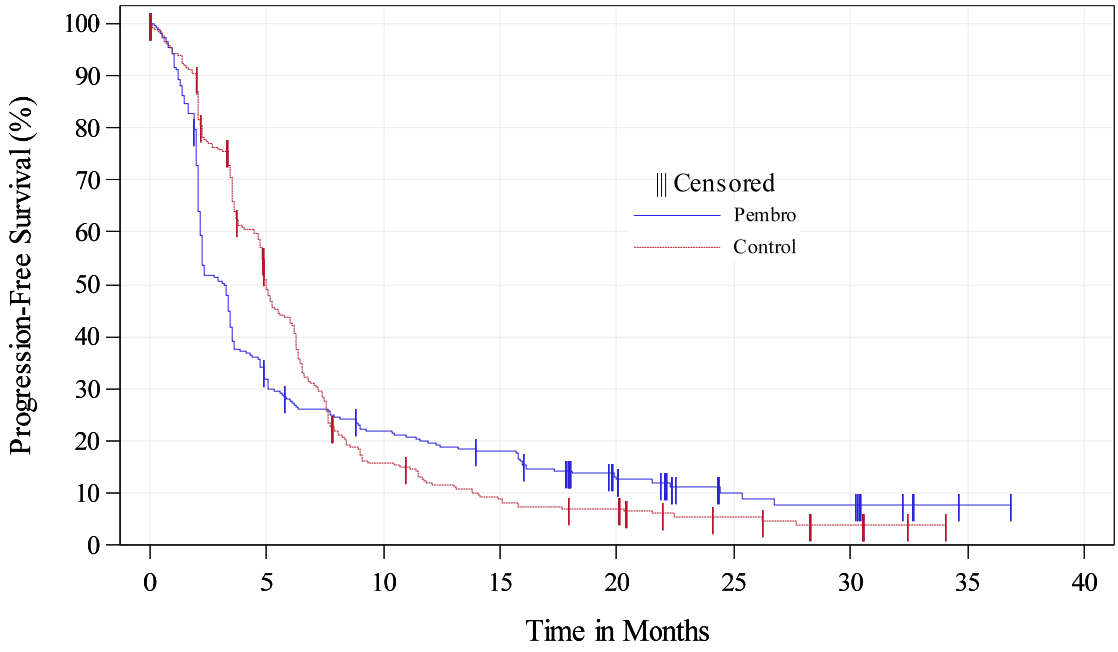
Table 20 Summary of PFS rate over time based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
PFS rate at 6 Months in (95% CI)†	28.1 (22.7, 33.7)	43.0 (36.8, 49.1)
PFS rate at 9 Months in (95% CI)†	22.5 (17.5, 27.8)	18.5 (13.8, 23.6)
PFS rate at 12 Months in (95% CI)†	19.6 (15.0, 24.7)	11.9 (8.2, 16.4)

BICR = Blinded Independent Central Review

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

Figure 9 Kaplan-Meier estimates of PFS based on BICR assessment per RECIST 1.1, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup



At Risk

Pembro	257	80	54	43	23	9	7	1	0
Control	255	119	37	20	15	8	4	0	0

Response rate

Comparing the populations of participants with PD-L1 CPS ≥1 in the pembrolizumab monotherapy group with the standard treatment group, the ORR was 19.1% (95% CI: 14.5, 24.4) versus 34.9% (95% CI: 29.1, 41.1) (Table 21). The BOR summary showed that a smaller proportion of participants treated with pembrolizumab achieved an objective response compared to participants treated with standard treatment. However, more participants achieved a complete response in the pembrolizumab monotherapy group than the standard treatment group (Table 22).

Table 21 Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1, pembrolizumab monotherapy vs. control, ITT population, CPS≥20 subgroup

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembrolizumab	257	49	19.1 (14.5,24.4)	-15.9 (-23.4, -8.3)	1.0000
Cetuximab + Chemotherapy	255	89	34.9 (29.1,41.1)		

BICR = Blinded Independent Central Review

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive); in case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is >=5; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Table 22 Summary of best objective response with confirmation based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	257		255	
Complete Response (CR)	14	(5.4)	7	(2.7)
Partial Response (PR)	35	(13.6)	82	(32.2)
Objective Response (CR+PR)	**49**	**(19.1)**	**89**	**(34.9)**
Stable Disease (SD)	72	(28.0)	83	(32.5)
Progressive Disease (PD)	100	(38.9)	34	(13.3)
Non-CR/Non-PD (NN)	11	(4.3)	11	(4.3)
Not Evaluable (NE)	5	(1.9)	2	(0.8)
No Assessment	20	(7.8)	36	(14.1)

BICR = Blinded Independent Central Review

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

Duration of response

Comparing the populations of all participants in the pembrolizumab monotherapy group with the standard treatment group:

- The median time to response was similar (approximately 2.1 months) (Table 23).
- Median response duration was longer, 20.9 months (range 1.5+ to 34.8+ months) versus 4.5 months (range 1.2+ to 30.6+ months) (Table 23).
- There was a higher proportion of responders with an estimated response duration ≥6 months (36 [75.7%] versus 32 [38.8%]) (Table 23 and Figure 10).

A summary of the reasons that participants with a response based on RECIST 1.1 per BICR were censored from the DOR analysis is provided in (Table 24).

Table 23 Summary of time to response and duration of response based on BICR per RECIST 1.1 in subjects with confirmed response, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
Number of subjects with response†	49	89
Time to Response (months)		
Mean (SD)	3.1 (1.8)	2.4 (0.8)
Median (Range)	2.1 (1.5-9.1)	2.1 (1.3-6.2)
Response Duration‡ (months)		
Median (Range)	20.9 (1.5+ - 34.8+)	4.5 (1.2+ - 28.6+)
Number (%‡) of Subjects with Extended Response Duration:		
≥6 months	36 (78.9)	24 (36.0)

† Includes subjects with confirmed complete response or partial response.

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

"+" indicates there is no progressive disease by the time of last disease assessment.

Figure 10 Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

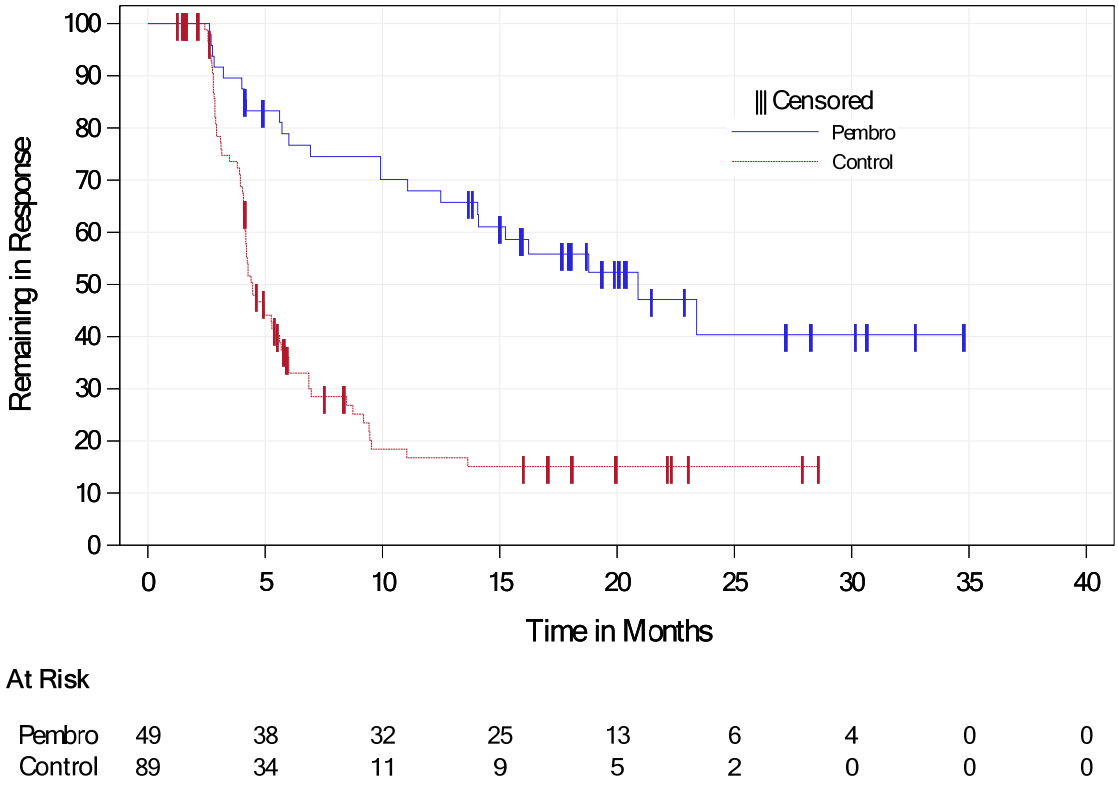


Table 24 Summary of response outcome in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
Number of Subjects with Response†	49	89
Subjects Who Progressed or Died‡ (%)	**23 (46.9)**	**65 (73.0)**
Range of DOR (months)	2.6 to 23.4	2.4 to 13.6
Censored Subjects (%)	**26 (53.1)**	**24 (27.0)**
Subjects who missed 2 or more consecutive disease assessments	1 (2.0)	9 (10.1)
Subjects who started new anti-cancer treatment	2 (4.1)	6 (6.7)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	0 (0.0)	2 (2.2)
Ongoing response§	23 (46.9)	7 (7.9)
≥6 months	23 (46.9)	7 (7.9)
Range of DOR (months)	13.6+ to 34.8+	16.0+ to 28.6+

† Includes subjects with a confirmed complete response or partial response.

‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment.

Health-related quality of life

EORTC QLQ-C30

The baseline global health status/QoL scores were similar between the pembrolizumab monotherapy and cetuximab in combination with chemotherapy groups (Table 25). At Week 15 no clinically meaningful differences were observed between groups, the mean change from baseline in the global health status/QOL score remained stable in both the pembrolizumab monotherapy group (LS mean=[redacted]) and the cetuximab in combination with chemotherapy group (LS mean=[redacted]). The difference in LS means between pembrolizumab monotherapy and cetuximab in combination with chemotherapy at Week 15 was -[redacted]) (Table 25). A summary of the empirical mean change from baseline over time for the EORTC QLQ-C30 global health status/QoL scores is displayed in Figure 11. Global health status/QoL scores remained stable over time in both treatment groups through Week 51.

Time to deterioration in the EORTC QLQ-C30 global health status/QoL score for pembrolizumab monotherapy was similar when compared with cetuximab in combination with chemotherapy ([redacted]) (Table 26 and Figure 12). Similarly, time to deterioration in the in the EORTC QLQ-H&N35 pain score ([redacted]

[redacted]) (Table 27 and Figure 13) and swallowing score ([redacted]) (Table 28 and Figure 14) for pembrolizumab monotherapy were similar when compared with cetuximab in combination with chemotherapy, respectively.

Table 25 Analysis of change from baseline of EORTC QLQ-C30 Global Health Status/QoL Scales at Week 15, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**LS Mean (95% CI)[†]**
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Means (95% CI)**	**p-Value**
Pembrolizumab vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

Figure 11 Empirical mean change from baseline in EORTC QLQ-C30 Global Health Status/QoL across time, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

Table 26 Analysis of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

	Pembrolizumab (N=252)	Cetuximab + Chemotherapy (N=238)
Number of Events (%)		
Number of Censored (%)		
Kaplan-Meier Estimates (Months)†		
Median (95% CI)	. (., .)	. (., .)
Q1, Q3		
vs Cetuximab + Chemotherapy		
Hazard Ratio (95% CI)‡		
p-value§		

	Pembrolizumab (N=252)	Cetuximab + Chemotherapy (N=238)

† 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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).

Figure 12 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

Table 27 Analysis of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

	Pembrolizumab (N=253)	Cetuximab + Chemotherapy (N=238)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)†		
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy		
Hazard Ratio (95% CI)‡	[redacted]	
p-value§	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).

Figure 13 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

Table 28 Analysis of time to true deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

	Pembrolizumab (N=253)	Cetuximab + Chemotherapy (N=238)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)[†]		
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy		
Hazard Ratio (95% CI)[‡]	[redacted]	
p-value[§]	[redacted]	

	Pembrolizumab (N=253)	Cetuximab + Chemotherapy (N=238)

† 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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).

Figure 14 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

EQ-5D

Analyses of the mean change from baseline to Week 15 in the EQ-5D visual analog scale and utility scores in the PRO FAS population are provided in Table 29 and Table 30. In the PRO FAS population, participants in both the pembrolizumab monotherapy and standard treatment groups exhibited generally stable scores in the EQ-5D visual analog scale and utility scores at Week 15.

Table 29 Analysis of change from baseline of EQ-5D VAS at Week 15, pembrolizumab monotherapy versus control, FAS population, CPS≥1 population

Treatment	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	247	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + chemotherapy	226	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Means (95% CI)**	**p-Value**
Pembrolizumab vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

Table 30 Analysis of change from baseline of EQ-5D Utility Score (using European Algorithm) at Week 15, pembrolizumab monotherapy versus control, FAS population, CPS≥1 population

Treatment	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Means (95% CI)**	**p-Value**
Pembrolizumab vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

Treatment	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.2.6.2 Pembrolizumab + chemotherapy combination therapy in patients with CPS≥1

Extent of exposure

The median duration of exposure was [redacted] days for pembrolizumab plus chemotherapy and 148 days for standard treatment (Table 31). The mean number of cycles was [redacted] (range: [redacted] to 35.0) for patients treated with pembrolizumab plus chemotherapy and 8.46 cycles (range: 1.00 to 48.0) for participants treated with standard treatment (Table 31). The mean number of chemotherapy cycles was also similar in the pembrolizumab plus chemotherapy and standard treatment groups (Table 32). More participants in the pembrolizumab plus chemotherapy group received treatment for ≥6 months and ≥12 months than those in the standard treatment group (Table 33).

Table 31 Extent of Exposure, pembrolizumab + chemotherapy combination therapy versus control, ASaT population, CPS≥1 population

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	237		245	
Number of administrations[†]				
1 Cycle	[redacted]	[redacted]	20	(8.2)
2 Cycles	[redacted]	[redacted]	9	(3.7)
3 Cycles	[redacted]	[redacted]	30	(12.2)
4 Cycles	[redacted]	[redacted]	18	(7.3)
5 Cycles	[redacted]	[redacted]	18	(7.3)
6 Cycles	[redacted]	[redacted]	22	(9.0)
>=7 Cycles	[redacted]	[redacted]	128	(52.2)
Mean	[redacted]		8.46	
Median	[redacted]		7.00	
SD	[redacted]		7.75	
Range	[redacted]		1.00 to 48.0	
Number of days on therapy (days)				
Mean	[redacted]		178.97	
Median	[redacted]		148.00	
SD	[redacted]		170.60	
Range	[redacted]		1.00 to 1073.0	

[†] For Pembro Combo and Control arms, if any drug was administered during a cycle, it is counted as one administration.

For subjects who received second course treatment, doses administered in second course are excluded.

Table 32 Summary of drug administration by dose regimen, pembrolizumab + chemotherapy combination therapy versus control, ASaT population, CPS≥1 population

Number of Cycles	Pembrolizumab + Chemotherapy (N = 237)			Cetuximab + Chemotherapy (N = 245)		
	Pembrolizumab n (%)	Platinum n (%)	5-FU n (%)	Cetuximab n (%)	Platinum n (%)	5-FU n (%)
1	[redacted]	[redacted]	[redacted]	24 (9.8)	20 (8.2)	22 (9.0)
2	[redacted]	[redacted]	[redacted]	9 (3.7)	14 (5.7)	17 (6.9)
3	[redacted]	[redacted]	[redacted]	30 (12.2)	32 (13.1)	31 (12.7)
4	[redacted]	[redacted]	[redacted]	18 (7.3)	25 (10.2)	26 (10.6)
5	[redacted]	[redacted]	[redacted]	19 (7.8)	20 (8.2)	17 (6.9)
6	[redacted]	[redacted]	[redacted]	18 (7.3)	132 (53.9)	130 (53.1)
>=7	[redacted]	[redacted]	[redacted]	127 (51.8)	0 (0.00)	0 (0.00)
Mean	[redacted]	[redacted]	[redacted]	8.4	4.7	4.6
SD	[redacted]	[redacted]	[redacted]	7.8	1.7	1.8
Median	[redacted]	[redacted]	[redacted]	7.0	6.0	6.0
Range	[redacted]	[redacted]	[redacted]	1 to 48	1 to 6	1 to 6

For subjects who received second course treatment, doses administered in second course are excluded.

Table 33 Exposure by Duration, pembrolizumab + chemotherapy combination therapy versus control, ASaT population, CPS≥1 population

	Pembrolizumab + Chemotherapy (N=237)		Cetuximab + Chemotherapy (N=245)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	[redacted]	[redacted]	245	120
≥ 1 m	[redacted]	[redacted]	221	119
≥ 3 m	[redacted]	[redacted]	173	111
≥ 6 m	[redacted]	[redacted]	90	80
≥ 12 m	[redacted]	[redacted]	17	32

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.
For subjects who received second course treatment, doses administered in second course are excluded.

Overall survival

Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

As of the database cutoff date for IA2, in participants whose tumours expressed PD-L1 CPS≥1, a clinically meaningful difference in OS was seen between pembrolizumab plus chemotherapy and standard treatment. No alpha was initially allocated to the OS hypothesis for the PD-L1 CPS≥1 population. The CPS≥1 OS hypothesis could only be tested if alpha was passed from a successful CPS≥20 hypothesis as per the multiplicity analysis strategy. Since the OS hypothesis for CPS≥20 was not statistically significant at IA2, the CPS≥1 hypothesis could not be tested statistically at this time.

The comparison between pembrolizumab plus chemotherapy group with the standard treatment group results in a HR for OS of 0.71 (95% CI: 0.57, 0.88), a clinically meaningful benefit that was not tested statistically, and a median OS of 13.6 months (95% CI: 10.7, 15.5 months) versus 10.4 months (95% CI: 9.1, 11.7 months) (Table 34). However, it should be noted that the clinically meaningful difference in OS seen between pembrolizumab plus chemotherapy and standard treatment in the PD-L1 CPS≥1 population has been confirmed to be statistically significant at the final analysis (HR 0.65, 95% CI 0.53-0.80, p<0.0001; median 13.6 months versus 10.4 months) (23).

The final analyses clinical effectiveness data will be provided at a later date. By KM estimation, OS rate at 12 months was 55.0% versus 43.5 %, and at 18 months was 39.1% versus 26.4% (Table 35 and Figure 15).The extended tail of the KM curve suggests long-term survival benefits from combination treatment (Figure 15).

Table 34 Analysis of OS, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

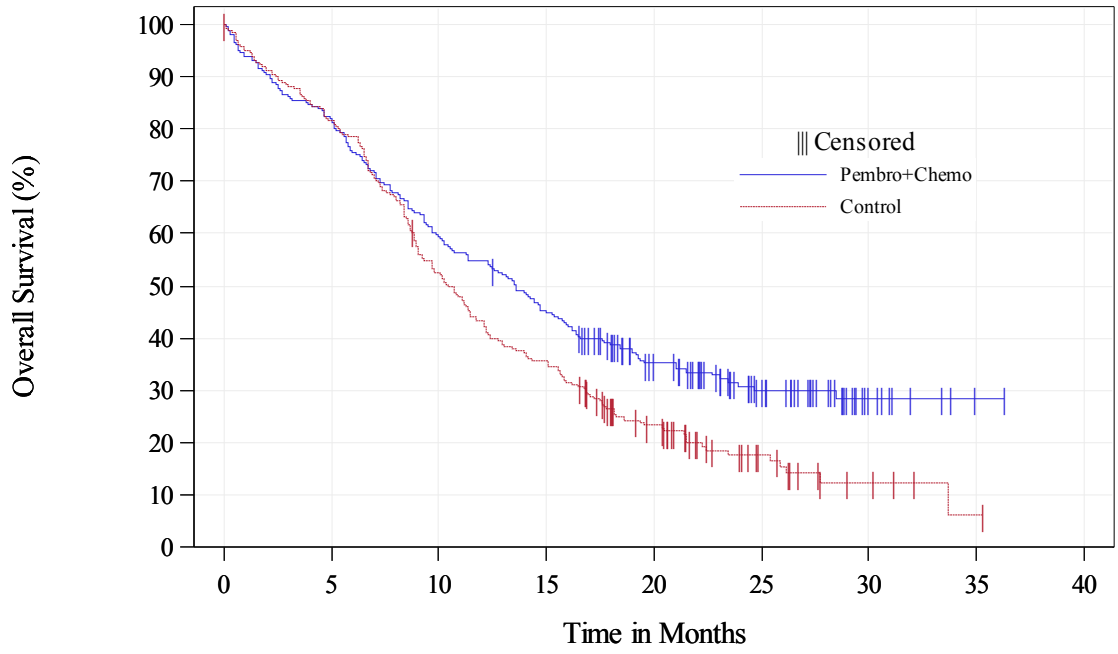
Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Chemotherapy	242	164 (67.8)	3416.4	4.8	13.6 (10.7, 15.5)	55.0 (48.5, 61.0)
Cetuximab + Chemotherapy	235	190 (80.9)	2827.6	6.7	10.4 (9.1, 11.7)	43.5 (37.0, 49.7)
Pairwise Comparisons					**Hazard Ratio‡ (95% CI)‡**	**p-Value**
Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					0.71 (0.57, 0.88)	0.00072§

† 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 ECOG and HPV status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status until event count in every stratum is ≥5.

§ One-sided p-value based on log-rank test stratified by ECOG and HPV status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status until event count in every stratum is ≥5.

Figure 15 Kaplan-Meier estimates of OS, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup



At Risk

Pembro+Chemo	242	197	144	109	67	36	9	1	0
Control	235	191	122	83	42	16	5	1	0

Table 35 OS rate, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
OS rate at 9 Months in (95% CI)†	64.0 (57.7, 69.7)	57.7 (51.1, 63.7)
OS rate at 12 Months in (95% CI)†	55.0 (48.5, 61.0)	43.5 (37.0, 49.7)
OS rate at 18 Months in (95% CI)†	39.1 (32.9, 45.2)	26.4 (20.9, 32.3)

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

Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

Table 36 and Figure 16 present the results of the analysis of OS adjusting for treatment post-study switch from control arm to immune checkpoint inhibitors including Kaplan-Meier estimates of OS and estimation of treatment effect (without re-censoring procedure applied). The number of events in control arm is the same in the adjusted analysis as in the unadjusted ITT analysis (85 events). The adjusted HR

for OS is 0.67 (95% CI: 0.48; 0.94) with a two-sided p-value of 0.0197 in the pembrolizumab + chemotherapy arm vs. the control arm comparison. Details of the 2-stage methodology for this analysis are provided in Appendix L.

Table 36 Analysis of overall survival, without recensoring, pembrolizumab + chemotherapy vs, cetuximab + chemotherapy, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population with CPS≥1

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)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio‡ (95% CI)‡	p-Value¶¶	p-Value‖
Cetuximab + Chemotherapy	235	190 (80.9)	2827.6	6.7	10.4 (9.1, 11.7)	43.5 (37.0, 49.7)	---	---	---
Cetuximab + Chemotherapy, 2-stage adjusted¶	235	190 (80.9)	2677.2	7.1	10.3 (9.0, 11.5)	42.5 (36.1, 48.8)	---	---	---
Pembrolizumab + Chemotherapy	242	164 (67.8)	3416.4	4.8	13.6 (10.7, 15.5)	55.0 (48.5, 61.0)	0.68 (0.54, 0.86)	0.0015	0.0014
Stage 1 model††							Acceleration factor‡‡		
§ Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching							1.607 (1.155, 2.235)		

¶ Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5. The 95% CI is derived by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

¶¶ Two sided p-value based on stratified Cox model, ITT population, analysis not adjusted for treatment switch.

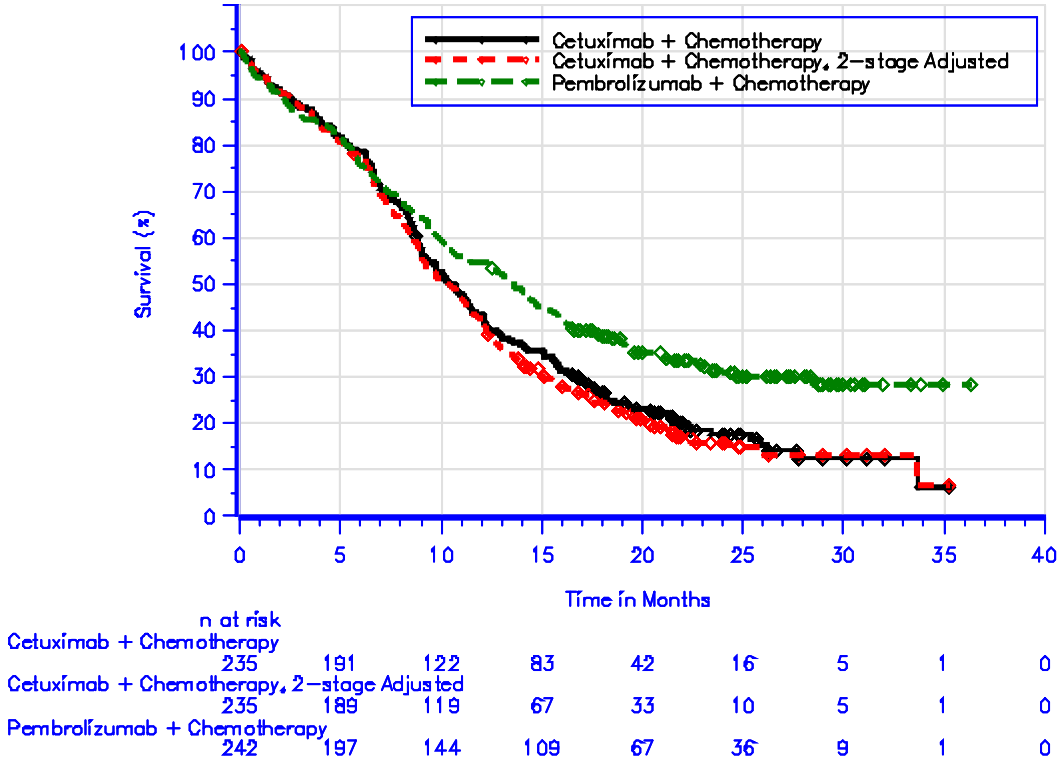
‖ Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for treatment switch.

†† Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS <20 vs. CPS≥20), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), haemoglobin at secondary baseline and tumour size at secondary baseline.

§ Patients were eligible to switch if they had documented progression.

‡‡ Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

Figure 16 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, without recensoring, pembrolizumab + chemotherapy vs. cetuximab + chemotherapy, ITT population with CPS≥1



Database Cutoff Date: 13JUN2018

Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the rank preserving structural failure (RPSFT) method

A total of 63/235 (26.8%) of control patients switched to an immune checkpoint inhibitor after discontinuation of the protocol treatment. Table 37 present the results of the OS analysis adjusting for receiving subsequent immune checkpoint inhibitors after discontinuation of protocol treatment for the control arm using RPSFT model without re-censoring.The RPSFT-adjusted HR for OS is 0.69 (95% CI: 0.55; 0.87) with a two-sided ITT log-rank p-value of 0.0014 in the pembrolizumab + chemotherapy vs. cetuximab + chemotherapy comparison.

Table 37 Analysis of overall survival, without recensoring, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, ITT population with CPS≥1, pembrolizumab + chemotherapy vs. cetuximab + chemotherapy

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS† (Months) (95% CI)	Survival Rate at Month 12† (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio‡ (95% CI)§	p-Value‖	p-Value¶
Cetuximab + Chemotherapy	235	190 (80.9)	2827.6	6.7	10.4 (9.1, 11.7)	43.5 (37.0, 49.7)	-	-	-
Cetuximab + Chemotherapy, RPSFT adjusted	235	190 (80.9)	2727.3	7.0	10.3 (9.0, 11.7)	43.0 (36.6, 49.2)	-	-	-
Pembrolizumab + Chemotherapy	242	164 (67.8)	3416.4	4.8	13.6 (10.7, 15.5)	55.0 (48.5, 61.0)	0.69 (0.55, 0.87)	0.0015	0.0014

Rank-preserving structural failure time (RPSFT) model is used to adjust for the effect in overall survival analysis for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors.

† From product-limit (Kaplan-Meier) method.

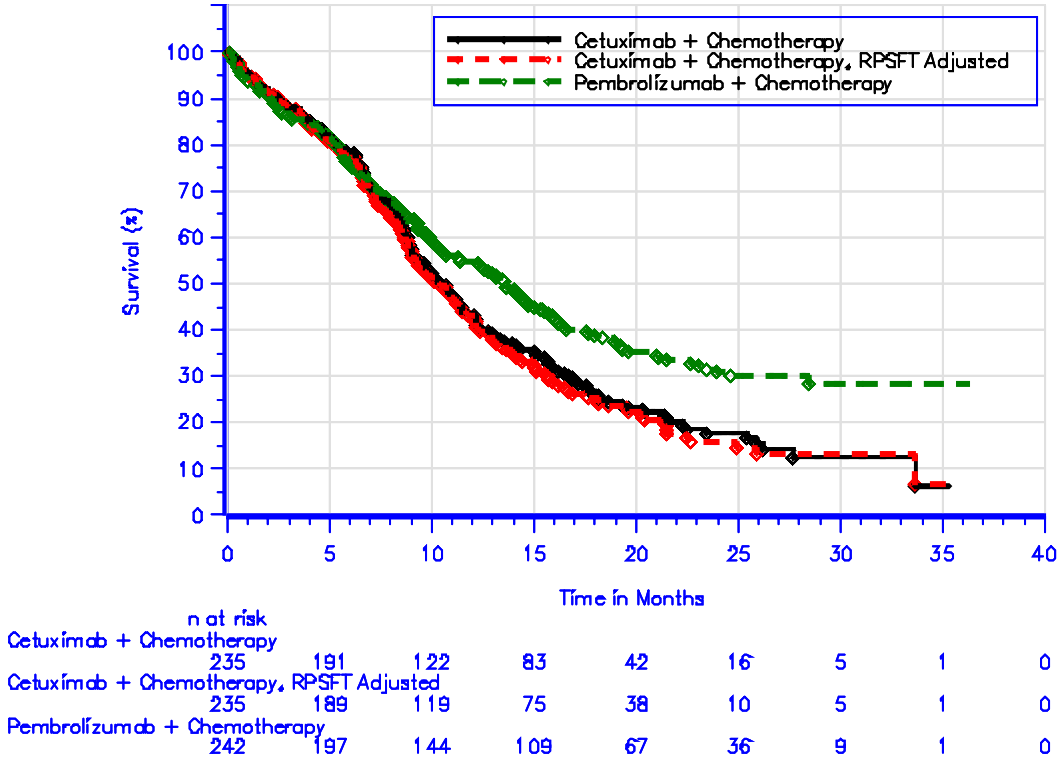
‡ Based on Cox regression model with Efron′s method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ Obtained by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

‖ Two sided p-value based on stratified Cox model, analysis not adjusted for treatment switch.

¶ Two-sided p-value based on stratified log-rank test, analysis not adjusted for treatment switch.

Figure 17 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, without recensoring, ITT population with CPS≥1, pembrolizumab + chemotherapy vs. cetuximab + chemotherapy



Database Cutoff Date: 13JUN2018

Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the inverse probability censored weighting (IPCW) method

Of those who switched in the cetuximab + chemotherapy arm, 44/63 (69.8%) patients died after switching, and therefore 44/190 (23.2%) observed events in the cetuximab + chemotherapy arm were lost due to censoring at the time of switch. Among those who did not switch in the cetuximab + chemotherapy arm, 146/172 (84.9%) deaths were observed, and included in the analysis. Table 38 summarises the results from the weighted Cox proportional hazard regression. The IPCW-adjusted hazard ratio of pembrolizumab versus cetuximab + chemotherapy is 0.77, with 95% bootstrap

percentile confidence interval of 0.61 to 0.97 (bootstrap p-value = 0.0340). Figure 18 shows the survival curves for the ITT-unadjusted and the IPCW-adjusted control arm compared to the pembrolizumab + chemotherapy arm.

Table 38 Analysis of overall survival adjusting for treatment switch to immune checkpoint inhibitors in standard treatment arm using IPCW model comparison, pembrolizumab + chemotherapy versus cetuximab + chemotherapy, intention-to-treat population with CPS≥1

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median OS† (Month) (95% CI)	Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy		
						Hazard Ratio†† (95% CI)	p-Value§	p-Value§§
Cetuximab + Chemotherapy	235	190 (80.9)	2827.6	6.7	10.4 (9.1, 11.7)	-	-	-
Cetuximab + Chemotherapy, IPCW Adjusted	235	146 (62.1)	2375.2	6.1	10.8 (9.7, 12.1)	-	-	-
Pembrolizumab + Chemotherapy	242	164 (67.8)	3416.4	4.8	13.6 (10.7, 15.5)	0.77 (0.61, 0.97)	0.0230	0.0340

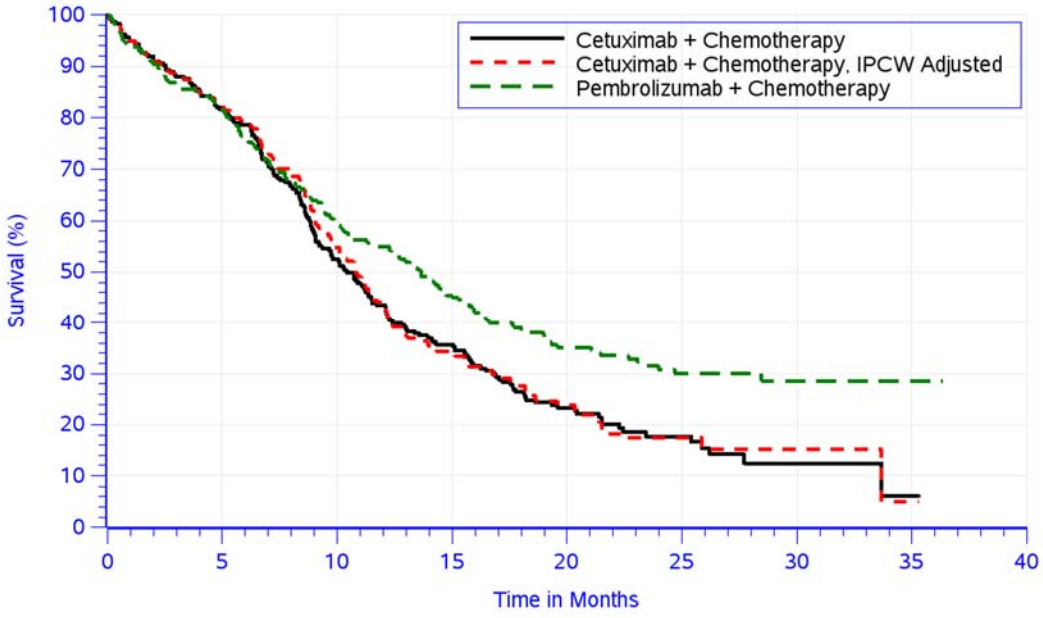
† From product-limit (Kaplan-Meier) method for censored data, if the median OS is reached

†† HR based on Cox regression model with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status, and bootstrap 95% CI. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ Two-sided p-value based on the IPCW log-rank test

§§ Two-sided p-value based on bootstrap percentiles

Figure 18 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received immune checkpoint inhibitors using IPCW comparison, pembrolizumab + chemotherapy versus cetuximab + chemotherapy, intention-to-treat population with CPS≥1



n at risk

Cetuximab + Chemotherapy	235	191	122	83	42	16	5	1	0
Cetuximab + Chemotherapy, IPCW Adjusted	235	179	101	58	28	10	5	1	0
Pembrolizumab + Chemotherapy	242	197	144	109	67	36	9	1	0

Database Cutoff Date: 13JUN2018

Progression-free survival (based on BICR assessment per RECIST 1.1)

No alpha was initially allocated to the PFS hypothesis for the PD-L1 CPS≥1 population. The CPS≥1 PFS hypothesis could only be tested if alpha was passed from a successful CPS≥20 hypothesis as per the multiplicity analysis strategy (as described in section B.2.4). Since the PFS hypothesis for CPS≥20 was not statistically significant at IA2 (see Appendix E section E.4), the CPS≥1 hypothesis could not be tested statistically at this time.

The comparison between pembrolizumab plus chemotherapy group with the standard treatment group shows a median PFS of 5.0 months for the pembrolizumab plus chemotherapy group (95% CI: 4.7, 6.2) and 5.0 months for the standard treatment group (95% CI: 4.8, 5.8) and a HR of 0.82 (95% CI: 0.67, 1.00) (Table 39). By KM estimation, PFS rates which were higher at 9 and 12 months (Table 40 and Figure 19).

Table 39 PFS based on BICR assessment per RECIST 1.1, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

Treatment	N	Number of Events (%)	Person-Months	Event Rate/100 Person-Months (%)	Median PFS [†] (Months) (95% CI)	PFS Rate at Months 6 in % [†] (95% CI)
Pembrolizumab + Chemotherapy	242	206 (85.1)	1772.2	11.6	5.0 (4.7, 6.2)	44.7 (38.3, 51.0)
Cetuximab + Chemotherapy	235	215 (91.5)	1437.5	15.0	5.0 (4.8, 5.8)	42.4 (35.9, 48.7)
Pairwise Comparisons					**Hazard Ratio[‡] (95% CI)[‡]**	**p-Value**
Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					0.82 (0.67, 1.00)	0.02286[§]

[†] 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

[§] One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

Table 40 Summary of PFS rate over time based on BICR per RECIST 1.1, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

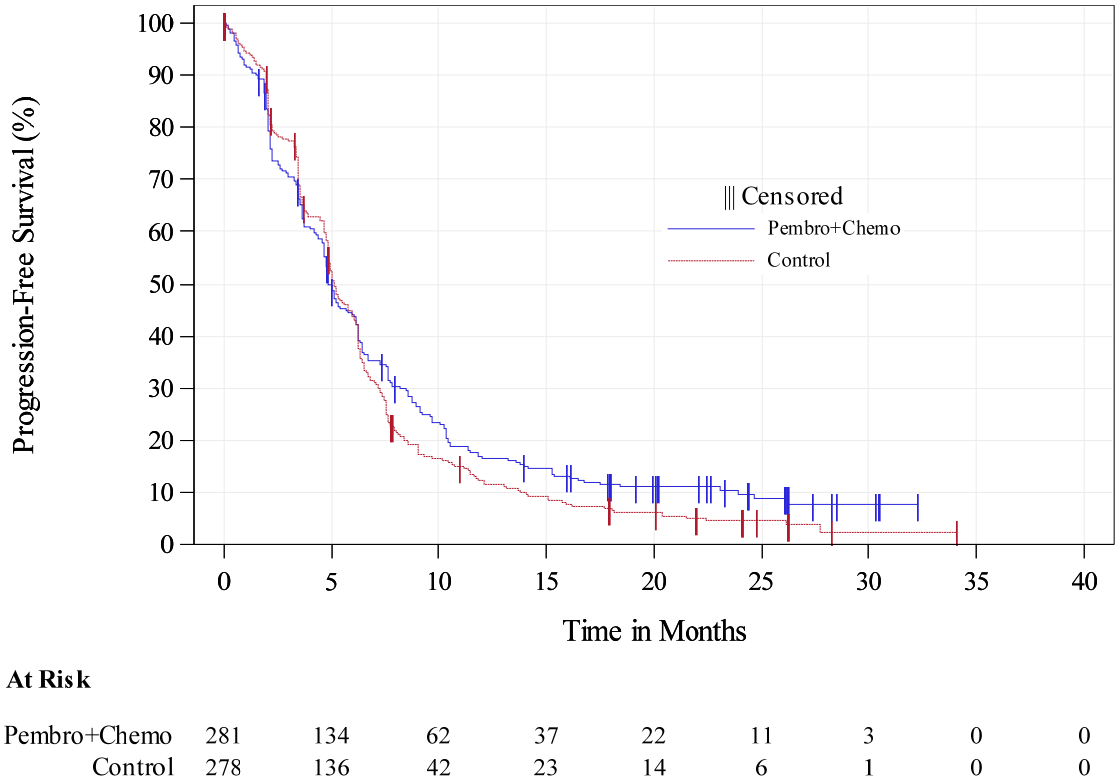
	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
PFS rate at 6 Months in (95% CI)†	44.7 (38.3, 51.0)	42.4 (35.9, 48.7)
PFS rate at 9 Months in (95% CI)†	27.6 (22.0, 33.5)	17.9 (13.1, 23.2)
PFS rate at 12 Months in (95% CI)†	19.2 (14.4, 24.5)	10.7 (7.0, 15.3)

BICR = Blinded Independent Central Review

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

(Database Cutoff Date: 13JUN2018).

Figure 19 Kaplan-Meier estimates of PFS based on BICR assessment per RECIST 1.1, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup



Response rate

Comparing the populations of participants with PD-L1 CPS≥1 in the pembrolizumab plus chemotherapy group with the standard treatment group, the (confirmed) ORR was similar: (36.4 % [95% CI: 30.3, 42.8] vs 35.7% [95% CI: 29.6, 42.2]) (Table 41). The best objective response (BOR) summary showed that a higher proportion of participants whose tumours express PD L1 CPS≥1 treated with pembrolizumab plus chemotherapy also achieved a complete response (Table 42).

Table 41 Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)†	p-Value††
Pembrolizumab + Chemotherapy	242	88	36.4 (30.3,42.8)	0.5 (-8.2,9.1)	0.4586
Cetuximab + Chemotherapy	235	84	35.7 (29.6,42.2)		

BICR = Blinded Independent Central Review

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

† Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive); in case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is >=5; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

†† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

Table 42 Summary of best objective response with confirmation based on BICR per RECIST 1.1, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	242		235	
Complete Response (CR)	16	(6.6)	7	(3.0)
Partial Response (PR)	72	(29.8)	77	(32.8)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Objective Response (CR+PR)	**88**	**(36.4)**	**84**	**(35.7)**
Stable Disease (SD)	64	(26.4)	76	(32.3)
Progressive Disease (PD)	42	(17.4)	30	(12.8)
Non-CR/Non-PD (NN)	11	(4.5)	9	(3.8)
Not Evaluable (NE)	4	(1.7)	2	(0.9)
No Assessment	33	(13.6)	34	(14.5)

BICR = Blinded Independent Central Review
Responses are based on BICR assessments per RECIST 1.1 with confirmation.
Database Cutoff Date: 13JUN2018

Duration of response

Comparing the populations of participants with PD-L1 CPS≥1 in the pembrolizumab plus chemotherapy group with the standard treatment group, the median time to response was similar (approximately 2.1 months), and the median response duration was longer, 6.7 months (range 1.6+ to 30.4+ months) versus 4.3 months (range 1.2+ months to 27.9+ months) (Table 43). There was a higher proportion of responders with an estimated response duration ≥6 months (44 [54.3%] versus 21 [34.3%]) (Table 43 and Figure 20). A summary of the reasons that participants with a response based on RECIST 1.1 per BICR were censored from the duration of response analysis is provided in Table 44.

Table 43 Summary of time to response and duration of response based on BICR per RECIST 1.1 in subjects with confirmed response, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

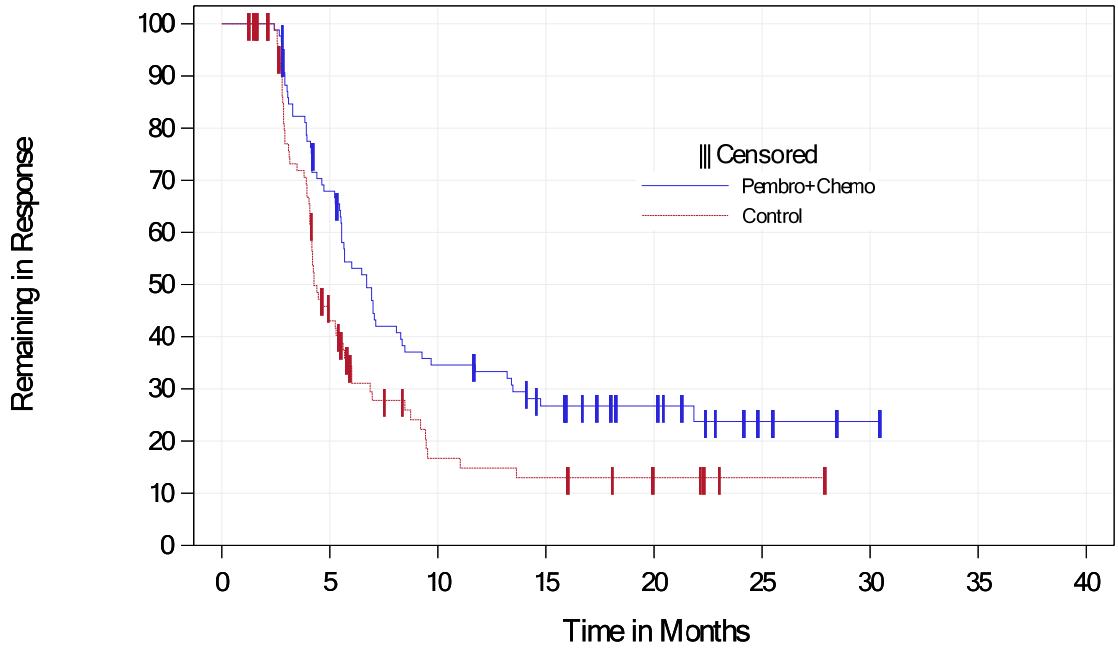
	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
Number of subjects with response†	88	84
Time to Response (months)		
Mean (SD)	2.6 (1.7)	2.4 (0.8)
Median (Range)	2.1 (1.4-13.7)	2.1 (1.3-6.2)
Response Duration‡ (months)		
Median (Range)	6.7 (1.6+ - 30.4+)	4.3 (1.2+ - 27.9+)
Number (%‡) of Subjects with Extended Response Duration:		
≥6 months	44 (54.3)	21 (34.3)

† Includes subjects with confirmed complete response or partial response.

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

"+" indicates there is no progressive disease by the time of last disease assessment.

Figure 20 Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup



At Risk

Pembro+Chemo	88	56	28	19	12	3	1	0	0
Control	84	31	9	7	4	1	0	0	0

Table 44 Summary of response outcome in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
Number of Subjects with Response†	88	84
Subjects Who Progressed or Died‡ (%)	**61 (69.3)**	**62 (73.8)**
Range of DOR (months)	2.4 to 21.8	2.4 to 13.6
Censored Subjects (%)	**27 (30.7)**	**22 (26.2)**
Subjects who missed 2 or more consecutive disease assessments	3 (3.4)	9 (10.7)
Subjects who started new anti-cancer treatment	3 (3.4)	5 (6.0)
Subjects who were lost to follow-up	0 (0.0)	0 (0.0)
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	1 (1.1)	2 (2.4)
Ongoing response§	20 (22.7)	6 (7.1)
≥6 months	20 (22.7)	6 (7.1)
Range of DOR (months)	14.1+ to 30.4+	16.0+ to 27.9+

† Includes subjects with a confirmed complete response or partial response.

‡ Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.

§ Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest.

'+' indicates there was no progressive disease by the time of last disease assessment.

Health-related quality of life

EORTC QLQ-C30

Over 15 weeks of follow up, participants receiving pembrolizumab plus chemotherapy and standard treatment had stable global health status/QoL. The mean change from baseline in the global health status/QOL score remained stable in both the pembrolizumab plus chemotherapy group (least squares [LS] mean = [redacted]) and the standard treatment group (LS mean = [redacted]).

The difference in LS means between pembrolizumab plus chemotherapy and standard treatment at Week 15 was [redacted] (Table 45). A summary of the empirical mean change from baseline over time for the EORTC QLQ-C30 global health status/QoL scores is displayed in Figure 21, global health status/QoL scores remained stable over time in both treatment groups through Week 51.

Time to deterioration in the EORTC QLQ-C30 global health status/QoL score for pembrolizumab plus chemotherapy was similar when compared with standard treatment (HR = [redacted]) (Table 46 and Figure 22). Similarly, time to deterioration in the EORTC QLQ H&N35 pain score (HR = [redacted]; Table 47 and Figure 23) and swallowing score (HR = [redacted]; Table 48 and Figure 24) for pembrolizumab plus chemotherapy were similar when compared with standard treatment.

Table 45 Analysis of change from baseline of EORTC QLQ-C30 Global Health Status/QoL Scales at Week 15, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

Treatment	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Means (95% CI)**	**p-Value**
Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

Figure 21 Empirical mean change from baseline in EORTC QLQ-C30 Global Health Status/QoL across time, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

Table 46 Analysis of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=231)	Cetuximab + Chemotherapy (N=220)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)†		
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy		

	Pembrolizumab + Chemotherapy (N=231)	Cetuximab + Chemotherapy (N=220)
Hazard Ratio (95% CI)‡	[redacted]	
p-value§	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).

Figure 22 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

Table 47 Analysis of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=230)	Cetuximab + Chemotherapy (N=220)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)†		
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy		
Hazard Ratio (95% CI)‡	[redacted]	
p-value§	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).

Figure 23 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

Table 48 Analysis of time to true deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=230)	Cetuximab + Chemotherapy (N=220)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)†		
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy		
Hazard Ratio (95% CI)‡	[redacted]	

p-value§	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).

Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).

Figure 24 Kaplan-Meier Plot of Time to True Deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab combination therapy vs. control, FAS population, CPS≥1 subgroup

EQ-5D

Analyses of the mean change from baseline to Week 15 in the EQ-5D visual analog scale and utility scores in the PRO FAS population are provided in Table 49 and Table

50. In the PRO FAS population, participants in both the pembrolizumab monotherapy and standard treatment groups exhibited stable scores in the EQ-5D visual analog scale and utility scores at Week 15.

Table 49 Analysis of change from baseline of EQ-5D VAS at Week 15, pembrolizumab combination therapy versus control, FAS population, CPS≥1 population

Treatment	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Means (95% CI)**	**p-Value**
Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

†Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

Table 50 Analysis of change from baseline of EQ-5D Utility Score (using European Algorithm) at Week 15, pembrolizumab + chemotherapy combination therapy versus control, FAS population, CPS≥1 population

Treatment	Baseline		Week 15		Change from Baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise Comparison					**Difference in LS Means (95% CI)**	**p-Value**
Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					[redacted]	[redacted]

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)) as covariates.

For baseline and Week 15, 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

The between-group treatment effect for OS, PFS, and ORR (with a nominal 95% CI) was estimated and plotted within each category of the following classification variables:

- Stratification factors
    - PD-L1 subgroup (strongly positive vs. not strongly positive, defined by TPS 50%, i.e. TPS≥50% vs. TPS<50%)
    - HPV status (HPV positive vs. HPV negative)
    - ECOG status (0 vs. 1)
- PD-L1 expression level defined by CPS (≥ 20 vs. not ≥ 20; and ≥ 1 vs. not ≥ 1)
- Age category (<65 vs. ≥65 years)
- Sex (female vs. male)
- Race (white vs. all others)
- Region (North America vs. Europe vs. rest of the world)
- Smoking status (never vs. former vs. current)
- Disease status (recurrent vs. metastatic)

These were pre-planned subgroup analyses as described in previously in section B.2.4. These analyses were performed for the subgroups listed above in the CPS≥1 population for pembrolizumab monotherapy and pembrolizumab + chemotherapy combination therapy. The results of these subgroup analyses are summarised in Appendix E. The results of subgroup analyses for each outcome analysed were consistent with the primary findings, as shown in the forest plots in Appendix E, with all confidence intervals for the results of each subgroup overlapping the primary/overall result.

Clinical effectiveness analyses results for the KEYNOTE-048 overall population (i.e. all patients regardless of PD-L1 expression status) are also summarised in Appendix M.

B.2.8 Meta-analysis

Pooling of study data via pair-wise meta-analysis was not performed because the KEYNOTE-048 trial is the one and only trial that compared pembrolizumab to comparators in the population of interest.

B.2.9 Indirect and mixed treatment comparisons

Network meta-analyses (NMAs) were conducted to compared pembrolizumab to platinum-based chemotherapy regimens. The methods used for these NMAs are described in Appendix D. An overview of the NMAs conducted are shown in Table 51.

The NMAs for the outcomes of OS and PFS were conducted via methods that used models that allowed for time-varying hazard ratios. This was done because NMA for survival outcomes based on constant HRs rely on the proportional hazards assumption, which was not appropriate in this case given that this assumption was shown to be violated for both OS and PFS where the Kaplan-Meier survival curves for pembrolizumab (as monotherapy and in combination therapy with chemotherapy) and for cetuximab + chemotherapy cross (as shown in section B.2.6). As an alternative to the constant HR, which is a univariate treatment effect measure, a multivariate treatment effect measure that describes how the relative treatment effect (e.g. HR) develops over time was used (details provided in Appendix D section D.1.1). Ouwens et al. and Jansen presented methods for NMA of survival data using a multi-dimensional or multivariate treatment effect as an alternative to the synthesis of one treatment effect (e.g. the constant HRs) (24, 25). By relaxing this proportional hazards assumption, and incorporating additional parameters for the treatment effect, the NMA model more closely fit the available data.

The OS results presented in this section are those from cross-over adjustment via the 2-stage method, as used in the base-case of the cost-effectiveness analysis (detailed in section B.3). Unadjusted results and results from adjustment via other methods are shown in Appendix N.

Table 51 Overview of NMAs conducted

Comparator	Survival outcome	Population	Network
Pembrolizumab monotherapy	Overall survival	CPS≥1	Full network (base case)
	Progression-free survival	CPS≥1	Full network (base case)
Pembrolizumab combination therapy	Overall survival	CPS≥1	Full network (base case)
	Progression-free survival	CPS≥1	Full network (base case)

Abbreviations: CPS, combined positive score.

B.2.9.1 Pembrolizumab monotherapy

Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

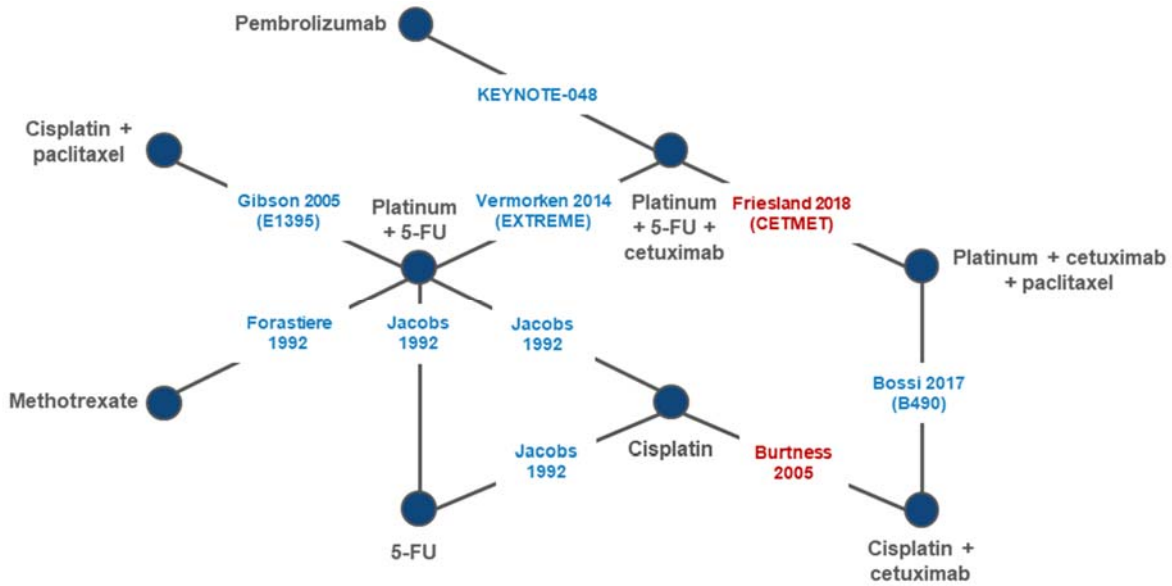
For OS, KM curves were presented in all of the eight included trials (see Appendix D section D1.1). All studies were included in the CPS≥1 population analyses. The NMA comparison network is presented in Figure 25. DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D section D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=0 and p2=0.5 for the CPS≥1 subgroup analysis. The results of time-varying OS HRs for pembrolizumab monotherapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 43.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment arms) in order to generate the OS proportions over time, which are summarised for each intervention in Figure 26.

Amongst patients in the CPS≥1 subgroup, and consistent with the results of the KEYNOTE-048 trial, OS NMA results showed a statistically meaningful improvement in OS with pembrolizumab monotherapy in comparison with the EXTREME regimen; the OS HRs and 95% CrIs were less than 1 for the majority of time points with OS

benefit increasing steadily from month 6 ([redacted]) through month 36 ([redacted]) in the CPS≥1 subgroup. Similarly, pembrolizumab monotherapy was consistently associated with a statistically meaningful improvement in OS in comparison with platinum + 5-FU, with the magnitude of OS benefit increasing over time from month 6 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. Additional indirect comparisons of pembrolizumab monotherapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying patient sample sizes to form the basis of the network connections. Among these comparisons in the CPS ≥1 subgroup, pembrolizumab monotherapy consistently showed a statistically meaningful improvement in OS in comparison with cisplatin, 5-FU, and methotrexate for the majority of time points, and showed a trend in OS benefit in comparison with cetuximab + cisplatin, cisplatin + paclitaxel, platinum + paclitaxel + cetuximab, and cisplatin comparators, although the 95% credible intervals were wide and did not exclude 1.

Figure 25 Full network of all randomised controlled trials for overall survival (pembrolizumab monotherapy)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 52 Estimated overall survival hazard ratios for pembrolizumab monotherapy versus comparators from fixed-effects network meta-analysis (P1=0, P2=0.5); PD-L1 CPS≥1 subgroup, crossover adjustment via the 2-stage method

Overall survival hazard ratio (95% credible interval)								
Timepoint (months)	Platinum+ 5-FU+ Cetuximab	Cetuximab+ Cisplatin	Platinum+ 5-FU	Cisplatin+ Paclitaxel	Platinum+ Paclitaxel+ Cetuximab	Cisplatin	5-FU	Methotrexate
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab monotherapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 26 Estimated overall survival from fixed-effects network meta-analysis (P0=0, P2=0.5); pembrolizumab monotherapy versus comparators, PD-L1 CPS≥1 subgroup, crossover adjustment via the 2-stage method

Progression-free survival

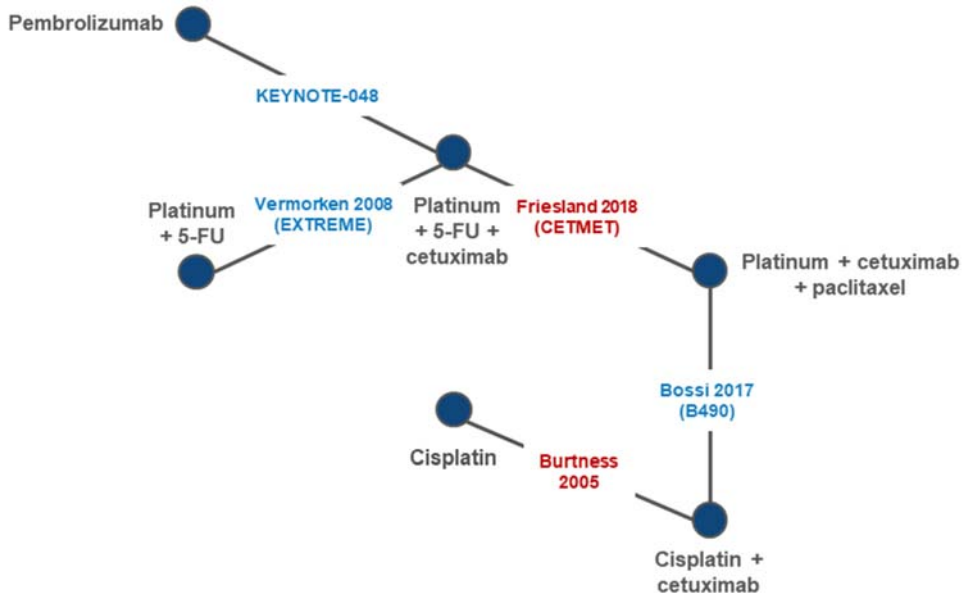
For PFS, KM curves were presented in five included trials, all of which were included in the CPS≥1 population analysis, the network of trials is presented in Figure 27. DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D section D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=0 and p2=--0.5 for the CPS≥1 analysis. The results of time-varying PFS HRs for pembrolizumab monotherapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 53.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment

arms) in order to generate the PFS proportions over time, which are summarised for each intervention in Figure 28.

Amongst patients in in CPS≥1 subgroup, and consistent with the results of the KEYNOTE-048, the NMA showed that the PFS benefit associated with pembrolizumab monotherapy compared with the EXTREME regimen is generally only seen at later time points, with a statistically meaningful PFS benefit observed from month 9 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. In addition, pembrolizumab monotherapy demonstrated a statistically meaningful PFS improvement compared with platinum + 5-FU for the majority of time points starting from month 6 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. Additional indirect comparisons of pembrolizumab monotherapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying patient sample sizes to form the basis of the network connections. PFS was comparable for pembrolizumab versus the remaining regimens (cisplatin, platinum + paclitaxel + cetuximab, and cetuximab + cisplatin) at all time points in both CPS subgroups.

Figure 27 Full network of all randomised controlled trials for progression-free survival (pembrolizumab monotherapy)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 53 Estimated progression-free survival hazard ratios for pembrolizumab monotherapy versus comparators from fixed-effects network meta-analysis (P1=0, P2=-0.5); PD-L1 CPS≥1 subgroup

Progression-free survival hazard ratio (95% credible interval)					
Timepoint (months)	Platinum+ 5-FU+ Cetuximab	Cetuximab+ Cisplatin	Platinum+5-FU	Platinum+ Paclitaxel+ Cetuximab	Cisplatin
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab monotherapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 28 Estimated progression-free survival from fixed-effects network meta-analysis (P1=0, P2=-0.5); pembrolizumab monotherapy versus comparators, PD-L1 CPS≥1 subgroup

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

B.2.9.2 Pembrolizumab + chemotherapy combination therapy

Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

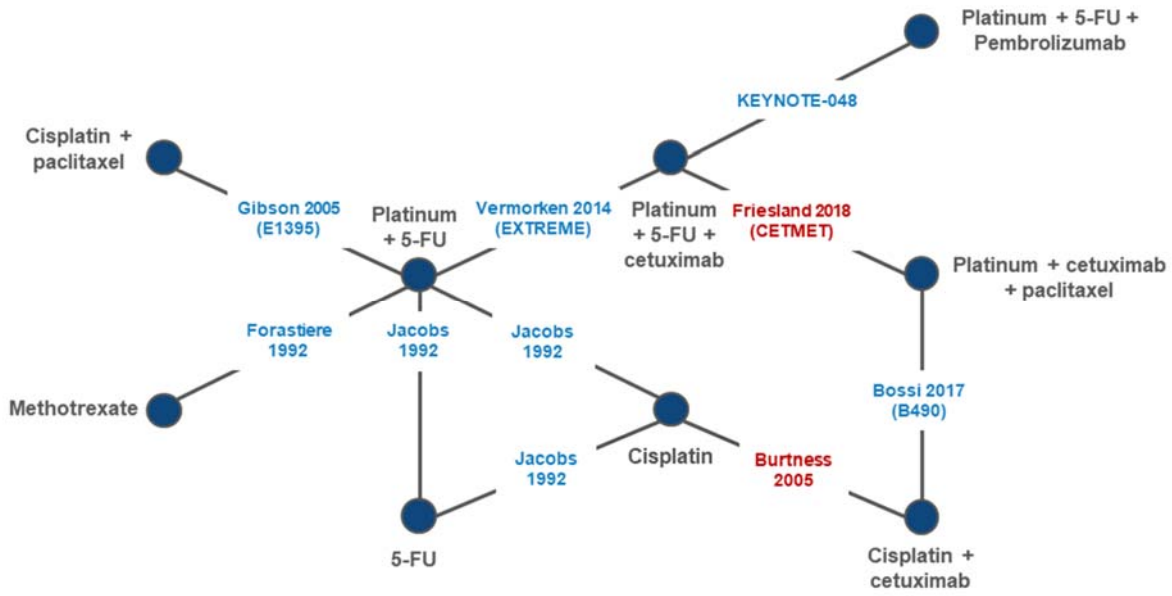
Network of the included trials for the OS outcome for the PD-L1 CPS≥1 population was the same as that of the overall population (Figure 29, see Appendix D for details). DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D section D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=1 and p2=0. The

results of time-varying OS HRs for pembrolizumab monotherapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 54.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment arms) in order to generate the OS proportions over time, which are summarised for each intervention in Figure 30.

In the CPS≥1 subgroup, and consistent with the results of the KEYNOTE-048 trial, OS NMA results showed a statistically meaningful improvement in OS with pembrolizumab combination therapy in comparison with the EXTREME regimen; the OS HRs and 95% CrI bounds were less than 1 for the majority of time points with OS benefit increasing steadily from month 9 (HR = [redacted]) through month 36 (HR = [redacted]) in the CPS ≥1 subgroup. Similarly, pembrolizumab combination therapy was consistently associated with a statistically meaningful improvement in OS in comparison with platinum + 5-FU, with the magnitude of OS benefit increasing over time from month 6 (HR = [redacted]) through month 36 (HR = [redacted]) in the CPS≥1 subgroup. Additional indirect comparisons of pembrolizumab combination therapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying patient sample sizes to form the basis of the network connections. Among these comparisons in the CPS≥1 subgroup, pembrolizumab combination therapy consistently showed a statistically meaningful improvement in OS in comparison with 5-FU and methotrexate for the majority of time points, and showed a trend in OS benefit in comparison with cisplatin + paclitaxel, and cisplatin comparators, although the 95% credible intervals were wide and did not exclude 1.

Figure 29 Full network of all randomised controlled trials for overall survival (pembrolizumab combination therapy)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 54 Estimated overall survival hazard ratios for pembrolizumab combination therapy versus comparators from fixed-effects network meta-analysis (P1=1, P2=0); PD-L1 CPS≥1 subgroup, crossover adjustment via the 2-stage method

Overall survival (95% credible intervals)								
Timepoint (months)	Platinum+ 5-FU+ Cetuximab	Cetuximab+ Cisplatin	Platinum+ 5-FU	Cisplatin+ Paclitaxel	Platinum+ Paclitaxel+ Cetuximab	Cisplatin	5-FU	Methotrexate
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab + chemotherapy combination therapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 30 Estimated overall survival from fixed-effects network meta-analysis (P1=1, P2=0); pembrolizumab combination therapy versus comparators, PD-L1 CPS≥1 subgroup

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Progression-free survival

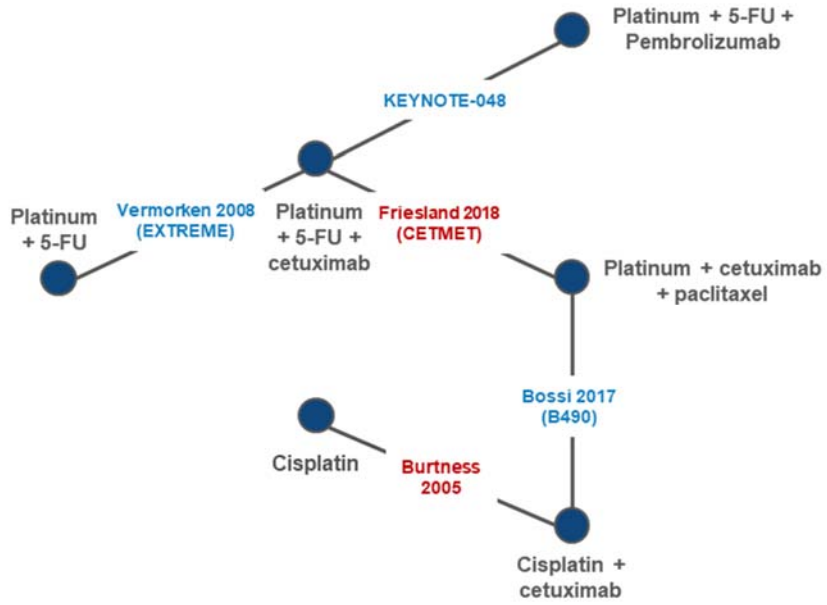
The network of the included trials for the PFS outcome for the PD-L1 CPS≥1 population was the same as that of the overall population (Figure 31). DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D section D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=0 and p2=0.5. The results of time-varying PFS HRs for pembrolizumab combination therapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 55.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment

arms) in order to generate the PFS proportions over time, which are summarised for each intervention in Figure 32.

The pembrolizumab combination therapy versus cetuximab in combination with chemotherapy PFS HRs and 95% CrI bounds were less than 1 for majority of time points with PFS benefit increasing steadily from month 6 (HR = [redacted] through month 36 (HR = [redacted]) in the CPS ≥1 subgroup. Similarly, pembrolizumab combination therapy was consistently associated with a statistically meaningful improvement in PFS in comparison with platinum + 5-FU, with the magnitude of PFS benefit increasing over time from month 3 (HR = [redacted]) through month 36 (HR = [redacted]) in the CPS ≥1 subgroup. Additional indirect comparisons of pembrolizumab combination therapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying patient sample sizes to form the basis of the network connections. PFS was comparable for pembrolizumab combination therapy versus the remaining regimens (cetuximab + cisplatin, platinum + paclitaxel + cetuximab, and cisplatin) at all time points.

Figure 31 Full network of all randomised controlled trials for progression-free survival (pembrolizumab combination therapy)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 55 Estimated progression-free survival hazard ratios for pembrolizumab combination therapy versus competing interventions from fixed-effects network meta-analysis (P1=0, P2=0.5); PD-L1 CPS≥1 subgroup

Progression-free survival (95% credible intervals)					
Timepoint (months)	Platinum+ 5-FU+ Cetuximab	Cetuximab+Cisplatin	Platinum+5-FU	Platinum+ Paclitaxel+ Cetuximab	Cisplatin
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab + chemotherapy combination therapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 32 Estimated progression-free survival from fixed-effects network meta-analysis (P1=0, P2=0.5); pembrolizumab combination therapy versus comparators, CPS≥1 subgroup population

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

A source of uncertainty in the NMAs is around the use of a full network of studies (used in the base case analyses) which included both “Tier 1” studies that closely reflected the patient population of the KEYNOTE-048 trial and the decision problem of relevance to this submission with regard to prior therapy (i.e. no prior systemic therapy in the R/M setting; systemic therapy for LA disease allowed if received >6 months before study entry) and “Tier 2” studies that included patients populations that were less reflective (i.e. no prior systemic therapy in the R/M setting; systemic therapy for LA disease allowed if received >3 months before study entry). Tier 2 studies were included in the base case analyses in order to expand the trial network in order to

compare pembrolizumab to a greater number of different platinum-containing chemotherapy regimens (described in greater detail in Appendix D section D.1.1).

With regard to other potential sources of uncertainty, outcome definitions (where reported) were similar across the included trials for both OS and PFS. Furthermore, the distribution of patients with different tumour locations as well as baseline demographics of populations were generally similar among the included studies. On the other hand, some variations were observed in other baseline patient characteristics such as the proportion of metastatic patients and the distribution of patients with ECOG PS of 0-1. Although our NMA used robust statistical methods to analyse the collected data (e.g. time-varying hazard ratios were used given the proportional hazards assumption was violated), it was not possible to account for the variation in the potential effect modifiers mentioned above. This would have been possible through incorporating random-effects models or performing meta-regressions; however, the limited available data for each head-to-head comparison in the network (i.e. only one trial for each direct comparison) did not allow for these alternative methods to account for the observed heterogeneity.

Another source of uncertainty was the small sample size in some of the trials included in the network; for example, while there were well over 250 patients in each treatment arm of KEYNOTE-048, the number of participants in the entire population was under 250 patients in B490 (n = 191), E1395 (n = 204), and Jacobs 1992 (n = 245), and even less than 150 patients in Burtness 2005 (n = 117) and CETMET (n = 85) (26-30). Another limitation was the small number of trials comparing the same pair of interventions (i.e. number of trials per direct comparison); each pair of interventions (nodes) was informed by only one study, as shown in the overall network of trials (shown in Appendix D section D.1.1). Both of the above limitations resulted in relatively small amount of data being available for each comparison, and consequently, estimated HRs with higher uncertainty (i.e. wider CrIs). Lastly, the majority of the trials included in our analyses were at least 10 years old (EXTREME, E1395, Burtness 2005) with a few being over 25 years old (Jacobs 1992 and Forastiere 1992); there is always a concern that standard of care and precision of data may not have been held to high standards in these trials, compared to more recent trials such as KEYNOTE-048 and CETMET (27-32).

B.2.10 Adverse reactions

Summaries of the AE data from the KEYNOTE-048 trial are provided in this section. Data tables showing the details of the adverse events from this trial are provided in Appendix F. Data for the (larger) overall population of the KEYNOTE-048 trial (including data from all patients, not just those in the CPS≥1 subgroups) are described; however, the overall summaries of adverse events between the CPS≥1 population versus the overall population are also compared to demonstrate that the AE profile in this subgroup does not differ substantially from that in the overall population.

B.2.10.1 Pembrolizumab monotherapy

The safety results from KEYNOTE-048 demonstrate that pembrolizumab monotherapy:

- Has a favourable adverse event profile compared with standard treatment.
- Is well tolerated with low rates of treatment discontinuation.
- The incidences and types of AEOSIs were generally consistent with the known safety profile of pembrolizumab monotherapy use in R/M HNSCC.

Summary of adverse events

In the overall population, a total of 290 participants (96.7%) in the pembrolizumab monotherapy group experienced at least 1 AE compared with 286 participants (99.7%) in the standard treatment group (Table 56). The favourable AE profile of pembrolizumab monotherapy compared with standard treatment was further demonstrated by the lower incidence of AEs for all of the AE categories in (Table 56). It can also be seen from Table 56 that the AE profile of pembrolizumab monotherapy in all of the AE categories, both considered on its own in and in terms of the difference between it and cetuximab + chemotherapy, in the CPS≥1 population does not differ substantially to that in the overall population.

Table 56 Adverse event summary, pembrolizumab monotherapy vs. control, ASaT population, comparison between the overall population and CPS≥1 subgroup

	Overall population					CPS≥1 subgroup				
	Pembrolizumab monotherapy		Cetuximab + chemotherapy		Difference in % vs control arm[†]	Pembrolizumab monotherapy		Cetuximab + chemotherapy		Difference in % vs control arm[†]
	n	(%)	n	(%)	Estimate (95% CI)	n	(%)	n	(%)	Estimate (95% CI)
Subjects in population	300		287			256		245		
with one or more adverse events	290	(96.7)	286	(99.7)	-3.0 (-5.7, -1.0)	248	(96.9)	244	(99.6)	-2.7 (-5.7, -0.5)
with no adverse event	10	(3.3)	1	(0.3)	3.0 (1.0, 5.7)	8	(3.1)	1	(0.4)	2.7 (0.5, 5.7)
with drug-related[‡] adverse events	175	(58.3)	278	(96.9)	-38.5 (-44.5, -32.6)	152	(59.4)	236	(96.3)	-37.0 (-43.4, -30.5)
with toxicity grade 3-5 adverse events	162	(54.0)	240	(83.6)	-29.6 (-36.6, -22.4)	137	(53.5)	204	(83.3)	-29.7 (-37.3, -21.9)
with toxicity grade 3-5 drug-related adverse events	50	(16.7)	198	(69.0)	-52.3 (-58.8, -45.2)	45	(17.6)	166	(67.8)	-50.2 (-57.3, -42.3)
with serious adverse events	121	(40.3)	141	(49.1)	-8.8 (-16.7, -0.7)	104	(40.6)	121	(49.4)	-8.8 (-17.4, -0.0)
with serious drug-related adverse events	27	(9.0)	73	(25.4)	-16.4 (-22.5, -10.5)	27	(10.5)	60	(24.5)	-13.9 (-20.6, -7.4)
with dose modification[§] due to an adverse event	113	(37.7)	240	(83.6)	-46.0 (-52.6, -38.7)	97	(37.9)	206	(84.1)	-46.2 (-53.4, -38.4)
who died	25	(8.3)	27	(9.4)	-1.1 (-5.8, 3.6)	18	(7.0)	27	(11.0)	-4.0 (-9.2, 1.1)
who died due to a drug-related adverse event	3	(1.0)	8	(2.8)	-1.8 (-4.5, 0.5)	3	(1.2)	8	(3.3)	-2.1 (-5.3, 0.6)
discontinued drug due to an adverse event	36	(12.0)	78	(27.2)	-15.2 (-21.6, -8.9)	30	(11.7)	67	(27.3)	-15.6 (-22.5, -8.8)
discontinued drug due to a drug-related adverse event	14	(4.7)	57	(19.9)	-15.2 (-20.6, -10.1)	14	(5.5)	48	(19.6)	-14.1 (-20.1, -8.5)
discontinued drug due to a serious adverse event	29	(9.7)	48	(16.7)	-7.1 (-12.7, -1.6)	23	(9.0)	45	(18.4)	-9.4 (-15.5, -3.4)

	Overall population					CPS≥1 subgroup				
	Pembrolizumab monotherapy		Cetuximab + chemotherapy		Difference in % vs control arm†	Pembrolizumab monotherapy		Cetuximab + chemotherapy		Difference in % vs control arm†
	n	(%)	n	(%)	Estimate (95% CI)	n	(%)	n	(%)	Estimate (95% CI)
discontinued drug due to a serious drug-related adverse event	9	(3.0)	28	(9.8)	-6.8 (-11.1, -2.9)	9	(3.5)	25	(10.2)	-6.7 (-11.5, -2.4)

†Based on Miettinen & Nurminen method.

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

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

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

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.

Adverse events by decreasing incidence

With the exception of hypothyroidism and dyspnoea, all other AEs were reported in a similar or lower proportion of participants receiving pembrolizumab monotherapy compared to standard treatment. The most common AEs reported in the pembrolizumab monotherapy group (>20% incidence) were fatigue and anaemia, whereas nausea, anaemia, hypomagnesemia, rash, fatigue, diarrhoea, constipation, and neutropenia were the most common AEs reported (>30% incidence) in the standard treatment group.

Drug-related adverse events

The proportion of participants with at least 1 drug-related AE (incidence ≥5%) was lower in the pembrolizumab monotherapy group (58.3% compared to 96.9% in the standard treatment group). With the exception of hypothyroidism (which were Grade 1 or 2), all other drug-related AEs (incidence ≥10%) were less frequently reported in the pembrolizumab monotherapy group.

Grade 3-5 adverse events

The proportion of participants with 1 or more Grade 3 to 5 AEs was lower in the pembrolizumab monotherapy group (54.0% compared with 83.6% in the standard treatment group). The main differences included a lower rate of neutropenia, neutrophil count decrease, anaemia, WBC decrease, thrombocytopenia, nausea, leukopenia, rash, febrile neutropenia, hypokalaemia, and mucosal inflammation events in the pembrolizumab monotherapy group. No Grade 3 to 5 AEs in pembrolizumab monotherapy group was reported in a higher proportion of participants than in the standard treatment group.

The most common Grade 3 to 5 AEs (>4% incidence) in the pembrolizumab monotherapy group were hyponatremia, pneumonia, and anaemia; whereas neutropenia, anaemia, and neutrophil count decrease were the most common Grade 3 to 5 AEs in the standard treatment group (>10% incidence).

Drug-related grade 3-5 adverse events

The proportion of participants with Grade 3 to 5 AEs considered to be drug-related was lower in the pembrolizumab monotherapy group (16.7% compared with 69.0% in

the standard treatment group). The most common drug-related Grade 3 to 5 AEs in the pembrolizumab monotherapy group were hyponatremia and pneumonitis (>1% incidence), whereas neutropenia, anaemia, and neutrophil count decrease were events most commonly reported in the standard treatment group (>10% incidence).

Serious adverse events

The proportion of participants with 1 or more SAE was lower in the pembrolizumab monotherapy group compared with the standard treatment group (40.3% versus 49.1%). The most frequently (≥2% incidence) reported SAEs in the pembrolizumab monotherapy group were pneumonia, tumour haemorrhage, dyspnoea, and sepsis, whereas pneumonia, febrile neutropenia, nausea, anaemia, and pulmonary embolism were commonly reported in the standard treatment group.

Drug-related serious adverse events

The proportion of participants with 1 or more drug-related SAE was lower in the pembrolizumab monotherapy group (9.0% compared to 25.4% in the standard treatment group). The most frequently reported drug-related SAEs by decreasing incidence was pneumonitis (which is a known AEOSI of pembrolizumab) in the pembrolizumab monotherapy group (≥1% incidence), whereas febrile neutropenia, anaemia, pneumonia, and nausea were commonly reported in the standard treatment group (>2% incidence).

Adverse events resulting in death

The proportion of participants with AEs resulting in death was similar in the 2 treatment groups. The most common reason for death in participants treated with pembrolizumab monotherapy was sepsis (3 participants [1.0%]). In the standard treatment group the most common reason for death was pneumonia (6 participants [2.1%]) and tumour haemorrhage (3 participants [1.0%]). Drug-related deaths were reported in 3 (1.0%) and 8 (2.8%) participants in the pembrolizumab monotherapy and standard treatment groups, respectively.

Drug-related adverse events resulting in discontinuation

The proportion of participants discontinuing study intervention due to an AE was lower in the pembrolizumab monotherapy group (12.0% compared to 27.2% in the standard

treatment group). The most common reason for the discontinuation of study treatment was sepsis in the pembrolizumab monotherapy group. The most common reasons for discontinuation of study treatment were infusion related reaction and rash, anaemia, and pneumonia in the standard treatment group.

Drug-related AEs resulting in discontinuation of study intervention were lower in the pembrolizumab monotherapy group (4.7% compared to 19.9% in the standard treatment group). The most common drug-related AE resulting in the discontinuation of study treatment was autoimmune hepatitis and pneumonitis in the pembrolizumab monotherapy group. Of the 2 Grade 4 autoimmune hepatitis events, 1 had resolved and 1 was resolving. Of the 2 pneumonitis events, 1 was not resolved and 1 was fatal. The most common drug-related AE resulting in the discontinuation of study treatment was infusion related reaction and rash and anaemia in the standard treatment group.

Adverse events of special interest

The overall incidence of AEOSI was similar in the pembrolizumab monotherapy group and the standard treatment group (30.3% and 23.7%, respectively) with the exception of a lower proportion of participants in the pembrolizumab monotherapy group discontinuing study intervention due to an AEOSI (including those considered to be drug-related).

The incidence rate of AEOSIs were similar between the two groups, except that pembrolizumab monotherapy group had a higher rate of hypothyroidism, pneumonitis and hyperthyroidism; whereas, the standard treatment group had a higher rate of infusion reactions and severe skin reactions. The majority of AEOSIs in the pembrolizumab monotherapy group were Grade 1 and 2, whereas in the standard treatment group AEOSIs were most commonly Grade 2 and 3.

B.2.10.2 Pembrolizumab + chemotherapy combination therapy in the overall population

The safety results from KEYNOTE-048 demonstrate that pembrolizumab plus chemotherapy:

- Has a comparable and tolerable safety profile compared with standard treatment. The results from the KEYNOTE-048 study are consistent with the

known safety profiles of pembrolizumab monotherapy and platinum plus 5-FU chemotherapy, with no new safety issues identified.

- Per exposure-adjusted event rates, pembrolizumab plus chemotherapy does not result in an additive effect in terms of the frequency and severity of several important chemotherapy-related toxicities, including neutropenia, anaemia, and thrombocytopenia.

- The exposure-adjusted event rates of Grade 3 to 5 stomatitis and mucosal inflammation were higher in the pembrolizumab plus chemotherapy group than in the standard treatment group. A shorter time from prior radiation and more current smokers are identified as 2 risk factors that may contribute to the higher rate of these events in the pembrolizumab plus chemotherapy group.

- Higher rates of SAEs (including those considered to be related to study intervention) were reported in the pembrolizumab plus chemotherapy group compared to standard treatment group.

- The proportion of participants discontinuing study treatment due to an AE was similar between the pembrolizumab plus chemotherapy and the standard treatment groups.

- The incidences and types of AEOSIs were generally consistent with the known safety profile of pembrolizumab monotherapy use in R/M HNSCC.

- The AEs observed for pembrolizumab plus chemotherapy were effectively managed by standard clinical practice as applicable for pembrolizumab monotherapy or platinum plus 5-FU.

Summary of adverse events

The AE summary profile observed for participants treated with pembrolizumab plus chemotherapy was generally consistent with the known safety profiles of pembrolizumab monotherapy and of chemotherapy.

The frequency of AEs by category was similar in the pembrolizumab plus chemotherapy group and in the standard treatment group, including all AEs, drug-

related AEs, Grade 3 to 5 AEs, dose modification due to AE, deaths due to AEs, and AEs leading to treatment discontinuation (Table 57). The pembrolizumab plus chemotherapy group experienced a higher frequency of SAEs and drug-related SAEs (58.7% and 37.0% compared with 49.1% and 25.4% in the standard treatment group, respectively) (Table 57). It can also be seen from Table 57 that the AE profile of pembrolizumab plus chemotherapy in all of the AE categories, both considered on its own in and in terms of the difference between it and cetuximab + chemotherapy, in the CPS≥1 population does not differ substantially to that in the overall population.

Table 57 Adverse event summary, pembrolizumab +chemotherapy combination therapy vs. control, ASaT population, comparison between the overall population and CPS≥1 subgroup

	Overall population					CPS≥1 subgroup				
	Pembrolizumab + chemotherapy		Cetuximab + chemotherapy		Difference in % vs control arm[†]	Pembrolizumab + chemotherapy		Cetuximab + chemotherapy		Difference in % vs control arm[†]
	n	(%)	n	(%)	Estimate (95% CI)	n	(%)	n	(%)	Estimate (95% CI)
Subjects in population	276		287			237		245		
with one or more adverse events	271	(98.2)	286	(99.7)	-1.5 (-3.9, 0.3)	233	(98.3)	244	(99.6)	-1.3 (-3.9, 0.8)
with no adverse event	5	(1.8)	1	(0.3)	1.5 (-0.3, 3.9)	4	(1.7)	1	(0.4)	1.3 (-0.8, 3.9)
with drug-related[‡] adverse events	263	(95.3)	278	(96.9)	-1.6 (-5.1, 1.7)	226	(95.4)	236	(96.3)	-1.0 (-4.9, 2.8)
with toxicity grade 3-5 adverse events	234	(84.8)	240	(83.6)	1.2 (-4.9, 7.2)	202	(85.2)	204	(83.3)	2.0 (-4.6, 8.5)
with toxicity grade 3-5 drug-related adverse events	196	(71.0)	198	(69.0)	2.0 (-5.6, 9.6)	171	(72.2)	166	(67.8)	4.4 (-3.8, 12.5)
with serious adverse events	162	(58.7)	141	(49.1)	9.6 (1.3, 17.7)	147	(62.0)	121	(49.4)	12.6 (3.8, 21.3)
with serious drug-related adverse events	102	(37.0)	73	(25.4)	11.5 (3.9, 19.1)	95	(40.1)	60	(24.5)	15.6 (7.3, 23.7)
with dose modification[§] due to an adverse event	229	(83.0)	240	(83.6)	-0.7 (-6.9, 5.5)	200	(84.4)	206	(84.1)	0.3 (-6.3, 6.9)
who died	32	(11.6)	27	(9.4)	2.2 (-2.9, 7.4)	30	(12.7)	27	(11.0)	1.6 (-4.2, 7.6)
who died due to a drug-related adverse event	10	(3.6)	8	(2.8)	0.8 (-2.2, 4.1)	8	(3.4)	8	(3.3)	0.1 (-3.4, 3.7)
discontinued drug due to an adverse event	85	(30.8)	78	(27.2)	3.6 (-3.9, 11.1)	77	(32.5)	67	(27.3)	5.1 (-3.0, 13.3)
discontinued drug due to a drug-related adverse event	63	(22.8)	57	(19.9)	3.0 (-3.8, 9.8)	56	(23.6)	48	(19.6)	4.0 (-3.3, 11.4)
discontinued drug due to a serious adverse event	54	(19.6)	48	(16.7)	2.8 (-3.5, 9.3)	51	(21.5)	45	(18.4)	3.2 (-4.0, 10.3)

	Overall population					CPS≥1 subgroup				
	Pembrolizumab + chemotherapy		Cetuximab + chemotherapy		Difference in % vs control arm†	Pembrolizumab + chemotherapy		Cetuximab + chemotherapy		Difference in % vs control arm†
	n	(%)	n	(%)	Estimate (95% CI)	n	(%)	n	(%)	Estimate (95% CI)
discontinued drug due to a serious drug-related adverse event	31	(11.2)	28	(9.8)	1.5 (-3.6, 6.7)	29	(12.2)	25	(10.2)	2.0 (-3.7, 7.8)

†Based on Miettinen & Nurminen method.

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

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

Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.

For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.

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.

Adverse events by decreasing incidence

The most frequently reported AEs (incidence >40%) in both treatment groups were anaemia and nausea, which are expected AEs of platinum and 5-FU chemotherapy, and additionally, in the standard treatment group, hypomagnesemia, which is consistent with the AE profiles of cetuximab.

Drug-related adverse events

The number of participants with at least 1 drug-related AE (incidence ≥5%) was comparable in both treatment groups. The most frequently reported drug-related AEs (incidence >40%) in participants in both treatment groups were anaemia and nausea, which are expected AEs of platinum and 5-FU chemotherapy. Treatment differences included a higher proportion of participants in the pembrolizumab plus chemotherapy group who had drug-related anaemia, thrombocytopenia, hypothyroidism, blood creatinine increase, peripheral sensory neuropathy, malaise, and acute kidney injury, and a higher proportion of participants in the standard treatment group who had various skin-related events, hypokalaemia, hypomagnesemia, hypophosphatemia, and infusion-related reactions.

Grade 3-5 adverse events

No substantial differences in the type and frequencies of Grade 3 to 5 AEs were reported between the 2 treatment groups, except for a higher rate of anaemia, stomatitis, and mucosal inflammation in the pembrolizumab plus chemotherapy group, and a higher rate of rash in the standard treatment group. The most frequently reported Grade 3 to 5 AEs (>10% incidence) by decreasing incidence were anaemia, neutropenia, and neutrophil count decrease in both treatment groups. The incidence of these most frequently reported Grade 3 or 5 events was comparable between the 2 treatment groups, with the exception of anaemia which was reported more frequently in the pembrolizumab plus chemotherapy group.

Drug-related grade 3-5 adverse events

The proportion of participants who experienced Grade 3 to 5 AEs considered to be drug-related were similar in both treatment groups. The most common drug-related Grade 3 to 5 AEs (>10% incidence) in both treatment groups were anaemia,

neutropenia, and neutrophil count decrease. The incidence of these events was comparable between the 2 treatment groups. The main difference was a higher rate of stomatitis, febrile neutropenia, and mucosal inflammation in the pembrolizumab plus chemotherapy group.

Serious adverse events

The proportion of participants with 1 or more SAE was higher in the pembrolizumab plus chemotherapy group (58.7% compared with 49.1% in the standard treatment group). The most frequently reported SAEs (>5% incidence in the pembrolizumab plus chemotherapy groups and >3% incidence in the standard treatment group) were febrile neutropenia, pneumonia, and anaemia in both treatment groups, and lung infection in the pembrolizumab plus chemotherapy group.

Drug-related serious adverse events

The number of participants with 1 or more drug-related SAE was higher in the pembrolizumab plus chemotherapy group (37.0% compared with 25.4% in the standard treatment group). The most frequently reported drug-related SAEs (≥3% incidence in the pembrolizumab plus chemotherapy group and >2.5% incidence in the standard treatment group), were febrile neutropenia and anaemia in both treatment groups. All 14 drug-related SAE of febrile neutropenia in pembrolizumab plus chemotherapy group occurred shortly after all 3 drugs (pembrolizumab, platinum, and 5-FU) were administered (10 to 20 days). All the events were considered by the investigator to be related to chemotherapy.

Adverse events resulting in death

The proportion of participants with AEs resulting in death was similar in the 2 treatment groups (11.6% in the pembrolizumab plus chemotherapy group and 9.4% in the standard treatment group). The most common reason for death in participants treated with pembrolizumab plus chemotherapy was septic shock (5 participants [1.8%]). In the standard treatment group the most common reason for death was pneumonia (6 participants [2.1%]). The incidence of death due to infection was similar in both treatment groups.

Drug-related AEs resulting in death were reported in a similar proportion of participants in both treatment groups (3.6% in the pembrolizumab plus chemotherapy group and 2.8% in the standard treatment group). The most common reason for death due to a drug-related AE was septic shock and pneumonia in the pembrolizumab plus chemotherapy group and standard treatment group, respectively.

Drug-related adverse events resulting in discontinuation

The proportion of participants discontinuing study treatment due to a drug-related AE was similar in the 2 treatment groups. The most common drug-related AEs resulting in the discontinuation of study treatment in the pembrolizumab plus chemotherapy group were blood creatinine increase, neutropenia, mucosal inflammation, pneumonia, and septic shock. The most common drug-related AEs resulting in the discontinuation of study treatment in the standard treatment group were infusion related reaction, rash, and anaemia.

Adverse events of special interest

The overall incidence of AEOSI was similar in the pembrolizumab plus chemotherapy group and the standard treatment group (25.7% and 23.7%, respectively). The incidence of drug-related AEOSIs was higher in the pembrolizumab plus chemotherapy group compared with the standard treatment group, whereas the incidence of Grade 3 to 5 AEOSIs (including those considered to be related to study intervention), AEOSIs resulting in dose modification (including all modifications and modifications due to cetuximab), and AEOSIs resulting in discontinuation of study intervention (including those considered to be related to study intervention) were lower in the pembrolizumab plus chemotherapy group.

The most common AEOSIs in pembrolizumab plus chemotherapy group were hypothyroidism, pneumonitis, hyperthyroidism, and colitis, which are currently known risks/AEOSI associated with pembrolizumab. Infusion reactions and severe skin reactions were the most common AEOSIs in the standard treatment group. The majority of AEOSIs in the pembrolizumab plus chemotherapy group were Grade 1 and 2, whereas in the standard treatment group AEOSIs were most commonly Grade 2 and 3.

B.2.11 Ongoing studies

For the KEYNOTE-048 study, more recent data from the full analysis (FA) will become available in the following days. The full set of FA data has not been released in time for incorporation into this submission document, however a recently published summary of the KEYNOTE-048 FA results are included in Appendix N. An important finding from the FA results is that the difference in OS between the pembrolizumab + chemotherapy arm and the cetuximab + chemotherapy arm in the PD-L1 CPS≥1 population is shown to be statistically significant (23).

There are no ongoing studies of pembrolizumab in addition to the KEYNOTE-048 study that will provide additional evidence in the next 12 months for the indication being appraised.

B.2.12 Innovation

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. This mode of action has been demonstrated for both pembrolizumab monotherapy and pembrolizumab + chemotherapy combination therapy in the PD-L1 CPS≥1 population as covered by this submission. As evident by clinical and safety data presented, pembrolizumab offers a durable and well tolerated treatment option for patients with R/M HNSCC and PD-L1 expression of CPS≥1.

Currently, first line-treatment options for R/M HNSCC in routine UK clinical practice is limited to platinum-based chemotherapy regimens which are associated with significantly poorer efficacy in terms of overall and progression-free survival compared to treatment with pembrolizumab (either as monotherapy or in combination with platinum-based chemotherapy) along with significantly worse adverse events rates compared to pembrolizumab monotherapy (as shown in section B.2.9). Patient who have R/M HNSCC originating in the oral cavity may be treated with cetuximab in combination with platinum-based chemotherapy regimens, as the results presented from the KEYNOTE-048 study show, treatment with pembrolizumab also results in significantly superior survival outcomes compared to this regimen along with a more

favourable safety profile (using pembrolizumab monotherapy, or a comparable safety profile using pembrolizumab in combination with platinum-based chemotherapy).

R/M HNSCC is a highly symptomatic disease that can exert a considerably negative effect on patients' health-related quality of life, in particular arising from pain, difficulties with swallowing and speech, breathing and social function. It is therefore notable that patients treated with pembrolizumab monotherapy or pembrolizumab in combination with platinum-based chemotherapy exhibited [redacted] health-related quality of life scores over 15 weeks of follow-up.

These facts therefore show that pembrolizumab offers a significant step-change in benefit for patients with R/M HNSCC in the UK.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Pembrolizumab monotherapy

Clinical effectiveness

KEYNOTE-048 is the first global study to demonstrate significant and meaningful benefit of pembrolizumab monotherapy in participants with R/M HNSCC over standard treatment, which included 3 medications.

Pembrolizumab monotherapy has demonstrated statistically significant and clinically meaningful OS advantage over standard treatment in participants with first-line R/M HNSCC whose tumours express PD-L1 CPS≥1 (HR 0.78 [0.64, 0.96], p = 0.00855) at the latest interim analysis (IA2).

Considerably higher OS rates at 12 months and 18 months by KM estimation favoured pembrolizumab monotherapy to standard treatment in all participants whose tumours express PD-L1 CPS≥1. Thus, treatment with pembrolizumab monotherapy resulted in long-term survival benefits beyond what has previously been reported for this population. Clinically meaningful benefit in OS was achieved with pembrolizumab across all other prognostic factors and demographic subgroups evaluated, providing further evidence of survival benefit with pembrolizumab monotherapy.

Pembrolizumab monotherapy did not show improvement in PFS compared with standard treatment however PFS rates were higher at 12 months in the pembrolizumab monotherapy arm compared to the cetuximab + chemotherapy arm (19.6% vs 11.9%). This PFS effect is consistent with the class effect of immunotherapy agents, where a delayed separation of PFS curves has been observed, evidenced by higher PFS rates at later months after treatment initiation.

Although there was no ORR benefit, pembrolizumab monotherapy demonstrated improved benefit in terms of durability of response, with 78.9% of responders to pembrolizumab monotherapy having response lasting ≥6 months, compared to 36.0% of responders to standard treatment.

R/M HNSCC is a symptomatic disease that notably affects daily life of patients, including pain, swallowing, speech, breathing, and social function. Participants treated with pembrolizumab monotherapy exhibited stable global health status/QoL, functioning, and symptoms over 15 weeks of follow-up.

The NMAs also showed that pembrolizumab monotherapy was generally more efficacious than the EXTREME regimen as well as methotrexate, 5-FU, and platinum + 5-FU interventions in terms of survival. PFS results were also generally favourable for pembrolizumab versus the EXTREME regimen and the platinum + 5-FU combination therapy.

Safety profile

Pembrolizumab monotherapy had a favourable safety profile that was generally well-tolerated compared to standard treatment, with a low rate of treatment discontinuation, and had a safety profile that was generally consistent with the established safety profile of pembrolizumab, in the R/M HNSCC population. Comparison of summary AE data between the CPS≥1 subgroup and the overall population showed that the safety profile of pembrolizumab monotherapy does not differ substantially between these populations.

Summary

In summary, pembrolizumab monotherapy was well tolerated in participants with R/M HNSCC, with a more favourable safety profile compared with standard treatment.

There were no new safety concerns identified with the use of pembrolizumab monotherapy in KEYNOTE-048. The safety profile of pembrolizumab monotherapy as observed in KEYNOTE-048 was generally consistent with the established safety profile for pembrolizumab monotherapy in R/M HNSCC.

B.2.13.2 Pembrolizumab + chemotherapy combination therapy

Clinical effectiveness

KEYNOTE-048 is the first global study to demonstrate that the combination of a checkpoint inhibitor with chemotherapy substantially and meaningfully improves efficacy endpoints in patients with 1L HNSCC.

KEYNOTE-048 demonstrated that, in the population of patients with CPS≥1, pembrolizumab plus chemotherapy resulted in a statistically significant, clinically meaningful improvement in OS for participants with 1L R/M HNSCC (HR 0.71; 95% CI: 0.57, 0.8; p=0.00072). The OS rate was 55.0% and 43.5% at 12 months and 39.1% and 26.4% at 18 months for participants receiving pembrolizumab plus chemotherapy and standard treatment, respectively, by KM estimation. Thus, treatment with pembrolizumab plus chemotherapy resulted in long-term survival benefits beyond what has previously been reported for this population. Clinically meaningful benefit in OS was achieved with pembrolizumab plus chemotherapy across all prognostic factors and demographic subgroups evaluated, providing further evidence of survival benefit with the pembrolizumab plus chemotherapy regimen.

The success criteria for PFS had not been reached at this interim analysis. As with what was observed in the pembrolizumab monotherapy arm, this PFS effect is consistent with the class effect of immunotherapy agents, where a delayed separation of PFS curves has been observed, evidenced by higher PFS rates at later months after treatment initiation. ORR by BICR of the experimental arm is comparable with standard treatment.

Pembrolizumab plus chemotherapy also demonstrated the improved benefit assessed by the durability of response. Approximately half of the responders to pembrolizumab plus chemotherapy (54.3%) had a response lasting ≥6 months, compared with 34.3% of responders to standard treatment.

R/M HNSCC is an aggressive and devastating disease that is symptomatic, significantly destructive, and severely impactful on the daily life of patients. Participants treated with pembrolizumab plus chemotherapy exhibited stable global health status/QoL, functionality and symptoms over 15 weeks of follow-up.

The NMAs also showed that pembrolizumab combination therapy generally showed improved survival compared to the EXTREME regimen as well as methotrexate and platinum + 5-FU, and cisplatin monotherapies. Similar to OS analyses, PFS results also favoured pembrolizumab combination therapy compared to the EXTREME regimen and platinum + 5-FU combination treatment.

Safety profile

Pembrolizumab plus chemotherapy had a comparable and manageable safety profile relative to standard treatment. No new safety issues were identified with the treatment of pembrolizumab plus chemotherapy beyond those known to occur with platinum plus 5-FU chemotherapy as well as pembrolizumab monotherapy in the R/M HNSCC population. The AEs observed for pembrolizumab plus chemotherapy were effectively managed by standard clinical practice as applicable for pembrolizumab monotherapy or platinum plus 5-FU. Comparison of summary AE data between the CPS≥1 subgroup and the overall population showed that the safety profile of pembrolizumab + chemotherapy does not differ substantially between these populations.

Summary

In summary, pembrolizumab plus chemotherapy has a positive benefit/risk profile in R/M HNSCC patients, demonstrated by a statistically significant and clinically meaningful OS advantage relative to standard treatment, along with comparable and manageable safety profiles.

B.2.13.3 End-of-life criteria

Both pembrolizumab monotherapy and pembrolizumab + chemotherapy in this indication meet the end-of-life criteria, the details are summarised in Table 58.

Table 58 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 overall survival in patients with PD-L1 CPS≥1 treated with standard therapy of cetuximab + chemotherapy is 10.3 (95% CI: 9.0, 11.5) months, as shown in the KEYNOTE-048 study.	Section B.2.6.1, page 59, Table 14.
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	The increase in overall survival in patients with PD-L1 CPS≥1 treated with pembrolizumab monotherapy is 1.06 years in patients treated with standard therapy of cetuximab + chemotherapy, and 1.44 years in patients treated with platinum + 5-FU.	Section B.3.7 Table 89
	Median overall survival in patients with PD-L1 CPS≥1 treated with pembrolizumab + chemotherapy is 1.19 years in patients treated with standard therapy of cetuximab + chemotherapy, and 1.61 years in patients treated with platinum + 5-FU.	Section B.3.7 page Table 90.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review was undertaken in April 2019 to identify relevant cost-effectiveness studies from the published literature. No cost-effectiveness studies meeting all the inclusion criteria were identified. Full details of the SLR search strategy, study selection process and results are presented in Appendix G.

B.3.2 Economic analysis

No cost-effectiveness study meeting the relevant inclusion criteria to this submission was identified, indicating that a de novo cost-effectiveness model is required to assess the cost-effectiveness of pembrolizumab compared with the relevant comparators.

Patient population

The patient population included in the economic evaluation consisted of patients with untreated recurrent or metastatic squamous cell carcinoma of the head and neck with CPS expression ≥1. The patient characteristics were based on KEYNOTE-048 trial and are presented in Table 59, below.

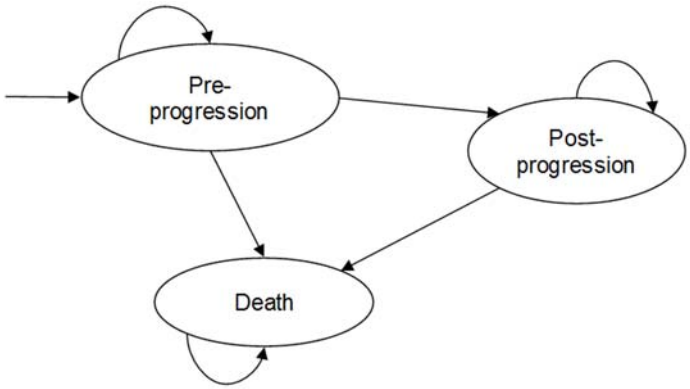
Table 59. Baseline characteristics of the population in the cost-effectiveness model

Patient characteristics	Mean Value		Source
	Monotherapy	Combination Therapy	
Patient Age	61.08	60.82	KEYNOTE-048
Proportion male	83.0%	83.4%	
Average patient weight (kg)	69.37	68.17	KEYNOTE-048 (patients from European sites)
Average body surface area (m^2)	1.75	1.74	

Model structure

A partitioned survival cohort simulation model was developed to estimate health outcomes and costs for pembrolizumab and comparator regimens in the target patient population. The transition diagram of the cohort simulation model is presented in Figure 33 below.

Figure 33. Transition Diagram for the Cohort Simulation



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

In the cost-effectiveness model, progression is defined by the primary censoring rule in KEYNOTE-048 trial, i.e. assessment by independent radiologist's review per the Response Evaluation Criteria in Solid Tumors [RECIST] V1.1.

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 analyses adopt a partitioned-survival model approach, which partitions the overall survival (OS) time into progression-free survival (PFS) and post-progression survival. This is in line with the clinical pathway of care described in section B.1.3 of the submission. Unlike a Markov model, in which transition probabilities between health states are needed, a partitioned-survival model directly estimates proportions of patients in each health state at each time point. The partitioned-survival approach has the advantage of utilising the PFS and OS survival data from KEYNOTE-048 directly, without requiring transition probabilities.

The proportion of patients in each health state at a certain time point is calculated as follows using the partitioned-survival approach:

- Pre-progression: proportion of patients who are in PFS, based on the estimates from PFS curve

- Death: 1 – proportion of alive patients based on the estimates from OS curve
- Post-progression: (proportion of alive patients based on estimates from OS curve) – (proportion of patients in PFS)

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(33).

Table 60. Features of the economic analysis

	Previous appraisals		Current appraisal	
Factor	**NICE [TA490]**	**NICE [TA473]**	**Chosen values**	**Justification**
Time horizon	20	5	20	Lifetime horizon for the defined population (NICE reference case)
Treatment waning effect?	No	No	No	Any treatment waning effect is reflected in the extrapolation of OS
Source of utilities	HRQoL data were collected in the CheckMate 141 trial using the EQ-5D-3L questionnaire	Collected from EXTREME trial using EORTC QLQ-C30 questionnaire	Utility values collected in KEYNOTE-048 trial using the EQ-5D-3L questionnaire	Consistent with NICE reference case
Source of costs	BNF 71 (2016), eMIT (2015), NHS reference costs schedule 2014-15,	NHS reference costs schedule 2014-15, PSSRU (2015), eMIT (2015), BNF 71 (2016)	NICE TA473, NICE TA490, NHS reference costs schedule 2017-18(34), eMIT 2018(35) and published literature, BNF 77(36)	Resource use was based on previous HTAs in metastatic HNSCC (TA490), (TA473) and published literature. Unit costs were taken from recognised national databases

Intervention technology and comparators

The intervention (i.e. pembrolizumab) was applied in the model as per the expected licensed dosing regimen. As a monotherapy this is administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]. It is also expected that the monotherapy licence will include an option to administer pembrolizumab at a fixed dose of 400mg over 30 minutes every 6 weeks [Q6W].

As a combination therapy this is at a fixed dose of 200mg over 30 minutes Q3W in combination with platinum and 5-FU. The licence states that pembrolizumab is to be administered until disease progression or unacceptable toxicity. The KEYNOTE-048 protocol established that treatment should continue until radiologic disease progression, toxicities leading to discontinuation, physician's decision or 24 months of uninterrupted treatment with pembrolizumab. The final scope specifies that there will be two pembrolizumab therapy options:

- Pembrolizumab monotherapy
- Pembrolizumab in combination with a platinum-based chemotherapeutic agent (cisplatin or carboplatin) and 5-Fluorouracil

This submission is for both the pembrolizumab monotherapy and combination therapy options for the first line treatment of adults with recurrent/metastatic head and neck squamous cell carcinoma with CPS≥1. The final scope specifies the following treatment regimens as relevant comparators:

- Platinum-based chemotherapy regimens
- Cetuximab in combination with platinum-based chemotherapy – the EXTREME regimen (only if the cancer started in the oral cavity)

Platinum plus 5-FU is the UK standard of care for patients not eligible for treatment with the EXTREME regimen (i.e. with cancer not starting in the oral cavity) and is included as the other main comparator.(16)

Discontinuation rules

In KEYNOTE-048, patients were to continue pembrolizumab until radiographic disease progression as determined by the central imaging vendor, unacceptable toxicity, unacceptable adverse events, intercurrent illness that prevents further administration of treatment, the subject has a confirmed positive serum pregnancy test or a maximum of 24 months of uninterrupted treatment with pembrolizumab. Additionally, the treatment durations of the platinum agents and 5-Fluorouracil are limited to 6 cycles (5 months), which is implemented for all treatment regimens including these agents.

B.3.3 Clinical parameters and variables

Overall Method of Modelling Effectiveness

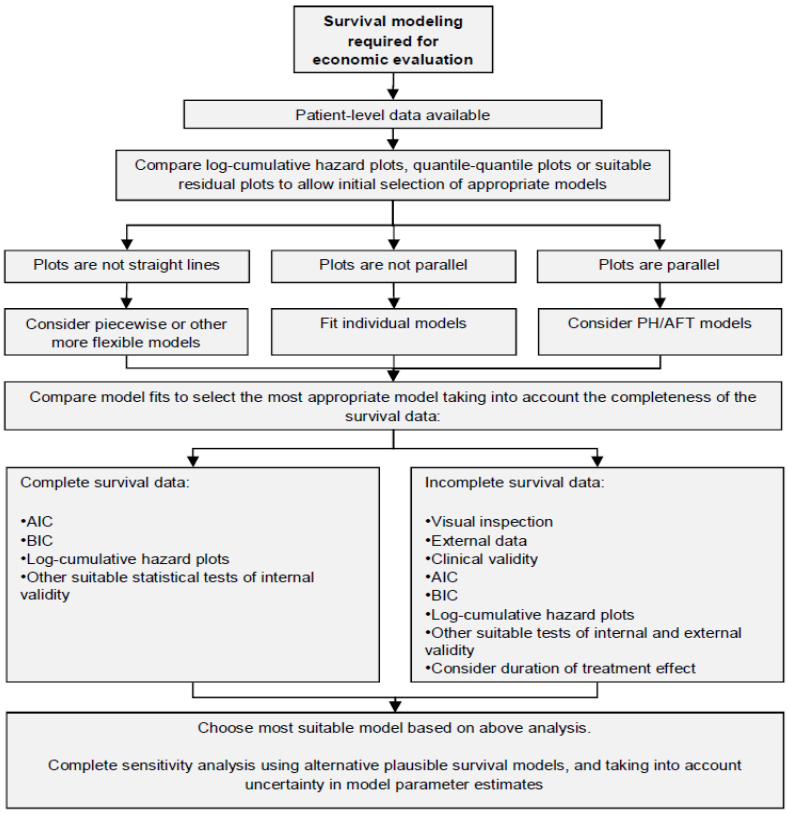
The clinical effectiveness parameters for pembrolizumab in the cost-effectiveness model were estimated from the KEYNOTE-048 patient-level data on OS, PFS and adverse event rates. Clinical effectiveness estimates for non-trial comparators (platinum + 5-FU) were applied using the hazard ratios from the network meta-analysis (please see section B.2.9).

The follow-up period in KEYNOTE-048 was shorter than the time horizon of the economic model. Therefore, extrapolation of the OS and PFS was required for the area-under-the-curve (AUC) partitioned survival approach.

Parametric models were fitted to the KEYNOTE-048 Kaplan–Meier (KM) data. The survival curve fitting was carried out in line with the NICE Decision Support Unit (DSU) guidelines outlined in Technical Support Document 14(37). In summary, the steps that were followed are presented in

Figure **33** below.

Figure 34. Survival Model Selection Process Algorithm (adapted from TSD 14)



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

Modelling Overall Survival

KEYNOTE-048 is a phase III trial, whereby patient level data are available for patients treated with pembrolizumab (monotherapy and in combination with platinum + 5-FU) and with the EXTREME regimen. Detailed below is a description of how the survival curve fitting exercise was implemented for these treatments.

Monotherapy

When comparing the log cumulative hazards for OS observed in the pembrolizumab and EXTREME arms (**Error! Reference source not found.**), the lines do not appear parallel and cross. The Grambsch and Therneau's test supports this interpretation since the result is statistically significant ($p < 0.05$), indicating a rejection of the proportional hazards assumption for OS. This is further validated, which is further validated in the analysis of the Schoenfeld residual plot reported in

Figure **36**.

Figure 35: Log cumulative hazards plot for OS (monotherapy, CPS ≥1)

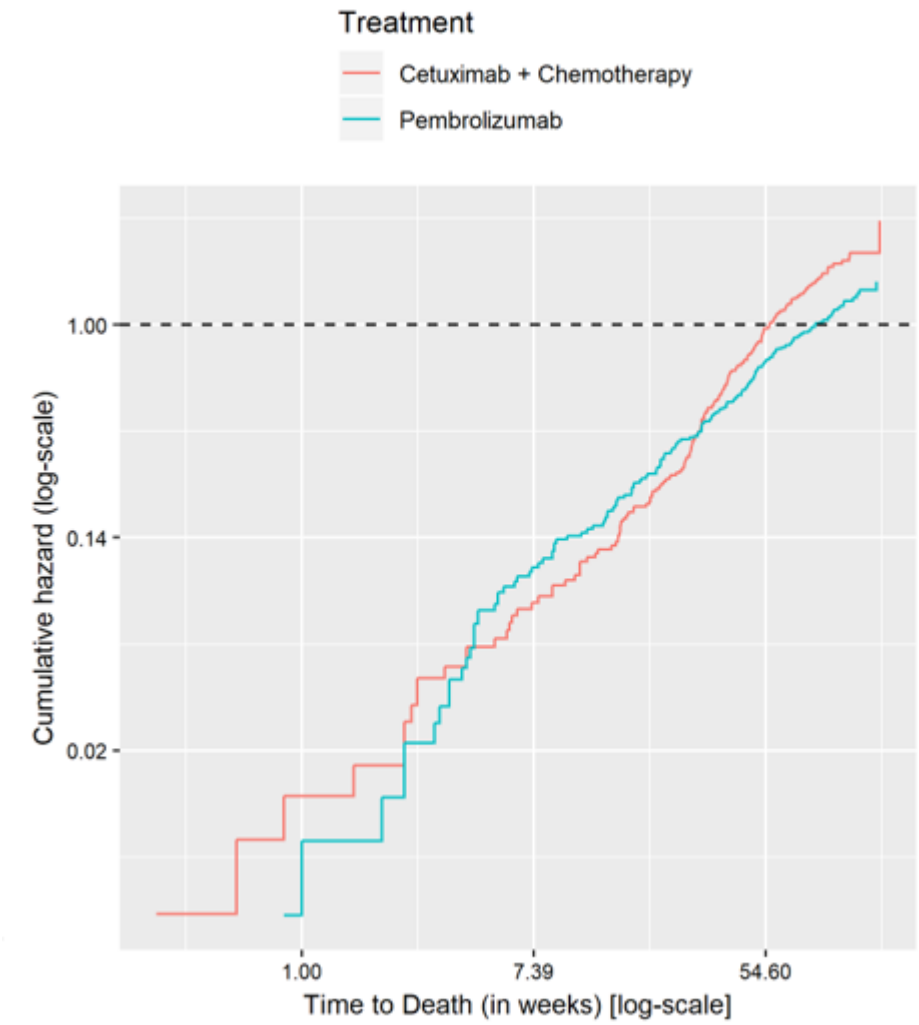
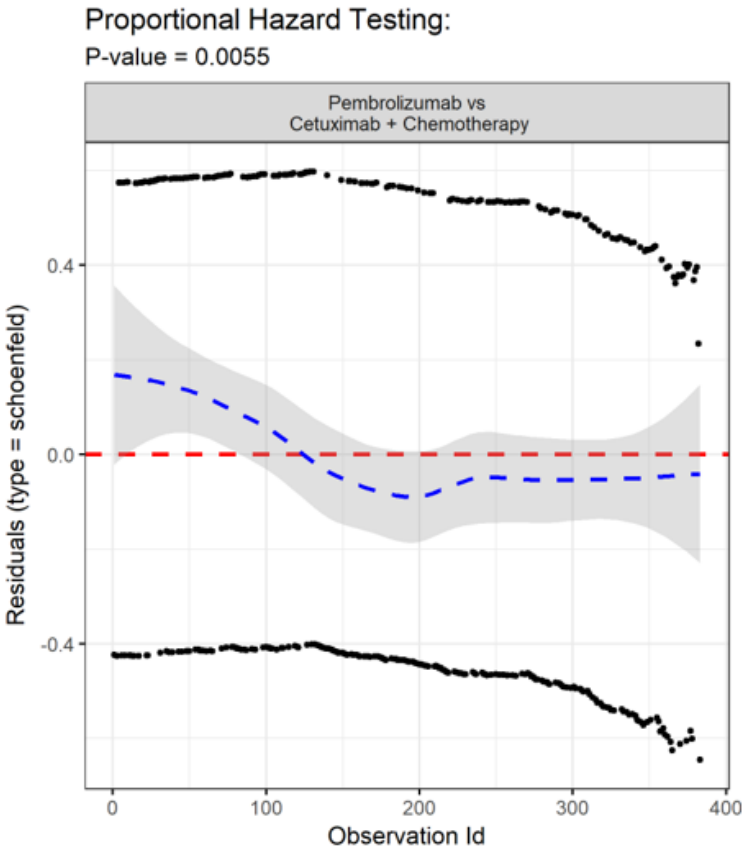


Figure 36: Schoenfeld residuals plot for OS (monotherapy, CPS ≥1)



This statistical and visual assessment suggests that a piecewise approach would be more appropriate for extrapolation. This was supported by the fact that none of the fully fitted parametric curves provided a good fit to the observed trial data (see Appendix P). The cut-off point for OS extrapolation was determined upon inspection of the cumulative hazard plot, where the change of hazard is more profound around weeks 30 and 45. Week 45 was selected to allow for a greater use of the observed trial data, whilst still allowing sufficient data from which to extrapolate the survival curve. 58.12% of pembrolizumab patients and 48.94% of EXTREME regimen patients are still alive. Alternative parametric approaches with a fully fitted parametric curve and extrapolation from a 30-week cut-off point were explored in scenario analyses. The figures and tables for the fully fitted parametric curves and the 30-week extrapolation are presented in Appendix P.

For the comparison with platinum + 5-FU, the best fit time-varying hazard ratios, based on the lowest DIC value, was the p1=0, p2=0.5. Please refer to section B.2.9 for more information.

Upon selection of the extrapolation point, the parametric models fitted were the Weibull, exponential, log-normal, log-logistic, Gompertz and generalised gamma distributions. Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information

criterion (BIC), combined with visual inspection were used to select the parametric distribution which provided the best-fit to the observed data. Next the external validity and clinical plausibility of the extrapolation was explored using external data. This information was then combined to make the final distribution selection for the model.

Goodness of fit – monotherapy

The statistical goodness of fit for each parametric distribution are provided in Table 61, showing good fit across both arms with the Gompertz, log-logistic and log-normal distributions.

Table 61. Summary of goodness-of-fit qualities of OS survival models at 45-week cut-off point – pembrolizumab monotherapy and EXTREME (CPS≥ 1)

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	775.43	778.42	6	802.34	805.18	1
Weibull	773.38	779.38	5	803.63	809.30	5
Gompertz	772.28	778.27	3	802.74	808.41	3
Log-logistic	771.90	777.90	2	802.57	808.24	2
Log-normal	769.92	775.91	1	803.24	808.91	4
Generalised Gamma	771.88	780.87	4	803.97	812.48	6

External validation – monotherapy

The clinical plausibility of the long-term extrapolations versus external data or longer-term data are key to appropriate selection of the base case distribution. The previous technology appraisal for cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA473) presented longer-term data from the relevant pivotal trial (EXTREME) to a time horizon of five years(32). Given this trial includes five-year data for both the EXTREME regimen and the platinum + 5-FU regimen, it provides a very useful validation of these longer-term survival estimates.

Table 62. Overall survival at random time points from the model and 5-year trial data *(replication of Table 7, page 36 from Submission template for the reconsideration of CDF drugs (TA473)(16)*

Treatment arm	% of patients alive at 28 months (1376 days)		% of patients alive at 36 months (1769 days)		% of patients alive at 42 months (2064 days)		% of patients alive at 59.5 months (2924 days)	
	Trial	Model	Trial	Model	Trial	Model	Trial	Model
Cetuximab	11.7	0.8	7.1	0.1	6.5	0.02	2.9	0
Standard of Care	8.3	0.08	4.4	0.01	4.4	0.002	1.7	0
Increment	**3.4**	**0.72**	**2.7**	**0.09**	**2.1**	**0.018**	**1.2**	**0**

To assess which of the distributions would provide a good projection of survival at longer term time points, the landmark time points of 3 and 5 years were summarised for each distribution to allow for comparison with the long-term EXTREME data. From this analysis, the exponential and Weibull distribution provide an underestimate of the survival at 5 years for both the EXTREME regimen and platinum + 5-FU and are not considered to be a good fit to the observe data. The Gompertz provides an overestimate of survival for both the EXTREME regimen and platinum 5-FU; whilst the lognormal, loglogistic and generalised gamma all provide reasonable estimates of survival for platinum + 5-FU (1.9%, 1.5% and 2.1% respectively versus an observed rate of 1.7%). The lognormal, loglogistic and Generalised Gamma do slightly overestimate 3- and 5-year survival for the EXTREME regimen by 2-3 percentage points. However, comparison of the EXTREME trial data to the KEYNOTE-048 trial data indicates that the survival curve in KEYNOTE-048 is already a few percentage points above survival curve from the EXTREME trial; implying that such an overestimate is to be expected and may reflect improvements in treatment practices in the 15 years since the trial was initiated.

Table 63. Overall survival at landmark time points for all distributions for pembrolizumab monotherapy and comparators (CPS≥ 1)

	Distributions using 45 week cut-point											
Treatment	**Exponential**		**Weibull**		**Gompertz**		**Lognormal**		**Loglogistic**		**Generalised Gamma**	
	3 year	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**
Pembrolizumab monotherapy	17.5%	5.7%	20.3%	9.6%	22.9%	18.2%	22.9%	15.3%	22.0%	14.2%	23.2%	15.9%
EXTREME	5.7%	0.8%	7.5%	1.8%	10.7%	7.8%	10.5%	5.5%	9.7%	5.2%	9.7%	4.5%
Platinum + 5-FU	2.9%	0.1%	4.3%	0.5%	5.9%	3.1%	5.9%	1.9%	5.3%	1.5%	6.1%	2.1%

Base case model selection – monotherapy

Given all the considerations outlined above, the lognormal distribution with 45-week cut off point was chosen as the base case survival model for the pembrolizumab monotherapy and comparator arms. The lognormal was the best fitting distribution across both arms from a statistical perspective, and most importantly the long-term extrapolations provided a good fit compared to the long-term data from the EXTREME trial, presented in TA473, for both the cetuximab + platinum + 5-FU (EXTREME) and the platinum + 5-FU arms.

Table 64. Overall survival at landmark time points from the base case distribution for pembrolizumab monotherapy and comparators (CPS ≥1)

	Timepoints					
Treatment	**1 year**	**2 years**	**28 months**	**3 years**	**5 years**	**10 years**
Pembrolizumab monotherapy	51.9%	30.8%	27.6%	22.9%	15.3%	8.3%
EXTREME	40.7%	17.0%	14.2%	10.5%	5.5%	2.1%
Platinum + 5-FU	36.9%	12.3%	9.4%	5.9%	1.9%	0.2%

Figure 37. Base case overall survival modelling for pembrolizumab monotherapy and EXTREME: piecewise model using lognormal distribution and 45 weeks cut off point (CPS ≥1)

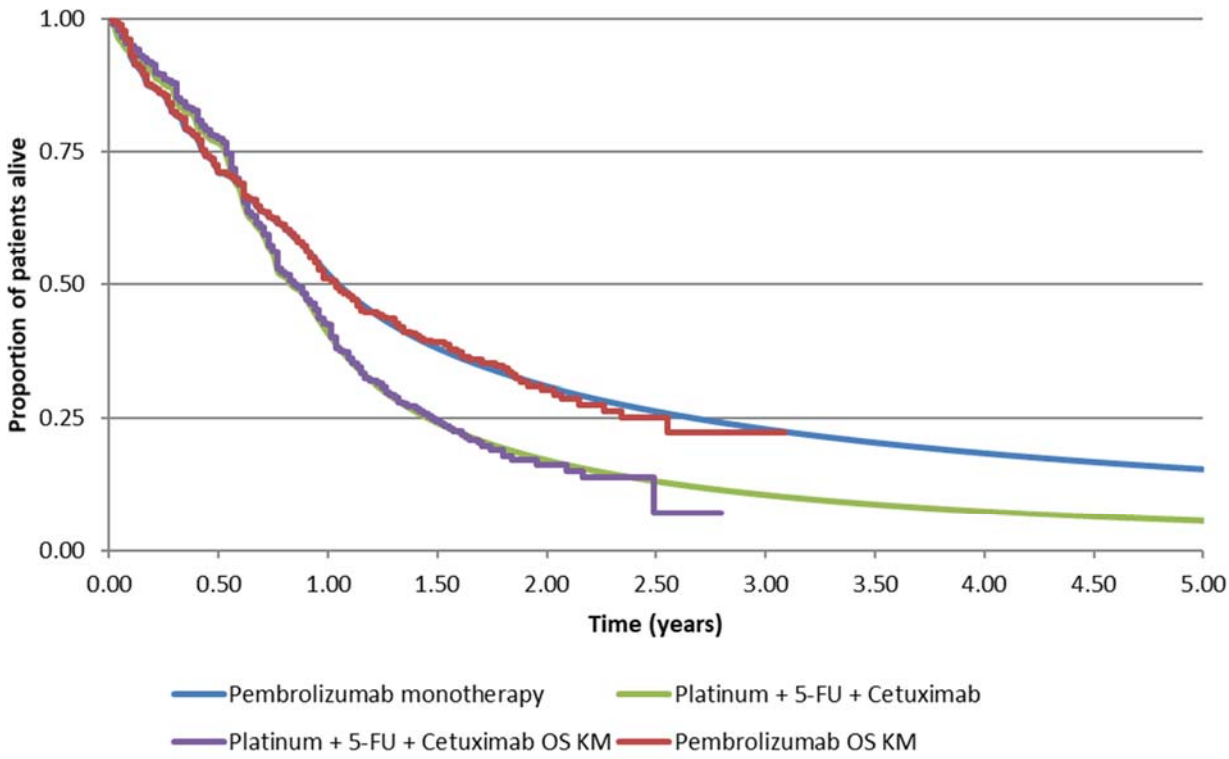
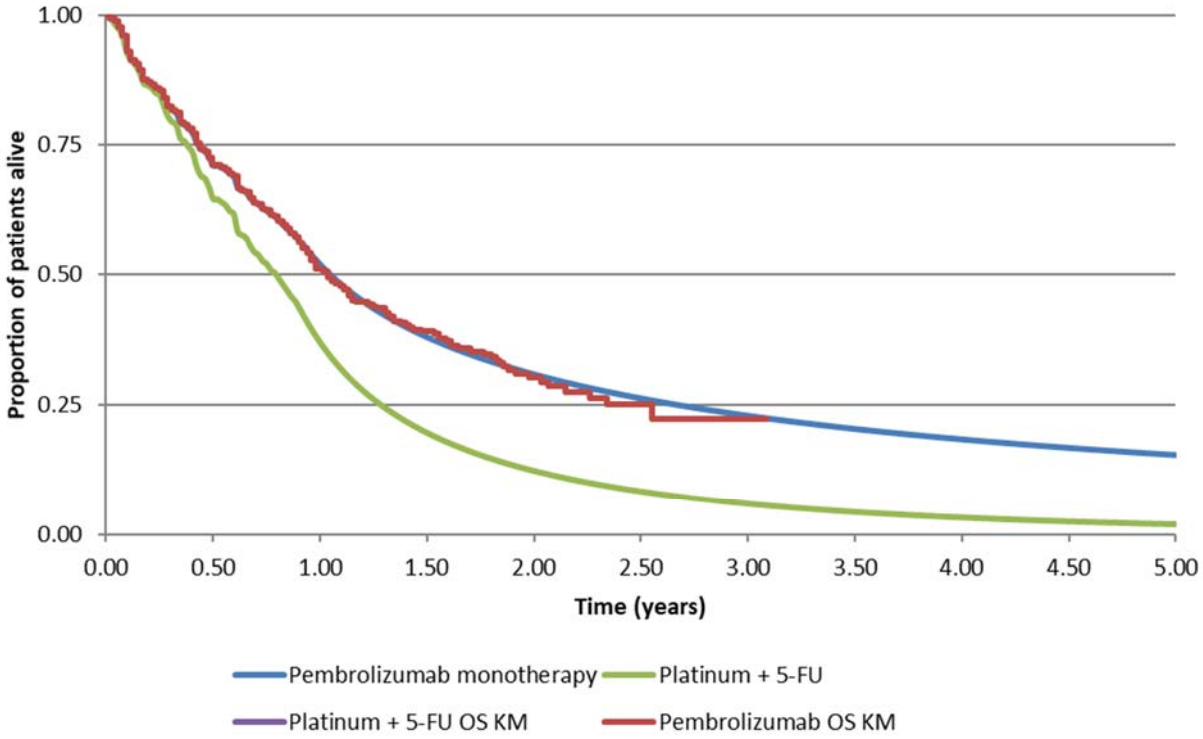


Figure 38. Base case overall survival modelling for pembrolizumab monotherapy and platinum + 5-FU: piecewise model using lognormal distribution and 45 weeks cut off point (CPS ≥1)



Combination therapy

When comparing the log cumulative hazards for OS observed in the pembrolizumab combination therapy and EXTREME arms (Figure 39), the lines do not appear parallel and cross. The Grambsch and Therneau's test supports this interpretation since the result is statistically significant ($p < 0.05$), indicating a rejection of the proportional hazards assumption for OS. This is also validated in the analysis of the Schoenfeld residual plot reported in Figure 40.

Figure 39: Log cumulative hazards plot for OS (combination therapy, CPS ≥1)

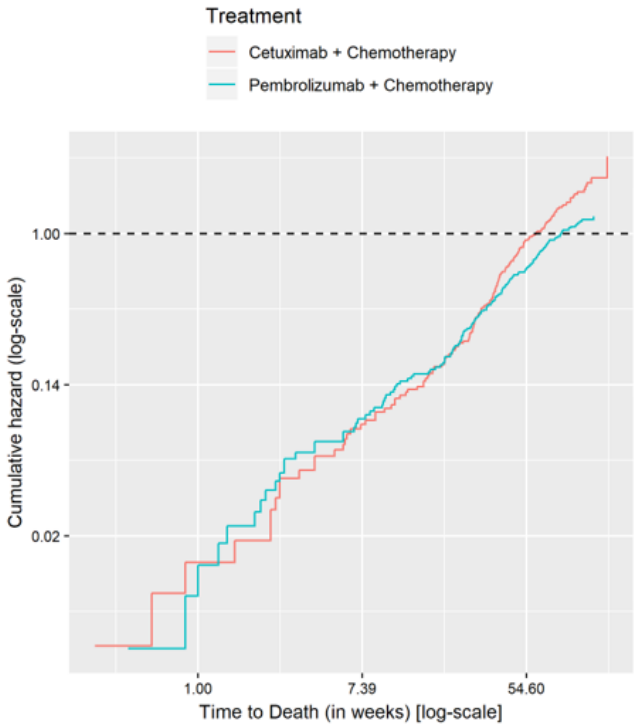
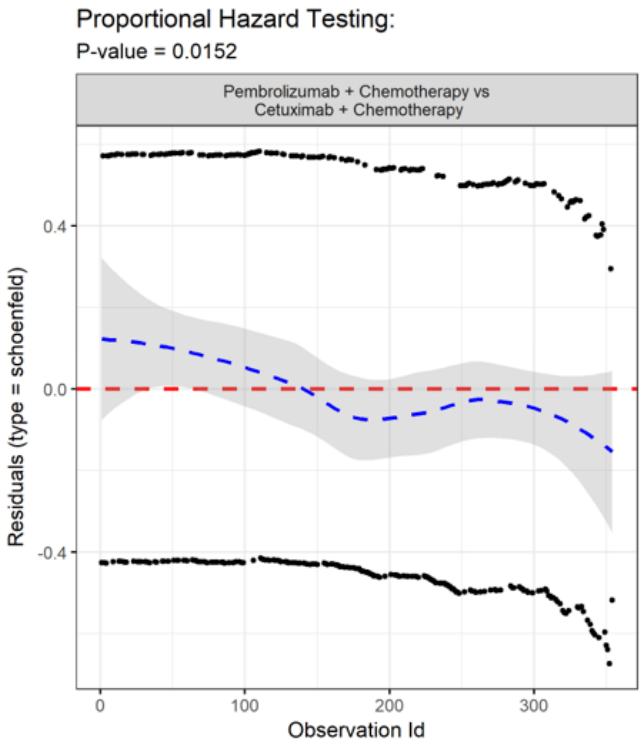


Figure 40: Schoenfeld residuals plot for OS (combination therapy, CPS ≥1)



This statistical and visual assessment suggests that a piecewise approach would be more appropriate for extrapolation. This was supported by the fact that none of the fully fitted parametric curves provided a good fit to the observed trial data (see Appendix P). The cut-off point for OS extrapolation was determined upon inspection of the cumulative hazard plot, where the change of hazard is more profound around weeks 30 and 45. Week 45 was selected to allow for a greater use of the observed trial data, whilst still allowing sufficient data with which to extrapolate the survival curve. 57.42% of pembrolizumab combination therapy patients and 49.19% of EXTREME regimen patients are still alive. Alternative parametric approaches with a fully fitted parametric curve and extrapolation from a 30-week cut-off point were explored in scenario analyses. The figures and tables for the fully fitted parametric curves and the 30-week extrapolation are presented in Appendix P.

For the comparison with platinum + 5-FU, the best fit time-varying hazard ratios, based on the lowest DIC value, was the p1=1, p2=0. Please refer to section B.2.9 for more information.

Upon selection of the extrapolation point, the parametric models fitted were the Weibull, exponential, log-normal, log-logistic, Gompertz and generalised gamma distributions. Statistical tests based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), combined with visual inspection were used to select the parametric distribution which provided the best-fit to the observed data. Next the external validity and clinical plausibility of the extrapolation was explored using external data. This information was then combined to make the final distribution selection for the model.

Goodness of fit – combination therapy

The statistical goodness of fit for each parametric distribution are provided in Table 65, showing the best fit across both arms with the Gompertz, exponential and loglogistic distributions.

Table 65. Summary of goodness-of-fit qualities of OS survival models at 45-week cut-off point – Pembrolizumab combination therapy and EXTREME (CPS ≥ 1)

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	698.18	701.12	3	742.70	745.46	1
Weibull	699.18	705.06	5	744.32	749.85	3
Gompertz	695.59	701.47	1	744.14	749.67	2
Log-logistic	696.24	702.13	2	744.85	750.37	4
Log-normal	697.70	703.58	4	745.61	751.13	5
Generalised Gamma	698.99	707.82	6	745.64	753.93	6

External validation – combination therapy

As previously discussed, the clinical plausibility of the long-term extrapolations versus external data or longer-term data are key to appropriate selection of the base case distribution. Again, validation was conducted against the long-term data provided from the EXTREME trial, presented in Table 62. By exploring the landmark survival with the different parametric distributions, an assessment of clinical plausibility was made.

Table 66. Overall survival at landmark time points for all distributions for pembrolizumab combination therapy and comparators (CPS ≥1)

	Distributions using 45 week cut-point											
Treatment	**Exponential**		**Weibull**		**Gompertz**		**Lognormal**		**Loglogistic**		**Generalised Gamma**	
	3 year	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**
Pembrolizumab combination therapy	19.1%	6.8%	20.7%	9.1%	25.0%	20.7%	24.0%	15.9%	22.1%	13.6%	22.7%	13.5%
EXTREME	4.9%	0.6%	6.3%	1.2%	9.1%	5.8%	9.6%	4.9%	9.1%	4.7%	8.8%	3.9%
Platinum + 5-FU	2.2%	0.0%	2.9%	0.0%	5.4%	2.1%	4.6%	0.5%	3.6%	0.3%	3.9%	0.2%

Base case model selection – combination therapy

Given all the considerations outlined above, the lognormal distribution with 45-week cut off point was chosen as the base case survival model for the pembrolizumab combination and comparator arms. Whilst the lognormal was not the best fitting distribution across both arms from a statistical perspective, the long-term extrapolations provided a plausible fit compared to the long-term data from the EXTREME trial, presented in TA473, for both the EXTREME arm and platinum + 5-FU arm. The Gompertz distribution provided a better statistical fit to the data and a better fit to the platinum + 5-FU arm. However, it was not selected as the base case due to concerns that the longer- term survival extrapolations (i.e. 10 and 20 years) across all treatment arms may be considered overly optimistic. Importantly, it also allows for consistency in the choice of distribution for the pembrolizumab combination therapy and monotherapy arms, as well as overall survival estimates which are similar in both sets of comparator arms (EXTREME regimen and platinum + 5-FU). The overall survival at landmark time points from the model for pembrolizumab combination therapy and the comparators are presented in Table 67.

Table 67. Overall survival at landmark time points from the model for combination therapy (CPS≥)

	Timepoints					
Treatment	**1 year**	**2 years**	**28 months**	**3 years**	**5 years**	**10 years**
Pembrolizumab combination	52.7%	32.3%	29.0%	24.0%	15.9%	8.4%
EXTREME	40.8%	16.2%	13.3%	9.6%	4.9%	1.7%
Platinum + 5-FU	34.6%	11.8%	8.7%	4.6%	0.5%	0.0%

The base case OS modelling is presented in Figure 41 for pembrolizumab combination therapy and EXTREME and in

Figure **42** for pembrolizumab combination therapy and platinum+5-FU.

Figure 41. Base case overall survival modelling for pembrolizumab combination therapy and EXTREME: piecewise model using lognormal distribution and 45 weeks cut off point (CPS ≥1)

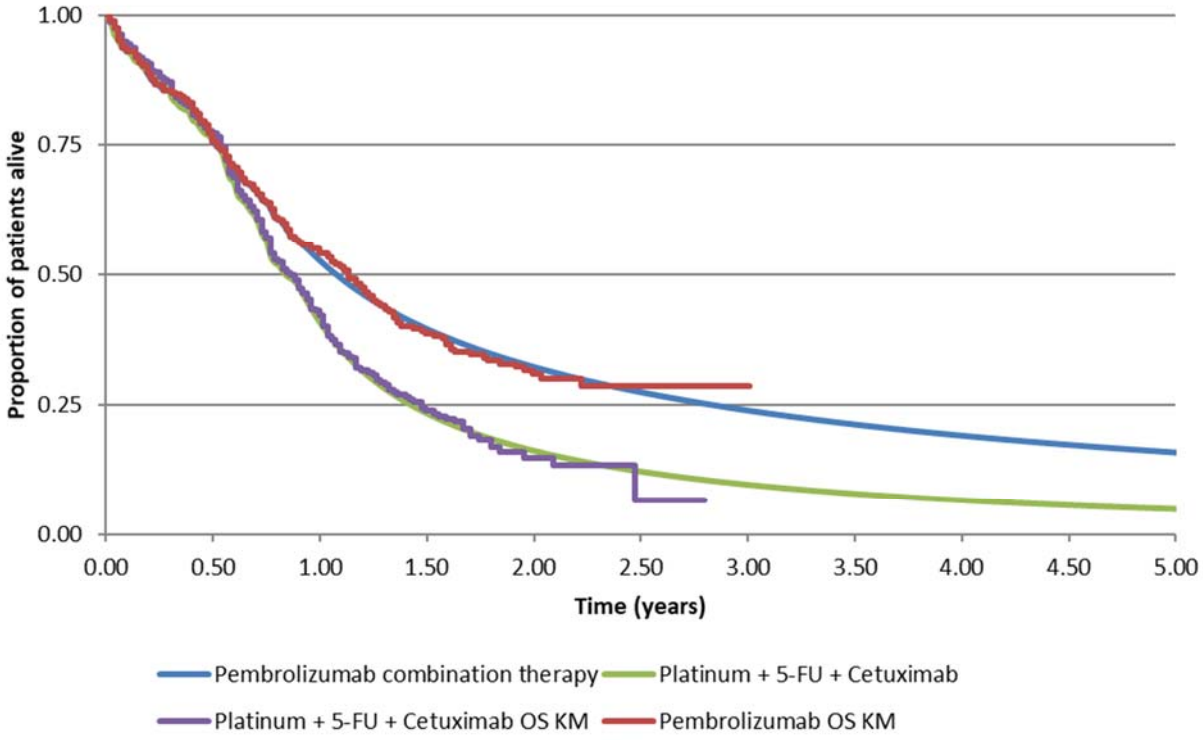
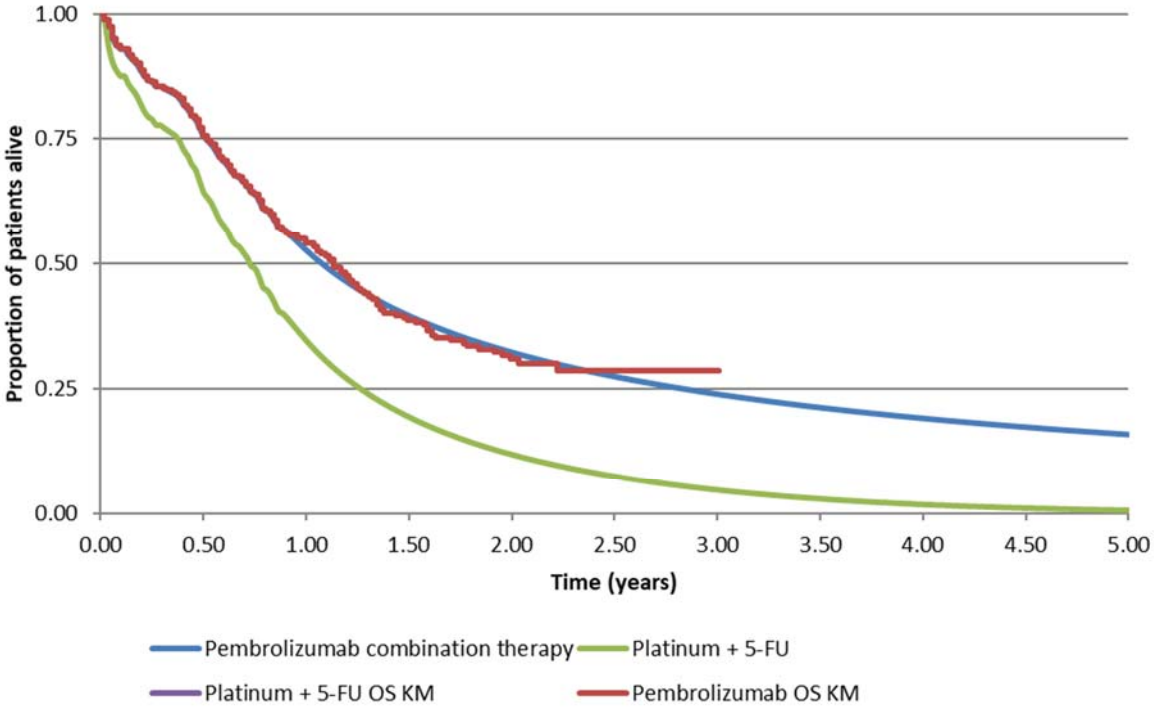


Figure 42. Base case overall survival modelling for pembrolizumab combination therapy and platinum + 5-FU: piecewise model using lognormal distribution and 45 weeks cut off point (CPS ≥1)



Modelling Progression-free Survival

Monotherapy

To identify the most plausible PFS curves among the standard parametric curves, the guidance from the NICE DSU was followed(37). The definition of PFS used for the economic modelling was based on the central assessment by independent review committee. Based on the trial protocol of KEYNOTE-048, the first tumour assessment was performed at week 9 and then every 6 weeks thereafter. This resulted in a sharp drop of PFS between weeks 0 and 9. The parametric model proportional hazards (PH) assumption was assessed visually using the log-cumulative hazards plot, and additionally, assessed using the Grambsch-Therneau correlation test. Visual assessment of the log-cumulative hazards plot (Figure 43), and results of the Grambsch and Therneau's test ($p < 0.05$), indicate a rejection of the proportional hazards assumption for PFS. This is also validated in the analysis of the Schoenfeld residual plot reported in Figure 44.

Figure 43. Log cumulative hazards plot for PFS (monotherapy, CPS ≥1)

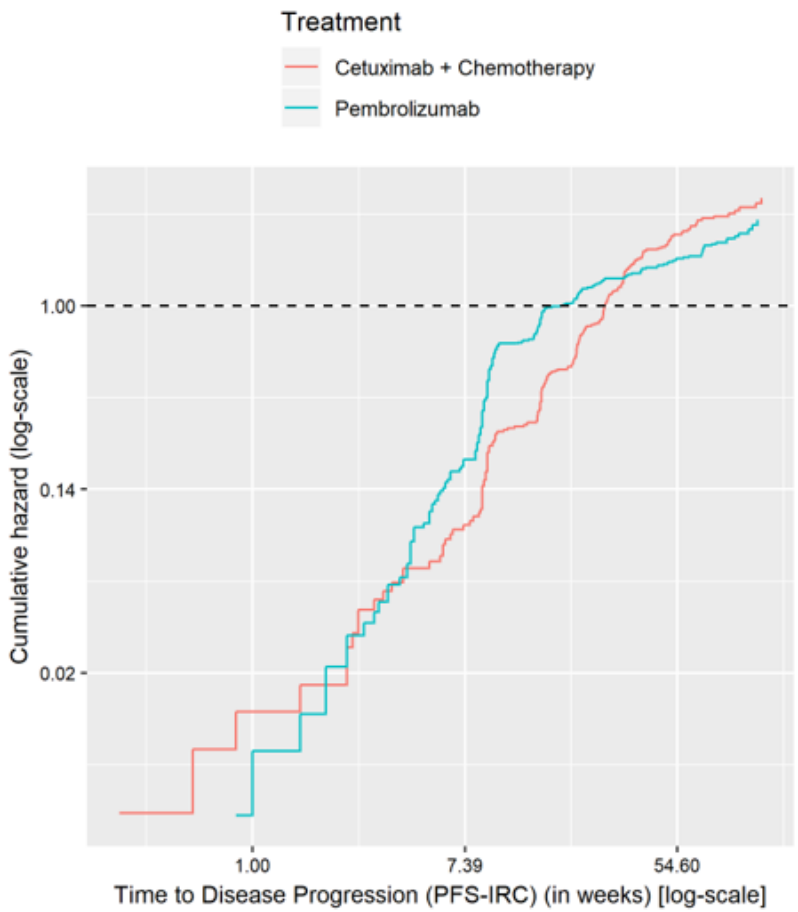
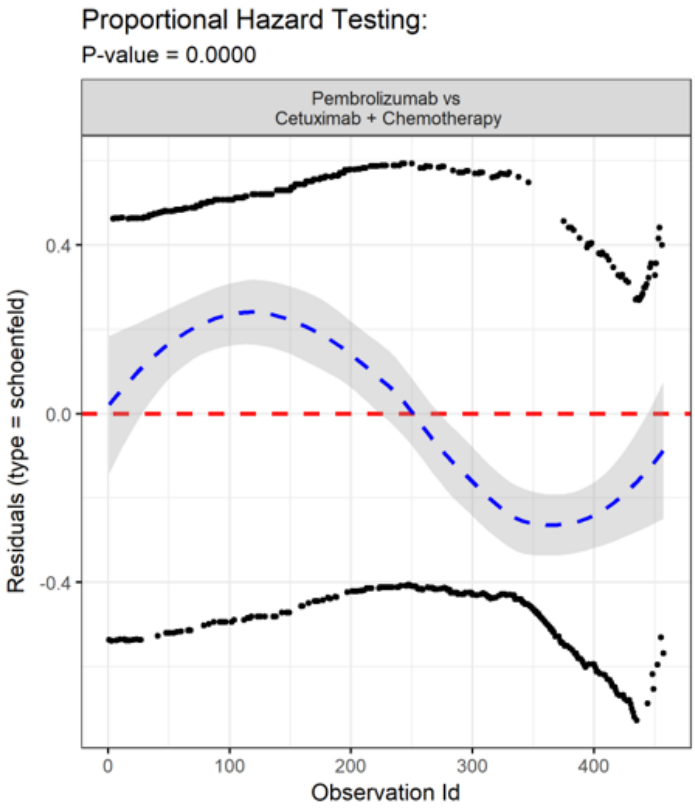


Figure 44: Schoenfeld residuals plot for PFS (monotherapy, CPS ≥1)



Given the shape of the curves, the direct use of KM data up until a point with fitted parametric functions was implemented. Based on the change in the hazard observed in the log-cumulative hazard plot the time periods of 10 and 25 weeks were explored as potential cut points. To allow the use of the most trial data, but with enough datapoints for extrapolation, the 25-week timepoint was selected. Scenario analysis is also presented for weeks 0 and 10 in the appendix.

Table 68 reports the AIC/BIC statistics for the second part of the PFS two-piece fit for pembrolizumab monotherapy and the EXTREME regimen based on KEYNOTE-048 PFS data from the 25-week cut-off point.

Table 68. Summary of goodness-of-fit measures of PFS as defined per RECIST v1.1 as assessed by BICR at a 25-week cut-off point – pembrolizumab monotherapy and EXTREME (CPS≥1)

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	464.85	467.13	1	797.27	799.95	6
Weibull	465.82	470.37	2	780.93	786.28	5
Gompertz	465.99	470.54	3	766.24	771.59	4
Log-logistic	466.73	471.28	4	763.31	768.66	2
Log-normal	468.72	473.27	5	762.35	767.70	1
Generalised Gamma	467.82	474.65	6	762.54	770.56	3

Figure 45. Plot of parametric fitting and extrapolation of long-term BIRC-assessed Progression-free Survival for the group treated with Pembrolizumab, with breaking point at Week 25 (monotherapy, CPS ≥1)

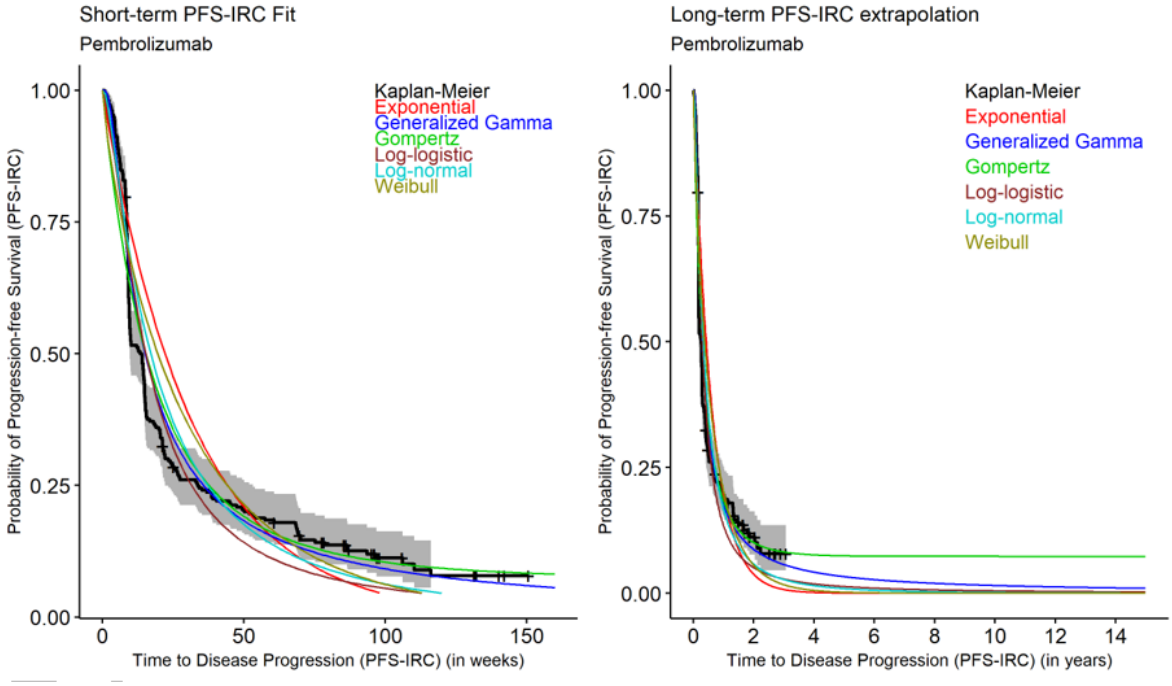
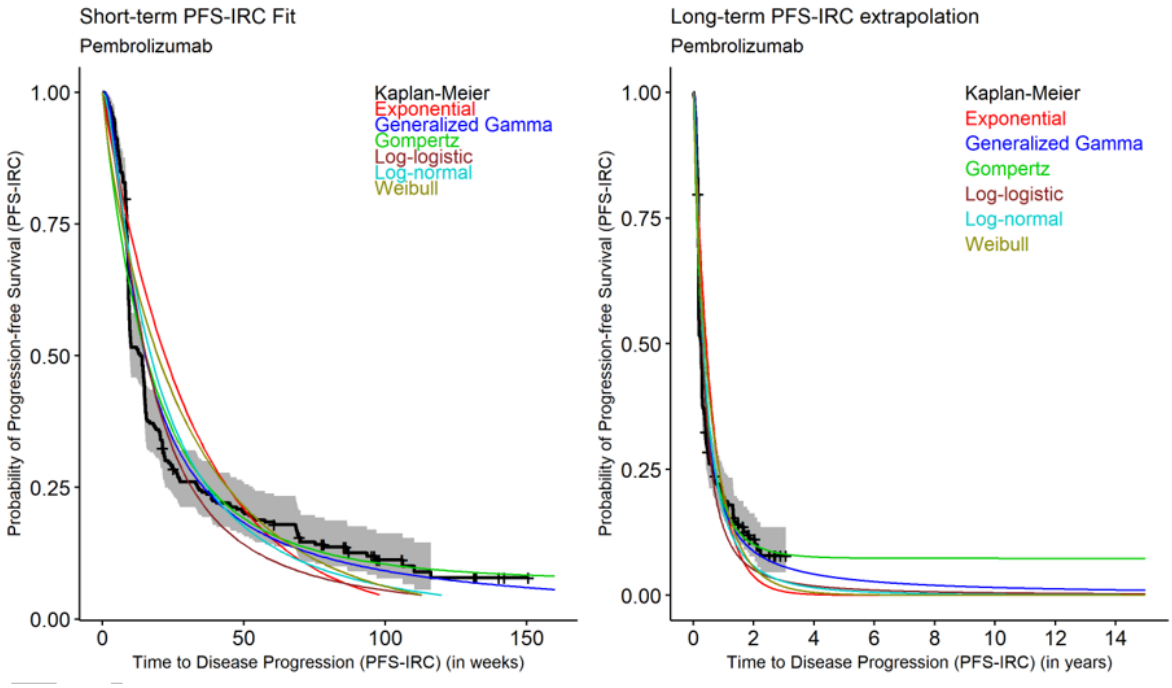
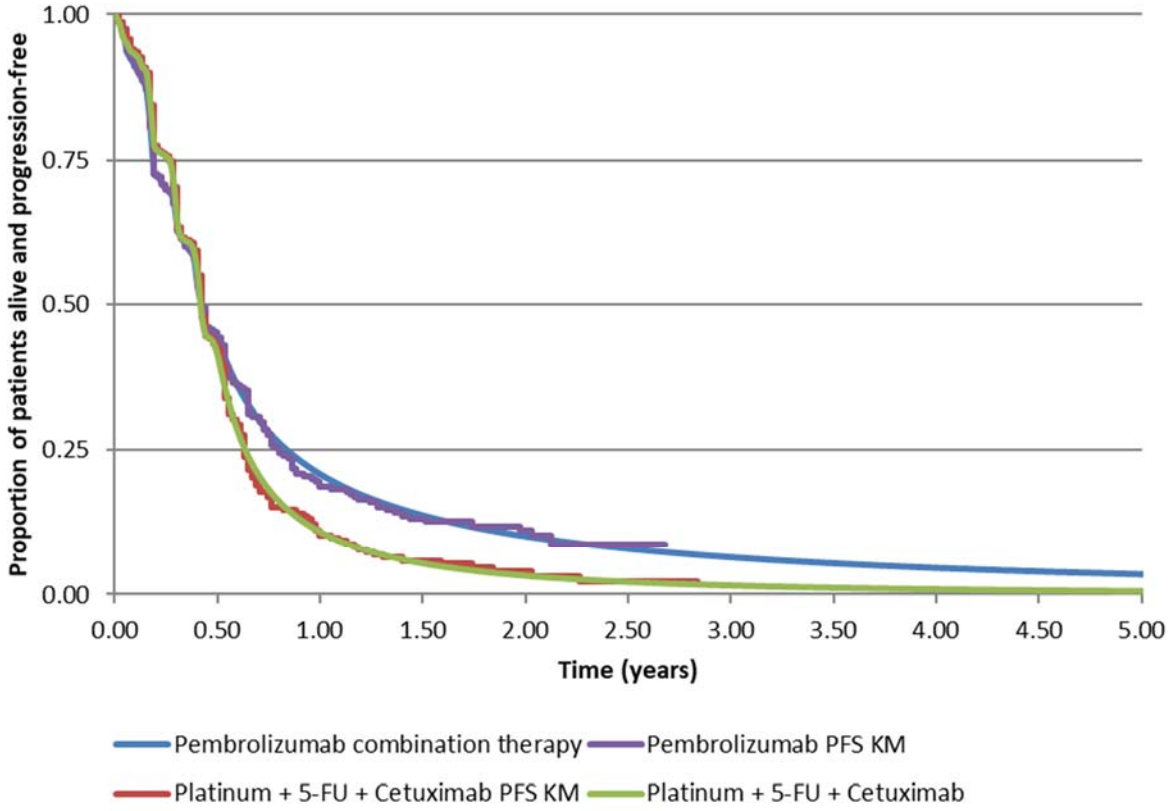


Figure 46: Plot of parametric fitting and extrapolation of long-term BIRC-assessed Progression-free Survival for the group treated with Cetuximab + Chemotherapy, with breaking point at Week 25 (monotherapy, CPS ≥1)



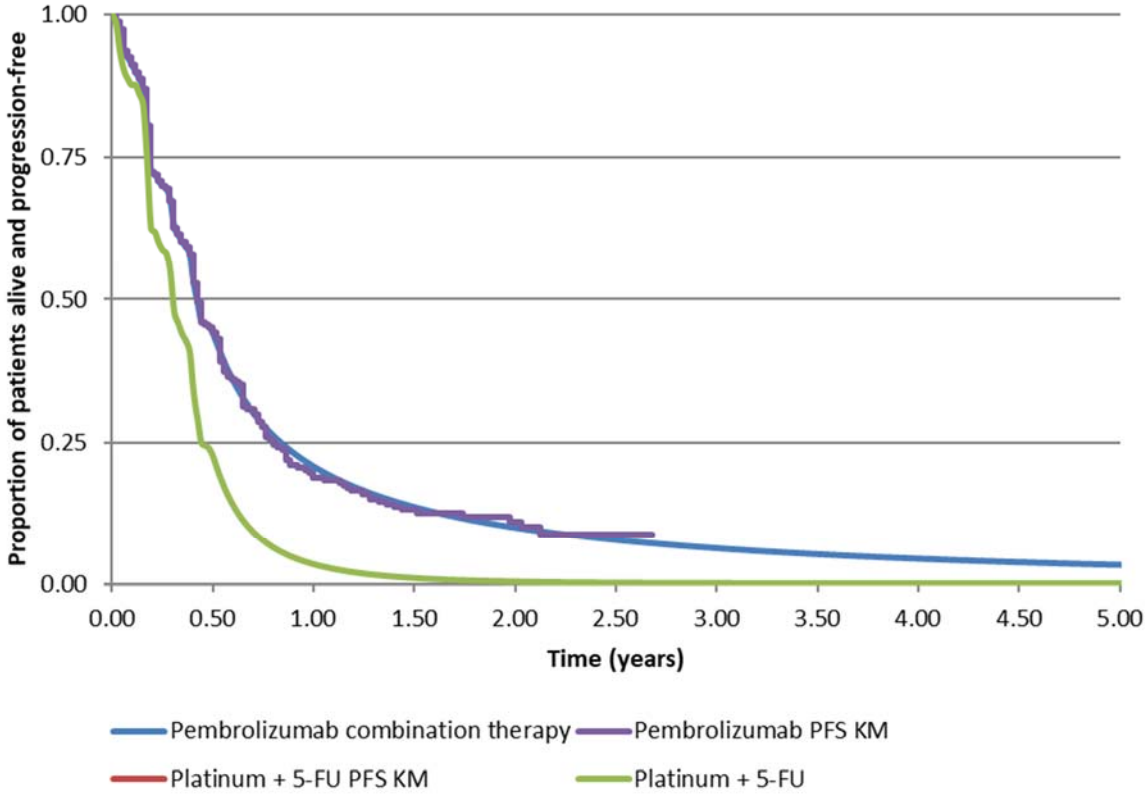
Considering the statistical and visual goodness of fit across both arms, the lognormal distribution with 25 week cut point was selected as the base case distribution. Alternative distributions are considered in scenario analyses.

Figure 47. Base case progression-free survival extrapolations for pembrolizumab vs. platinum + 5 FU + cetuximab (lognormal with 25 week cut-off point) (monotherapy, CPS ≥1)



For the comparison with platinum/5-FU, progression-free survival is modelled by applying time-varying HRs. The model allows up for a fractional polynomial up to the second order to be used to express the logarithm of the instantaneous hazard ratios. The best fit time-varying hazard ratios, based on the lowest DIC value, were the p1=0, p2=-0.5. Please refer to section B.2.9 for more information.

Figure 48. Base case progression-free survival extrapolations for pembrolizumab vs. platinum + 5 FU (lognormal with 25 week cut-off point) (monotherapy, CPS ≥1)



Pembrolizumab Combination Therapy

When comparing the PFS outcomes observed in the pembrolizumab combination therapy and the EXTREME arm, the PH assumption does not appear to hold based on the visual assessment of the log-cumulative hazards plot in Figure 49, since the curves do not appear parallel. The Grambsch and Therneau's test supports this interpretation since the result is statistically significant ($p < 0.05$), indicating a rejection of the proportional hazards assumption for PFS. This is also validated in the analysis of the Schoenfeld residual plot reported in Figure 50.

Figure 49: Log cumulative hazards plot for PFS (combination therapy, CPS ≥1)

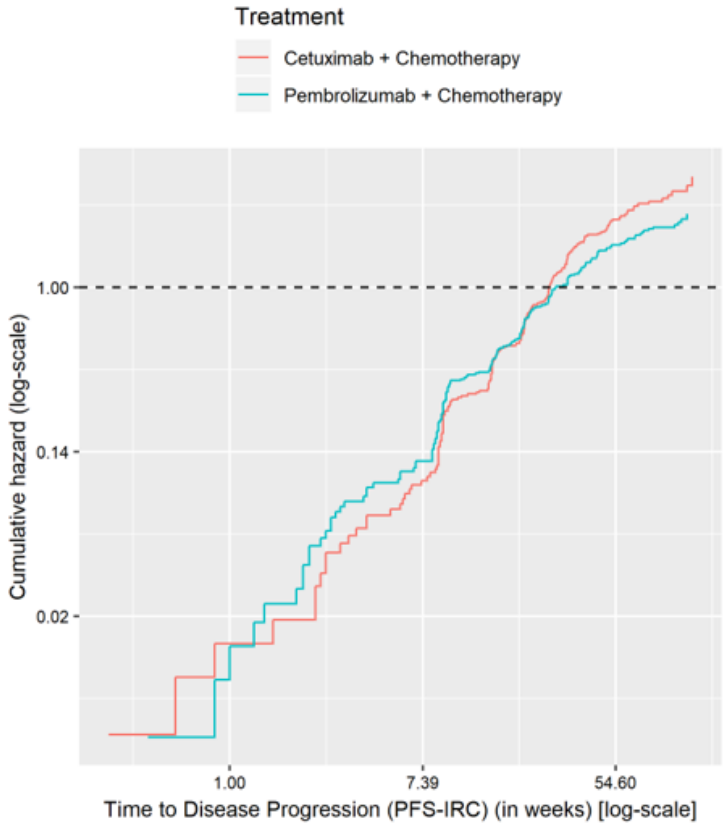
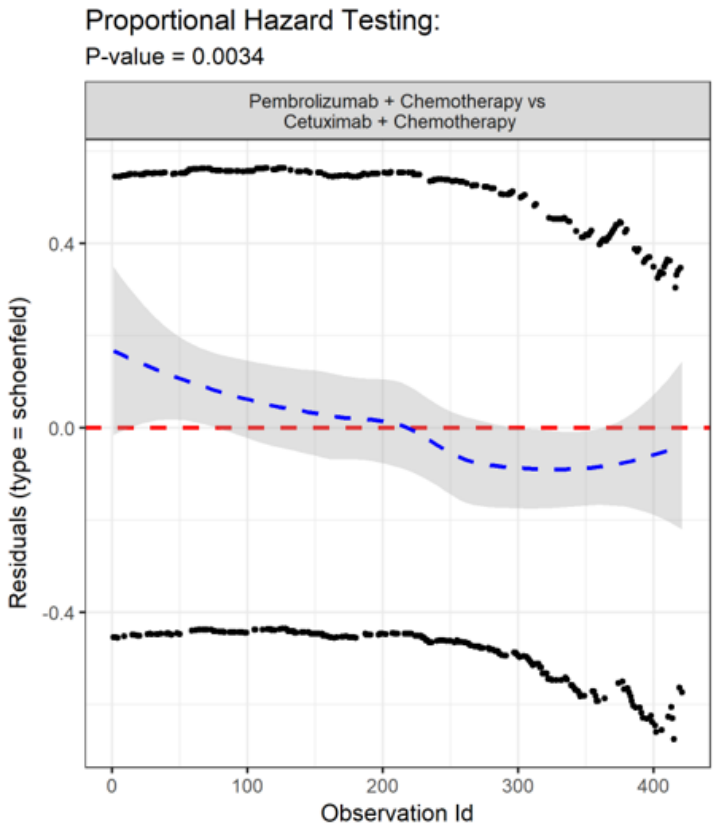


Figure 50: Schoenfeld residuals plot for PFS (combination therapy, CPS ≥1)



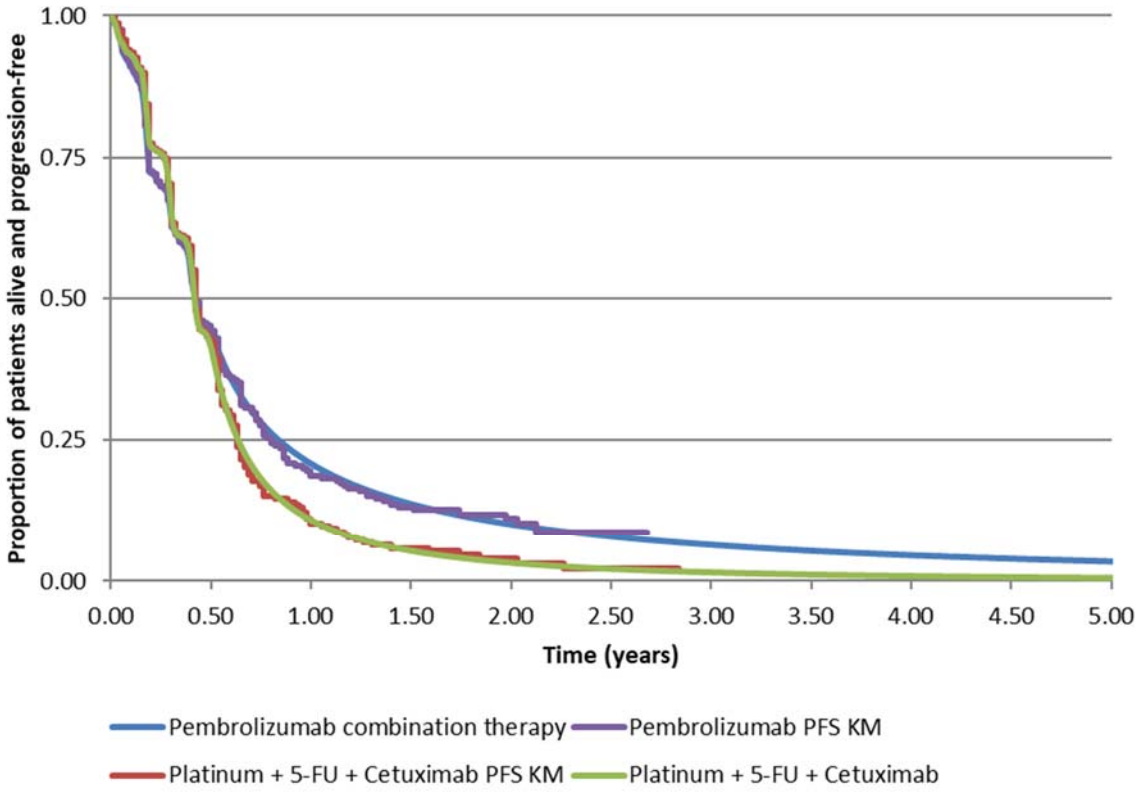
Again, given the shape of the curves, the direct use of KM data up until a point with fitted parametric functions was implemented. Based on the change in the hazard observed in the cumulative and log-cumulative hazard plots (see Figure 49), the time periods of 10 and 25 weeks were explored as potential cut points. To allow the use of the most trial data, but with enough datapoints for extrapolating, the 25-week timepoint was selected. Scenario analysis is also presented for weeks 0 and 10 in the appendix. Table 69 reports the AIC/BIC statistics for the pembrolizumab combination therapy and EXTREME regimen.

Table 69. Summary of goodness-of-fit measures of PFS as defined per RECIST v1.1 as assessed by BICR at a 25-week cut-off point – pembrolizumab combination therapy and EXTREME

Fitted Function	Pembrolizumab combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	740.19	742.84	6	720.35	722.93	6
Weibull	731.76	737.05	5	711.03	716.18	5
Gompertz	723.12	728.41	2	702.48	707.63	4
Log-logistic	723.34	728.63	3	697.92	703.07	2
Log-normal	721.33	726.62	1	696.79	701.94	1
Generalised Gamma	722.39	730.32	4	698.37	706.09	3

Considering the statistical and visual goodness of fit across both arms, the lognormal distribution with 25 week cut point was selected as the base case distribution. Alternative distributions are considered in scenario analyses.

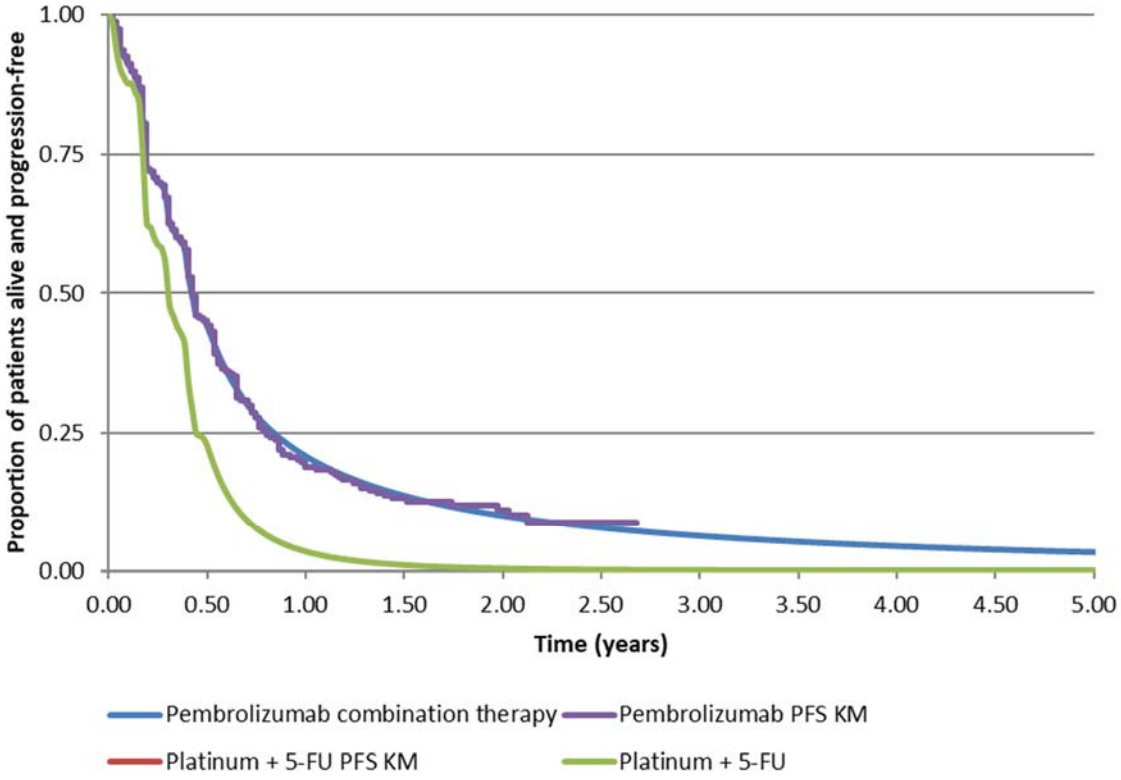
Figure 51. Base case progression-free survival extrapolations for pembrolizumab combination therapy vs. platinum + 5 FU + cetuximab (lognormal with 25 week cut-off point) (combination therapy, CPS ≥1)



Platinum/5-FU

For the comparison with platinum/5-FU, progression-free survival is modelled by applying time-varying HRs. The model allows up for a fractional polynomial up to the second order to be used to express the logarithm of the instantaneous hazard ratios. The best fit time-varying hazard ratios, based on the lowest DIC value, were the p1=0, p2=0.5. Please refer to section B.2.9 for more information.

Figure 52. Base case progression-free survival extrapolations for pembrolizumab combination therapy vs. platinum + 5 FU + cetuximab (lognormal with 25 week cut-off point) (combination therapy, CPS ≥1)



Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients in any treatment arm. Treatment related adverse event costs (TRAE) were ascribed in each model cycle by applying the weekly incidence of these AEs, multiplied by the respective costs, to the time on treatment curve in each treatment arm. AE data for non-trial comparators were obtained from the published literature used in the NMA. The unit cost and the disutility associated with the individual AEs were assumed to be the same for all treatment arms, therefore the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 70. This was consistent with the methods used in previous oncology submissions and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting(38, 39).

Table 70: AEs incidence - grade ≥3 5%+ incidence TRAEs per week of treatment exposure

Treatment	KN-048 Monotherapy arm				KN-048 Combination therapy arm				External comparator
	Pembrolizumab		Cetuximab + platinum + 5-FU		Pembrolizumab + platinum + 5-FU		Cetuximab + platinum + 5-FU		Platinum + 5-FU(40)
	Incidence	SE	Incidence	SE	Incidence	SE	Incidence	SE	Incidence
ALT/AST increase	NR	NR	NR	NR	NR	NR	NR	NR	NR
Anemia	0.0017	0.0005	0.0062	0.0009	0.0077	0.0010	0.0070	0.0010	0.0040
Asthenia	0.0004	0.0002	0.0012	0.0004	0.0011	0.0004	0.0013	0.0004	0.0006
Cardiac event	NR	NR	NR	NR	NR	NR	NR	NR	NR
Decreased appetite	0.0004	0.0002	0.0013	0.0004	0.0015	0.0004	0.0015	0.0004	NR
Dehydration	NR	NR	NR	NR	0.0008	0.0003	0.0012	0.0004	0.0006
Diarrhoea	NR	NR	NR	NR	NR	NR	NR	NR	0.0003
Fatigue	0.0011	0.0004	0.0019	0.0005	0.0023	0.0005	0.0021	0.0005	NR
Febrile Neutropenia	NR	NR	0.0020	0.0005	0.0026	0.0006	0.0022	0.0005	0.0014
Hypokalemia	0.0007	0.0003	0.0022	0.0005	0.0019	0.0005	0.0025	0.0006	0.0019
Hypomagnesemia	NR	NR	0.0019	0.0005	0.0007	0.0003	0.0021	0.0005	0.0010
Hyponatraemia	0.0021	0.0005	0.0024	0.0005	0.0025	0.0005	0.0027	0.0006	NR
Leukopenia	NR	NR	0.0021	0.0005	0.0010	0.0003	0.0024	0.0006	NR
Dysphagia/Mucositis	0.0005	0.0002	0.0020	0.0005	0.0031	0.0006	0.0022	0.0006	NR
Nausea/vomiting	NR	NR	0.0022	0.0005	0.0018	0.0005	0.0025	0.0006	NR
Neutropenia	0.0001	0.0001	0.0082	0.0009	0.0057	0.0007	0.0092	0.0011	0.0101

Neutrophil count decreased	NR	NR	0.0049	0.0008	0.0035	0.0006	0.0055	0.0009	NR
White bloodcell count decreased	NR	NR	0.0034	0.0007	0.0017	0.0004	0.0039	0.0007	NR
Phlebitis	NR	NR	NR	NR	NR	NR	NR	NR	0.0010
Platelet count decrease	NR	NR	NR	NR	0.0017	0.0004	0.0015	0.0004	NR
Pneumonia	0.0020	0.0005	0.0025	0.0006	0.0016	0.0004	0.0028	0.0007	NR
Pneumonia aspiration	NR	NR	NR	NR	0.0010	0.0003	0.0004	0.0003	NR
Skin reaction	0.0002	0.0002	0.0022	0.0005	0.0001	0.0001	0.0025	0.0006	0.0005
Stomatitis	0.0001	0.0001	NR	NR	0.0026	0.0005	0.0015	0.0005	0.0023
Thrombocytopenia	0.0001	0.0001	0.0034	0.0007	0.0028	0.0006	0.0039	0.0008	0.0021

NR: not reported, SE: standard error

Subsequent treatment

Prior to the introduction of immunotherapy for the treatment of head and neck cancer, there were no effective treatment options for patients following platinum-containing therapy. Nivolumab has been approved as a treatment option for patients with squamous cell carcinoma of the head and neck after platinum-based chemotherapy (TA490) since November 2017. UK market share data indicates that nivolumab is used in 38% of patients post platinum-based therapy and 43% of patients following the EXTREME regimen(41). However, this indication is approved in the Cancer Drugs Fund and as per the NICE position statement it should not be included in the treatment pathway(21).

The distribution of second line treatments is taken from KEYNOTE-048. The five most commonly used subsequent treatments were taken from the trial but any treatments not available in the UK (i.e. cetuximab or cetuximab containing regimens) were excluded. For nivolumab, it is also removed as a possible subsequent treatment and its percentage usage is split equally between the remaining subsequent therapies, as outlined in Table 71 and Table 72.

Table 71. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab monotherapy) – base case assumptions

Primary treatment	Subsequent treatment			
	Docetaxel	Paclitaxel	Carboplatin + Paclitaxel	Methotrexate
Pembrolizumab	13.39%	11.61%	18.04%	8.39%
EXTREME regimen	25.83 %	26.82%	14.90%	5.96%
Platinum + 5-FU	25.83 %	26.82%	14.90%	5.96%
Mean duration (months)	2.89	4.06	2.80	3.45
Weekly cost (£)	80.35	90.68	94.33	59.78
AE costs associated (£)	9.85	31.02	31.02	0.30

Table 72. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab combination therapy) – base case assumptions

Primary treatment	Subsequent treatment		
	Docetaxel	Paclitaxel	Methotrexate
Pembrolizumab + chemotherapy	20.32%	25.08%	18.41%
EXTREME regimen	31.52%	28.26%	19.20%
Platinum + 5-FU	31.52%	28.26%	19.20%
Mean duration (months)	2.66	2.69	1.77
Weekly cost (£)	80.35	90.68	59.78
AE costs associated (£)	9.85	31.02	0.30

A scenario is presented which includes post-platinum nivolumab usage, in line with the subsequent treatments administered in KEYNOTE-048 and currently clinical practice in England.

Table 73 and Table 74 below show the subsequent treatments received in KEYNOTE-048 following combination and monotherapy which includes nivolumab usage as it was received in the trial.

Table 73. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab monotherapy) – nivolumab scenario analysis

Primary treatment	Subsequent treatment				
	Docetaxel	Nivolumab	Paclitaxel	Carboplatin + Paclitaxel	Methotrexate
Pembrolizumab	12.50%	3.57%	10.71%	17.14%	7.50%
EXTREME regimen	20.20%	22.52%	21.19%	9.27%	0.33%
Platinum + 5-FU	20.20%	22.52%	21.19%	9.27%	0.33%
Mean duration (months)	2.89	2.56	4.06	2.80	3.45
Weekly cost (£)	80.35	1,403.70	90.68	94.33	59.78
AE costs associated (£)	9.85	1.04	31.02	31.02	0.30

Table 74. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab combination therapy) – nivolumab scenario analysis

Primary treatment	Subsequent treatment			
	Docetaxel	Nivolumab	Paclitaxel	Methotrexate
Pembrolizumab + chemotherapy	19.05%	3.81%	23.81%	17.14%
EXTREME regimen	23.55%	23.91%	20.29%	11.23%
Platinum + 5-FU	23.55%	23.91%	20.29%	11.23%
Mean duration (months)	2.66	4.05	2.69	1.77
Weekly cost (£)	80.35	1,403.70	90.68	59.78
AE costs associated (£)	9.85	1.04	31.02	0.30

B.3.4 Measurement and valuation of health effects

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

Health-related quality-of-life (HRQoL) was evaluated in the KEYNOTE-048 trial using the EuroQoL EQ-5D-3L. The estimated utilities were used in the cost-effectiveness model as evaluation of HRQoL using EQ-5D directly from patients is consistent with the NICE reference case.(42)

In KEYNOTE-048, the EQ-5D questionnaire was administered at treatment cycle 1, 2, 3, 4, and every 2 cycles thereafter (e.g., Cycle 6, Cycle 8, Cycle 10) up to a year or End of Treatment, whichever occurred first, as well as discontinuation visit, and the 30-day post-treatment discontinuation follow-up visit. The EQ-5D analysis below is based on the PRO Full Analysis Set (PRO FAS) population. UK preference-based scores were used for all patients analysed from the KEYNOTE-048 clinical trial. The UK scoring functions were developed based on the time trade-off (TTO) technique.

When estimating utilities, two approaches were considered:

- Mixed regression model
- Estimation of mean utility values

Mixed regression model

Health state utility values (HSUVs) and the event-specific utility decrements are derived from a linear mixed effect regression model of EQ-5D-3L data. The fixed effect regression model includes a covariate for Grade ≥3 TRAEs and categorized variable of time-to-death, in addition to disease progression and key baseline covariates (i.e. sex, Eastern Cooperative Oncology Group (ECOG) score).

This approach reflects the known decline in cancer patients' quality of life during the terminal phase of the disease. The approach has been used previously in the estimation of HRQoL in patients with urothelial cancer and in advanced melanoma patients (38, 43, 44).

Based on KEYNOTE-048 EQ-5D data, time to death was categorised into the following groups:

- 180 to 365 days to death
- 90 to 180 days to death
- 60 to 90 days to death

- 30 to 60 days to death
- 0 to 30 days to death

The analyses of the intervals related to time to death lower than 360 days included only patients with observed death dates. The justification to exclude patients whose death dates were censored was that their EQ-5D values could not be linked to their time-to-death category. The same mixed effects regression model is used across both intervention arms.

The coefficient for Grade ≥3 TRAEs derived from the regression analysis is -0.0277, adjusted for the weekly model cycle length and ascribed to those patients experiencing events in each cycle. The time-to-death coefficients were estimated for discrete time intervals prior to death, however only 0-30 days and 90-180 were found to be statistically significant at the 95% confidence interval; all other time intervals have a coefficient of 0. The respective disutilities are ascribed in the respective time period for those patients who die in the model simulation, adjusted for the weekly cycle length.

Table 75. Fixed effects utility model with time-to-death, no age, no interactions (UK algorithm)

Coefficient	Estimate	SE
Intercept (PFS)	0.8192	0.0109
Disease progression	0.7046	0.0156
ECOG score: 1	-0.0908	-0.0136
TRAEs: grade 3-5	-0.0277	0.0077
Time prior to death: 180-365 days	-0.0000	0.0000
Time prior to death: 90-180 days	-0.0430	0.0103
Time prior to death: 60-90 days	-0.0000	0.0000
Time prior to death: 30-60 days	0.0000	0.0000
Time prior to death: 0-30 days	0.3186	0.0216

Estimation of mean utility values for monotherapy and combination therapy

Another approach was to calculate the health state utility values as mean values for both intervention arms. In this approach, the same time to death categories were used as well as grade 3-5 TRAEs. HSUVs and the event-specific utility decrements are mean values of the monotherapy sample, presented below.

Table 76: Mean utility values - monotherapy subgroup

Utility	Mean	SE
PFS	07650	0.0080
PD	0.6890	0.0130
TRAEs: grade 3-5	0.126	0.016
Time prior to death: 180-365 days	0.0260	0.0144
Time prior to death: 90-180 days	0.1234	0.0301
Time prior to death: 60-90 days	0.2110	0.0437
Time prior to death: 30-60 days	0.2980	0.0496
Time prior to death: 0-30 days	0.3490	0.0576

HSUVs and the event-specific utility decrements are mean values of the combination therapy sample, presented below.

Table 77: Mean utility values - combination subgroup

Utility	Mean	SE
PFS	0.7730	0.0070
PD	0.6790	0.0150
TRAEs: grade 3-5	0.1260	0.0201
Time prior to death: 180-365 days	0.0240	0.0139
Time prior to death: 90-180 days	0.1174	0.0428
Time prior to death: 60-90 days	0.2510	0.0485
Time prior to death: 30-60 days	0.3070	0.0594
Time prior to death: 0-30 days	0.3500	0.0703

Mapping

Not applicable as HRQoL was derived from the KEYNOTE-048 EQ-5D data.

Health-related quality-of-life studies

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

Adverse reactions

To assess the potential disutility associated with Grade ≥3 AEs, the disutility associated with patients experiencing Grade ≥3 AEs were analysed as a fixed effect in both regression models.

The coefficient for Grade ≥3 TRAEs derived from the regression analysis is -0.0277, adjusted for the weekly model cycle length and ascribed to those patients experiencing events in each cycle. For the mean utility values, the coefficient for ≥3 TRAEs is 0.1260 for both the monotherapy and combination therapy regimens. The disutility used in the model is dependent on the utility method selected; in the base case, this is the mix regression model.

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

EQ-5D analyses based on KEYNOTE-048 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-progression health state. A constant value for HRQoL is applied in each cycle. A study by Ara and Brazier (2010) suggests that average utility decreases with age therefore age-adjusted utilities are applied in the model to account for the impact of age on utilities using the formula provided by Ara and Brazier (45), re-weighted using the starting age of patients in the model, i.e. 61 years of age.

The age-related utility decrements are calculated based on the age of the cohort in each model cycle and the proportion who are male; the equation used is derived from a regression analysis of a patient population with cardiovascular disease, published in Ara and Brazier.

The utility values chosen for the cost-effectiveness model are presented in Table 78. The applicability of the selected health state utility values was not assessed by clinical experts as these values were consistent with the NICE reference case.

Table 78. Summary of utility values for base case cost-effectiveness analysis

	Utilities		Reference in submission (section and page number)	Justification
	Mean	Standard Error		
PFS	0.8192	0.0109	Page XXX	NICE Reference Case
Disease progression	0.7046	0.0156		
ECOG score 1	-0.0908	-0.0136		
TRAEs: grade 3-5	-0.0277	0.0077		
Time prior to death: 180-365 days	-0.0000	0.0000		
Time prior to death: 90-180 days	-0.0430	0.0103		
Time prior to death: 60-90 days	-0.0000	0.0000		
Time prior to death: 30-60 days	0.0000	0.0000		
Time prior to death: 0-30 days	0.3186	0.0216		

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

There are no NHS reference costs or payment-by-results (PbR) tariffs specific for costing pembrolizumab. Details about the cost estimation of treatment with pembrolizumab in terms of acquisition and administration are reported below.

Input from clinical experts

The costing approach adopted in this submission was previously validated with clinical experts in previous HTA submissions of pembrolizumab(38, 39).

Intervention and comparators' costs and resource use

Intervention

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) (see Appendix A). As a monotherapy, it is anticipated that pembrolizumab can also be administered at a 400mg fixed dose every six weeks (Q6W) which is explored in a sensitivity analysis. The list price of a 100mg vial 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]

Comparators

For each of the comparators, because the dose may be administered based on patients' body surface area (BSA) or body weight, the distribution of vials minimizing the acquisition costs can differ depending on the patients' profile. In the base-case model, the analysis will assume that any remaining vial that is not administered to a patient will be discarded; as vial sharing is not commonly accepted by NICE committee's for decision making. The following methodology is used to determine the optimal cost-minimizing vial mix under the assumption of no sharing of vials between patients. The optimal vial mix is estimated for each patient profile, based on weight or body surface area; therefore, a different target dose for each patient profile is estimated and potentially a different optimal vial mix. The solutions are then averaged to obtain the population estimate, with weights equal to the expected proportion of patients in each profile based on the distribution of the dose-defining characteristic. This is to account for

variations in the target population and a similar conceptual approach has been used in previous HTAs(20, 39). The probability distribution associated with both weight and body surface area is assumed to be log-normal and the result may be a non-integer number of vials.

An alternative approach is also used in a scenario analysis which is as follows; the number of vials used is estimated based on the average target dose across all patients, calculated in correspondence with the average of the dose-defining characteristics, e.g. weight or body surface area. The result is restricted to an integer number of vials since no vial sharing is allowed. The costs for both methods are shown in Table 79 and drug acquisition costs are calculated per cycle, by ascribing the weekly acquisition cost to the time on treatment curve (see below).

Table 79: Drug acquisition cost

Treatment	Formulation per vial/cap (pack size)	Unit cost (£)	Dosage	Total average dose	Average of profiles method			Average profile method		
					Vials used	Total cost per dose (£)	Cost per week (£)	Vials used	Total cost per dose (£)	Cost per week (£)
Pembrolizumab	100mg	[redacted]	200mg	200mg	2.00	[redacted]	[redacted]	2	[redacted]	[redacted]
Cetuximab	100mg/20ml	178.10	Loading: 400mg/m^2 Subsequent: 250 mg/m^2	437.20mg	2.94 (loading) 1.32 (subsequent)	Loading dose: 1,334.89 Subsequent dose: 867.62	867.22	3 (loading) 0 (subsequent)	1,424.80 (loading) 890.50 (subsequent)	1,781.00
	500mg/100ml	890.50			0.91 (loading) 0.71(subsequent)			1 (loading) 1 (subsequent)		
Cisplatin	10mg	1.84	100mg/m^2	174.88mg/m^2	0.62	8.62	2.87	0	8.96	2.99
	50mg	4.48			3.59			4		
	100mg	10.13			0			0		
Cisplatin[a]	10mg/	1.84	75mg/m^2	131.16mg/m^2	0.59	13.36	4.45	0	13.44	4.48
	50mg/	4.48			2.74			3		
	100mg	10.13			0			0		
Cisplatin[b]	10mg	1.84	3mg/kg	197.29mg	0.60	19.23	4.81	0	17.92	4.48
	50mg	4.48			4.05			4		
	100mg	10.13			0			0		
Carboplatin	50mg	3.18	500mg/m^2	500.00mg/m^2	3.18	10.96	3.65	1	10.96	3.65
	150mg	6.35			0			0		
	450mg	18.73			1.00			1		
	600mg	28.24			0			0		
Carboplatin*	50mg	3.18	100mg/m^2	174.88mg/m^2	0.69	4.76	1.59	1	4.77	1.59
	150mg	6.35			1.16			1		
	450mg	18.73			0			0		

	600mg	28.24			0			0		
5-FU	500	1.36	1,000mg/m^2	1,748.80	0	2.78	3.71	0	2.59	3.44
	1,000	1.29			1.29			2		
	2,500	5.16			0			0		
	5,000	5.83			0			0		
Methotrexate	5mg	6.44	60mg/m^2	104.93mg/m^2	6.44	4.31	4.31	0	4.95	4.95
	50mg	5.3			2.61			3		
	500mg	8.76			0			0		
	1000mg	9.22			0			0		
	5000mg	149.50			0			0		
Paclitaxel	30mg	3.44	135mg/m^2	135mg/m^2	0	10.52	3.51	0	10.52	3.51
	100mg	9.85			0			0		
	150mg	10.52			1.00			1		
	300mg	19.68			0			0		
Paclitaxel[c]	30mg	3.44	175mg/m^2	306.04mg/m^2	0.59	22.79	7.60	1	23.12	7.71
	100mg	9.85			0.09			0		
	150mg	10.52			0.03			0		
	300mg	19.68			1.00			1		

BNF: British national formulary.

Source: BNF(36)

a. A different cisplatin dosage is used for each comparator. Cisplatin 75mg/m2 is used in combination of paclitaxel
b. A different cisplatin dosage is used for each comparator. Cisplatin 3mg/kg is used as a monotherapy
c. Paclitaxel 175mg/m^2 is used with platinum + cetuximab while paclitaxel 135mg/m2 is used only in combination with platinum

*weekly cost per dose for Q6W monotherapy administration will be the same

Treatment duration

Pembrolizumab monotherapy

As per the licensed indication, patients treated with pembrolizumab are expected to be treated until disease progression or unacceptable toxicity. In line with the KEYNOTE-048 protocol, a stopping rule has been implemented in the model whereby patients do not receive therapy beyond 24 months. To estimate the duration of treatment of pembrolizumab, time on treatment (ToT) data from KEYNOTE-048 was used to reflect both early discontinuations caused by AEs and other reasons for discontinuations before progression in addition to the additional weeks of treatment that some patients may receive until confirmation of progression. Given the maturity of the data, no further extrapolation was required, and the direct KM data were used in the economic model.

Figure 53. Time on treatment (ToT) data for monotherapy (CPS ≥1)

Pembrolizumab combination therapy

Figure 54.Time on treatment (ToT) for combination therapy (CPS ≥1)

EXTREME Regimen

The EXTREME regimen was assumed to be administered until disease progression or unacceptable toxicity. A maximum treatment duration of 18 weeks (i.e. 6 cycles administered every 3 weeks) was used for the platinum compounds (i.e. cisplatin and carboplatin) and 5-FU to reflect the clinical practice in England. Given the maturity of the data, no further extrapolation was required, and the direct KM data were used in the economic model. The time on treatment for the EXTREME regimen is shown in Figure 53 and Figure 54.

Platinum+5-FU

The time on treatment duration for platinum+5-FU is assumed to be equal to the PFS curve in the absence of alternative data. PFS was estimated as outlined in Section 3.3 using the output of the NMA described in Section 2.9.

Administration Costs

Drug administration costs include the cost of therapy infusions required at each treatment administration. With the exception of cetuximab, which requires an initial loading dose of 400mg/m2, all treatment strategies include a fixed dose single infusion at each treatment administration. The administration codes and costs by treatment are outlined below. Drug administration costs are applied in the cycle that drug administration occurs to the time on treatment curve for each intervention. The weekly cetuximab administration cost only occurs in those cycles where other treatments are not administered.

Pembrolizumab Monotherapy

The time required for the administration of pembrolizumab is 30 minutes, the Health Resource Groups (HRG) code for SB12Z: *Deliver Simple Parenteral Chemotherapy at First Attendance* based on the latest NHS reference costs 2017-2018 was used to reflect administration costs for pembrolizumab. The assumption had been previously agreed with NHS England and used in previous NICE submissions for pembrolizumab.(38, 39)

Pembrolizumab Combination Therapy

The administration of cisplatin requires pre and post hydration and its co-administration with 5-FU and pembrolizumab would likely be conducted in an inpatient setting. The administration of 5-FU is continuous over four days and is also assumed to be administered in an inpatient setting, consistent with TA472 (16). Therefore, the administration code of SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment*, at First Attendance* was applied for the first administration, with SB15Z used for administrations on day 2-4.

EXTREME Regimen

As above and in keeping with TA472, an administration code of SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment*, at First Attendance* was applied for the first and subsequent administrations.

Platinum plus 5-FU

As above and in keeping with TA472, an administration cost of SB14Z: Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, *at First Attendance* was applied for the first and subsequent administrations.

Table 80. Administration costs for first-line treatment regimens

	Type of administration required	NHS reference cost code	Setting	Cost
Pembrolizumab Monotherapy	Simple Chemotherapy, at First Attendance	SB12Z	Outpatient	£174.40
Pembrolizumab Combination Therapy	Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance (Day 1) Deliver Subsequent Elements of a Chemotherapy Cycle (Day 2, 3 and 4)	SB14Z; SB15Z	Daycase and reg day/night	£374.52*; £312.34** x 3 Total: £1,311.53
	Pembrolizumab monotherapy	SB12Z	Outpatient	£174.40
Extreme Regimen	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance (Day 1) Deliver Subsequent Elements of a Chemotherapy Cycle (Day 2, 3 and 4)	SB14Z; SB15Z	Daycase and reg day/night	£374.52*; £312.34** x 3 Total: £1,311.53
	Cetuximab monotherapy	SB12Z	Outpatient	£174.40
Platinum + 5-FU	Deliver complex chemotherapy, including prolonged infusion treatment at first attendance (Day 1) Deliver Subsequent Elements of a Chemotherapy Cycle (Day 2, 3 and 4)	SB14Z; SB15Z	Daycase and reg day/night	£374.52*; £312.34** x 3 Total: £1,311.53

*First administration of prolonged infusion in the outpatient setting (SB14Z) is an option (£252.36) in the model

** Subsequent administration within the first chemotherapy cycle in the outpatient setting (SB15Z) is an option (£233.23) in the model

Health-state unit costs and resource use

A comprehensive literature search was conducted in April 2019, to identify costs and resource use in the treatment of and on-going management of recurrent or metastatic HNSCC. Please see Appendix I for details of the search strategy and literature identified.

There are three health states included in the model – progression free (PFS), post-progression (PPS) and death (see section 3.2).

Patients incur disease management costs whilst in the progression free and progressed disease health states. Table 81 and

Table **82** shows the resource use for monitoring and disease management in the progression free health state and the post-progression health state, taken from TA490 (20).

Table 81 and

Table **82** present the unit costs for individual resource use items, which were updated based on the latest NHS reference costs 2017-2018(34) and the Personal and Personal and Social Services Research Unit (PSSRU) 2018 report(46). The estimated monitoring and disease management costs per month were £123.26 and £64.31 respectively for the pre-progression (PFS) and post-progression periods.

Table 81. Resource use and unit costs for progression free HNSCC

Resource	Usage per week	Reference	Unit cost	Reference
Dental therapy for radiotherapy effects	0.06	NICE TA490	£121.94	NHS Reference Costs 2017-2018: Total Outpatient Attendances (450) Dental Medicine Specialities
Depression assessment & management	0.03		£81.31	NHS Reference Costs 2017-2018: Community Health Services, Allied Health Professionals (A06A1): occupational health, adult, one-to-one
Nutritional support	0.20		£110.23	NHS Reference Costs 2017-2018: Total other currencies (N16AF): specialist nursing, eternal feeding, nursing services, adult, face-to-face.
Pain and symptom management / any supportive care	0.17		£104.17	NHS Reference Costs 2017-2018: Community Health Services, (N21AF): specialist nursing, palliative/respite care, adult, face-to-face.
Speech and swallowing therapy	0.06		£95.52	NHS Reference Costs 2017-2018: Community Health Services (A13A1): speech and language therapist, adult, one-to-one.
Management of oral and gastrointestinal mucositis	0.08		£5.65	BNF 2017, 15ml four times a day for 7 days (assuming one 300ml bottle of benzydamine hydrochloride per cycle)
Antiemetics	0.20		£6.41	8mg Ondansetron per day for 5 days, eMit (2018)
Xerostomia Management	0.07		£41.89	BNF 2017: Pilocarpine 5-10mg three times per day
Hematologic Growth Factor/Transfusion	0.07		£174.65	NICE costing template NG24 (2015), Inflated to 2018 using ONS (2018) CPI health index D7BZ
Oncologist Visit	0.25		£132.10	NHS Reference costs – Outpatient attendances data. Service code 370:Non-Consultant Led(47)
CT Scan	0.13		£132.66	RD22Z: Computerised Tomography Scan of one area, with pre and post contrast, NHS reference costs 2017/18
Cell blood count	0.25		£2.51	DAPS05 (Total HRG) Haematology, Dental Medicine Specialties, 2017/18 NHS reference costs
Total cost per week				**£123.26**

Table 82. Resource use and unit costs for post-progression HNSCC

Resource	Usage per week	Reference	Unit cost	Reference
Dental therapy for radiotherapy effects	0.03	NICE TA490	£121.94	NHS Reference Costs 2017-2018: Total Outpatient Attendances (450) Dental Medicine Specialities
Depression assessment & management	0.03		£81.31	NHS Reference Costs 2017-2018: Community Health Services, Allied Health Professionals (A06A1): occupational health, adult, one-to-one
Nutritional support	0.16		£110.23	NHS Reference Costs 2017-2018: Total other currencies (N16AF): specialist nursing, eternal feeding, nursing services, adult, face-to-face.
Pain and symptom management / any supportive care	0.19		£104.17	NHS Reference Costs 2017-2018: Community Health Services, (N21AF): specialist nursing, palliative/respite care, adult, face-to-face.
Speech and swallowing therapy	0.02		£95.52	NHS Reference Costs 2017-2018: Community Health Services (A13A1): speech and language therapist, adult, one-to-one.
Management of oral and gastrointestinal mucositis	0.04		£5.65	BNF 2017, 15ml four times a day for 7 days (assuming one 300ml bottle of Benzydamine hydrochloride per cycle)
Antiemetics	0.12		£6.41	8mg Ondansetron per day for 5 days, eMIT (2018)
Xerostomia Management	0.04		£41.89	BNF 2017: Pilocarpine 5-10mg three times per day
Hematologic Growth Factor/Transfusion	0.03		£174.65	NICE costing template NG24 (2015), Inflated to 2018 using ONS (2018) CPI health index D7BZ
Oncologist Visit	0.08		£132.10	NHS Reference costs – Outpatient attendances data. Service code 370:Non-Consultant Led(47)
CT Scan	0.00		£132.66	RD22Z: Computerised Tomography Scan of one area, with pre and post contrast, NHS reference costs 2017/18
Cell blood count	0.08		£2.51	DAPS05 (Total HRG) Haematology, Dental Medicine Specialties, 2017/18 NHS reference costs
Total cost per week				**£64.31**

A one-off cost relating to the confirmation of progression is also included in the model and assumed for all patients. This includes an oncologist visit and CT scan to confirm disease progression, as outlined in Table 83.

Table 83. One-off progression costs

Resource	Reference	Costs (£)
Oncologist Visit (Monitoring)	WF01A (total HRG) Non-Admitted Face to Face Attendance, Follow-Up	132.10
CT Scan (Monitoring)	RD22Z (Total HRG) Computerised Tomography Scan of one area	132.66
One-off progression costs per patient		**264.76**

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 approach used to consider the HRQoL impact of AEs as part of the cost-effectiveness assessment is described in B.3.4.

The costs of managing TRAEs are derived from the NHS Reference costs 2017-2018, with previous NICE submissions in HNSCC used as a guide for the appropriate HRG codes(16, 20). The costs of treating each AE and the associated HRG code and descriptions are provided in Table 84.

Table 84. Unit costs of adverse events

AE	AE Details		Unit Cost (£)	Source
	HRG Code	Description		
ALT/ASL increase	GC17A-K	Non-Malignant, Hepatobiliary or Pancreatic Disorders, average of those with single, Multiple or no Interventions, with CC Score 0-9+, short stay cost used when available	530.46	NHS reference costs 2017-2018
Anemia	SA01G-K	Acquired Pure Red Cell Aplasia or Other Aplastic Anemia. Weighted cost of non-elective long stay, short stay and day case	631.88	NHS reference costs 2017-2018
Asthenia	WA17X	One hospital admission during chemotherapy, corresponding to HRG code WA17X (other admissions related to neoplasms with intermediate complicating conditions) as a non-elective long-stay episode of 8–9 days costing £2536.95	2,863.70	Brown et al.(2013) (48) Inflated 2018
Cardiac event	EB03A - EB10E	Average of all relevant cardiac related	497.58	NHS reference costs 2017-2018
Decreased appetite	SPHMSEDSAAPC	Adult Specialist Eating Disorder Services, Admitted Patient; Most relevant NHS reference cost HRG code	461.74	NHS reference costs 2017-2018
Dehydration	KC05G-H	Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ (Most relevant HRG code)	1,104.28	NHS reference costs 2017-2018
Diarrhea	FD10M	FD10M Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2	894.04	Assumed that a typical patient will have two hospital admissions as a non-elective short-stay episode, corresponding to NHS reference costs 2017-2018
Dyspnoea	-	Assumed to be £0 (TA490 - aligned with HNSCC - 2L)	0.00	Assumption
Fatigue	SA01K, J,H,G	Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia. Average cost of non-elective long stay, short stay and day case	631.88	NHS reference costs 2017-2018

AE	AE Details		Unit Cost (£)	Source
	HRG Code	Description		
Febrile Neutropenia	-	The NICE DSU report on the cost of febrile neutropenia 2007 (£2,286) has been inflated to 2017-2018 prices using the Hospital & community health services (HCHS) index	3,171.57	Morgan 2007.(49)
Granulocytopenia	WJ11Z	Assume equal to Neutropenia. Assumed that 10% of patient require hospital treatment, each requiring two episodes during chemotherapy	78.69	NHS reference costs 2017-2018
Hypokalemia	KC05G-H	Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ (TA490)	1,104.28	NHS reference costs 2017-2018(50)
Hypomagnesemia	KC05G-H	Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ (TA490)	1,104.28	NHS reference costs 2017-2018
Hyponatremia	KC05G-H	Fluid or Electrolyte Disorders, with Interventions, CC Score 0-5+ (TA490)	1,104.28	NHS reference costs 2017-2018
Hypotension	EB04Z	Hypotension	364.49	NHS reference costs 2017-2018
Infection	WH07A-G	Infections or Other Complications of Procedures, with no intervention, Single Intervention or multiple interventions with cc 0 - 2+	489.65	NHS reference costs 2017-2018
Leukopenia	WJ11Z	Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	78.69	Assumed that 10% of patients require hospital treatment, each requiring two episodes during chemotherapy NHS reference costs 2017-2018
Lymphopenia	WJ11Z	Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	78.69	Assumed that 10% of patients require hospital treatment, each requiring two episodes during chemotherapy
Dysphagia/Mucositis	FZ80C	Average of complex, Very Complex and major Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 0-6+ Non-elected short stay	3,237.20	NHS reference costs 2017-2018

AE	AE Details		Unit Cost (£)	Source
	HRG Code	Description		
Nausea/vomitting	FZ91M	Assumed that a typical patient will have two hospital admissions, corresponding to Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2 as a non-elective short-stay episode, each costing £365	894.04	NHS reference costs 2017-2018
Neutropenia	WJ11Z	Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	78.69	Assumed that 10% of patients require hospital treatment, each requiring two episodes during chemotherapy NHS reference costs 2017-2018
Neutrophil count decreased	WJ11Z	Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	78.69	Assumed that 10% of patients require hospital treatment, each requiring two episodes during chemotherapy NHS reference costs 2017-2018
White blood cell count decreased	WJ11Z	Weighted average of mean costs for HRG code WJ11Z Other disorders of immunity across non-elective long- and short-stay episodes and day-case admissions	78.69	Assumed that 10% of patients require hospital treatment, each requiring two episodes during chemotherapy NHS reference costs 2017-2018
Phlebitis	YQ51A-E	Average of Deep Vein Thrombosis with CC Score 0-12+ using the reduced short stay cost where this is available	373.72	NHS reference costs 2017-2018
Platelet count decrease	-	-	0.00	Assume equal to Thrombocytopenia
Pneumonia	DK11K-V	Lobar, atypical or viral pneumonia cc score 0-14+ DZ11K-V, Weighted cost of non-elective long stay, short stay and day case	495.81	NHS reference costs 2017-2018
Pneumonia aspiration	DK11K-V	Lobar, atypical or viral pneumonia cc score 0-14+ DZ11K-V, Weighted cost of non-elective long stay, short stay and day case	495.81	NHS reference costs 2017-2018
Skin reaction		It is assumed that a typical patient will have one additional outpatient consultation during chemotherapy	148.02	Brown et el. 2013(48)

AE	AE Details		Unit Cost (£)	Source
	HRG Code	Description		
		for this condition (skin rash). A weighted average reference cost of is used, based on codes 370 (medical oncology) and 800 (clinical oncology) from NHS reference costs 2017-2018		
Stomatitis	-	-	0.00	Assumption
Thrombocytopenia	-	-	0.00	Assumption

BNF: British National Formulary; CC: Complication and Comorbidity score; eMIT: Drugs and pharmaceutical electronic market information; DSU: Decision support unit; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; w/a: Weighted average

Miscellaneous unit costs and resource use

Subsequent Treatment Costs

In the economic model, upon disease progression patients were assumed to incur the costs of subsequent therapies, in line with clinical practice. The proportions, both including and excluding nivolumab (which is available in the Cancer Drugs Fund) are presented Table 71-Table 74.

Drug and administration costs

The average cost of subsequent treatment is calculated by weighting the proportions of patients receiving each treatment, the unit cost of each subsequent treatment and treatment duration. The mean duration of subsequent treatment, also derived from the KEYNOTE-048 clinical data, is assumed to be independent of the primary treatment used across each intervention arm. The drug acquisition costs of subsequent treatments are sourced from eMIT(35) or the BNF(36), if generic costs are unavailable from eMIT. The dose and frequency of administration for second line treatments is based on their use in UK clinical practice. The treatment duration and weekly costs are reported in Table 71 and Table 72.

Adverse events are also costed and included in the economic model for second line therapies, taken from the relevant clinical trials.

Table 85. AE cost associated with second line therapies

Subsequent Treatment	AE Cost (£)
Docetaxel	9.85
Methotrexate	0.30
Nivolumab	1.04
Paclitaxel	31.02
Carboplatin + Paclitaxel	31.02

Terminal Care Costs

Patients who die from recurrent or advance HNSCC were assumed to require a one-off cost for palliative/terminal care. This one-off cost of £7,797.92 is applied at the point of death to reflect the cost of terminal care and is taken from a Kings Fund Report (2004)(51) and inflated up to 2018(52).

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

Summary of base-case analysis inputs

The full list of variables used in the cost-effectiveness analysis is presented in Table 86 below.

Table 86. Summary of variables applied in the economic model for pembrolizumab monotherapy

Variable	Base case value	Lower bound	Upper bound	Reference to section of submission
Discount rate (costs)	3.50%	0.00%	6.00%	Section 3.2 Page XX-XX
Discount rate (outcomes)	3.50%	0.00%	6.00%	
Age (years)	61.08	42.09	80.07	
Weight (kg)	69.37	40.34	98.40	
Body surface area (m²)	1.75	1.26	2.24	
PFS utility score	0.76	0.74	0.79	Section 3.4 Page XX-XX
PD utility score	0.70	0.67	0.74	
TTD disutilities: 180-365 days prior to death	0	0	0	
TTD disutilities: 90-180 days prior to death	0.04297	0.0228408	0.0630992	
TTD disutilities: 60-90 days prior to death	0.1554	0.1288812	0.1819188	
TTD disutilities: 30-60 days prior to death	0.1554	0.1288812	0.1819188	
TTD disutilities: 0-30 days prior to death	0.3186	0.2763228	0.3608772	
PF health state costs	123.26	98.61	147.91	Section 3.5 Page XX-XX
PD health state costs	64.31	51.45	77.18	
Terminal care health state costs	7797.92	6238.34	9357.51	
Pembrolizumab Overall survival parameters: alpha	4.22	3.84	4.59	Section 3.3 Page
Pembrolizumab Overall survival parameters: beta	0.60	0.42	0.79	
Pembrolizumab Overall survival parameters: Q	x	x	x	
Pembrolizumab Progression-free survival parameters: alpha	3.96	3.51	4.41	
Pembrolizumab Progression-free survival parameters: beta	0.54	0.32	0.77	
Pembrolizumab Progression-free survival parameters: Q	x	x	x	
Pembrolizumab Time on treatment parameters: alpha	2.67	2.47	2.87	
Pembrolizumab Time on treatment parameters: beta	0.49	0.40	0.58	
Pembrolizumab Time on treatment parameters: Q	x	x	x	
Platinum + 5-FU Overall survival parameters: alpha	4.22	3.84	4.59	
Platinum + 5-FU Overall survival parameters: beta	0.60	0.42	0.79	
Platinum + 5-FU Overall survival parameters: Q	x	x	x	

Variable	Base case value	Lower bound	Upper bound	Reference to section of submission
Platinum + 5-FU Progression-free survival parameters: alpha	3.96	3.51	4.41	
Platinum + 5-FU Progression-free survival parameters: beta	0.54	0.32	0.77	
Platinum + 5-FU Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU Time on treatment parameters: alpha	2.79	2.65	2.93	
Platinum + 5-FU Time on treatment parameters: beta	0.14	0.05	0.23	
Platinum + 5-FU Time on treatment parameters: Q	x	x	x	
Pembrolizumab Time on treatment HR	1.00	0.80	1.20	
Platinum + 5-FU Time on treatment HR	1.00	0.80	1.20	
Platinum + 5-FU + Cetuximab Overall survival parameters: alpha	3.46	3.15	3.77	
Platinum + 5-FU + Cetuximab Overall survival parameters: beta	0.46	0.29	0.62	
Platinum + 5-FU + Cetuximab Overall survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: alpha	2.46	2.17	2.74	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: beta	0.39	0.24	0.54	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment parameters: alpha	2.79	2.65	2.93	
Platinum + 5-FU + Cetuximab Time on treatment parameters: beta	0.14	0.05	0.23	
Platinum + 5-FU + Cetuximab Time on treatment parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment HR	1.00	0.80	1.20	
ALT/AST increase weekly incidence rate, pembrolizumab	0	0	0	Section 3.3. Page XX
Anaemia weekly incidence rate, pembrolizumab	0.00171	0.00078684	0.00263316	
Asthenia weekly incidence rate, pembrolizumab	0.000367	-0.00001912	0.00075312	
Cardiac event weekly incidence rate, pembrolizumab	0	0	0	

Variable	Base case value	Lower bound	Upper bound	Reference to section of submission
Decreased appetite weekly incidence rate, pembrolizumab	0.000367	-0.00004068	0.00077468	
Dehydration weekly incidence rate, pembrolizumab	0	0	0	
Diarrhoea weekly incidence rate, pembrolizumab	0	0	0	
Dyspnoea weekly incidence rate, pembrolizumab	0	0	0	
Fatigue weekly incidence rate, pembrolizumab	0.0011	0.00035324	0.00184676	
Febrile Neutropenia weekly incidence rate, pembrolizumab	0	0	0	
Granulocytopenia weekly incidence rate, pembrolizumab	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, pembrolizumab	0.000733	0.00014108	0.00132492	
Hypomagnesemia (low magnesium) weekly incidence rate, pembrolizumab	0	0	0	
Hyponatraemia weekly incidence rate, pembrolizumab	0.002077	0.0010676	0.0030864	
Hypotension weekly incidence rate, pembrolizumab	0	0	0	
ALT/AST increase Platinum + 5-FU	0	0	0	
AnaemiaPlatinum + 5-FU	4.0052325292077E-03	4.0052325292077E-03	4.0052325292077E-03	
AstheniaPlatinum + 5-FU	6.39061755191201E-04	6.39061755191201E-04	6.39061755191201E-04	
Cardiac eventPlatinum + 5-FU	0	0	0	
Decreased appetitePlatinum + 5-FU	0	0	0	
DehydrationPlatinum + 5-FU	5.58302552552836E-04	5.58302552552836E-04	5.58302552552836E-04	
DiarrhoeaPlatinum + 5-FU	3.17539979480043E-04	3.17539979480043E-04	3.17539979480043E-04	
DyspnoeaPlatinum + 5-FU	0	0	0	
FatiguePlatinum + 5-FU	0	0	0	
Febrile NeutropeniaPlatinum + 5-FU	1.37757434246572E-03	1.37757434246572E-03	1.37757434246572E-03	
GranulocytopeniaPlatinum + 5-FU	0	0	0	
Hypokalemia (low potassium)Platinum + 5-FU	0.001882004229612	0.001882004229612	0.001882004229612	
Hypomagnesemia (low magnesium)Platinum + 5-FU	9.64666456143187E-04	9.64666456143187E-04	9.64666456143187E-04	
HyponatraemiaPlatinum + 5-FU	0	0	0	
HypotensionPlatinum + 5-FU	0	0	0	

Variable	Base case value	Lower bound	Upper bound	Reference to section of submission
ALT/AST increase Platinum + 5-FU + Cetuximab	0	0	0	
AnaemiaPlatinum + 5-FU + Cetuximab	0.006212	0.00444408	0.00797992	
AstheniaPlatinum + 5-FU + Cetuximab	0.00119	0.00040012	0.00197988	
Cardiac eventPlatinum + 5-FU + Cetuximab	0	0	0	
Decreased appetitePlatinum + 5-FU + Cetuximab	0.001322	0.00046548	0.00217852	
DehydrationPlatinum + 5-FU + Cetuximab	0	0	0	
DiarrhoeaPlatinum + 5-FU + Cetuximab	0	0	0	
DyspnoeaPlatinum + 5-FU + Cetuximab	0	0	0	
FatiguePlatinum + 5-FU + Cetuximab	0.00185	0.00089156	0.00280844	
Febrile NeutropeniaPlatinum + 5-FU + Cetuximab	0.001983	0.00095792	0.00300808	
GranulocytopeniaPlatinum + 5-FU + Cetuximab	0	0	0	
Hypokalemia (low potassium) Platinum + 5-FU + Cetuximab	0.002247	0.0011788	0.0033152	
Hypomagnesemia (low magnesium) Platinum + 5-FU + Cetuximab	0.00185	0.0008308	0.0028692	
Hyponatraemia Platinum + 5-FU + Cetuximab	0.002379	0.00131668	0.00344132	
Hypotension Platinum + 5-FU + Cetuximab	0	0	0	
ALT/AST increase disutility	0.02772	0.0126476	0.0427924	Section 3.4. Page XX
Anaemia disutility	0.02772	0.0126476	0.0427924	
Asthenia disutility	0.02772	0.0126476	0.0427924	
Cardiac event disutility	0.02772	0.0126476	0.0427924	
Decreased appetite disutility	0.02772	0.0126476	0.0427924	
Dehydration disutility	0.02772	0.0126476	0.0427924	
Diarrhoea disutility	0.02772	0.0126476	0.0427924	
Dyspnoea disutility	0.02772	0.0126476	0.0427924	
Fatigue disutility	0.02772	0.0126476	0.0427924	
Febrile Neutropenia disutility	0.02772	0.0126476	0.0427924	

Table 87. Summary of variables applied in the economic model for pembrolizumab combination therapy

Company evidence submission for pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Variable	Base case value	Lower bound	Upper bound	Reference to section of submission
Discount rate (costs)	3.50%	0.00%	6.00%	Section 3.2 Page XX-XX
Discount rate (outcomes)	3.50%	0.00%	6.00%	
Age (years)	60.82	41.49	80.15	
Weight (kg)	68.17	40.04	96.30	
Body surface area (m^2)	1.74	1.28	2.19	
PFS utility score	0.76	0.74	0.79	Section 3.4 Page XX-XX
PD utility score	0.70	0.67	0.74	
TTD disutilities: 180-365 days prior to death	0	0	0	
TTD disutilities: 90-180 days prior to death	0.04297	0.0228408	0.0630992	
TTD disutilities: 60-90 days prior to death	0.1554	0.1288812	0.1819188	
TTD disutilities: 30-60 days prior to death	0.1554	0.1288812	0.1819188	
TTD disutilities: 0-30 days prior to death	0.3186	0.2763228	0.3608772	
PF health state costs	123.26	98.61	147.91	Section 3.5 Page XX-XX
PD health state costs	64.31	51.45	77.18	
Terminal care health state costs	7797.92	6238.34	9357.51	
Pembrolizumab Overall survival parameters: alpha	4.35	3.97	4.73	Section 3.3 Page
Pembrolizumab Overall survival parameters: beta	0.55	0.35	0.74	
Pembrolizumab Overall survival parameters: Q	x	x	x	
Pembrolizumab Progression-free survival parameters: alpha	3.13	2.81	3.46	
Pembrolizumab Progression-free survival parameters: beta	0.48	0.31	0.65	
Pembrolizumab Progression-free survival parameters: Q	x	x	x	
Pembrolizumab Time on treatment parameters: alpha	2.91	2.74	3.08	
Pembrolizumab Time on treatment parameters: beta	0.30	0.21	0.39	
Pembrolizumab Time on treatment parameters: Q	x	x	x	
Platinum + 5-FU Overall survival parameters: alpha	4.35	3.97	4.73	
Platinum + 5-FU Overall survival parameters: beta	0.55	0.35	0.74	
Platinum + 5-FU Overall survival parameters: Q	x	x	x	

Platinum + 5-FU Progression-free survival parameters: alpha	3.13	2.81	3.46	
Platinum + 5-FU Progression-free survival parameters: beta	0.48	0.31	0.65	
Platinum + 5-FU Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU Time on treatment parameters: alpha	2.78	2.64	2.93	
Platinum + 5-FU Time on treatment parameters: beta	0.11	0.02	0.20	
Platinum + 5-FU Time on treatment parameters: Q	x	x	x	
Pembrolizumab Time on treatment HR	1.00	0.80	1.20	
Platinum + 5-FU Time on treatment HR	1.00	0.80	1.20	
Platinum + 5-FU + Cetuximab Overall survival parameters: alpha	3.40	3.09	3.71	
Platinum + 5-FU + Cetuximab Overall survival parameters: beta	0.43	0.25	0.60	
Platinum + 5-FU + Cetuximab Overall survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: alpha	2.36	2.07	2.64	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: beta	0.34	0.19	0.49	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment parameters: alpha	2.78	2.64	2.93	
Platinum + 5-FU + Cetuximab Time on treatment parameters: beta	0.11	0.02	0.20	
Platinum + 5-FU + Cetuximab Time on treatment parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment HR	1.00	0.80	1.20	
ALT/AST increase weekly incidence rate, pembrolizumab	0	0	0	Section 3.3. Page XX
Anaemia weekly incidence rate, pembrolizumab	0.007729	0.00584936	0.00960864	
Asthenia weekly incidence rate, pembrolizumab	0.001137	0.00044904	0.00182496	
Cardiac event weekly incidence rate, pembrolizumab	0	0	0	
Decreased appetite weekly incidence rate, pembrolizumab	0.001478	0.00068616	0.00226984	
Dehydration weekly incidence rate, pembrolizumab	0.000796	0.00017664	0.00141536	

Diarrhoea weekly incidence rate, pembrolizumab	0	0	0	
Dyspnoea weekly incidence rate, pembrolizumab	0	0	0	
Fatigue weekly incidence rate, pembrolizumab	0.002273	0.001244	0.003302	
Febrile Neutropenia weekly incidence rate, pembrolizumab	0.002614	0.00151836	0.00370964	
Granulocytopenia weekly incidence rate, pembrolizumab	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, pembrolizumab	0.001932	0.00096768	0.00289632	
Hypomagnesemia (low magnesium) weekly incidence rate, pembrolizumab	0.000682	0.00014692	0.00121708	
Hyponatraemia weekly incidence rate, pembrolizumab	0.002501	0.0014328	0.0035692	
Hypotension weekly incidence rate, pembrolizumab	0	0	0	
ALT/AST increase Platinum + 5-FU	0	0	0	
AnaemiaPlatinum + 5-FU	4.0052325292077E-03	4.0052325292077E-03	4.0052325292077E-03	
AstheniaPlatinum + 5-FU	6.39061755191201E-04	6.39061755191201E-04	6.39061755191201E-04	
Cardiac eventPlatinum + 5-FU	0	0	0	
Decreased appetitePlatinum + 5-FU	0	0	0	
DehydrationPlatinum + 5-FU	5.58302552552836E-04	5.58302552552836E-04	5.58302552552836E-04	
DiarrhoeaPlatinum + 5-FU	3.17539979480043E-04	3.17539979480043E-04	3.17539979480043E-04	
DyspnoeaPlatinum + 5-FU	0	0	0	
FatiguePlatinum + 5-FU	0	0	0	
Febrile NeutropeniaPlatinum + 5-FU	1.37757434246572E-03	1.37757434246572E-03	1.37757434246572E-03	
GranulocytopeniaPlatinum + 5-FU	0	0	0	
Hypokalemia (low potassium)Platinum + 5-FU	0.001882004229612	0.001882004229612	0.001882004229612	
Hypomagnesemia (low magnesium)Platinum + 5-FU	9.64666456143187E-04	9.64666456143187E-04	9.64666456143187E-04	
HyponatraemiaPlatinum + 5-FU	0	0	0	
HypotensionPlatinum + 5-FU	0	0	0	
ALT/AST increase Platinum + 5-FU + Cetuximab	0	0	0	
AnaemiaPlatinum + 5-FU + Cetuximab	0.00701	0.0050794	0.0089406	
AstheniaPlatinum + 5-FU + Cetuximab	0.001342	0.00050116	0.00218284	
Cardiac eventPlatinum + 5-FU + Cetuximab	0	0	0	

Decreased appetitePlatinum + 5-FU + Cetuximab	0.001491	0.00063252	0.00234948	
DehydrationPlatinum + 5-FU + Cetuximab	0.001193	0.00037764	0.00200836	
DiarrhoeaPlatinum + 5-FU + Cetuximab	0	0	0	
DyspnoeaPlatinum + 5-FU + Cetuximab	0	0	0	
FatiguePlatinum + 5-FU + Cetuximab	0.002088	0.00102764	0.00314836	
Febrile NeutropeniaPlatinum + 5-FU + Cetuximab	0.002237	0.0011786	0.0032954	
GranulocytopeniaPlatinum + 5-FU + Cetuximab	0	0	0	
Hypokalemia (low potassium)Platinum + 5-FU + Cetuximab	0.002535	0.00132176	0.00374824	
Hypomagnesemia (low magnesium)Platinum + 5-FU + Cetuximab	0.002088	0.00105508	0.00312092	
HyponatraemiaPlatinum + 5-FU + Cetuximab	0.002685	0.00143452	0.00393548	
HypotensionPlatinum + 5-FU + Cetuximab	0	0	0	
ALT/AST increase disutility	0.02772	0.0126476	0.0427924	Section 3.4. Page XX
Anaemia disutility	0.02772	0.0126476	0.0427924	
Asthenia disutility	0.02772	0.0126476	0.0427924	
Cardiac event disutility	0.02772	0.0126476	0.0427924	
Decreased appetite disutility	0.02772	0.0126476	0.0427924	
Dehydration disutility	0.02772	0.0126476	0.0427924	
Diarrhoea disutility	0.02772	0.0126476	0.0427924	
Dyspnoea disutility	0.02772	0.0126476	0.0427924	
Fatigue disutility	0.02772	0.0126476	0.0427924	
Febrile Neutropenia disutility	0.02772	0.0126476	0.0427924	

Assumptions

Table 88 summarises the assumptions used in the economic model.

Table 88: List of assumptions used in the economic model

Assumption	Justification
Use KM data for the first 25 weeks from KEYNOTE-048 trial to model PFS for pembrolizumab and EXTREME, then extrapolate	Based on the shape of the survival curves, 2-phases piecewise approach was considered appropriate. Given the data maturity and hazards over time, 25 weeks was considered an appropriate point to begin the extrapolation.
Use KM data for the first 45 weeks from KEYNOTE-048 trial to model OS for pembrolizumab and EXTREME, the extrapolate	Based on the shape of the survival curves, 2-phases piecewise approach was considered appropriate. For the first 45 weeks OS KM data provides robust and reliable estimate and at that point patient numbers are sufficient to implement parametric fitting based on KEYNOTE-048 data.
Use KM data for the time-to-treatment discontinuation curves	The KM data from KN-048 are fully mature for time to treatment continuation, therefore extrapolation via parametric models is not required.
The incidence of AEs from KEYNOTE-048 and published trials was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-048 trial and the published trials for platinum plus 5-FU for the indication under consideration. The same method and criteria were applied in a recent NICE oncology appraisals of pembrolizumab.(38, 39)
The quality of life of patients is appropriately captured by considering time to death utilities	Previous studies have suggested there is a decline in HRQL in the final months of life of patients which may not appropriately be captured solely through the use of progression-based health state(43, 44). 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.
Utilities were adjusted by UK general population utility where utility deceases with age	Based on the Ara and Brazier study suggesting the impact of age on HRQoL.(45)
Resource use is assumed to be equal between pembrolizumab and EXTREME/platinum plus 5-FU arms	Due to paucity of data, resource use was assumed to be equal per treatment arm in the pre- and post- progression health states.
Pembrolizumab will be administered for a maximum of 35 cycles (24 months).	This assumption is in line with KEYNOTE-048 clinical trial
Platinum plus 5-FU will be administered for up to 6 cycles	This assumption was implemented to reflect UK clinical practice.

Assumption	Justification
Cetuximab is assumed to be administered with an initial loading dose of and then subsequent doses every week. No vial sharing is assumed.	This is the assumption used in the appraisal TA472 for cetuximab.(16)
No use of nivolumab as a subsequent therapy despite its use in KEYNOTE-048.	NICE position statement requests the exclusion as comparators or subsequent treatments, any drugs currently available in the Cancer Drugs Fund.(21) Therefore, a cross-over adjustment was conducted to remove its effect on the overall survival curve and its cost was not included in the economic model. A scenario including the efficacy and cost of nivolumab was presented, given the use of nivolumab in current NHS practice.
Comparison with EXTREME regimen is based on full KEYNOTE-048 population.	KEYNOTE-048 was not designed to analyse subgroups by cancer origin, such as the oral cavity. Therefore, the comparison to the EXTREME regimen was based on all cancer subgroups to maintain randomisation and powering.

B.3.7 Base-case results

The results of the economic model for the CPS ≥1 population are presented below. In the base case analysis, the estimated mean overall survival was 2.49 years with pembrolizumab monotherapy, 1.44 years for EXTREME and 1.05 years for platinum + 5-FU. Patients treated with pembrolizumab monotherapy accrued 1.76 QALYs compared to 1.02 QALYs for the EXTREME regimen and 0.75 QALYs for platinum + 5-FU.

The estimated mean overall survival was 2.56 years with pembrolizumab combination therapy, 1.37 years with the EXTREME regimen and 0.93 years with platinum + 5-FU. Patients treated with pembrolizumab combination therapy accrued 1.80 QALYs compared to 0.98 QALYs for EXTREME and 0.68 QALYs for platinum + 5-FU.

Base-case incremental cost-effectiveness analysis results

Table 89 below presents the base case incremental cost-effectiveness results for pembrolizumab monotherapy in the CPS ≥1 population, incorporating the discount of the CAA. The results show pembrolizumab monotherapy to be cost-effective compared to both the EXTREME regimen and platinum + 5-FU when considering a willingness to pay threshold of £50,000 per QALY. When pembrolizumab monotherapy is compared to EXTREME, pembrolizumab dominates the EXTREME regimen; the incremental-cost-effectiveness ratio (ICER) for pembrolizumab monotherapy is £29,057 when compared to platinum + 5-FU.

Table 89. Base-case results – monotherapy (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	49,695	2.49	1.76	-	-	-	-
EXTREME regimen	53,008	1.44	1.02	-3,313	1.06	0.74	Dominant
Platinum + 5-FU	20,319	1.05	0.75	29,376	1.44	1.01	29,057
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table **90** below presents the base case incremental cost-effectiveness results for pembrolizumab combination therapy in the CPS ≥1 population, incorporating the discount of the CAA. The results show pembrolizumab combination therapy to be cost-effective compared to both the EXTREME regimen and platinum + 5-FU when considering a willingness to pay threshold of £50,000 per QALY. The corresponding incremental-cost-effectiveness ratio

(ICER) when pembrolizumab combination therapy is compared to EXTREME is £11,829 and £37,286 when compared to platinum + 5-FU. These ICERs should be considered in the context of pembrolizumab being an innovative new treatment option for patients at the end of their life.

Table 90. Base-case results - combination therapy (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	61,430	2.56	1.80	-	-	-	-
EXTREME regimen	51,694	1.37	0.98	9,735	1.19	0.83	11,791
Platinum + 5-FU	19,497	0.95	0.68	41,964	1.61	1.13	37,258
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

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 Table 86.

Monotherapy

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis for pembrolizumab monotherapy are presented in Table 91 and Table 92 and the corresponding scatterplots and cost-effectiveness acceptability curves (CEAC) are presented in Figure 55 to Figure 58.

The cost-effectiveness acceptability curve shows that there is an approximately 100% probability that pembrolizumab monotherapy therapy is cost-effective when compared to the EXTREME regimen and a 99.8% probability that it is cost-effective compared to platinum + 5-FU at the £50,000 per QALY gained threshold.

Table 91. Probability sensitivity analyses for pembrolizumab monotherapy vs EXTREME (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	49,865	2.47	1.75	-	-	-	-
EXTREME regimen	52,917	1.45	1.03	-3,052	1.02	0.72	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 55. CEAC for pembrolizumab monotherapy vs EXTREME

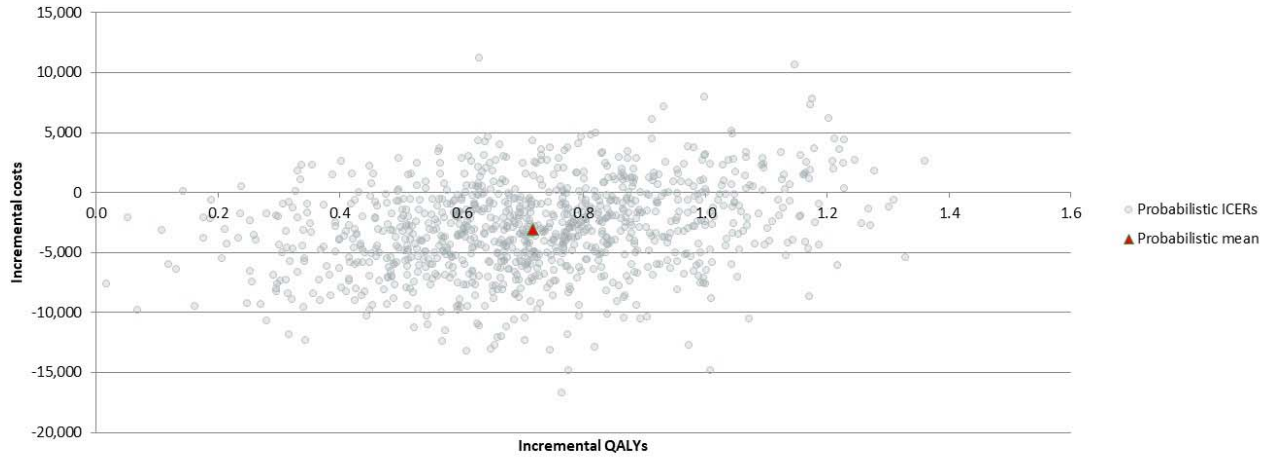


Figure 56. Scatterplot for pembrolizumab monotherapy vs EXTREME (CPS ≥1)

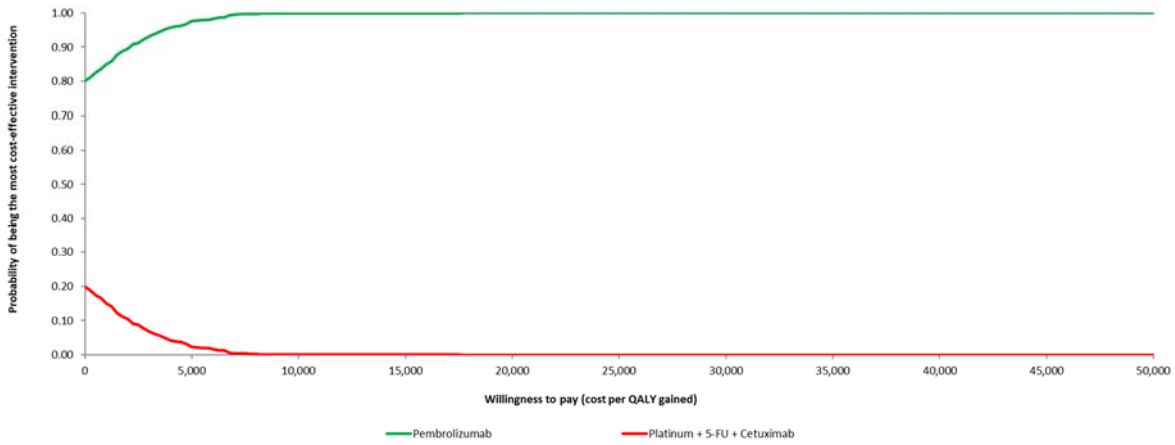


Table 92. Probability sensitivity analyses for pembrolizumab monotherapy vs platinum +5-FU (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	49,633	2.47	1.75	-	-	-	-
Platinum + 5-FU	20,310	1.06	0.75	23,323	0.42	0.99	29,474
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 57. CEAC for pembrolizumab monotherapy vs platinum + 5-FU (CPS ≥1)

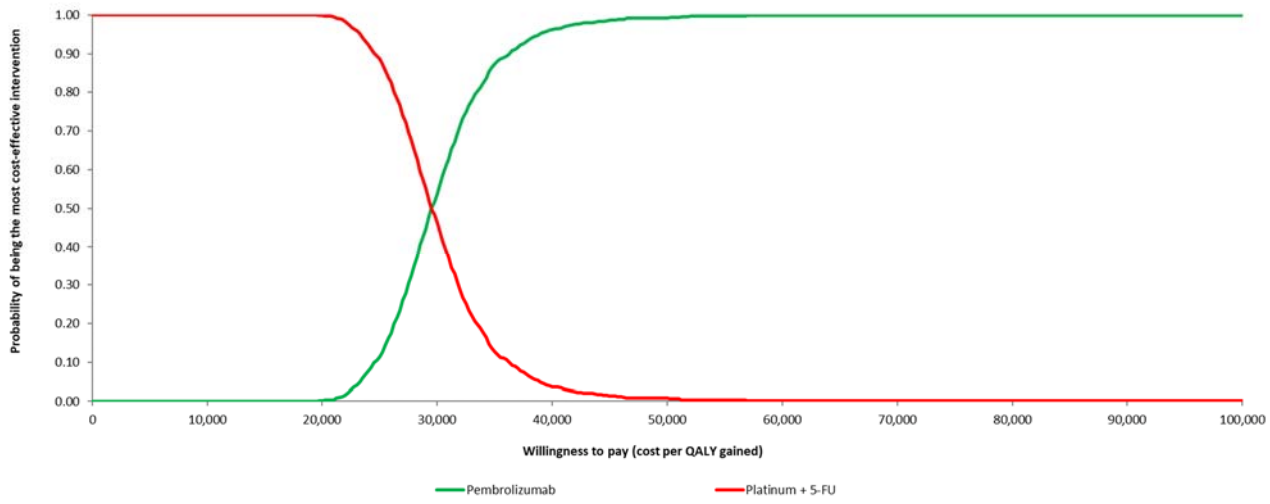
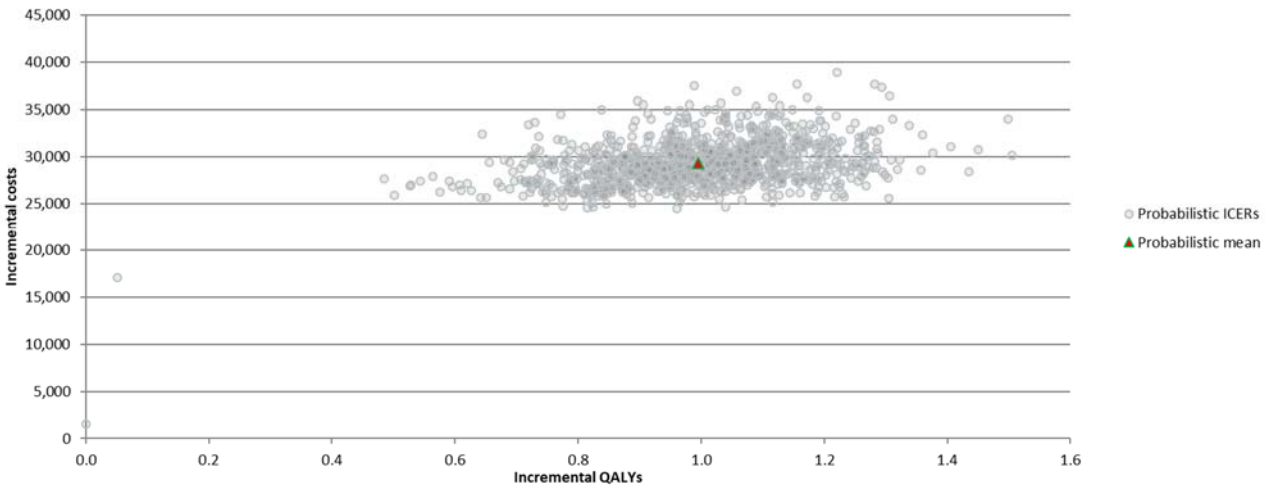


Figure 58. Scatterplot for pembrolizumab monotherapy vs platinum + 5-FU (CPS ≥1)



Combination therapy

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis for pembrolizumab combination therapy are presented in Table 93 to

and the corresponding scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 59 and Figure 60.

The cost-effectiveness acceptability curve shows that there is an approximately 100% probability that pembrolizumab combination therapy is cost-effective when compared to the EXTREME regimen and a 100% probability that it is cost-effective compared to platinum + 5-FU at the £50,000 per QALY gained threshold.

Table 93. Probability sensitivity analyses for pembrolizumab combination therapy vs EXTREME (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	61,534	2.56	1.81	-	-	-	-
EXTREME regimen	51,628	1.38	0.98	9,908	1.18	0.82	12,038
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 59. Scatterplot for pembrolizumab combination therapy vs EXTREME (CPS ≥1)

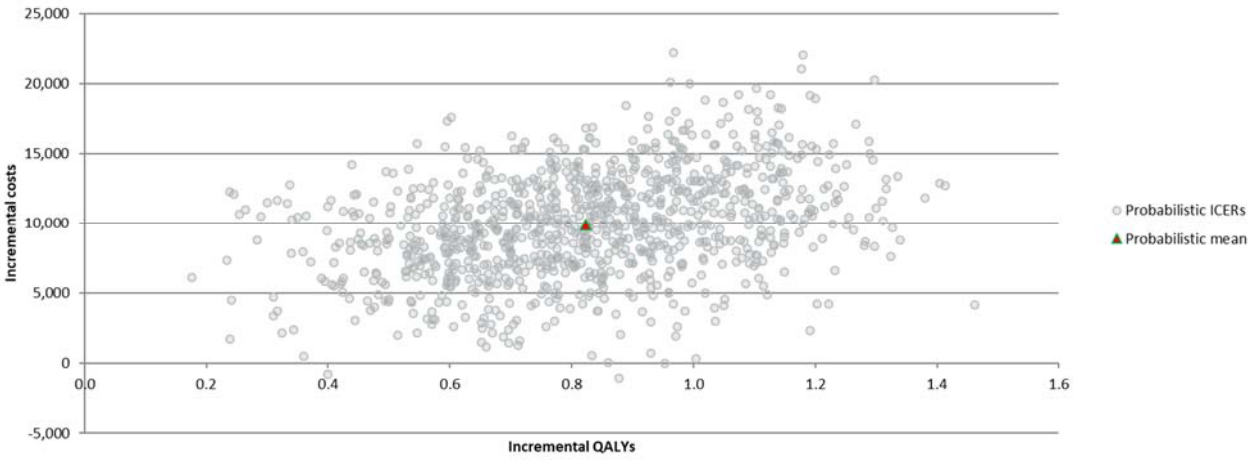


Figure 60. CEAC for pembrolizumab combination therapy vs EXTREME (CPS ≥1)

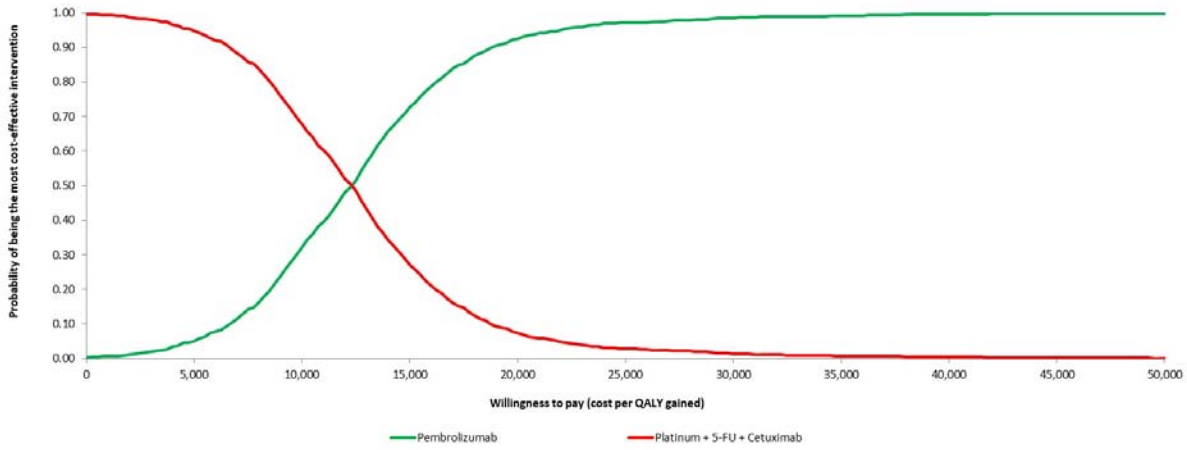


Table 94. Probability sensitivity analyses for pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	61,372	2.54	1.79	-	-	-	-
Platinum + 5-FU	19,474	0.95	0.68	41,898	1.59	1.11	37,671
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 61. Scatterplot for pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)

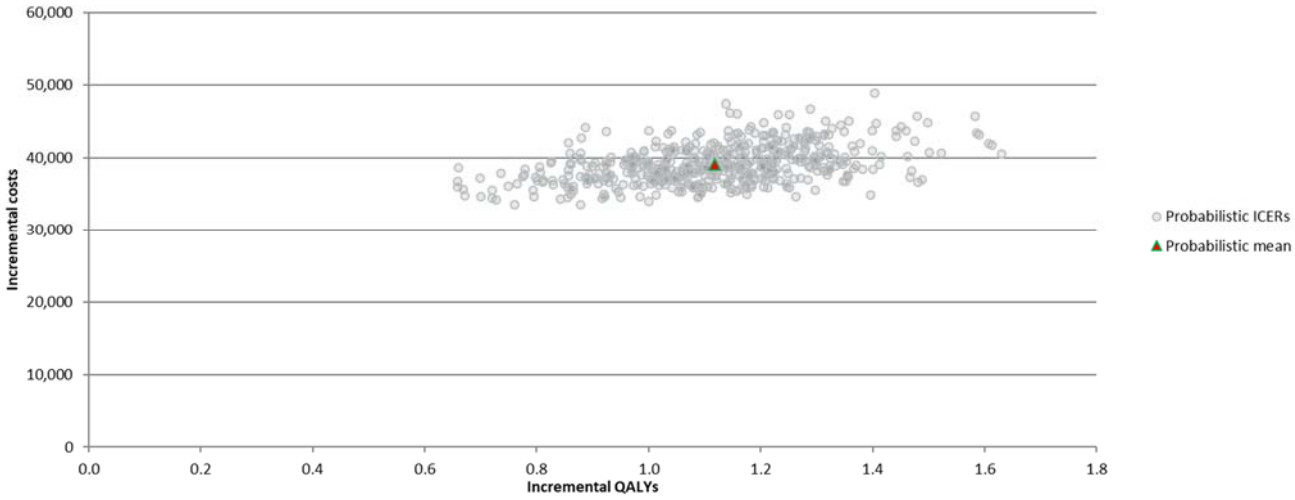
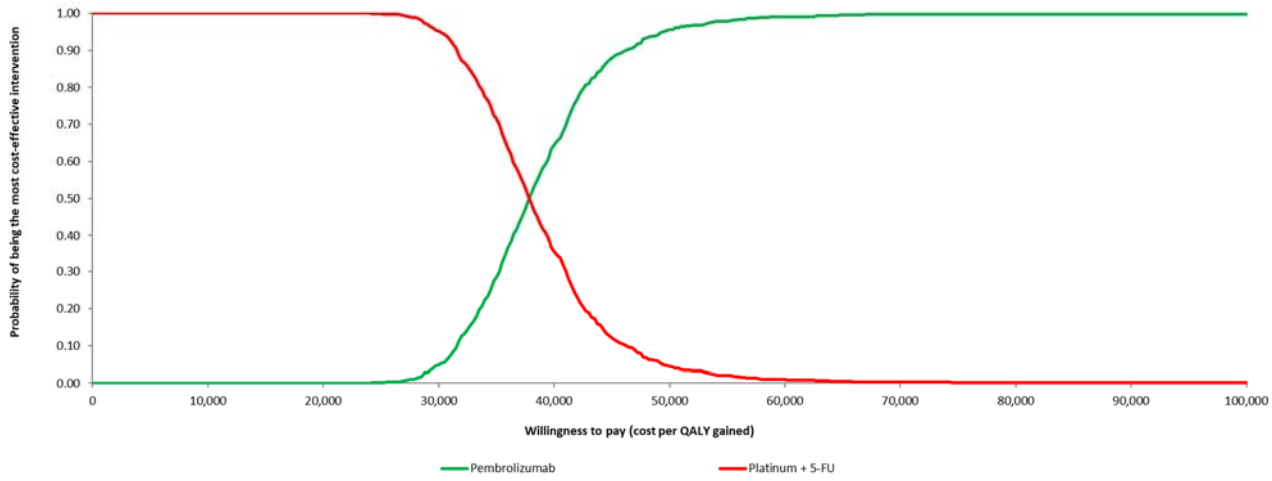


Figure 62. CEAC for pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)



Deterministic sensitivity analysis

Extensive sensitivity analyses were conducted to explore the uncertainty associated with the estimates of cost-effectiveness. One-way deterministic sensitivity analysis (DSA) was conducted using the parameters outlined in Table 86 and Table 87, and the associated lower and upper bound. The tornado diagrams of these one-way DSA are presented in Figure Figure 63 to

Figure ***66*** and the full table of results are presented in Appendix Q.

Figure 63. Tornado diagram presenting one-way DSA results: pembrolizumab monotherapy vs EXTREME (CPS ≥1)

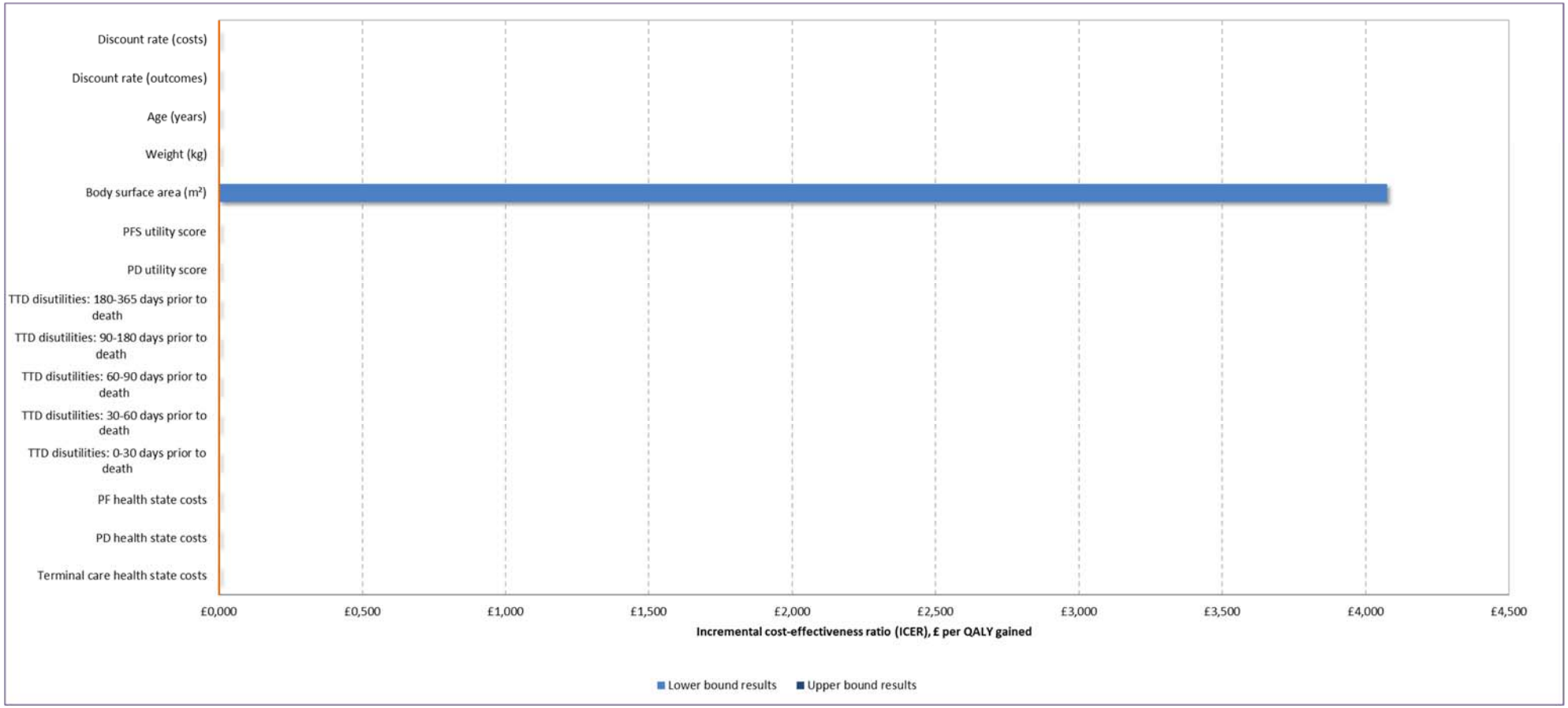


Figure 64. Tornado diagram presenting one-way DSA results: pembrolizumab monotherapy vs platinum + 5-FU (CPS ≥1)

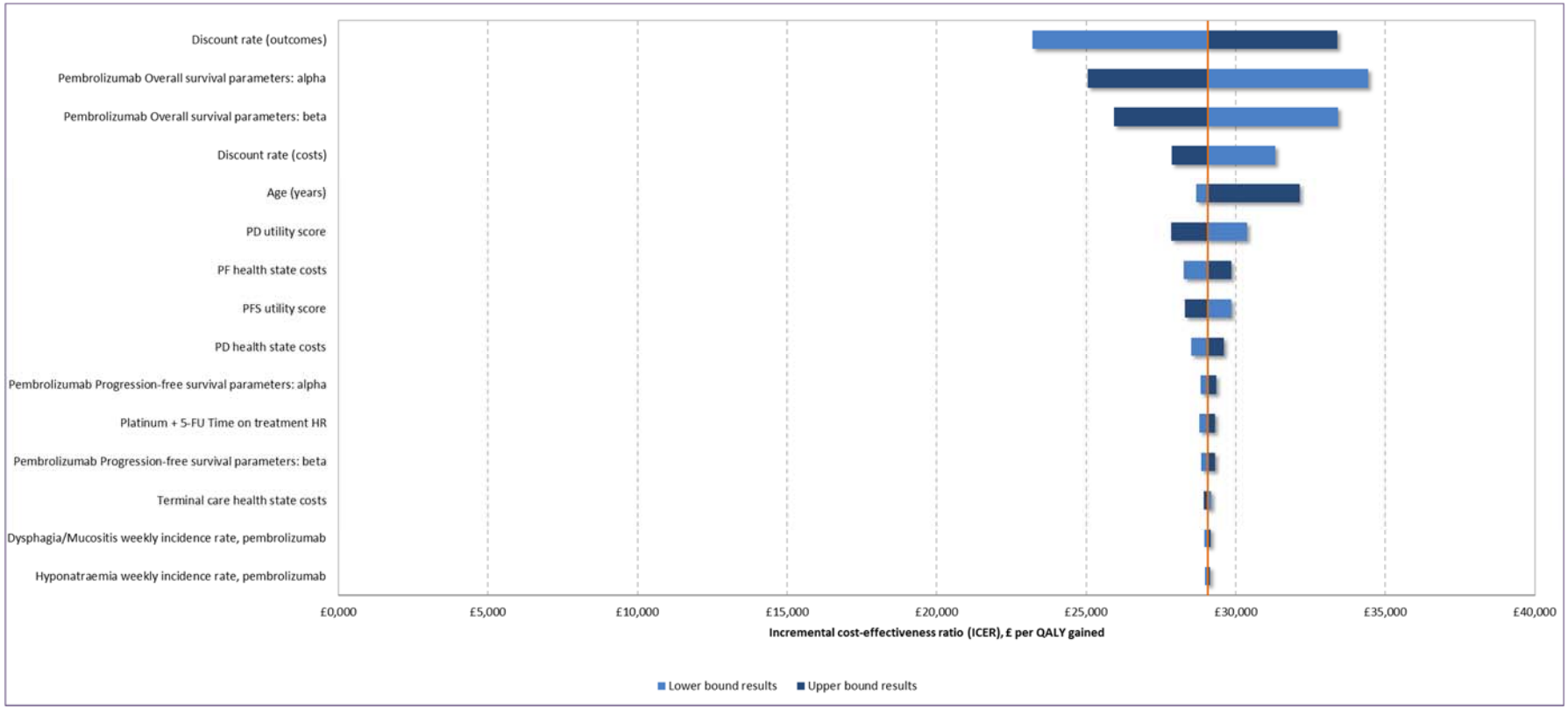


Figure 65. Tornado diagram presenting one-way DSA results: pembrolizumab combination therapy y vs EXTREME (CPS ≥1)

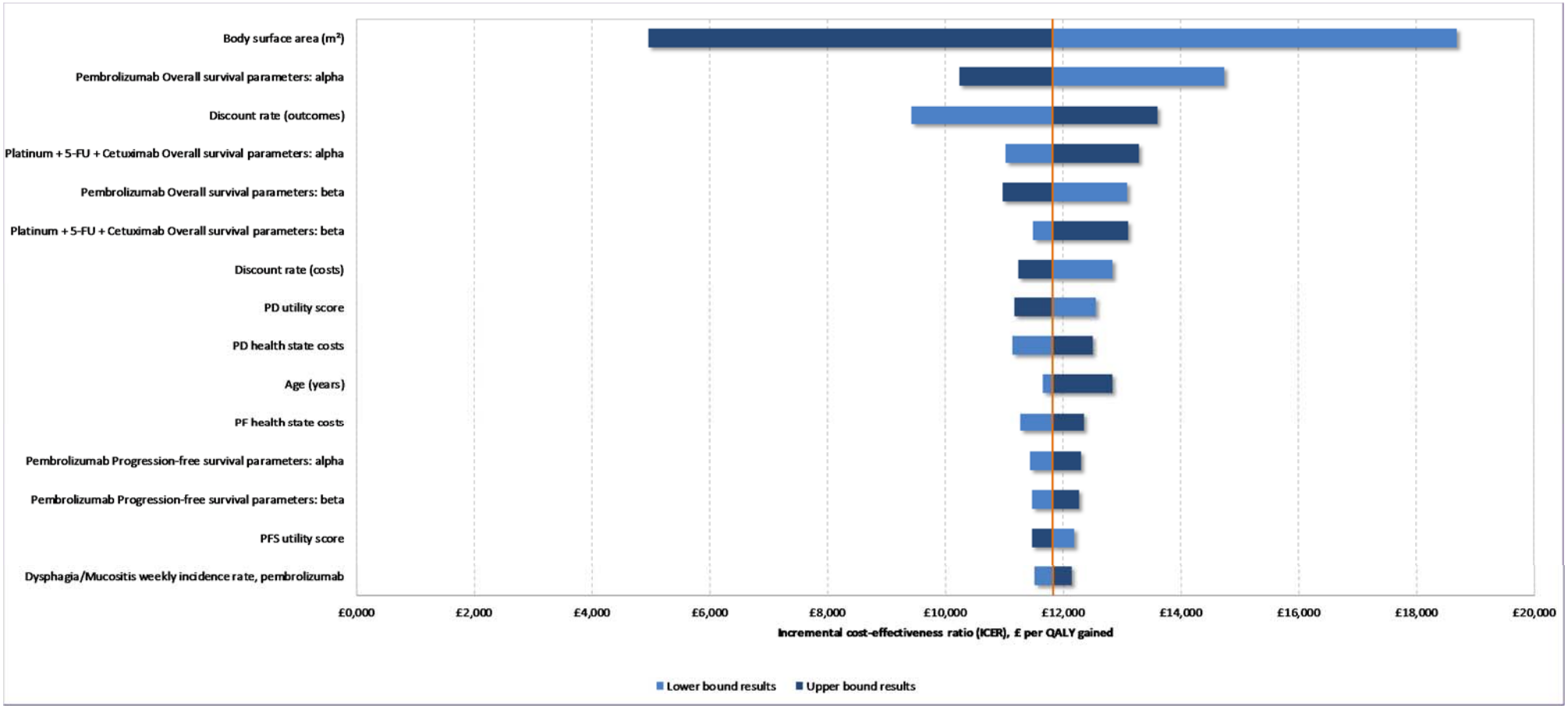
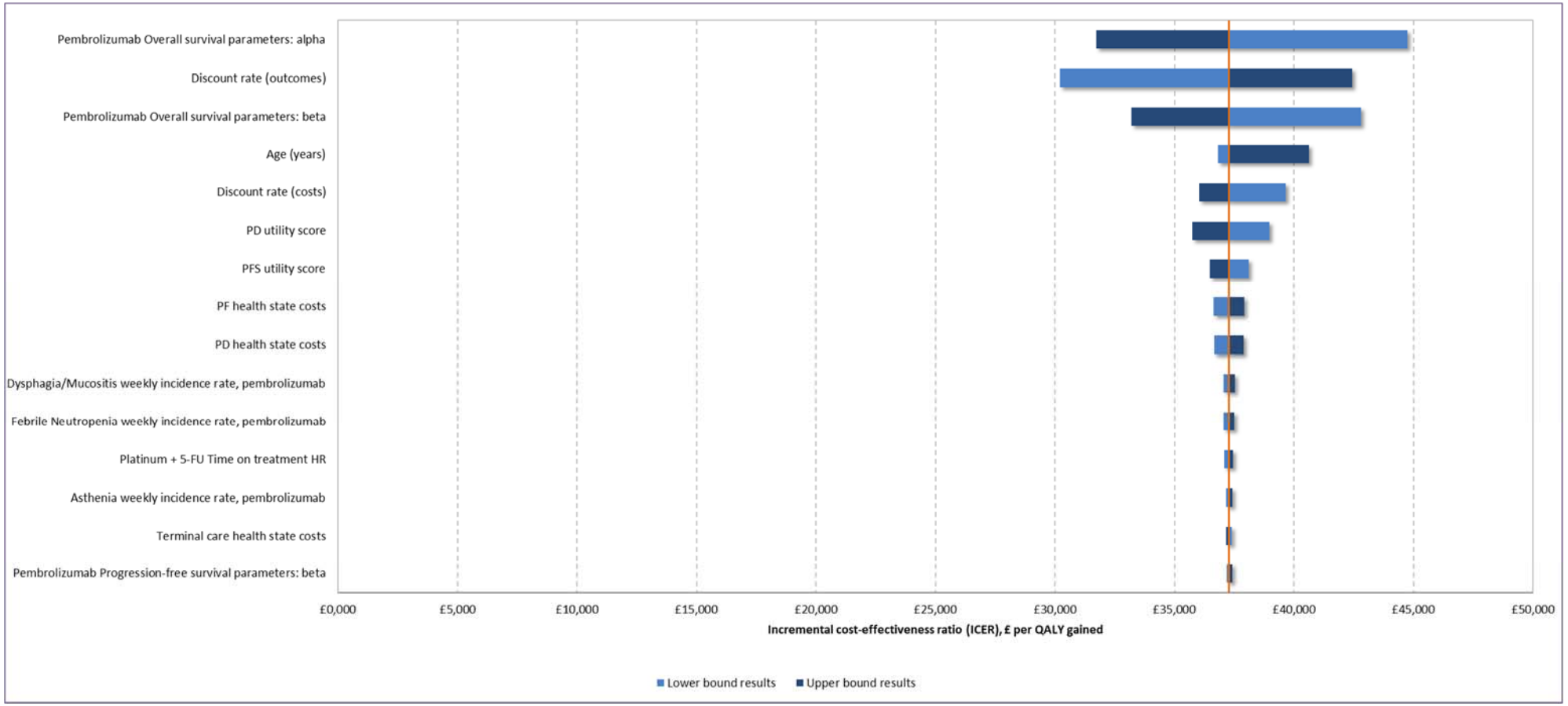


Figure 66. Tornado diagram presenting one-way DSA results: pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)



The one-way DSA shows the economic model is robust to a wide range of variables explored for uncertainty. In all comparisons the ICER remained below the range considered cost-effective for an end of life treatment.

Scenario analysis

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

The parameters explored are summarized below.

Model structure

- Time horizon (reduced to 10 years)

Efficacy estimates

- Overall survival
    - Pembrolizumab monotherapy: 45 weeks with loglogistic distribution (alternative good statistical fit)
    - Pembrolizumab monotherapy: 45 weeks with Weibull distribution (conservative extrapolation)
    - Pembrolizumab monotherapy: 30 weeks with Gompertz distribution (best statistical fit)
    - Pembrolizumab monotherapy: 30 weeks with Weibull distribution (conservative extrapolation)
    - Pembrolizumab monotherapy: full parametric with loglogistic (best statistical fit)
    - Pembrolizumab combination therapy: 45 weeks with Gompertz distribution (alternative good statistical fit)
    - Pembrolizumab combination therapy: 45 weeks with exponential distribution (conservative extrapolation)
    - Pembrolizumab combination therapy: 30 weeks with loglogistic distribution (best statistical fit)

    - Pembrolizumab combination therapy: 30 weeks with exponential distribution (conservative extrapolation)
    - Pembrolizumab combination therapy: full parametric with Gompertz (best statistical fit)
- Progression free survival
    - Pembrolizumab monotherapy: 10 weeks with lognormal distribution (alternative cut-point)
    - Pembrolizumab monotherapy: fully parametric with generalized gamma (best statistical fit)
    - Pembrolizumab combination therapy: 10 weeks with loglogistic distribution (alternative cut-point))
    - Pembrolizumab combination therapy: fully parametric with loglogistic (best statistical fit)
- Treatment effect waning
    - Three and five years

Scenario for subsequent therapies

- Including the cost and efficacy of nivolumab

Utilities

- Use mean health state utilities

Treatment Costs

- Q6W dosing (monotherapy only)
- Allow vial sharing
- Time to treatment discontinuation
    - Pembrolizumab monotherapy: fully parametric with Weibull (best statistical fit)
    - Pembrolizumab combination therapy: fully parametric with generalized gamma (best statistical fit)

Scenario analyses results

The scenario analysis results are all presented in the tables below.

Table 95. Scenarios analysis results: pembrolizumab monotherapy vs EXTREME

Pembrolizumab monotherapy vs platinum + 5-fu + cetuximab	Pembrolizumab		EXTREME		Cost differential	QALY differential	ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs				
Pembrolizumab Monotherapy Versus Extreme base case	£49,695	1.76	£53,008	1.02	-£3,313	0.74	Dominant	
Time horizon (reduced to 10 years)	£47,786	1.52	£51,179	0.97	-£3,393	0.55	Dominant	N/A
Pembrolizumab monotherapy: 45 weeks with loglogistic distribution (alternative good statistical fit)	£49,433	1.71	£53,001	1.02	-£3,568	0.68	Dominant	N/A
Pembrolizumab monotherapy: 45 weeks with Weibull distribution (conservative extrapolation)	£47,341	1.32	£50,495	0.84	-£3,154	0.48	Dominant	N/A
Pembrolizumab monotherapy: 30 weeks with Gompertz distribution (best statistical fit)	£50,790	2.01	£53,626	1.19	-£2,836	0.81	Dominant	N/A
Pembrolizumab monotherapy: 30 weeks with Weibull distribution (conservative extrapolation)	£46,765	1.24	£50,196	0.83	-£3,431	0.42	Dominant	N/A
Pembrolizumab monotherapy: full parametric with loglogistic (best statistical fit)	£48,756	1.59	£52,850	1.00	-£4,095	0.59	Dominant	N/A
PFS - Pembrolizumab monotherapy: 10 weeks with lognormal distribution (alternative cut-point)	£49,211	1.75	£52,885	1.02	-£3,674	0.73	Dominant	N/A
PFS -Pembrolizumab monotherapy: fully parametric with generalized gamma (best statistical fit)	£49,135	1.75	£52,871	1.02	-£3,736	0.73	Dominant	N/A
Treatment Waning 3 years	£49,692	1.76	£53,008	1.02	-£3,317	0.74	Dominant	N/A
Treatment Waning 5 years	£49,693	1.76	£53,008	1.02	-£3,315	0.74	Dominant	N/A
Subsequent treatment: Including the cost and efficacy of nivolumab	£50,045	1.76	£55,283	1.02	-£5,238	0.74	Dominant	N/A
Use mean health state utilities	£49,695	1.73	£53,008	1.00	-£3,313	0.73	Dominant	N/A
Q6W dosing (monotherapy only)	£50,485	1.76	£53,008	1.02	-£2,523	0.74	Dominant	N/A
Allow vial sharing	£49,689	1.76	£50,503	1.02	-£814	0.74	Dominant	N/A
TTD Fully parametric distribution with best statistical fit	£48,540	1.76	£50,252	1.02	-£1,712	0.74	Dominant	N/A

Table 96. Scenarios analysis results: pembrolizumab monotherapy vs platinum + 5-FU

Pembrolizumab monotherapy vs platinum + 5-FU	Pembrolizumab		Platinum + 5-FU		Cost differential	QALY differential	ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs				
Pembrolizumab Monotherapy Versus Platinum + 5-FU	£49,695	1.76	£20,319	0.75	£29,376	1.01	£29,057	
Time horizon (reduced to 10 years)	£47,786	1.52	£20,289	0.75	£27,497	0.78	£35,462	£6,404
Pembrolizumab monotherapy: 45 weeks with loglogistic distribution (alternative good statistical fit)	£49,433	1.71	£20,281	0.74	£29,152	0.97	£30,144	£1,087
Pembrolizumab monotherapy: 45 weeks with Weibull distribution (conservative extrapolation)	£47,341	1.32	£20,147	0.71	£27,195	0.61	£44,597	£15,540
Pembrolizumab monotherapy: 30 weeks with Gompertz distribution (best statistical fit)	£50,790	2.01	£20,381	0.79	£30,409	1.22	£24,909	-£4,149
Pembrolizumab monotherapy: 30 weeks with Weibull distribution (conservative extrapolation)	£46,765	1.24	£19,958	0.70	£26,806	0.55	£48,985	£19,928
Pembrolizumab monotherapy: full parametric with loglogistic (best statistical fit)	£48,756	1.59	£20,023	0.73	£28,733	0.86	£33,277	£4,220
PFS - Pembrolizumab monotherapy: 10 weeks with lognormal distribution (alternative cut-point)	£49,211	1.75	£20,321	0.75	£28,890	1.00	£28,834	-£224
PFS -Pembrolizumab monotherapy: fully parametric with generalized gamma (best statistical fit)	£49,135	1.75	£20,315	0.75	£28,820	1.00	£28,803	-£254
Treatment Waning 3 years	£49,679	1.76	£20,319	0.75	£29,359	1.01	£29,166	£108
Treatment Waning 5 years	£49,684	1.76	£20,319	0.75	£29,365	1.01	£29,124	£67
Subsequent treatment: Including the cost and efficacy of nivolumab	£50,045	1.76	£22,360	0.75	£27,686	1.01	£27,385	-£1,672
Use mean health state utilities	£49,695	1.73	£20,319	0.73	£29,376	1.00	£29,382	£324
Q6W dosing (monotherapy only)	£50,485	1.76	£20,319	0.75	£30,166	1.01	£29,834	£781
Allow vial sharing	£49,689	1.76	£20,302	0.75	£29,387	1.01	£29,068	£11
TTD Fully parametric distribution with best statistical fit	£48,540	1.76	£19,974	0.75	£28,566	1.01	£28,250	-£807

Table 97. Scenarios analysis results: pembrolizumab combination vs EXTREME

Pembrolizumab combination therapy vs EXTREME	Pembrolizumab		Platinum + 5-FU		Cost differential	QALY differential	ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs				
Base case	£61,430	1.80	£51,694	0.98	£9,735	0.83	£11,791	
Time horizon (reduced to 10 years)	£59,153	1.57	£49,833	0.94	£9,320	0.63	£14,757	£2,967
Pembrolizumab combination therapy: 45 weeks with Gompertz distribution (alternative good statistical fit)	£66,140	2.48	£52,439	1.16	£13,701	1.32	£10,379	-£1,411
Pembrolizumab combination therapy: 45 weeks with exponential distribution (conservative extrapolation)	£57,500	1.23	£48,479	0.79	£9,021	0.44	£20,276	£8,486
Pembrolizumab combination therapy: 30 weeks with loglogistic distribution (best statistical fit)	£60,629	1.68	£51,672	0.99	£8,957	0.69	£12,945	£1,154
Pembrolizumab combination therapy: 30 weeks with exponential distribution (conservative extrapolation)	£57,251	1.19	£48,342	0.78	£8,909	0.41	£21,617	£9,826
Pembrolizumab combination therapy: full parametric with Gompertz (best statistical fit)	£59,595	1.52	£47,822	0.76	£11,772	0.76	£15,439	£3,649
PFS - Pembrolizumab combination therapy: 10 weeks with loglogistic distribution (alternative cut-point))	£61,057	1.80	£51,645	0.98	£9,412	0.82	£11,485	-£306
PFS - Pembrolizumab combination therapy: fully parametric with loglogistic (best statistical fit)	£61,179	1.80	£51,759	0.98	£9,420	0.82	£11,494	-£296
Treatment Waning 3 years	£61,424	1.80	£51,694	0.98	£9,729	0.82	£11,803	£12
Treatment Waning 5 years	£61,426	1.80	£51,694	0.98	£9,731	0.82	£11,796	£5
Subsequent treatment: Including the cost and efficacy of nivolumab	£62,049	1.80	£55,723	0.98	£6,325	0.83	£7,661	-£4,130
Use mean health state utilities	£61,430	1.76	£51,694	0.95	£9,735	0.81	£12,087	£296
Allow vial sharing	£61,418	1.80	£49,265	0.98	£12,152	0.83	£14,718	£2,927
TTD Fully parametric distribution with best statistical fit	£59,345	1.80	£48,469	0.98	£10,876	0.83	£13,158	£1,368

Table 98. Scenarios analysis results: pembrolizumab combination vs platinum + 5-FU

Pembrolizumab combination therapy vs Platinum + 5-FU	Pembrolizumab		Platinum + 5-FU		Cost differential	QALY differential	ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs				
Base	£61,430	1.80	£19,497	0.68	£41,933	1.13	£37,258	
Time horizon (reduced to 10 years)	£59,153	1.57	£19,497	0.68	£39,656	0.89	£44,482	£7,224
Pembrolizumab combination therapy: 45 weeks with Gompertz distribution (alternative good statistical fit)	£66,140	2.48	£19,881	0.76	£46,258	1.72	£26,907	-£10,351
Pembrolizumab combination therapy: 45 weeks with exponential distribution (conservative extrapolation)	£57,500	1.23	£19,395	0.65	£38,105	0.58	£65,784	£28,526
Pembrolizumab combination therapy: 30 weeks with loglogistic distribution (best statistical fit)	£60,629	1.68	£19,449	0.67	£41,180	1.01	£40,651	£3,392
Pembrolizumab combination therapy: 30 weeks with exponential distribution (conservative extrapolation)	£57,251	1.19	£19,410	0.66	£37,841	0.54	£70,217	£32,958
Pembrolizumab combination therapy: full parametric with Gompertz (best statistical fit)	£59,595	1.52	£19,523	0.67	£40,072	0.85	£47,133	£9,874
PFS - Pembrolizumab combination therapy: 10 weeks with loglogistic distribution (alternative cut-point))	£61,057	1.80	£19,491	0.68	£41,566	1.12	£37,163	-£95
PFS - Pembrolizumab combination therapy: fully parametric with loglogistic (best statistical fit)	£61,179	1.80	£19,495	0.68	£41,683	1.12	£37,193	-£65
Treatment Waning 3 years	£60,954	1.72	£19,497	0.68	£41,457	1.05	£39,586	£2,328
Treatment Waning 5 years	£60,971	1.73	£19,497	0.68	£41,474	1.05	£39,457	£2,198
Subsequent treatment: Including the cost and efficacy of nivolumab	£62,049	1.80	£22,938	0.68	£39,110	1.13	£34,750	-£2,508
Use mean health state utilities	£61,430	1.76	£19,497	0.66	£41,933	1.10	£38,117	£859
Allow vial sharing	£61,418	1.80	£19,481	0.68	£41,936	1.13	£37,261	£3
TTD Fully parametric distribution with best statistical fit	£59,345	1.80	£18,979	0.68	£40,366	1.13	£35,835	-£1,423

The results show that pembrolizumab monotherapy and pembrolizumab combination remains a cost-effectiveness treatment option versus the EXTREME regimen and platinum + 5-FU in the vast majority of scenarios explored. The results are robust to changes in the time horizon, estimation of treatment costs and utility values; and pembrolizumab becomes more cost-effective when second-line treatment with nivolumab is included, as is current NHS practice. Exploration of the efficacy assumptions is where the greatest variation in cost-effectiveness is observed – though pembrolizumab remains cost-effective in the majority of scenarios explored. Most alternative survival distributions and cut-off points provide similar results of cost-effectiveness. The use of the Weibull and exponential distribution increase the ICER over the £50,000 cost per QALY threshold for the comparison of pembrolizumab combination therapy and platinum + 5-FU. However, these survival curves were shown to be a poor fit to real world data and should not be considered plausible considering the evidence available.

The results are also robust to the exploration of a "treatment waning effect" which is implemented to explore the loss of treatment efficacy with pembrolizumab over longer time periods. It works by setting the hazard rate equal to the hazard in the comparator arm after the pre-specified time. Even when implemented after a very short time, such as three years, there is limited impact on the ICER. The reason for this is because after the initial 1-2 years, the condition survival between both arms is similar; therefore, setting the pembrolizumab arm equal to the comparator arm has minimal impact. This is supported by the 5-year data from the EXTREME trial which shows the EXTREME and platinum + 5-FU arms flattening out over the long-term.

B 3.8.3 Summary of sensitivity analyses results

We have conducted extensive sensitivity analyses to understand the key determinants of the cost-effectiveness of pembrolizumab monotherapy and combination therapy for r/m HNSCC. The results demonstrate that the model is robust to the vast majority of scenarios explored, with pembrolizumab monotherapy and combination remaining a cost-effective end of life treatment option for patients with r/m HNSCC.

One of the key drivers of cost-effectiveness is the choice of survival extrapolation used for overall survival for the pembrolizumab monotherapy, pembrolizumab combination therapy and

comparator arms. The choice of the model selection process for extrapolating overall survival was explored extensively in section B.3.3, where evidence to support the base case assumptions was provided. Alternative scenarios using a range of different distributions and approaches were also explored, and these showed that pembrolizumab remains a cost-effective treatment option, either as a monotherapy or in combination with chemotherapy, in the majority of scenarios explored.

B.3.9 Subgroup analysis

Subgroup analysis for the CPS 20 population is presented below. The same survival modelling assumptions have been used as on the base case (summarized below). All other variables remain the same.

Table 99. Survival modelling used for CPS 20 subgroup analysis

Treatment arm	Overall Survival	Progression-free survival	Time to treatment discontinuation
Pembrolizumab monotherapy	45-week cut-off with lognormal	25-week cut-off with lognormal	KM only
Pembrolizumab combination therapy	45-week cut-off with lognormal	25-week cut-off with lognormal	KM only
EXTREME	45-week cut-off with lognormal	25-week cut-off with lognormal	KM only
Platinum + 5-FU	45-week cut-off with lognormal	25-week cut-off with lognormal	PFS extrapolation

Table 100. Sub-group analysis results: Monotherapy (CPS ≥20)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	56,765	3.20	2.25	-	-	-	-
EXTREME regimen	56,765	1.57	1.11	-468	1.63	1.14	Dominant
Platinum + 5-FU	21,185	1.27	0.90	£35,580	1.93	1.36	£26,210
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 101. Sub-group analysis results: Combination therapy (CPS ≥20)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	67,236	2.78	1.97	-	-	-	-
EXTREME regimen	57,305	1.57	1.11	9,931	1.21	0.86	11,546
Platinum + 5-FU	20,511	1.21	0.86	46,725	1.57	1.11	42,057
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

These results show that pembrolizumab remains a cost-effective treatment option for patients with r/m HNSCC at both CPS ≥1 and CPS 20 cut-off levels.

B.3.10 Validation

B 3.10.1 Validation of cost-effectiveness analysis

Comparison with published economic literature

This is the first economic evaluation focused on assessing the cost-effectiveness of pembrolizumab for the treatment of patients with recurrent or metastatic HNSCC. The economic evaluation reflects patients assessed in KEYNOTE-048 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 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.

Clinical benefit

The validation of the model was assessed by comparing the efficacy outcomes of pembrolizumab observed in the KEYNOTE-048 trial to the outcomes from the cost-effectiveness model. The PFS and OS curves predicted for the pembrolizumab arms and the EXTREME arm were compared to the observed Kaplan-Meier curves to ensure that the curves were well-aligned during the trial period. For more details comparing the results generated from the model to the outcomes from the model please refer to Appendix J1.1.

Model predictions were also compared against observed data from an external study. Specifically, long term data from the EXTREME trial was used to validate the model predictions of OS for the EXTREME arm and the platinum + 5-FU arm.

Expert validation

To verify the results of the cost-effectiveness model, internal quality control procedures were undertaken by the model developers to ensure that the mathematical calculations were performed correctly and were consistent with the model's specifications.

B.3.11 Interpretation and conclusions of economic evidence

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-048 and the de novo economic evaluation are reflective of patients with recurrent or metastatic HNSCC in the UK.
- 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.
- 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 and weaknesses of the evaluation

The cost-effectiveness analysis makes use of the best available evidence to inform the model.

- OS, PFS and ToT data for pembrolizumab were used from KEYNOTE-048 trial. For the comparators not included in the trial, a network meta-analysis was conducted. However, the EXTREME regimen is only approved for use in patients with HNSCC beginning in the oral cavity, meaning the results for this comparator are only relevant for the oral cavity patient population.

- OS and PFS extrapolation: The approaches to OS and PFS extrapolation were based on statistical and clinical considerations; validated against external data.
- Estimation of utilities: Utility values were obtained from EQ-5D KEYNOTE-048 data.
- Treatment duration of pembrolizumab: The model assumed that patients will be treated for up to 24 months, i.e. 35 cycles, as defined as part of the KEYNOTE-048 protocol.
- Resource utilisation and unit costs used in the analysis are reflective of UK clinical practice.

Extensive sensitivity analyses were conducted to inform the uncertainty around the above, which helped in understanding the key variables that could potentially have a major impact on the cost-effectiveness results.

The results presented here support the conclusion that, within the context of innovative end-of-life therapies, pembrolizumab is a cost-effective therapeutic option for the treatment of patients with recurrent or metastatic HNSCC.

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MSD
Hertford Road
Hoddesdon, Hertfordshire
EN11 9BU, UK
Telephone +44 (0)1992 452644
Facsimile +44 (0)1992 468175

22nd July 2019

Dear Jasdeep,

Re. Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Please find enclosed MSD's responses to the clarification questions from the ERG and the NICE technical team, concerning the clinical and cost effectiveness data for the above mentioned submission.

We believe that we have addressed all of the questions (now including those that require the provision of the KEYNOTE-048 final analysis [the latest data cut]), but should you or the ERG require any further clarification, please do not hesitate to contact us.

Best regards,

Sarah Breen, Team Leader HTA&OR

Section A: Clarification on effectiveness data

A1. Please provide details of disease stage at diagnosis and previous treatments for patients in each arm of the KEYNOTE-048 trial (PD-L1 CPS≥1 subgroup).

Data on patient disease stage at diagnosis were not collected as part of the KEYNOTE-048 trial (though disease stage at study baseline were collected and are shown in Document B section B.2.3.3 of the submission) and so we are not able to provide this information.

Previous treatments that patient had received at baseline of the KEYNOTE-048 trial for the PD-L1 CPS≥1 subgroup are shown in the tables in Appendix 1, A1. Response additional data.

A2. Priority question. Using data from the most recent KEYNOTE-048 trial data cut please provide clinical effectiveness results for all outcomes presented in Section B.2.6.1 of the company submission (CS). Please provide these results for the comparisons of pembrolizumab monotherapy with cetuximab + chemotherapy and pembrolizumab + chemotherapy with cetuximab + chemotherapy for people with cancer that started in the oral cavity (PD-L1 CPS≥1 subgroup). Where possible please perform statistical tests at the 5% significance level.

The KEYNOTE-048 clinical effectiveness results for all outcomes presented in Section B.2.6.1 of the original CS from the latest trial data cut (i.e. the final analysis [FA] data), as well as the equivalent clinical effectiveness results specific to the population of patients with cancer that started in the oral cavity (PD-L1 CPS≥1 subgroup) from the FA data are provided in the Supplementary Document and Supplementary Document - Appendices.

The Supplementary Document and Supplementary Document – Appendices are structured to present only those sections from the original CS that have been revised with the FA data, in sections/headings/appendices numbered in line with those used in the original company submission to facilitate cross-checking. The FA data on the population of patients with cancer started in the oral cavity (PD-L1 CPS≥1 subgroup) are presented in Appendix S of the Supplementary Document - Appendices. It should be noted that the KEYNOTE-048 study was not powered to detect statistically

significant differences in outcomes in this particular subpopulation, nor was this a pre-specified subgroup analysis.

A3. The expected number of progression free survival (PFS) and OS events at the time of the final analysis, for various patient populations, are provided in the CS (pp47-49). For example, "…for patients with PD-L1 CPS≥20, it was expected that approximately 237 PFS events will have been observed between one experimental treatment and standard treatment". Please clarify what is meant by "…between one experimental treatment and standard treatment".

Where "between one experimental treatment and standard treatment" is stated, it means between either pembrolizumab monotherapy or pembrolizumab plus chemotherapy and cetuximab plus chemotherapy.

i.e. "it was expected that approximately 237 PFS events will have been observed between one experimental treatment and standard treatment" means that at that particular analysis either that 237 PFS events were observed between pembrolizumab monotherapy and cetuximab plus chemotherapy or that 237 PFS events were observed between pembrolizumab plus chemotherapy and cetuximab plus chemotherapy.

A4. On pages 50, 51 and 53 of the CS, it is stated: "For analyses in the PD-L1 strongly positive subgroup, HPV status and ECOG status were used as the stratification factors". There is no mention of any analyses performed in the PD-L1 strongly positive subgroup elsewhere in the CS. Please clarify whether any analyses were performed in this subgroup and provide results if possible.

These are errors on our part in the descriptions of the analyses conducted, no analyses were conducted specifically with the PD-L1 strongly positive (TPS ≥50%) subgroup as a stratification factor for the PD-L1 CPS≥1 population.

Subgroup analysis of the overall population of the KEYNOTE-048 study were performed with PD-L1 TPS strongly positive/not strongly positive for the OS, PFS, and response rate outcomes. The results of these analyses are shown in Appendix M of the Supplementary Document - Appendices.

A5. A re-censoring protocol is referred to on pages 60, 63, 91 and 95 of the CS.

I. Please provide more details on this re-censoring procedure.

II. If any analyses were performed on data that had been re-censored, please provide details and results.

These instances are where we've indicated that re-censoring procedures have not been applied to our analyses that adjusted for post-study treatment switch-over of cetuximab plus chemotherapy arm patients to another immune checkpoint inhibitor via either the simplified 2-stage method or the rank preserving structural failure (RPSFT) method. There are no details or results of analyses that were performed on data that had been re-censored as no analyses incorporating a re-censoring procedure have been performed.

A6. In the CS, p-values are provided from both the stratified Cox model and the stratified log-rank test for the analysis of OS in the comparisons of pembrolizumab with cetuximab + chemotherapy (Table 16 and Table 17) and pembrolizumab + chemotherapy with cetuximab + chemotherapy (Table 36 and Table 37). It is stated that the analyses were not adjusted for treatment switching. Please clarify why unadjusted p-values have been presented alongside OS results which have been generated using data that have been adjusted for treatment switching.

For the tabulation of the adjusted OS analysis results, the p-value from the unadjusted ITT analysis (log-rank test) is maintained in the 2-stage/RPSFT model approach, by design. Specifically, under the null hypothesis of no treatment effect, the distribution of the test statistic used in the 2-stage/RPSFT model is identical to the distribution of test statistic in the unadjusted ITT model (no treatment effect implies no effect of receiving subsequent immune checkpoint inhibitors). The principle of the retention of the p-value is valid when the same test statistic is used in the 2-stage/RPSFT method and in the unadjusted ITT analysis.

A7. Please explain why two-sided tests of statistical significance were used when analysing the crossover-adjusted OS data when all other efficacy analyses of KEYNOTE-048 data were performed using one-sided tests.

Our analysis of the unadjusted data was performed in alignment with the KEYNOTE-048 statistical analysis plan where the hypothesis we were testing was that treatment with pembrolizumab is an improvement over treatment with the comparator in terms of overall survival (as described in hypotheses H7 to H14 in Document B section B.2.4 in our submission) and one-sided tests are appropriated and were presented. It should be noted that the type I error allowed in the direction of interest (i.e. the pembrolizumab arm superior to the comparator arm) is the same for the cross-over adjusted analyses results as the unadjusted results. The same test-statistic was computed for both and the p-value should be evaluated at the appropriate alpha level (5% for 2-sided and 2.5% for one-sided, ignoring the multiplicity strategy). The p-value should be interpreted together with the estimated HR and CI, both presentations (one-sided/two-sided) will provide the same type of information to evaluate the effectiveness.

For transparency, the results of both two-sided and one-sided tests for the OS analyses for the PD-L1 CPS≥1 population are summarised in ***Table 1*** and ***Table 2*** below.

Table 1 Summary of results of OS analyses – pembrolizumab monotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, PD-L1 CPS≥1 population

Analysis Method	Hazard Ratio	95% CI	P-value (2-sided)	P-value (1-sided)
ITT	0.74	(0.61; 0.90)	0.0027	0.0014
Simplified two-stage	0.71	(0.57; 0.89)	0.0027*	0.0014*
RPSFT	0.71	(0.57; 0.89)	0.0027*	0.0014*
IPCW	0.83	(0.67; 1.02)	0.0850§	0.0425§

* P-value retained from the ITT analysis (log-rank test) based on distribution of the test statistic under the null hypothesis of no treatment effect.

§ P-value based on bootstrap percentiles.

IPCW: inverse probability of censoring weighting method; ITT: intention-to-treat (no adjustment for crossover); RPSFT: rank preserving structural failure time method

Table 2 Summary of results of OS analyses – pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, PD-L1 CPS≥1 population

Analysis Method	Hazard Ratio	95% CI	P-value (2-sided)	P-value (1-sided)
ITT	0.65	(0.53; 0.80)	<0.0001	<0.0001
Simplified two-stage (no re-censoring)	0.62	(0.50; 0.78)	<0.0001*	<0.0001*
RPSFT (no re-censoring)	0.62	(0.50; 0.78)	<0.0001*	0.0001*
IPCW	0.72	(0.58; 0.91)	0.0050§	0.0025§

* P-value retained from the ITT analysis (log-rank test) based on distribution of the test statistic under the null hypothesis of no treatment effect.

§ P-value based on bootstrap percentiles.

IPCW: inverse probability of censoring weighting method; ITT: intention-to-treat (no adjustment for crossover); RPSFT: rank preserving structural failure time method

A8. Please clarify the rationale for using the two-stage adjusted OS results from the KEYNOTE-048 trial in the network meta-analyses, instead of other recognised methods (such as, the RPSFTM- or IPCW-adjusted OS data).

We conducted network meta-analyses using OS results from the KEYNOTE-048 trial that had been adjusted for treatment switching via the RPSFT and IPCW methods as well via the 2-stage method. The results of these network meta-analyses are presented in Appendix N of our initial submission. We chose to use the results of OS analysis using the 2-stage methodology because we believe this to be the most appropriate methodology for adjustment based on the guidance given in NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching:

The IPCW method represents a type of Marginal Structural Model that was originally developed for use with observational data, and has “no unmeasured confounder” (i.e. data must be available on all baseline and time-dependent prognostic factors for mortality that independently predict informative censoring [switching] and models of censoring risk must be correctly specified) as a key assumption. This assumption is particularly problematic in the context of an RCT such as KEYNOTE-048 as the RCT dataset is much smaller than observational datasets, some key predictors of treatment switching (e.g. patient preference for switching) may not be collected, and data collection of key indicators is stopped at some point (e.g. upon treatment discontinuation or disease progression even in patients who do not switch).

Furthermore, a large proportion of patients who switched from the cetuximab in combination with platinum and 5-FU arm died after switching (≥90%), as such >25% of observed events in the cetuximab in combination with platinum and 5-FU arm were lost due to censoring at the time of switch. With such a large proportion the weight compensation used for IPCW is prone to bias. Consequently, the IPCW method is unlikely to be the most appropriate method for the analysis of data from KEYNOTE-048.

The RPSFT method was designed primarily to address the issue of treatment non-compliance in RCTs (not very relevant in the context of the KEYNOTE-048 trial) and is primarily limited by the "common treatment effect" assumption which becomes invalid if patients who switch on to the experimental treatment part way through a trial experience a different treatment effect compared to patients originally randomised to the experimental group. Given that switching in the KEYNOTE-048 trial is permitted only after disease progression, at which time the capacity for a patient to benefit from pembrolizumab is likely to be different compared to pre-progression (and different to that of a patient who had been on pembrolizumab for while, given that it is known that the body's response to immune-oncology drugs may be delayed), the "common treatment effect" assumption is unlikely to be clinically plausible and consequently the RPSFT method is unlikely to be the most appropriate.

The simplified 2-stage model approach is particularly suitable for adjusting for the type of treatment switching observed in oncology RCTs when switching is only permitted soon after disease progress, i.e. a timepoint that can be used as a secondary "baseline" under the assumption that all patients are at a similar stage of disease at the point of disease progression (a reasonable assumption in the context of the KEYNOTE-048 trial design). Unlike the RPSFT method, the simple 2-stage method does require the "common treatment effect" assumption (which is unlikely to be clinically plausible as described previously) as the initial step of this approach involves estimating a treatment effect specifically for switchers.

We chose to use the results of OS analysis using the 2-stage methodology because we believe this is in general the most appropriate methodology for adjustment. For KEYNOTE-048, no deviation from the common treatment effect could be

demonstrated therefore estimates from RPSFT can be considered with the same validity as the one from 2-stage. Adjusted estimates from both methods are very similar. The 2-stage method of adjustment was also chosen as the most appropriate and used as the base-case for two earlier successful pembrolizumab NICE appraisals (TA428 for treating PD-L1-positive non-small-cell lung cancer after chemotherapy and TA519 for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy).

A9. Please provide the date of the first interim analysis of the KEYNOTE-048 trial.

The data cut-off for the first interim analysis (IA1) was 17-OCT-2017 (database lock on 27-NOV-2017). However, no data analysis was conducted at that time-point.

Section B: Clarification on cost-effectiveness data

B1. Priority request:

Please provide the following Kaplan-Meier analyses:

A. Time to death from any cause (OS)

B. Time to progression (based on central assessment by independent review) or death from any cause (PFS)

C. Time to study treatment discontinuation (TTD)

to the following specifications:

Trial data set: *KEYNOTE-048*

Data cut: *Final clinical effectiveness data*

Format: *Please present analysis outputs using the format used in the sample table below (p5)*

Populations: *(i) The population with PD-L1 CPS≥1 including all patients lost to follow-up or withdrawing from the trial and*

(ii) The population with PD-L1 CPS≥1 with cancer originating in the oral cavity only, including all patients lost to follow-up or withdrawing from the trial and

(iii) The population with PD-L1 CPS≥1 with cancer not originating in the oral cavity only, including all patients lost to follow-up or withdrawing from the trial

Trial arms: *(i) Pembrolizumab monotherapy*

(ii) Pembrolizumab+platinum+5-FU

(iii) Cetuximab+platinum+5-FU

Crossover adjustment: Please provide the Kaplan-Meier OS and PFS analyses for the cetuximab+platinum+5-FU arm of the KEYNOTE-048 trial using the following adjustments for crossover:

1. *No adjustment*
2. *RPFST adjusted population*
3. *Two-stage adjusted population*
4. *ICPW adjusted population*

Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Kaplan-Meier analyses have been provided in the zip folders in Appendix 2 (separate file), the key for to aid with cross-referencing can be viewed below. Please note, the ERG had requested if possible to provide disaggregated ToT KM curves for the different components. Unfortunately, MSD was unable to separate out the aggregated data.

The ERG also requested KM dataset for the population with PD-L1 CPS≥1 with cancer not originating in the oral cavity only. As mentioned, oral cavity was not a pre-specified subgroup in the KN048 trial and therefore any analysis including or excluding this subgroup is highly questionable. Additionally, the scope of the

appraisal does not list platinum-based comparators for non-oral cavity patients only, therefore the data for this subgroup is not provided.

PFS-IRC: independent review committee
PFS-INV: investigator assessed

Appendix 1

A1. Response additional data

Pembrolizumab monotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy (PD-L1 CPS≥1 population)

Table 3 Summary of prior line of systemic therapy, pembrolizumab monotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, ITT population, PD-L1 CPS≥1 population

	Pembrolizumab		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	257		255		512	
Subjects with no prior systemic therapy	127	(49.4)	130	(51.0)	257	(50.2)
Primary/Locally Advanced/With Curative Intent	**122**	**(47.5)**	**122**	**(47.8)**	**244**	**(47.7)**
Cetuximab	17	(6.6)	14	(5.5)	31	(6.1)
Platinum	105	(40.9)	117	(45.9)	222	(43.4)
Recurrent/With Curative Intent	**11**	**(4.3)**	**5**	**(2.0)**	**16**	**(3.1)**
Cetuximab	3	(1.2)	0	(0.0)	3	(0.6)
Platinum	9	(3.5)	4	(1.6)	13	(2.5)

A subject can have multiple prior systemic therapies and be counted in different rows that are applicable. But every subject is counted a single time for each applicable row and column.

Table 4 Patients with specific prior medications (incidence >0% in one or more treatment groups) pembrolizumab monotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, ASaT population, PD-L1 CPS≥1 population

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	256		245	
With one or more prior medications	235	(91.8)	237	(96.7)
With no prior medication	21	(8.2)	8	(3.3)
alimentary tract and metabolism				
antidiarrheals, intestinal antiinflammatory/antiinfective agents	**4**	**(1.6)**	**4**	**(1.6)**
Clostridium butyricum	0	(0.0)	1	(0.4)
Lactobacillus acidophilus	1	(0.4)	0	(0.0)
Lactobacillus acidophilus (+) Lactobacillus bulgaricus	1	(0.4)	0	(0.0)
Saccharomyces boulardii	2	(0.8)	0	(0.0)
ast-120	0	(0.0)	1	(0.4)
loperamide hydrochloride	1	(0.4)	1	(0.4)
pectin	0	(0.0)	1	(0.4)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
antiemetics and antinauseants	**16**	**(6.3)**	**149**	**(60.8)**
aprepitant	0	(0.0)	36	(14.7)
fosaprepitant dimeglumine	0	(0.0)	12	(4.9)
granisetron	0	(0.0)	25	(10.2)
granisetron hydrochloride	0	(0.0)	4	(1.6)
ondansetron	6	(2.3)	46	(18.8)
ondansetron hydrochloride	10	(3.9)	23	(9.4)
palonosetron hydrochloride	0	(0.0)	48	(19.6)
ramosetron	0	(0.0)	5	(2.0)
bile and liver therapy	**0**	**(0.0)**	**1**	**(0.4)**
ursodiol	0	(0.0)	1	(0.4)
digestives, incl. enzymes	**1**	**(0.4)**	**2**	**(0.8)**
pancreatin	1	(0.4)	2	(0.8)
drugs for acid related disorders	**76**	**(29.7)**	**133**	**(54.3)**
alginic acid (+) aluminum hydroxide	1	(0.4)	0	(0.0)
alginic acid (+) aluminum hydroxide (+) magnesium carbonate	0	(0.0)	1	(0.4)
alginic acid (+) aluminum hydroxide (+) magnesium carbonate (+) silicon dioxide	1	(0.4)	0	(0.0)
almagate	1	(0.4)	0	(0.0)
aluminum hydroxide (+) calcium carbonate (+) magnesium carbonate (+) oxethazaine	1	(0.4)	2	(0.8)
aluminum hydroxide (+) magnesium hydroxide (+) simethicone	1	(0.4)	0	(0.0)
bismuth subcitrate	1	(0.4)	0	(0.0)
calcium carbonate	1	(0.4)	3	(1.2)
cimetidine	0	(0.0)	2	(0.8)
esomeprazole	4	(1.6)	5	(2.0)
esomeprazole magnesium	5	(2.0)	6	(2.4)
famotidine	4	(1.6)	13	(5.3)
hydrotalcite	1	(0.4)	0	(0.0)
irsogladine maleate	1	(0.4)	0	(0.0)
lansoprazole	16	(6.3)	8	(3.3)
magaldrate	0	(0.0)	1	(0.4)
magnesium hydroxide	0	(0.0)	2	(0.8)
magnesium oxide	7	(2.7)	11	(4.5)
omeprazole	23	(9.0)	29	(11.8)
omeprazole magnesium	0	(0.0)	1	(0.4)
omeprazole sodium	0	(0.0)	2	(0.8)
pantoprazole	10	(3.9)	8	(3.3)
pantoprazole sodium	7	(2.7)	5	(2.0)
rabeprazole sodium	1	(0.4)	0	(0.0)
ranitidine	3	(1.2)	25	(10.2)
ranitidine hydrochloride	5	(2.0)	31	(12.7)
rebamipide	2	(0.8)	3	(1.2)
sodium bicarbonate (+) Swertia japonica	1	(0.4)	0	(0.0)
sodium gualenate	1	(0.4)	6	(2.4)
sucralfate	1	(0.4)	0	(0.0)
teprenone	0	(0.0)	1	(0.4)
drugs for constipation	**51**	**(19.9)**	**43**	**(17.6)**
bisacodyl	7	(2.7)	3	(1.2)
citric acid (+) magnesium oxide (+) sodium picosulfate	0	(0.0)	1	(0.4)
coriander (+) Indian laburnum (+) licorice (+) senna (+) tamarind	0	(0.0)	1	(0.4)
docusate calcium	0	(0.0)	1	(0.4)
docusate sodium	7	(2.7)	5	(2.0)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
docusate sodium (+) senna	3	(1.2)	0	(0.0)
docusate sodium (+) sennosides	1	(0.4)	0	(0.0)
electrolytes (unspecified) (+) polyethylene glycol 3350	1	(0.4)	0	(0.0)
fiber (unspecified)	1	(0.4)	0	(0.0)
glycerin	2	(0.8)	0	(0.0)
lactulose	14	(5.5)	10	(4.1)
mineral oil	1	(0.4)	0	(0.0)
polyethylene glycol	1	(0.4)	2	(0.8)
polyethylene glycol 3350	9	(3.5)	6	(2.4)
polyethylene glycol 3350 (+) potassium chloride (+) sodium bicarbonate (+) sodium chloride	3	(1.2)	10	(4.1)
polyethylene glycol 3350 (+) potassium chloride (+) sodium bicarbonate (+) sodium chloride (+) sodium sulfate	0	(0.0)	1	(0.4)
psyllium husk	1	(0.4)	0	(0.0)
senna	5	(2.0)	0	(0.0)
sennosides	10	(3.9)	15	(6.1)
sodium phosphate, dibasic (+) sodium phosphate, monobasic	0	(0.0)	1	(0.4)
sodium picosulfate	3	(1.2)	2	(0.8)
drugs for functional gastrointestinal disorders	**27**	**(10.5)**	**33**	**(13.5)**
acetaminophen (+) butylscopolamine bromide	1	(0.4)	0	(0.0)
atropine	2	(0.8)	0	(0.0)
bromopride	1	(0.4)	0	(0.0)
butylscopolamine bromide	1	(0.4)	0	(0.0)
chlordiazepoxide hydrochloride (+) clidinium bromide	1	(0.4)	0	(0.0)
dimethicone	2	(0.8)	1	(0.4)
dipyrone (+) fenpiverinium bromide (+) pitofenone hydrochloride	1	(0.4)	0	(0.0)
domperidone	1	(0.4)	4	(1.6)
drotaverine hydrochloride	1	(0.4)	0	(0.0)
glycopyrrolate	1	(0.4)	0	(0.0)
mebeverine hydrochloride	1	(0.4)	0	(0.0)
metoclopramide	2	(0.8)	17	(6.9)
metoclopramide hydrochloride	15	(5.9)	12	(4.9)
drugs used in diabetes	**26**	**(10.2)**	**15**	**(6.1)**
alogliptin benzoate (+) metformin hydrochloride	1	(0.4)	0	(0.0)
alogliptin benzoate (+) pioglitazone hydrochloride	1	(0.4)	0	(0.0)
carbutamide	0	(0.0)	1	(0.4)
dapagliflozin propanediol	1	(0.4)	0	(0.0)
empagliflozin	1	(0.4)	0	(0.0)
gliclazide	3	(1.2)	1	(0.4)
glimepiride	6	(2.3)	1	(0.4)
glipizide	0	(0.0)	1	(0.4)
glyburide	1	(0.4)	0	(0.0)
glyburide (+) metformin hydrochloride	0	(0.0)	1	(0.4)
insulin	0	(0.0)	1	(0.4)
insulin aspart	3	(1.2)	2	(0.8)
insulin degludec	0	(0.0)	1	(0.4)
insulin detemir	4	(1.6)	0	(0.0)
insulin glargine	2	(0.8)	2	(0.8)
insulin human	1	(0.4)	1	(0.4)
insulin human (+) insulin human, isophane	1	(0.4)	1	(0.4)
insulin, neutral	1	(0.4)	0	(0.0)
linagliptin	1	(0.4)	0	(0.0)
metformin	10	(3.9)	7	(2.9)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
metformin hydrochloride	4	(1.6)	3	(1.2)
metformin hydrochloride (+) saxagliptin hydrochloride	1	(0.4)	0	(0.0)
metformin hydrochloride (+) sitagliptin phosphate	1	(0.4)	0	(0.0)
pioglitazone	1	(0.4)	0	(0.0)
pioglitazone hydrochloride	2	(0.8)	0	(0.0)
repaglinide	1	(0.4)	0	(0.0)
sitagliptin phosphate	0	(0.0)	2	(0.8)
mineral supplements	**17**	**(6.6)**	**36**	**(14.7)**
calcium (unspecified)	0	(0.0)	3	(1.2)
calcium carbonate (+) calcium glubionate	0	(0.0)	1	(0.4)
calcium carbonate (+) calcium lactate gluconate	1	(0.4)	0	(0.0)
calcium carbonate (+) cholecalciferol	1	(0.4)	1	(0.4)
calcium gluconate	0	(0.0)	2	(0.8)
calcium lactate	1	(0.4)	0	(0.0)
citric acid (+) potassium bicarbonate	1	(0.4)	0	(0.0)
citric acid (+) potassium bicarbonate (+) potassium citrate	1	(0.4)	0	(0.0)
magnesium (unspecified)	0	(0.0)	4	(1.6)
magnesium aspartate	1	(0.4)	1	(0.4)
magnesium chloride	1	(0.4)	0	(0.0)
magnesium citrate (+) magnesium glutamate	0	(0.0)	2	(0.8)
magnesium sulfate	1	(0.4)	13	(5.3)
minerals (unspecified)	0	(0.0)	1	(0.4)
potassium (unspecified)	2	(0.8)	3	(1.2)
potassium chloride	5	(2.0)	16	(6.5)
selenium (unspecified)	1	(0.4)	0	(0.0)
zinc (unspecified)	2	(0.8)	0	(0.0)
zinc sulfate	0	(0.0)	1	(0.4)
other alimentary tract and metabolism products	**4**	**(1.6)**	**3**	**(1.2)**
arginine (+) beta-hydroxyisovaleric acid (+) glutamine	1	(0.4)	0	(0.0)
gastrointestinal preparations (unspecified)	3	(1.2)	1	(0.4)
glutamine (+) maltodextrin	0	(0.0)	1	(0.4)
hemp seed oil	0	(0.0)	1	(0.4)
stomatological preparations	**7**	**(2.7)**	**10**	**(4.1)**
aluminum hydroxide (+) diphenhydramine hydrochloride (+) lidocaine (+) magnesium hydroxide	1	(0.4)	0	(0.0)
aluminum hydroxide (+) diphenhydramine hydrochloride (+) lidocaine hydrochloride (+) magnesium hydroxide (+) simethicone	1	(0.4)	1	(0.4)
aluminum hydroxide (+) lidocaine (+) magnesium hydroxide (+) nystatin	0	(0.0)	1	(0.4)
benzydamine hydrochloride (+) chlorhexidine gluconate	0	(0.0)	1	(0.4)
carbomer (+) glycerin (+) hyetellose (+) sorbitol (+) xylitol	0	(0.0)	1	(0.4)
chlorhexidine gluconate (+) polyethylene glycol 1500 (+) polyethylene glycol 300	1	(0.4)	3	(1.2)
dexamethasone (+) lidocaine (+) nystatin	0	(0.0)	1	(0.4)
diphenhydramine hydrochloride (+) lidocaine hydrochloride (+) magnesium hydroxide	1	(0.4)	0	(0.0)
glucose oxidase (as drug) (+) lactoferrin (as drug) (+) lysozyme chloride (+) peroxidase (as drug)	1	(0.4)	2	(0.8)
lidocaine (+) nystatin	0	(0.0)	1	(0.4)
sodium fluoride	3	(1.2)	2	(0.8)
vitamins	**41**	**(16.0)**	**19**	**(7.8)**
alfacalcidol	2	(0.8)	0	(0.0)
ascorbic acid	3	(1.2)	1	(0.4)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
ascorbic acid (+) calcium (unspecified) (+) chromium (unspecified) (+) folic acid (+) magnesium (unspecified) (+) manganese (unspecified) (+) potassium (unspecified) (+) thioctic acid (+) vitamin B complex (+) zinc (unspecified)	1	(0.4)	0	(0.0)
ascorbic acid (+) calcium phosphate, dibasic (+) cholecalciferol	1	(0.4)	0	(0.0)
biotin	1	(0.4)	1	(0.4)
calcitriol	0	(0.0)	1	(0.4)
cholecalciferol	8	(3.1)	4	(1.6)
cyanocobalamin (+) lidocaine hydrochloride (+) thiamine hydrochloride	1	(0.4)	0	(0.0)
cyanocobalamin (+) pyridoxine (+) thiamine	1	(0.4)	1	(0.4)
dexpanthenol (+) vitamin A	0	(0.0)	1	(0.4)
eldecalcitol	1	(0.4)	0	(0.0)
ergocalciferol	1	(0.4)	2	(0.8)
hydroxocobalamin acetate (+) pyridoxine hydrochloride (+) thiamine disulfide	2	(0.8)	0	(0.0)
minerals (unspecified) (+) vitamins (unspecified)	4	(1.6)	3	(1.2)
thiamine	5	(2.0)	1	(0.4)
vitamin A	0	(0.0)	1	(0.4)
vitamin B complex	2	(0.8)	4	(1.6)
vitamin D (unspecified)	8	(3.1)	6	(2.4)
vitamin E	2	(0.8)	1	(0.4)
vitamins (unspecified)	11	(4.3)	2	(0.8)
antiinfectives for systemic use				
antibacterials for systemic use	**44**	**(17.2)**	**54**	**(22.0)**
amoxicillin	8	(3.1)	6	(2.4)
amoxicillin (+) clavulanate potassium	7	(2.7)	7	(2.9)
ampicillin	0	(0.0)	1	(0.4)
ampicillin sodium (+) sulbactam sodium	2	(0.8)	1	(0.4)
antimicrobial (unspecified)	0	(0.0)	1	(0.4)
azithromycin	0	(0.0)	1	(0.4)
cefaclor	0	(0.0)	1	(0.4)
cefadroxil	1	(0.4)	1	(0.4)
cefazolin	3	(1.2)	5	(2.0)
cefazolin sodium	9	(3.5)	4	(1.6)
cefazolin sodium (+) dextrose	0	(0.0)	1	(0.4)
cefcapene pivoxil hydrochloride	1	(0.4)	1	(0.4)
cefditoren pivoxil	0	(0.0)	1	(0.4)
cefonicid sodium	0	(0.0)	1	(0.4)
cefoxitin	0	(0.0)	1	(0.4)
ceftriaxone	1	(0.4)	1	(0.4)
ceftriaxone sodium	2	(0.8)	0	(0.0)
cefuroxime	3	(1.2)	2	(0.8)
cephalexin	3	(1.2)	1	(0.4)
cephalothin sodium	0	(0.0)	1	(0.4)
cephradine	0	(0.0)	1	(0.4)
ciprofloxacin	2	(0.8)	5	(2.0)
clarithromycin	1	(0.4)	1	(0.4)
clavulanate potassium	1	(0.4)	1	(0.4)
clindamycin	4	(1.6)	5	(2.0)
clindamycin hydrochloride	3	(1.2)	2	(0.8)
clindamycin phosphate	1	(0.4)	0	(0.0)
dicloxacillin	1	(0.4)	1	(0.4)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
doxycycline	0	(0.0)	1	(0.4)
doxycycline hyclate	0	(0.0)	2	(0.8)
erythromycin	1	(0.4)	1	(0.4)
floxacillin	0	(0.0)	1	(0.4)
gentamicin sulfate	1	(0.4)	1	(0.4)
levofloxacin	2	(0.8)	5	(2.0)
metronidazole	4	(1.6)	5	(2.0)
minocycline	0	(0.0)	1	(0.4)
minocycline hydrochloride	0	(0.0)	2	(0.8)
moxifloxacin	3	(1.2)	0	(0.0)
moxifloxacin hydrochloride	1	(0.4)	0	(0.0)
piperacillin sodium (+) tazobactam sodium	5	(2.0)	6	(2.4)
sulbactam	0	(0.0)	1	(0.4)
sulfamethoxazole (+) trimethoprim	0	(0.0)	3	(1.2)
tetracycline	0	(0.0)	1	(0.4)
tobramycin	1	(0.4)	0	(0.0)
vancomycin	2	(0.8)	0	(0.0)
antimycobacterials	**0**	**(0.0)**	**1**	**(0.4)**
isoniazid	0	(0.0)	1	(0.4)
antimycotics for systemic use	**2**	**(0.8)**	**4**	**(1.6)**
amphotericin B	0	(0.0)	1	(0.4)
fluconazole	2	(0.8)	3	(1.2)
antivirals for systemic use	**1**	**(0.4)**	**0**	**(0.0)**
valacyclovir hydrochloride	1	(0.4)	0	(0.0)
vaccines	**1**	**(0.4)**	**0**	**(0.0)**
influenza virus vaccine (unspecified)	1	(0.4)	0	(0.0)
antineoplastic and immunomodulating agents				
endocrine therapy	**1**	**(0.4)**	**1**	**(0.4)**
anastrozole	1	(0.4)	0	(0.0)
megestrol acetate	0	(0.0)	1	(0.4)
blood and blood forming organs				
antianemic preparations	**14**	**(5.5)**	**10**	**(4.1)**
cyanocobalamin	5	(2.0)	1	(0.4)
ferrous fumarate	2	(0.8)	0	(0.0)
ferrous gluconate	1	(0.4)	0	(0.0)
ferrous glycine sulfate	0	(0.0)	1	(0.4)
ferrous sulfate	4	(1.6)	1	(0.4)
folic acid	3	(1.2)	5	(2.0)
folic acid (+) iron (unspecified)	0	(0.0)	1	(0.4)
iron polymaltose	1	(0.4)	0	(0.0)
iron sucrose	0	(0.0)	1	(0.4)
antihemorrhagics	**6**	**(2.3)**	**6**	**(2.4)**
carbazochrome sodium sulfonate	1	(0.4)	0	(0.0)
phytonadione	1	(0.4)	2	(0.8)
tranexamic acid	5	(2.0)	4	(1.6)
antithrombotic agents	**20**	**(7.8)**	**28**	**(11.4)**
acenocoumarol	1	(0.4)	1	(0.4)
alteplase	1	(0.4)	0	(0.0)
apixaban	1	(0.4)	2	(0.8)
aspirin (+) magnesium hydroxide	1	(0.4)	0	(0.0)
bemiparin sodium	1	(0.4)	1	(0.4)
cilostazol	0	(0.0)	1	(0.4)
clopidogrel	0	(0.0)	2	(0.8)
clopidogrel bisulfate	1	(0.4)	3	(1.2)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
dabigatran etexilate mesylate	0	(0.0)	1	(0.4)
dalteparin sodium	1	(0.4)	0	(0.0)
enoxaparin sodium	6	(2.3)	11	(4.5)
heparin	2	(0.8)	4	(1.6)
heparin low molecular weight	0	(0.0)	1	(0.4)
heparin sodium	2	(0.8)	2	(0.8)
rivaroxaban	2	(0.8)	2	(0.8)
warfarin	3	(1.2)	2	(0.8)
warfarin sodium	1	(0.4)	0	(0.0)
blood substitutes and perfusion solutions	**27**	**(10.5)**	**54**	**(22.0)**
albumin human	1	(0.4)	0	(0.0)
amino acids (unspecified) (+) dextrose (+) electrolytes (unspecified)	0	(0.0)	1	(0.4)
amino acids (unspecified) (+) dextrose (+) electrolytes (unspecified) (+) lipids (unspecified)	1	(0.4)	1	(0.4)
amino acids (unspecified) (+) dextrose (+) electrolytes (unspecified) (+) thiamine hydrochloride	1	(0.4)	1	(0.4)
blood cells, red	3	(1.2)	3	(1.2)
blood, plasma	1	(0.4)	1	(0.4)
calcium chloride (+) magnesium chloride (+) potassium chloride (+) sodium acetate (+) sodium chloride	0	(0.0)	1	(0.4)
calcium gluconate (+) dextrose (+) magnesium chloride (+) potassium chloride (+) sodium acetate (+) sodium chloride (+) sodium citrate	2	(0.8)	0	(0.0)
cupric chloride (+) manganese chloride (+) potassium iodide (+) sodium fluoride (+) sodium selenate (+) zinc chloride	0	(0.0)	1	(0.4)
dextrose (+) electrolytes (unspecified)	2	(0.8)	1	(0.4)
dextrose (+) electrolytes (unspecified) (+) sodium lactate	2	(0.8)	0	(0.0)
dextrose (+) mannitol (+) potassium chloride	0	(0.0)	3	(1.2)
dextrose (+) potassium chloride (+) sodium chloride	0	(0.0)	1	(0.4)
dextrose (+) sodium chloride	0	(0.0)	2	(0.8)
electrolytes (unspecified)	2	(0.8)	4	(1.6)
electrolytes (unspecified) (+) sodium acetate	1	(0.4)	1	(0.4)
electrolytes (unspecified) (+) sodium lactate	4	(1.6)	4	(1.6)
electrolytes (unspecified) (+) sodium lactate (+) sorbitol	1	(0.4)	0	(0.0)
magnesium sulfate (+) potassium chloride (+) sodium chloride	1	(0.4)	0	(0.0)
mannitol	0	(0.0)	10	(4.1)
mannitol (+) potassium chloride (+) sodium chloride	0	(0.0)	3	(1.2)
medium-chain triglycerides (+) olive oil (+) omega-3 marine triglycerides (+) soybean oil	0	(0.0)	1	(0.4)
nitrofurazone	1	(0.4)	0	(0.0)
parenteral nutrition (unspecified)	1	(0.4)	0	(0.0)
potassium chloride (+) sodium chloride	0	(0.0)	2	(0.8)
potassium phosphate, dibasic	0	(0.0)	1	(0.4)
sodium bicarbonate	2	(0.8)	0	(0.0)
sodium chloride	13	(5.1)	42	(17.1)
sodium chloride (+) tetrastarch	1	(0.4)	0	(0.0)
sodium phosphate, dibasic	1	(0.4)	0	(0.0)
cardiovascular system				
agents acting on the renin-angiotensin system	**55**	**(21.5)**	**41**	**(16.7)**
amlodipine besylate (+) candesartan cilexetil	1	(0.4)	0	(0.0)
amlodipine besylate (+) hydrochlorothiazide (+)	1	(0.4)	1	(0.4)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
valsartan				
amlodipine besylate (+) olmesartan medoxomil	2	(0.8)	1	(0.4)
amlodipine besylate (+) perindopril arginine	2	(0.8)	0	(0.0)
amlodipine besylate (+) telmisartan	1	(0.4)	0	(0.0)
amlodipine besylate (+) valsartan	1	(0.4)	2	(0.8)
azilsartan	2	(0.8)	0	(0.0)
benazepril hydrochloride (+) hydrochlorothiazide	1	(0.4)	0	(0.0)
candesartan	1	(0.4)	0	(0.0)
candesartan cilexetil	2	(0.8)	0	(0.0)
candesartan cilexetil (+) hydrochlorothiazide	0	(0.0)	1	(0.4)
captopril	1	(0.4)	1	(0.4)
enalapril	3	(1.2)	4	(1.6)
enalapril maleate	2	(0.8)	0	(0.0)
fosinopril sodium	1	(0.4)	0	(0.0)
hydrochlorothiazide (+) irbesartan	1	(0.4)	0	(0.0)
hydrochlorothiazide (+) lisinopril	1	(0.4)	1	(0.4)
hydrochlorothiazide (+) losartan potassium	0	(0.0)	3	(1.2)
hydrochlorothiazide (+) olmesartan medoxomil	0	(0.0)	1	(0.4)
hydrochlorothiazide (+) quinapril hydrochloride	1	(0.4)	0	(0.0)
hydrochlorothiazide (+) telmisartan	1	(0.4)	0	(0.0)
irbesartan	1	(0.4)	2	(0.8)
lisinopril	6	(2.3)	3	(1.2)
losartan	7	(2.7)	8	(3.3)
losartan potassium	2	(0.8)	2	(0.8)
olmesartan medoxomil	2	(0.8)	2	(0.8)
perindopril	0	(0.0)	1	(0.4)
perindopril arginine	2	(0.8)	1	(0.4)
perindopril erbumine	2	(0.8)	0	(0.0)
ramipril	6	(2.3)	4	(1.6)
telmisartan	1	(0.4)	3	(1.2)
valsartan	3	(1.2)	2	(0.8)
antihypertensives	**4**	**(1.6)**	**2**	**(0.8)**
clonidine	0	(0.0)	1	(0.4)
doxazosin mesylate	1	(0.4)	0	(0.0)
methyldopa	1	(0.4)	1	(0.4)
moxonidine	2	(0.8)	0	(0.0)
beta blocking agents	**26**	**(10.2)**	**24**	**(9.8)**
atenolol	4	(1.6)	5	(2.0)
bisoprolol	1	(0.4)	1	(0.4)
bisoprolol fumarate	3	(1.2)	5	(2.0)
bisoprolol fumarate (+) hydrochlorothiazide	0	(0.0)	1	(0.4)
carteolol hydrochloride	1	(0.4)	0	(0.0)
carvedilol	4	(1.6)	3	(1.2)
metoprolol	3	(1.2)	2	(0.8)
metoprolol succinate	4	(1.6)	2	(0.8)
metoprolol tartrate	4	(1.6)	4	(1.6)
nebivolol hydrochloride	0	(0.0)	1	(0.4)
propranolol	1	(0.4)	0	(0.0)
sotalol	1	(0.4)	0	(0.0)
calcium channel blockers	**26**	**(10.2)**	**17**	**(6.9)**
amlodipine	11	(4.3)	10	(4.1)
amlodipine besylate	5	(2.0)	3	(1.2)
azelnidipine	0	(0.0)	1	(0.4)
benidipine hydrochloride	0	(0.0)	1	(0.4)
diltiazem	1	(0.4)	0	(0.0)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
diltiazem hydrochloride	1	(0.4)	0	(0.0)
lacidipine	1	(0.4)	0	(0.0)
lercanidipine hydrochloride	2	(0.8)	2	(0.8)
nicardipine hydrochloride	1	(0.4)	0	(0.0)
nifedipine	3	(1.2)	0	(0.0)
nitrendipine	1	(0.4)	0	(0.0)
verapamil	1	(0.4)	1	(0.4)
cardiac therapy	**4**	**(1.6)**	**3**	**(1.2)**
amezinium metilsulfate	1	(0.4)	0	(0.0)
digoxin	1	(0.4)	0	(0.0)
nicorandil	0	(0.0)	1	(0.4)
nitroglycerin	1	(0.4)	1	(0.4)
propafenone hydrochloride	0	(0.0)	1	(0.4)
ubiquinol	1	(0.4)	0	(0.0)
diuretics	**11**	**(4.3)**	**19**	**(7.8)**
bumetanide	1	(0.4)	0	(0.0)
chlorthalidone	0	(0.0)	1	(0.4)
eplerenone	0	(0.0)	1	(0.4)
furosemide	6	(2.3)	11	(4.5)
furosemide sodium	0	(0.0)	1	(0.4)
hydrochlorothiazide	3	(1.2)	3	(1.2)
indapamide	1	(0.4)	2	(0.8)
spironolactone	2	(0.8)	1	(0.4)
lipid modifying agents	**40**	**(15.6)**	**38**	**(15.5)**
atorvastatin	11	(4.3)	4	(1.6)
atorvastatin calcium	8	(3.1)	5	(2.0)
bezafibrate	0	(0.0)	1	(0.4)
ezetimibe	2	(0.8)	1	(0.4)
ezetimibe (+) simvastatin	0	(0.0)	2	(0.8)
icosapent ethyl	0	(0.0)	1	(0.4)
krill oil	1	(0.4)	0	(0.0)
lovastatin	0	(0.0)	1	(0.4)
omega-3 marine triglycerides	2	(0.8)	1	(0.4)
pitavastatin calcium	2	(0.8)	0	(0.0)
pravastatin	1	(0.4)	1	(0.4)
pravastatin sodium	0	(0.0)	1	(0.4)
rosuvastatin	2	(0.8)	2	(0.8)
rosuvastatin calcium	2	(0.8)	3	(1.2)
simvastatin	10	(3.9)	17	(6.9)
vasoprotectives	**2**	**(0.8)**	**3**	**(1.2)**
diosmin	1	(0.4)	0	(0.0)
diosmin (+) hesperidin	1	(0.4)	0	(0.0)
escin	0	(0.0)	1	(0.4)
heparinoid	0	(0.0)	2	(0.8)
dermatologicals				
antibiotics and chemotherapeutics for dermatological use	**3**	**(1.2)**	**4**	**(1.6)**
bacitracin	2	(0.8)	0	(0.0)
bacitracin (+) neomycin sulfate (+) polymyxin B sulfate	1	(0.4)	3	(1.2)
mupirocin	0	(0.0)	1	(0.4)
antifungals for dermatological use	**9**	**(3.5)**	**3**	**(1.2)**
efinaconazole	1	(0.4)	0	(0.0)
ketoconazole	0	(0.0)	1	(0.4)
nystatin	8	(3.1)	2	(0.8)
antipruritics, incl. antihistamines, anesthetics, etc.	**2**	**(0.8)**	**2**	**(0.8)**

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
chlorhexidine gluconate (+) lidocaine hydrochloride	1	(0.4)	0	(0.0)
diphenhydramine hydrochloride (+) enoxolone (+) vitamin A palmitate	0	(0.0)	1	(0.4)
diphenhydramine hydrochloride (+) lidocaine hydrochloride	1	(0.4)	1	(0.4)
antiseptics and disinfectants	**6**	**(2.3)**	**6**	**(2.4)**
carbamide peroxide	1	(0.4)	0	(0.0)
chlorhexidine gluconate	3	(1.2)	3	(1.2)
guaiazulene	1	(0.4)	1	(0.4)
iodine	1	(0.4)	0	(0.0)
povidone-iodine	0	(0.0)	2	(0.8)
corticosteroids, dermatological preparations	**5**	**(2.0)**	**8**	**(3.3)**
betamethasone dipropionate (+) calcipotriene	0	(0.0)	2	(0.8)
betamethasone valerate	3	(1.2)	0	(0.0)
betamethasone valerate (+) gentamicin sulfate	1	(0.4)	0	(0.0)
desonide	1	(0.4)	0	(0.0)
difluprednate	0	(0.0)	1	(0.4)
diphenhydramine hydrochloride (+) hydrocortisone acetate (+) neomycin sulfate	0	(0.0)	1	(0.4)
hydrocortisone acetate	0	(0.0)	1	(0.4)
hydrocortisone butyrate	0	(0.0)	1	(0.4)
mometasone furoate	0	(0.0)	2	(0.8)
emollients and protectives	**3**	**(1.2)**	**0**	**(0.0)**
ceramide (+) coconut oil (+) glycerin (+) medium-chain triglycerides (+) phospholipids (+) shea butter	1	(0.4)	0	(0.0)
mineral oil (+) petrolatum	1	(0.4)	0	(0.0)
petrolatum, white	1	(0.4)	0	(0.0)
other dermatological preparations	**1**	**(0.4)**	**2**	**(0.8)**
dermatologic (unspecified)	1	(0.4)	2	(0.8)
preparations for the treatment of wounds and ulcers	**1**	**(0.4)**	**0**	**(0.0)**
castor oil (+) Peruvian balsam	1	(0.4)	0	(0.0)
genitourinary system and sex hormones				
other gynecologicals	**1**	**(0.4)**	**0**	**(0.0)**
quinagolide hydrochloride	1	(0.4)	0	(0.0)
sex hormones and modulators of the genital system	**2**	**(0.8)**	**0**	**(0.0)**
estradiol	1	(0.4)	0	(0.0)
testosterone	1	(0.4)	0	(0.0)
urologicals	**13**	**(5.1)**	**12**	**(4.9)**
alfuzosin hydrochloride	0	(0.0)	2	(0.8)
dutasteride	0	(0.0)	1	(0.4)
finasteride	3	(1.2)	3	(1.2)
sildenafil citrate	1	(0.4)	1	(0.4)
tamsulosin hydrochloride	11	(4.3)	6	(2.4)
tolterodine tartrate	0	(0.0)	1	(0.4)
musculoskeletal system				
antigout preparations	**5**	**(2.0)**	**6**	**(2.4)**
allopurinol	5	(2.0)	2	(0.8)
benzbromarone	0	(0.0)	1	(0.4)
colchicine	1	(0.4)	2	(0.8)
febuxostat	0	(0.0)	1	(0.4)
antiinflammatory and antirheumatic products	**56**	**(21.9)**	**66**	**(26.9)**
aceclofenac	2	(0.8)	0	(0.0)
acemetacin	2	(0.8)	4	(1.6)
benzydamine hydrochloride	1	(0.4)	0	(0.0)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
celecoxib	2	(0.8)	3	(1.2)
dexibuprofen	1	(0.4)	0	(0.0)
dexketoprofen tromethamine	1	(0.4)	6	(2.4)
diclofenac	5	(2.0)	3	(1.2)
diclofenac diethylamine	1	(0.4)	0	(0.0)
diclofenac epolamine	0	(0.0)	1	(0.4)
diclofenac potassium	2	(0.8)	2	(0.8)
diclofenac sodium	5	(2.0)	4	(1.6)
etoricoxib	1	(0.4)	1	(0.4)
flurbiprofen axetil	1	(0.4)	0	(0.0)
ibuprofen	23	(9.0)	18	(7.3)
indomethacin	0	(0.0)	2	(0.8)
ketoprofen	2	(0.8)	3	(1.2)
ketorolac tromethamine	2	(0.8)	3	(1.2)
loxoprofen	0	(0.0)	1	(0.4)
loxoprofen sodium	4	(1.6)	4	(1.6)
mefenamic acid	1	(0.4)	2	(0.8)
meloxicam	2	(0.8)	0	(0.0)
mucopolysaccharide polysulfate	0	(0.0)	7	(2.9)
naproxen	5	(2.0)	4	(1.6)
naproxen sodium	2	(0.8)	2	(0.8)
nimesulide	2	(0.8)	2	(0.8)
parecoxib	0	(0.0)	1	(0.4)
drugs for treatment of bone diseases	**7**	**(2.7)**	**6**	**(2.4)**
alendronate sodium	3	(1.2)	0	(0.0)
alendronate sodium (+) calcium (unspecified) (+) cholecalciferol	0	(0.0)	1	(0.4)
alendronic acid	1	(0.4)	0	(0.0)
denosumab	0	(0.0)	1	(0.4)
pamidronate disodium	2	(0.8)	2	(0.8)
zoledronic acid	1	(0.4)	2	(0.8)
muscle relaxants	**7**	**(2.7)**	**10**	**(4.1)**
acetaminophen (+) methocarbamol	0	(0.0)	1	(0.4)
baclofen	0	(0.0)	1	(0.4)
carisoprodol	0	(0.0)	2	(0.8)
chlorzoxazone	2	(0.8)	1	(0.4)
cyclobenzaprine hydrochloride	2	(0.8)	0	(0.0)
eperisone hydrochloride	1	(0.4)	0	(0.0)
methocarbamol	0	(0.0)	1	(0.4)
onabotulinumtoxinA	0	(0.0)	1	(0.4)
rocuronium bromide	2	(0.8)	1	(0.4)
tizanidine hydrochloride	0	(0.0)	2	(0.8)
other drugs for disorders of musculo-skeletal system	**1**	**(0.4)**	**0**	**(0.0)**
pronase	1	(0.4)	0	(0.0)
nervous system				
analgesics	**174**	**(68.0)**	**162**	**(66.1)**
acetaminophen	67	(26.2)	72	(29.4)
acetaminophen (+) caffeine (+) codeine	1	(0.4)	0	(0.0)
acetaminophen (+) caffeine (+) codeine phosphate	1	(0.4)	0	(0.0)
acetaminophen (+) caffeine (+) codeine phosphate (+) meprobamate	2	(0.8)	0	(0.0)
acetaminophen (+) chlorpheniramine maleate (+) phenylephrine hydrochloride	0	(0.0)	1	(0.4)
acetaminophen (+) ciclonium bromide (+) codeine phosphate	0	(0.0)	1	(0.4)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
acetaminophen (+) codeine	2	(0.8)	2	(0.8)
acetaminophen (+) codeine phosphate	13	(5.1)	6	(2.4)
acetaminophen (+) codeine phosphate (+) ibuprofen	0	(0.0)	1	(0.4)
acetaminophen (+) dextromethorphan hydrobromide (+) doxylamine succinate (+) ephedrine sulfate	0	(0.0)	1	(0.4)
acetaminophen (+) diphenhydramine hydrochloride	1	(0.4)	0	(0.0)
acetaminophen (+) hydrocodone bitartrate	12	(4.7)	4	(1.6)
acetaminophen (+) oxycodone hydrochloride	6	(2.3)	2	(0.8)
acetaminophen (+) tramadol hydrochloride	5	(2.0)	11	(4.5)
adiphenine hydrochloride (+) dipyrone sodium (+) promethazine hydrochloride	1	(0.4)	1	(0.4)
anise oil (+) antimony potassium tartrate (+) benzoic acid (+) camphor (+) licorice (+) opium	2	(0.8)	0	(0.0)
anise oil (+) benzoic acid (+) camphor (+) glycerin (+) opium	0	(0.0)	1	(0.4)
ascorbic acid (+) aspirin (+) chlorpheniramine maleate (+) moroxydine hydrochloride (+) phenylephrine hydrochloride	0	(0.0)	1	(0.4)
aspirin	30	(11.7)	30	(12.2)
aspirin (+) magnesium oxide	1	(0.4)	1	(0.4)
belladonna (+) codeine	1	(0.4)	0	(0.0)
buprenorphine	5	(2.0)	4	(1.6)
cyclizine tartrate (+) morphine tartrate	0	(0.0)	1	(0.4)
dihydrocodeine	1	(0.4)	0	(0.0)
dipyrone	18	(7.0)	18	(7.3)
dipyrone (+) pitofenone hydrochloride	1	(0.4)	1	(0.4)
dipyrone magnesium	2	(0.8)	1	(0.4)
fentanyl	25	(9.8)	24	(9.8)
fentanyl citrate	5	(2.0)	10	(4.1)
hydromorphone	6	(2.3)	0	(0.0)
hydromorphone hydrochloride	2	(0.8)	6	(2.4)
meperidine hydrochloride	2	(0.8)	0	(0.0)
morphine	12	(4.7)	11	(4.5)
morphine hydrochloride	5	(2.0)	6	(2.4)
morphine sulfate	20	(7.8)	17	(6.9)
nalbuphine hydrochloride	1	(0.4)	0	(0.0)
naloxone hydrochloride (+) oxycodone hydrochloride	6	(2.3)	5	(2.0)
oxycodone	10	(3.9)	11	(4.5)
oxycodone hydrochloride	14	(5.5)	18	(7.3)
tramadol hydrochloride	38	(14.8)	30	(12.2)
anesthetics	**18**	**(7.0)**	**17**	**(6.9)**
bupivacaine hydrochloride	0	(0.0)	1	(0.4)
epinephrine (+) lidocaine hydrochloride	2	(0.8)	3	(1.2)
lidocaine	8	(3.1)	5	(2.0)
lidocaine (+) prilocaine	2	(0.8)	2	(0.8)
lidocaine (+) sodium bicarbonate	0	(0.0)	2	(0.8)
lidocaine hydrochloride	6	(2.3)	7	(2.9)
mepivacaine hydrochloride	2	(0.8)	0	(0.0)
propofol	3	(1.2)	5	(2.0)
remifentanil hydrochloride	2	(0.8)	1	(0.4)
ropivacaine	1	(0.4)	0	(0.0)
ropivacaine hydrochloride	1	(0.4)	0	(0.0)
sevoflurane	1	(0.4)	1	(0.4)
anti-Parkinson drugs	**1**	**(0.4)**	**1**	**(0.4)**
biperiden hydrochloride	1	(0.4)	0	(0.0)
rotigotine	0	(0.0)	1	(0.4)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
antiepileptics	**30**	**(11.7)**	**31**	**(12.7)**
carbamazepine	1	(0.4)	3	(1.2)
clonazepam	5	(2.0)	4	(1.6)
gabapentin	12	(4.7)	9	(3.7)
levetiracetam	2	(0.8)	1	(0.4)
phenobarbital	0	(0.0)	1	(0.4)
phenytoin	1	(0.4)	2	(0.8)
pregabalin	10	(3.9)	13	(5.3)
topiramate	1	(0.4)	0	(0.0)
valproate sodium	1	(0.4)	0	(0.0)
other nervous system drugs	**6**	**(2.3)**	**5**	**(2.0)**
atropine sulfate (+) neostigmine methylsulfate	1	(0.4)	0	(0.0)
disulfiram	0	(0.0)	1	(0.4)
methadone hydrochloride	4	(1.6)	4	(1.6)
nicotine	1	(0.4)	0	(0.0)
psychoanaleptics	**37**	**(14.5)**	**28**	**(11.4)**
amitriptyline hydrochloride	7	(2.7)	5	(2.0)
atomoxetine hydrochloride	0	(0.0)	1	(0.4)
bupropion hydrochloride	0	(0.0)	1	(0.4)
caffeine	0	(0.0)	1	(0.4)
citalopram	6	(2.3)	3	(1.2)
citalopram hydrobromide	2	(0.8)	0	(0.0)
citicoline sodium	1	(0.4)	0	(0.0)
desvenlafaxine succinate	1	(0.4)	0	(0.0)
duloxetine hydrochloride	3	(1.2)	3	(1.2)
escitalopram	1	(0.4)	1	(0.4)
escitalopram oxalate	2	(0.8)	1	(0.4)
fluoxetine	1	(0.4)	0	(0.0)
flupentixol hydrochloride (+) melitracen hydrochloride	1	(0.4)	0	(0.0)
imipramine	0	(0.0)	1	(0.4)
methylphenidate	1	(0.4)	0	(0.0)
mirtazapine	6	(2.3)	6	(2.4)
nortriptyline	2	(0.8)	0	(0.0)
nortriptyline hydrochloride	0	(0.0)	1	(0.4)
paroxetine	1	(0.4)	0	(0.0)
paroxetine hydrochloride	1	(0.4)	0	(0.0)
piracetam	0	(0.0)	1	(0.4)
sertraline hydrochloride	3	(1.2)	5	(2.0)
trazodone hydrochloride	2	(0.8)	1	(0.4)
venlafaxine hydrochloride	3	(1.2)	2	(0.8)
psycholeptics	**70**	**(27.3)**	**72**	**(29.4)**
alprazolam	8	(3.1)	12	(4.9)
amisulpride	1	(0.4)	0	(0.0)
aripiprazole	0	(0.0)	1	(0.4)
bromazepam	2	(0.8)	1	(0.4)
brotizolam	1	(0.4)	3	(1.2)
chlordiazepoxide hydrochloride	1	(0.4)	0	(0.0)
clorazepate dipotassium	1	(0.4)	0	(0.0)
clotiazepam	1	(0.4)	0	(0.0)
diazepam	5	(2.0)	3	(1.2)
estazolam	3	(1.2)	3	(1.2)
etizolam	1	(0.4)	0	(0.0)
flunitrazepam	1	(0.4)	1	(0.4)
haloperidol	3	(1.2)	0	(0.0)
hydroxyzine	1	(0.4)	0	(0.0)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
hydroxyzine hydrochloride	1	(0.4)	0	(0.0)
lorazepam	13	(5.1)	27	(11.0)
lormetazepam	0	(0.0)	2	(0.8)
melatonin	1	(0.4)	1	(0.4)
midazolam	6	(2.3)	3	(1.2)
midazolam hydrochloride	4	(1.6)	3	(1.2)
nitrazepam	0	(0.0)	1	(0.4)
olanzapine	2	(0.8)	1	(0.4)
oxazepam	3	(1.2)	1	(0.4)
prazepam	1	(0.4)	0	(0.0)
prochlorperazine	3	(1.2)	4	(1.6)
prochlorperazine maleate	3	(1.2)	4	(1.6)
prothipendyl hydrochloride	1	(0.4)	0	(0.0)
quetiapine fumarate	5	(2.0)	1	(0.4)
ramelteon	1	(0.4)	0	(0.0)
risperidone	0	(0.0)	1	(0.4)
sulpiride	0	(0.0)	2	(0.8)
suvorexant	1	(0.4)	0	(0.0)
triazolam	4	(1.6)	3	(1.2)
zolpidem	2	(0.8)	4	(1.6)
zolpidem tartrate	6	(2.3)	7	(2.9)
zopiclone	12	(4.7)	6	(2.4)
respiratory system				
antihistamines for systemic use	**21**	**(8.2)**	**147**	**(60.0)**
bisulepin hydrochloride	0	(0.0)	6	(2.4)
cetirizine hydrochloride	1	(0.4)	3	(1.2)
chloropyramine hydrochloride	2	(0.8)	7	(2.9)
chlorpheniramine	0	(0.0)	1	(0.4)
chlorpheniramine maleate	1	(0.4)	15	(6.1)
clemastine	0	(0.0)	10	(4.1)
clemastine fumarate	0	(0.0)	5	(2.0)
cyclizine	0	(0.0)	1	(0.4)
cyproheptadine hydrochloride	0	(0.0)	1	(0.4)
dexchlorpheniramine maleate	1	(0.4)	14	(5.7)
dimenhydrinate	0	(0.0)	1	(0.4)
dimethindene maleate	4	(1.6)	6	(2.4)
diphenhydramine	3	(1.2)	33	(13.5)
diphenhydramine hydrochloride	3	(1.2)	39	(15.9)
fexofenadine hydrochloride	1	(0.4)	3	(1.2)
levocetirizine	1	(0.4)	0	(0.0)
levocetirizine dihydrochloride	0	(0.0)	3	(1.2)
loratadine	3	(1.2)	4	(1.6)
meclizine	2	(0.8)	0	(0.0)
pheniramine maleate	0	(0.0)	2	(0.8)
promethazine	1	(0.4)	0	(0.0)
promethazine hydrochloride	1	(0.4)	0	(0.0)
cough and cold preparations	**27**	**(10.5)**	**23**	**(9.4)**
acetylcysteine	9	(3.5)	8	(3.3)
ambroxol	0	(0.0)	1	(0.4)
ambroxol hydrochloride	3	(1.2)	3	(1.2)
carbocysteine	2	(0.8)	1	(0.4)
cocillana (+) ethylmorphine hydrochloride (+) Seneca snakeroot	1	(0.4)	0	(0.0)
codeine	7	(2.7)	7	(2.9)
codeine phosphate	3	(1.2)	2	(0.8)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
cough, cold, and flu therapies (unspecified)	1	(0.4)	1	(0.4)
dextromethorphan	1	(0.4)	1	(0.4)
dextromethorphan hydrobromide	1	(0.4)	1	(0.4)
dextromethorphan hydrobromide (+) ephedrine hydrochloride	1	(0.4)	1	(0.4)
dextromethorphan hydrobromide (+) lysozyme chloride (+) potassium cresolsulfonate	1	(0.4)	0	(0.0)
dextromethorphan hydrobromide (+) potassium cresolsulfonate	1	(0.4)	0	(0.0)
guaifenesin	4	(1.6)	1	(0.4)
hydrocodone	1	(0.4)	1	(0.4)
drugs for obstructive airway diseases	**27**	**(10.5)**	**22**	**(9.0)**
aclidinium bromide (+) formoterol fumarate	1	(0.4)	0	(0.0)
albuterol	9	(3.5)	6	(2.4)
albuterol (+) ipratropium bromide	0	(0.0)	2	(0.8)
albuterol sulfate	4	(1.6)	4	(1.6)
albuterol sulfate (+) ipratropium bromide	1	(0.4)	1	(0.4)
budesonide	0	(0.0)	2	(0.8)
budesonide (+) formoterol fumarate	3	(1.2)	1	(0.4)
ephedrine hydrochloride	1	(0.4)	0	(0.0)
epinephrine	2	(0.8)	3	(1.2)
fenoterol hydrobromide (+) ipratropium bromide	1	(0.4)	1	(0.4)
fluticasone	1	(0.4)	0	(0.0)
fluticasone furoate	0	(0.0)	1	(0.4)
fluticasone propionate	3	(1.2)	1	(0.4)
fluticasone propionate (+) formoterol fumarate	0	(0.0)	1	(0.4)
fluticasone propionate (+) salmeterol xinafoate	4	(1.6)	3	(1.2)
indacaterol	1	(0.4)	0	(0.0)
indacaterol maleate	1	(0.4)	0	(0.0)
ipratropium bromide	2	(0.8)	3	(1.2)
montelukast sodium	1	(0.4)	0	(0.0)
theophylline	2	(0.8)	1	(0.4)
tiotropium bromide	3	(1.2)	4	(1.6)
nasal preparations	**1**	**(0.4)**	**2**	**(0.8)**
hydrocortisone (+) oxytetracycline calcium (+) polymyxin B sulfate	0	(0.0)	1	(0.4)
loratadine (+) pseudoephedrine hydrochloride	1	(0.4)	0	(0.0)
pseudoephedrine hydrochloride (+) triprolidine hydrochloride	1	(0.4)	0	(0.0)
sea water	0	(0.0)	1	(0.4)
sensory organs				
ophthalmologicals	**5**	**(2.0)**	**4**	**(1.6)**
bimatoprost	0	(0.0)	1	(0.4)
carboxymethylcellulose sodium	0	(0.0)	1	(0.4)
ectoine (+) hyaluronate sodium	0	(0.0)	1	(0.4)
latanoprost	1	(0.4)	0	(0.0)
perfluorohexyloctane	0	(0.0)	1	(0.4)
pilocarpine	2	(0.8)	0	(0.0)
pilocarpine hydrochloride	0	(0.0)	1	(0.4)
tafluprost	1	(0.4)	0	(0.0)
timolol	0	(0.0)	1	(0.4)
timolol maleate	1	(0.4)	0	(0.0)
timolol maleate (+) travoprost	1	(0.4)	0	(0.0)
systemic hormonal preparations, excl. sex hormones and insulins				

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
corticosteroids for systemic use	**17**	**(6.6)**	**150**	**(61.2)**
betamethasone sodium phosphate	1	(0.4)	4	(1.6)
dexamethasone	7	(2.7)	100	(40.8)
dexamethasone phosphate	1	(0.4)	2	(0.8)
dexamethasone sodium phosphate	0	(0.0)	32	(13.1)
dexamethasone sodium phosphate (+) sodium chloride	0	(0.0)	1	(0.4)
hydrocortisone	3	(1.2)	2	(0.8)
hydrocortisone sodium succinate	1	(0.4)	4	(1.6)
methylprednisolone	2	(0.8)	5	(2.0)
methylprednisolone sodium succinate	0	(0.0)	3	(1.2)
prednisolone	2	(0.8)	3	(1.2)
prednisolone valerate acetate	0	(0.0)	1	(0.4)
prednisone	3	(1.2)	3	(1.2)
thyroid therapy	**55**	**(21.5)**	**45**	**(18.4)**
Thyroxine	0	(0.0)	1	(0.4)
carbimazole	1	(0.4)	0	(0.0)
levothyroxine sodium	53	(20.7)	43	(17.6)
methimazole	0	(0.0)	1	(0.4)
propylthiouracil	1	(0.4)	0	(0.0)
thyroid	1	(0.4)	0	(0.0)
various				
all other therapeutic products	**22**	**(8.6)**	**12**	**(4.9)**
Cannabis sativa oil	1	(0.4)	0	(0.0)
Enterococcus faecalis	2	(0.8)	1	(0.4)
European mistletoe	1	(0.4)	0	(0.0)
Fragaria vesca (+) grape	1	(0.4)	0	(0.0)
Veratrum nigrum	1	(0.4)	0	(0.0)
[composition unspecified]	1	(0.4)	1	(0.4)
acetyl tyrosine (+) caffeine (+) citicoline (+) cyanocobalamin (+) folic acid (+) glucurolactone (+) malic acid (+) niacinamide (+) phenylalanine (+) pyridoxine hydrochloride (+) taurine	0	(0.0)	1	(0.4)
alcohol (+) alum, potassium (+) benzoin (+) camphor (+) cinnamon oil (+) eucalyptol (+) menthol (+) methyl salicylate (+) pine oil (+) potassium chlorate (+) sodium bicarbonate (+) sodium chloride (+) spearmint oil (+) thymol	0	(0.0)	1	(0.4)
ammonium glycyrrhizate (+) cysteine (+) glycine	1	(0.4)	0	(0.0)
antioxidants (+) artichoke (+) bioflavonoids (+) bitter melon (+) blueberry (+) cassia (+) coffee (+) grape seeds (+) Indian gum arabic tree (+) minerals (+) plum (+) pomegranate (+) resveratrol (+) rosemary (+) tea (+) vitamins (+) watercress	1	(0.4)	0	(0.0)
arnica	1	(0.4)	0	(0.0)
black cohosh	1	(0.4)	0	(0.0)
calcium polystyrene sulfonate	1	(0.4)	1	(0.4)
catechu (+) Chinese skullcap (+) chondroitin sulfate sodium (+) dimethyl sulfone (+) glucosamine hydrochloride (+) hyaluronic acid	1	(0.4)	0	(0.0)
choline bitartrate (+) cyanocobalamin (+) cysteine hydrochloride (+) inositol (+) lecithin (+) liver extract	0	(0.0)	1	(0.4)
chondroitin sulfate sodium	1	(0.4)	0	(0.0)
cranberry	0	(0.0)	1	(0.4)
dietary supplement (unspecified)	1	(0.4)	0	(0.0)
flumazenil	1	(0.4)	0	(0.0)
ginkgo	0	(0.0)	1	(0.4)
glucosamine	0	(0.0)	1	(0.4)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
hemp	2	(0.8)	2	(0.8)
meglumine thioctate	0	(0.0)	1	(0.4)
neurotropin	1	(0.4)	0	(0.0)
oxygen	0	(0.0)	1	(0.4)
platycodin	1	(0.4)	0	(0.0)
rasburicase	0	(0.0)	1	(0.4)
saw palmetto	1	(0.4)	0	(0.0)
sugammadex sodium	1	(0.4)	1	(0.4)
syrup of figs	1	(0.4)	0	(0.0)
tea	1	(0.4)	0	(0.0)
turmeric	4	(1.6)	0	(0.0)
water, tap	1	(0.4)	0	(0.0)
contrast media	**2**	**(0.8)**	**1**	**(0.4)**
iohexol	2	(0.8)	0	(0.0)
iopamidol	0	(0.0)	1	(0.4)
general nutrients	**23**	**(9.0)**	**23**	**(9.4)**
amino acids (unspecified) (+) carbohydrates (unspecified) (+) fat (unspecified) (+) fructooligosaccharides (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
amino acids (unspecified) (+) carbohydrates (unspecified) (+) fat (unspecified) (+) lecithin (+) medium-chain triglycerides (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	0	(0.0)	1	(0.4)
amino acids (unspecified) (+) carbohydrates (unspecified) (+) fat (unspecified) (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	0	(0.0)	1	(0.4)
beta-hydroxyisovaleric acid (+) carbohydrates (unspecified) (+) fat (unspecified) (+) fructooligosaccharides (+) levocarnitine (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	0	(0.0)	1	(0.4)
carbohydrates (unspecified) (+) fat (unspecified) (+) fiber (unspecified) (+) minerals (unspecified) (+) omega-3 marine triglycerides (+) protein (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
carbohydrates (unspecified) (+) fat (unspecified) (+) fiber (unspecified) (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	2	(0.8)	2	(0.8)
carbohydrates (unspecified) (+) fat (unspecified) (+) minerals (unspecified) (+) omega-3 marine triglycerides (+) protein (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
carbohydrates (unspecified) (+) fat (unspecified) (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	10	(3.9)	12	(4.9)
dextrose	1	(0.4)	5	(2.0)
lecithin (+) protein (unspecified)	2	(0.8)	0	(0.0)
minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	5	(2.0)	3	(1.2)
nutritional supplements	0	(0.0)	1	(0.4)
rapeseed oil (+) sunflower oil	1	(0.4)	0	(0.0)

Every subject is counted a single time for each applicable specific prior medication. A subject with multiple prior medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

Pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy

Table 5 Summary of prior line of systemic therapy, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, ITT population, PD-L1 CPS≥1 population

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	242		235		477	
Subjects with no prior systemic therapy	124	(51.2)	117	(49.8)	241	(50.5)
Primary/Locally Advanced/With Curative Intent	**113**	**(46.7)**	**116**	**(49.4)**	**229**	**(48.0)**
Cetuximab	17	(7.0)	13	(5.5)	30	(6.3)
Platinum	104	(43.0)	111	(47.2)	215	(45.1)
Recurrent/With Curative Intent	**9**	**(3.7)**	**4**	**(1.7)**	**13**	**(2.7)**
Cetuximab	0	(0.0)	0	(0.0)	0	(0.0)
Platinum	8	(3.3)	3	(1.3)	11	(2.3)

A subject can have multiple prior systemic therapies and be counted in different rows that are applicable. But every subject is counted a single time for each applicable row and column.

Table 6 Patients with specific prior medications (incidence >0% in one or more treatment groups) pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, ASaT population, PD-L1 CPS≥1 population

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	237		245	
With one or more prior medications	235	(99.2)	237	(96.7)
With no prior medication	2	(0.8)	8	(3.3)
alimentary tract and metabolism				
antidiarrheals, intestinal antiinflammatory/antiinfective agents	**6**	**(2.5)**	**4**	**(1.6)**
Clostridium butyricum	2	(0.8)	1	(0.4)
ast-120	0	(0.0)	1	(0.4)
loperamide	4	(1.7)	0	(0.0)
loperamide hydrochloride	0	(0.0)	1	(0.4)
pectin	0	(0.0)	1	(0.4)
antiemetics and antinauseants	**134**	**(56.5)**	**149**	**(60.8)**
aprepitant	47	(19.8)	36	(14.7)
fosaprepitant dimeglumine	15	(6.3)	12	(4.9)
granisetron	6	(2.5)	25	(10.2)
granisetron hydrochloride	10	(4.2)	4	(1.6)
netupitant	2	(0.8)	0	(0.0)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
netupitant (+) palonosetron hydrochloride	1	(0.4)	0	(0.0)
ondansetron	48	(20.3)	46	(18.8)
ondansetron hydrochloride	17	(7.2)	23	(9.4)
palonosetron hydrochloride	54	(22.8)	48	(19.6)
ramosetron	0	(0.0)	5	(2.0)
bile and liver therapy	**0**	**(0.0)**	**1**	**(0.4)**
ursodiol	0	(0.0)	1	(0.4)
digestives, incl. enzymes	**0**	**(0.0)**	**2**	**(0.8)**
pancreatin	0	(0.0)	2	(0.8)
drugs for acid related disorders	**96**	**(40.5)**	**133**	**(54.3)**
alginic acid (+) aluminum hydroxide (+) magnesium carbonate	0	(0.0)	1	(0.4)
aluminum hydroxide (+) calcium carbonate (+) magnesium carbonate (+) oxethazaine	1	(0.4)	2	(0.8)
aluminum hydroxide (+) magnesium carbonate	1	(0.4)	0	(0.0)
bismuth subcarbonate (+) calcium carbonate (+) magnesium carbonate (+) sodium bicarbonate	1	(0.4)	0	(0.0)
calcium carbonate	2	(0.8)	3	(1.2)
cimetidine	0	(0.0)	2	(0.8)
ecabet sodium	1	(0.4)	0	(0.0)
esomeprazole	7	(3.0)	5	(2.0)
esomeprazole magnesium	7	(3.0)	6	(2.4)
famotidine	7	(3.0)	13	(5.3)
lansoprazole	5	(2.1)	8	(3.3)
magaldrate	1	(0.4)	1	(0.4)
magnesium hydroxide	4	(1.7)	2	(0.8)
magnesium oxide	8	(3.4)	11	(4.5)
omeprazole	33	(13.9)	29	(11.8)
omeprazole magnesium	1	(0.4)	1	(0.4)
omeprazole sodium	0	(0.0)	2	(0.8)
pantoprazole	8	(3.4)	8	(3.3)
pantoprazole sodium	4	(1.7)	5	(2.0)
rabeprazole sodium	3	(1.3)	0	(0.0)
ranitidine	12	(5.1)	25	(10.2)
ranitidine hydrochloride	9	(3.8)	31	(12.7)
rebamipide	0	(0.0)	3	(1.2)
sodium gualenate	2	(0.8)	6	(2.4)
teprenone	1	(0.4)	1	(0.4)
drugs for constipation	**44**	**(18.6)**	**43**	**(17.6)**
bisacodyl	3	(1.3)	3	(1.2)
citric acid (+) magnesium oxide (+) sodium picosulfate	0	(0.0)	1	(0.4)
coriander (+) Indian laburnum (+) licorice (+) senna (+) tamarind	0	(0.0)	1	(0.4)
docusate calcium	0	(0.0)	1	(0.4)
docusate sodium	8	(3.4)	5	(2.0)
docusate sodium (+) senna	2	(0.8)	0	(0.0)
electrolytes (unspecified) (+) polyethylene glycol 3350	1	(0.4)	0	(0.0)
lactulose	11	(4.6)	10	(4.1)
lubiprostone	1	(0.4)	0	(0.0)
polyethylene glycol	3	(1.3)	2	(0.8)
polyethylene glycol 3350	2	(0.8)	6	(2.4)
polyethylene glycol 3350 (+) potassium chloride (+) sodium bicarbonate (+) sodium chloride	6	(2.5)	10	(4.1)
polyethylene glycol 3350 (+) potassium chloride (+) sodium bicarbonate (+) sodium chloride (+) sodium sulfate	0	(0.0)	1	(0.4)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
sennosides	17	(7.2)	15	(6.1)
sodium bicarbonate (+) sodium phosphate, monobasic	1	(0.4)	0	(0.0)
sodium phosphate, dibasic (+) sodium phosphate, monobasic	1	(0.4)	1	(0.4)
sodium picosulfate	5	(2.1)	2	(0.8)
drugs for functional gastrointestinal disorders	**38**	**(16.0)**	**33**	**(13.5)**
alizapride	1	(0.4)	0	(0.0)
bromopride	1	(0.4)	0	(0.0)
butylscopolamine bromide	4	(1.7)	0	(0.0)
dimethicone	0	(0.0)	1	(0.4)
domperidone	6	(2.5)	4	(1.6)
metoclopramide	17	(7.2)	17	(6.9)
metoclopramide hydrochloride	11	(4.6)	12	(4.9)
mosapride citrate	1	(0.4)	0	(0.0)
trimebutine maleate	1	(0.4)	0	(0.0)
drugs used in diabetes	**19**	**(8.0)**	**15**	**(6.1)**
acarbose	1	(0.4)	0	(0.0)
carbutamide	0	(0.0)	1	(0.4)
gliclazide	0	(0.0)	1	(0.4)
glimepiride	3	(1.3)	1	(0.4)
glipizide	1	(0.4)	1	(0.4)
glyburide	2	(0.8)	0	(0.0)
glyburide (+) metformin hydrochloride	0	(0.0)	1	(0.4)
insulin	0	(0.0)	1	(0.4)
insulin aspart	2	(0.8)	2	(0.8)
insulin degludec	0	(0.0)	1	(0.4)
insulin glargine	1	(0.4)	2	(0.8)
insulin human	1	(0.4)	1	(0.4)
insulin human (+) insulin human, isophane	0	(0.0)	1	(0.4)
insulin lispro	1	(0.4)	0	(0.0)
insulin, isophane	1	(0.4)	0	(0.0)
metformin	10	(4.2)	7	(2.9)
metformin hydrochloride	4	(1.7)	3	(1.2)
metformin hydrochloride (+) saxagliptin hydrochloride	1	(0.4)	0	(0.0)
metformin hydrochloride (+) vildagliptin	1	(0.4)	0	(0.0)
miglitol	1	(0.4)	0	(0.0)
sitagliptin	2	(0.8)	0	(0.0)
sitagliptin phosphate	0	(0.0)	2	(0.8)
vildagliptin	1	(0.4)	0	(0.0)
mineral supplements	**29**	**(12.2)**	**36**	**(14.7)**
calcium (unspecified)	1	(0.4)	3	(1.2)
calcium (unspecified) (+) vitamin D (unspecified)	1	(0.4)	0	(0.0)
calcium carbonate (+) calcium glubionate	0	(0.0)	1	(0.4)
calcium carbonate (+) cholecalciferol	2	(0.8)	1	(0.4)
calcium chloride	1	(0.4)	0	(0.0)
calcium gluconate	0	(0.0)	2	(0.8)
calcium lactate	1	(0.4)	0	(0.0)
magnesium (unspecified)	3	(1.3)	4	(1.6)
magnesium aspartate	0	(0.0)	1	(0.4)
magnesium citrate (+) magnesium glutamate	0	(0.0)	2	(0.8)
magnesium lactate	1	(0.4)	0	(0.0)
magnesium lactate (+) pyridoxine hydrochloride	1	(0.4)	0	(0.0)
magnesium sulfate	8	(3.4)	13	(5.3)
magnesium sulfate (+) procaine hydrochloride	1	(0.4)	0	(0.0)
minerals (unspecified)	0	(0.0)	1	(0.4)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
potassium (unspecified)	4	(1.7)	3	(1.2)
potassium chloride	10	(4.2)	16	(6.5)
selenium (unspecified)	1	(0.4)	0	(0.0)
selenium (unspecified) (+) zinc (unspecified)	1	(0.4)	0	(0.0)
zinc sulfate	0	(0.0)	1	(0.4)
other alimentary tract and metabolism products	**2**	**(0.8)**	**3**	**(1.2)**
arginine (+) beta-hydroxyisovaleric acid (+) glutamine	1	(0.4)	0	(0.0)
gastrointestinal preparations (unspecified)	1	(0.4)	1	(0.4)
glutamine (+) maltodextrin	0	(0.0)	1	(0.4)
hemp seed oil	0	(0.0)	1	(0.4)
stomatological preparations	**10**	**(4.2)**	**10**	**(4.1)**
alcohol (+) benzocaine (+) hyetellose (+) peppermint oil (+) sorbitol	1	(0.4)	0	(0.0)
aloe vera (+) calcium lactate (+) glucose oxidase (as drug) (+) hyetellose (+) lactoferrin (as drug) (+) lysozyme chloride (+) peroxidase (as drug) (+) propylene glycol (+) zinc gluconate	1	(0.4)	0	(0.0)
aluminum hydroxide (+) diphenhydramine hydrochloride (+) lidocaine (+) magnesium hydroxide	3	(1.3)	0	(0.0)
aluminum hydroxide (+) diphenhydramine hydrochloride (+) lidocaine hydrochloride (+) magnesium hydroxide (+) simethicone	1	(0.4)	1	(0.4)
aluminum hydroxide (+) lidocaine (+) magnesium hydroxide (+) nystatin	0	(0.0)	1	(0.4)
benzydamine hydrochloride (+) chlorhexidine gluconate	0	(0.0)	1	(0.4)
carbomer (+) glycerin (+) hyetellose (+) sorbitol (+) xylitol	0	(0.0)	1	(0.4)
chlorhexidine gluconate (+) polyethylene glycol 1500 (+) polyethylene glycol 300	1	(0.4)	3	(1.2)
dexamethasone (+) lidocaine (+) nystatin	0	(0.0)	1	(0.4)
diphenhydramine hydrochloride (+) lidocaine (+) sodium bicarbonate	1	(0.4)	0	(0.0)
diphenhydramine hydrochloride (+) lidocaine hydrochloride (+) magnesium hydroxide	1	(0.4)	0	(0.0)
glucose oxidase (as drug) (+) lactoferrin (as drug) (+) lysozyme chloride (+) peroxidase (as drug)	1	(0.4)	2	(0.8)
lidocaine (+) nystatin	0	(0.0)	1	(0.4)
malic acid (+) sodium fluoride (+) xylitol	1	(0.4)	0	(0.0)
sodium fluoride	1	(0.4)	2	(0.8)
vitamins	**28**	**(11.8)**	**19**	**(7.8)**
acetylcysteine (+) bilberry (+) bioflavonoids (+) broccoli (+) bromelains (+) choline (+) cinnamon (+) inositol (+) lycopene (+) minerals (+) olive (+) pomegranate (+) tea (+) thioctic acid (+) turmeric (+) ubidecarenone (+) vitamins (+) xanthophyll	1	(0.4)	0	(0.0)
alfacalcidol	3	(1.3)	0	(0.0)
ascorbic acid	6	(2.5)	1	(0.4)
ascorbic acid (+) calcium (unspecified) (+) chromium (unspecified) (+) folic acid (+) magnesium (unspecified) (+) manganese (unspecified) (+) potassium (unspecified) (+) thioctic acid (+) vitamin B complex (+) zinc (unspecified)	1	(0.4)	0	(0.0)
ascorbic acid (+) folic acid (+) vitamin B complex (+) zinc (unspecified)	1	(0.4)	0	(0.0)
ascorbic acid (+) zinc citrate	1	(0.4)	0	(0.0)
beet (+) bioflavonoids (+) broccoli (+) ginger (+) grape (+) lycopene (+) minerals (unspecified) (+) omega-3 marine triglycerides (+) pomegranate (+) tea (+)	1	(0.4)	0	(0.0)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
turmeric (+) vitamins (unspecified) (+) xanthophyll				
biotin	0	(0.0)	1	(0.4)
calcitriol	1	(0.4)	1	(0.4)
calcium ascorbate	1	(0.4)	0	(0.0)
cholecalciferol	3	(1.3)	4	(1.6)
cyanocobalamin (+) pyridoxine (+) thiamine	2	(0.8)	1	(0.4)
dexpanthenol (+) vitamin A	0	(0.0)	1	(0.4)
ergocalciferol	1	(0.4)	2	(0.8)
lycopene (+) minerals (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
lycopene (+) minerals (unspecified) (+) vitamins (unspecified) (+) xanthophyll	1	(0.4)	0	(0.0)
minerals (unspecified) (+) vitamins (unspecified)	1	(0.4)	3	(1.2)
pantethine	1	(0.4)	0	(0.0)
pyridoxine	1	(0.4)	0	(0.0)
sodium ascorbate	1	(0.4)	0	(0.0)
sodium ascorbate (+) vitamin A (+) vitamin E (+) zinc sulfate	1	(0.4)	0	(0.0)
thiamine	0	(0.0)	1	(0.4)
vitamin A	0	(0.0)	1	(0.4)
vitamin B (unspecified)	2	(0.8)	0	(0.0)
vitamin B complex	5	(2.1)	4	(1.6)
vitamin D (unspecified)	2	(0.8)	6	(2.4)
vitamin E	0	(0.0)	1	(0.4)
vitamins (unspecified)	9	(3.8)	2	(0.8)
antiinfectives for systemic use				
antibacterials for systemic use	**44**	**(18.6)**	**54**	**(22.0)**
amoxicillin	6	(2.5)	6	(2.4)
amoxicillin (+) clavulanate potassium	7	(3.0)	7	(2.9)
ampicillin	0	(0.0)	1	(0.4)
ampicillin sodium (+) sulbactam sodium	4	(1.7)	1	(0.4)
antimicrobial (unspecified)	0	(0.0)	1	(0.4)
azithromycin	0	(0.0)	1	(0.4)
cefaclor	1	(0.4)	1	(0.4)
cefadroxil	0	(0.0)	1	(0.4)
cefazolin	8	(3.4)	5	(2.0)
cefazolin sodium	4	(1.7)	4	(1.6)
cefazolin sodium (+) dextrose	0	(0.0)	1	(0.4)
cefcapene pivoxil hydrochloride	2	(0.8)	1	(0.4)
cefditoren pivoxil	1	(0.4)	1	(0.4)
cefonicid sodium	0	(0.0)	1	(0.4)
cefotiam hexetil hydrochloride	1	(0.4)	0	(0.0)
cefoxitin	0	(0.0)	1	(0.4)
ceftazidime	1	(0.4)	0	(0.0)
ceftriaxone	1	(0.4)	1	(0.4)
ceftriaxone sodium	1	(0.4)	0	(0.0)
cefuroxime	2	(0.8)	2	(0.8)
cephalexin	2	(0.8)	1	(0.4)
cephalothin sodium	0	(0.0)	1	(0.4)
cephradine	0	(0.0)	1	(0.4)
chloramphenicol	1	(0.4)	0	(0.0)
ciprofloxacin	1	(0.4)	5	(2.0)
clarithromycin	0	(0.0)	1	(0.4)
clavulanate potassium	0	(0.0)	1	(0.4)
clindamycin	4	(1.7)	5	(2.0)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
clindamycin hydrochloride	0	(0.0)	2	(0.8)
clindamycin phosphate	1	(0.4)	0	(0.0)
dicloxacillin	0	(0.0)	1	(0.4)
doxycycline	1	(0.4)	1	(0.4)
doxycycline hyclate	1	(0.4)	2	(0.8)
erythromycin	0	(0.0)	1	(0.4)
flomoxef sodium	1	(0.4)	0	(0.0)
floxacillin	0	(0.0)	1	(0.4)
gentamicin sulfate	3	(1.3)	1	(0.4)
levofloxacin	4	(1.7)	5	(2.0)
metronidazole	1	(0.4)	5	(2.0)
minocycline	0	(0.0)	1	(0.4)
minocycline hydrochloride	0	(0.0)	2	(0.8)
neomycin	1	(0.4)	0	(0.0)
piperacillin sodium (+) tazobactam sodium	0	(0.0)	6	(2.4)
sulbactam	0	(0.0)	1	(0.4)
sulfamethoxazole (+) trimethoprim	1	(0.4)	3	(1.2)
tetracycline	0	(0.0)	1	(0.4)
tetracycline hydrochloride	1	(0.4)	0	(0.0)
antimycobacterials	**0**	**(0.0)**	**1**	**(0.4)**
isoniazid	0	(0.0)	1	(0.4)
antimycotics for systemic use	**4**	**(1.7)**	**4**	**(1.6)**
amphotericin B	0	(0.0)	1	(0.4)
fluconazole	4	(1.7)	3	(1.2)
antivirals for systemic use	**1**	**(0.4)**	**0**	**(0.0)**
entecavir	1	(0.4)	0	(0.0)
antineoplastic and immunomodulating agents				
antineoplastic agents	**4**	**(1.7)**	**0**	**(0.0)**
cisplatin	3	(1.3)	0	(0.0)
methotrexate	1	(0.4)	0	(0.0)
endocrine therapy	**2**	**(0.8)**	**1**	**(0.4)**
megestrol acetate	2	(0.8)	1	(0.4)
blood and blood forming organs				
antianemic preparations	**15**	**(6.3)**	**10**	**(4.1)**
DL-serine (+) ferrous sulfate (+) folic acid	1	(0.4)	0	(0.0)
cyanocobalamin	2	(0.8)	1	(0.4)
ferrous glycine sulfate	1	(0.4)	1	(0.4)
ferrous sulfate	5	(2.1)	1	(0.4)
ferrous sulfate (+) magnesium sulfate (+) manganese sulfate (+) potassium sulfate (+) zinc sulfate	1	(0.4)	0	(0.0)
folic acid	3	(1.3)	5	(2.0)
folic acid (+) iron (unspecified)	0	(0.0)	1	(0.4)
hydroxocobalamin	1	(0.4)	0	(0.0)
iron polymaltose	2	(0.8)	0	(0.0)
iron sucrose	0	(0.0)	1	(0.4)
mecobalamin	1	(0.4)	0	(0.0)
antihemorrhagics	**7**	**(3.0)**	**6**	**(2.4)**
phytonadione	0	(0.0)	2	(0.8)
tranexamic acid	7	(3.0)	4	(1.6)
antithrombotic agents	**24**	**(10.1)**	**28**	**(11.4)**
acenocoumarol	0	(0.0)	1	(0.4)
alteplase	2	(0.8)	0	(0.0)
apixaban	2	(0.8)	2	(0.8)
bemiparin sodium	0	(0.0)	1	(0.4)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
cilostazol	0	(0.0)	1	(0.4)
clopidogrel	3	(1.3)	2	(0.8)
clopidogrel besylate	1	(0.4)	0	(0.0)
clopidogrel bisulfate	1	(0.4)	3	(1.2)
dabigatran etexilate mesylate	1	(0.4)	1	(0.4)
dalteparin sodium	2	(0.8)	0	(0.0)
enoxaparin sodium	4	(1.7)	11	(4.5)
heparin	3	(1.3)	4	(1.6)
heparin low molecular weight	0	(0.0)	1	(0.4)
heparin sodium	0	(0.0)	2	(0.8)
prasugrel hydrochloride	1	(0.4)	0	(0.0)
rivaroxaban	3	(1.3)	2	(0.8)
ticagrelor	1	(0.4)	0	(0.0)
warfarin	1	(0.4)	2	(0.8)
warfarin sodium	1	(0.4)	0	(0.0)
blood substitutes and perfusion solutions	**40**	**(16.9)**	**54**	**(22.0)**
amino acids (unspecified) (+) carbohydrates (unspecified) (+) electrolytes (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
amino acids (unspecified) (+) dextrose (+) electrolytes (unspecified)	0	(0.0)	1	(0.4)
amino acids (unspecified) (+) dextrose (+) electrolytes (unspecified) (+) lipids (unspecified)	0	(0.0)	1	(0.4)
amino acids (unspecified) (+) dextrose (+) electrolytes (unspecified) (+) thiamine hydrochloride	1	(0.4)	1	(0.4)
blood cells, red	5	(2.1)	3	(1.2)
blood, plasma	0	(0.0)	1	(0.4)
calcium chloride (+) magnesium chloride (+) potassium chloride (+) sodium acetate (+) sodium chloride	0	(0.0)	1	(0.4)
calcium chloride (+) potassium chloride (+) sodium chloride (+) sodium lactate	1	(0.4)	0	(0.0)
calcium gluconate (+) dextrose (+) magnesium chloride (+) potassium chloride (+) sodium acetate (+) sodium chloride (+) sodium citrate	1	(0.4)	0	(0.0)
cupric chloride (+) manganese chloride (+) potassium iodide (+) sodium fluoride (+) sodium selenate (+) zinc chloride	0	(0.0)	1	(0.4)
dextrose (+) electrolytes (unspecified)	1	(0.4)	1	(0.4)
dextrose (+) electrolytes (unspecified) (+) sodium lactate	1	(0.4)	0	(0.0)
dextrose (+) mannitol (+) potassium chloride	1	(0.4)	3	(1.2)
dextrose (+) potassium chloride (+) sodium chloride	0	(0.0)	1	(0.4)
dextrose (+) potassium chloride (+) sodium chloride (+) sodium lactate	1	(0.4)	0	(0.0)
dextrose (+) sodium chloride	1	(0.4)	2	(0.8)
dextrose (+) sodium chloride (+) sodium lactate	1	(0.4)	0	(0.0)
electrolytes (unspecified)	3	(1.3)	4	(1.6)
electrolytes (unspecified) (+) sodium acetate	0	(0.0)	1	(0.4)
electrolytes (unspecified) (+) sodium lactate	4	(1.7)	4	(1.6)
mannitol	7	(3.0)	10	(4.1)
mannitol (+) potassium chloride (+) sodium chloride	1	(0.4)	3	(1.2)
medium-chain triglycerides (+) olive oil (+) omega-3 marine triglycerides (+) soybean oil	0	(0.0)	1	(0.4)
potassium chloride (+) sodium chloride	2	(0.8)	2	(0.8)
potassium phosphate, dibasic	0	(0.0)	1	(0.4)
sodium bicarbonate	1	(0.4)	0	(0.0)
sodium chloride	26	(11.0)	42	(17.1)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
sodium phosphate, dibasic	1	(0.4)	0	(0.0)
cardiovascular system				
agents acting on the renin-angiotensin system	**44**	**(18.6)**	**41**	**(16.7)**
amlodipine besylate (+) benazepril hydrochloride	1	(0.4)	0	(0.0)
amlodipine besylate (+) hydrochlorothiazide (+) valsartan	0	(0.0)	1	(0.4)
amlodipine besylate (+) olmesartan medoxomil	0	(0.0)	1	(0.4)
amlodipine besylate (+) valsartan	2	(0.8)	2	(0.8)
candesartan	3	(1.3)	0	(0.0)
candesartan cilexetil (+) hydrochlorothiazide	0	(0.0)	1	(0.4)
captopril	1	(0.4)	1	(0.4)
enalapril	3	(1.3)	4	(1.6)
enalapril maleate	2	(0.8)	0	(0.0)
enalapril maleate (+) hydrochlorothiazide	1	(0.4)	0	(0.0)
hydrochlorothiazide (+) lisinopril	0	(0.0)	1	(0.4)
hydrochlorothiazide (+) losartan potassium	3	(1.3)	3	(1.2)
hydrochlorothiazide (+) olmesartan medoxomil	0	(0.0)	1	(0.4)
indapamide (+) perindopril arginine	1	(0.4)	0	(0.0)
irbesartan	1	(0.4)	2	(0.8)
lisinopril	4	(1.7)	3	(1.2)
losartan	4	(1.7)	8	(3.3)
losartan potassium	4	(1.7)	2	(0.8)
olmesartan medoxomil	1	(0.4)	2	(0.8)
perindopril	3	(1.3)	1	(0.4)
perindopril arginine	1	(0.4)	1	(0.4)
perindopril erbumine	1	(0.4)	0	(0.0)
ramipril	5	(2.1)	4	(1.6)
telmisartan	2	(0.8)	3	(1.2)
valsartan	3	(1.3)	2	(0.8)
antihypertensives	**3**	**(1.3)**	**2**	**(0.8)**
clonidine	0	(0.0)	1	(0.4)
doxazosin	2	(0.8)	0	(0.0)
methyldopa	0	(0.0)	1	(0.4)
naftopidil	1	(0.4)	0	(0.0)
beta blocking agents	**29**	**(12.2)**	**24**	**(9.8)**
atenolol	6	(2.5)	5	(2.0)
bisoprolol	2	(0.8)	1	(0.4)
bisoprolol fumarate	3	(1.3)	5	(2.0)
bisoprolol fumarate (+) hydrochlorothiazide	0	(0.0)	1	(0.4)
carvedilol	5	(2.1)	3	(1.2)
metoprolol	6	(2.5)	2	(0.8)
metoprolol succinate	4	(1.7)	2	(0.8)
metoprolol tartrate	2	(0.8)	4	(1.6)
nebivolol hydrochloride	0	(0.0)	1	(0.4)
propranolol	1	(0.4)	0	(0.0)
calcium channel blockers	**21**	**(8.9)**	**17**	**(6.9)**
amlodipine	12	(5.1)	10	(4.1)
amlodipine besylate	4	(1.7)	3	(1.2)
azelnidipine	0	(0.0)	1	(0.4)
benidipine hydrochloride	1	(0.4)	1	(0.4)
diltiazem hydrochloride	3	(1.3)	0	(0.0)
efonidipine hydrochloride	1	(0.4)	0	(0.0)
lercanidipine hydrochloride	1	(0.4)	2	(0.8)
verapamil	0	(0.0)	1	(0.4)
cardiac therapy	**4**	**(1.7)**	**3**	**(1.2)**

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
digoxin	1	(0.4)	0	(0.0)
isosorbide mononitrate	1	(0.4)	0	(0.0)
nicorandil	2	(0.8)	1	(0.4)
nitroglycerin	1	(0.4)	1	(0.4)
propafenone hydrochloride	0	(0.0)	1	(0.4)
diuretics	**16**	**(6.8)**	**19**	**(7.8)**
chlorthalidone	1	(0.4)	1	(0.4)
eplerenone	0	(0.0)	1	(0.4)
furosemide	8	(3.4)	11	(4.5)
furosemide sodium	0	(0.0)	1	(0.4)
hydrochlorothiazide	6	(2.5)	3	(1.2)
indapamide	0	(0.0)	2	(0.8)
spironolactone	1	(0.4)	1	(0.4)
lipid modifying agents	**48**	**(20.3)**	**38**	**(15.5)**
atorvastatin	9	(3.8)	4	(1.6)
atorvastatin calcium	8	(3.4)	5	(2.0)
bezafibrate	0	(0.0)	1	(0.4)
ezetimibe	1	(0.4)	1	(0.4)
ezetimibe (+) simvastatin	0	(0.0)	2	(0.8)
fenofibrate	1	(0.4)	0	(0.0)
icosapent ethyl	1	(0.4)	1	(0.4)
inositol niacinate	1	(0.4)	0	(0.0)
lovastatin	1	(0.4)	1	(0.4)
omega-3 marine triglycerides	6	(2.5)	1	(0.4)
pravastatin	0	(0.0)	1	(0.4)
pravastatin sodium	0	(0.0)	1	(0.4)
rosuvastatin	3	(1.3)	2	(0.8)
rosuvastatin calcium	7	(3.0)	3	(1.2)
simvastatin	11	(4.6)	17	(6.9)
vitamin E nicotinate	1	(0.4)	0	(0.0)
vasoprotectives	**3**	**(1.3)**	**3**	**(1.2)**
diosmin (+) hesperidin	1	(0.4)	0	(0.0)
escin	1	(0.4)	1	(0.4)
heparinoid	1	(0.4)	2	(0.8)
dermatologicals				
antibiotics and chemotherapeutics for dermatological use	**4**	**(1.7)**	**4**	**(1.6)**
bacitracin (+) neomycin sulfate (+) polymyxin B sulfate	2	(0.8)	3	(1.2)
mupirocin	2	(0.8)	1	(0.4)
antifungals for dermatological use	**7**	**(3.0)**	**3**	**(1.2)**
clotrimazole	1	(0.4)	0	(0.0)
ketoconazole	0	(0.0)	1	(0.4)
nystatin	6	(2.5)	2	(0.8)
antipruritics, incl. antihistamines, anesthetics, etc.	**0**	**(0.0)**	**2**	**(0.8)**
diphenhydramine hydrochloride (+) enoxolone (+) vitamin A palmitate	0	(0.0)	1	(0.4)
diphenhydramine hydrochloride (+) lidocaine hydrochloride	0	(0.0)	1	(0.4)
antiseptics and disinfectants	**9**	**(3.8)**	**6**	**(2.4)**
3-methyl-4-isopropylphenol (+) phenol (+) salicylic acid (+) zinc oxide	1	(0.4)	0	(0.0)
chlorhexidine gluconate	5	(2.1)	3	(1.2)
guaiazulene	2	(0.8)	1	(0.4)
iodine	1	(0.4)	0	(0.0)
polihexanide (+) undecylenamidopropyl betaine	1	(0.4)	0	(0.0)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
povidone-iodine	0	(0.0)	2	(0.8)
corticosteroids, dermatological preparations	**3**	**(1.3)**	**8**	**(3.3)**
Enterococcus faecalis (+) Escherichia coli (+) hydrocortisone (+) Pseudomonas aeruginosa (+) Staphylococcus aureus	1	(0.4)	0	(0.0)
betamethasone dipropionate (+) calcipotriene	0	(0.0)	2	(0.8)
difluprednate	0	(0.0)	1	(0.4)
diphenhydramine hydrochloride (+) hydrocortisone acetate (+) neomycin sulfate	0	(0.0)	1	(0.4)
hydrocortisone acetate	0	(0.0)	1	(0.4)
hydrocortisone butyrate	1	(0.4)	1	(0.4)
mometasone furoate	1	(0.4)	2	(0.8)
emollients and protectives	**2**	**(0.8)**	**0**	**(0.0)**
aloe vera	1	(0.4)	0	(0.0)
mineral oil (+) polyethylene	1	(0.4)	0	(0.0)
other dermatological preparations	**1**	**(0.4)**	**2**	**(0.8)**
dermatologic (unspecified)	1	(0.4)	2	(0.8)
genitourinary system and sex hormones				
sex hormones and modulators of the genital system	**2**	**(0.8)**	**0**	**(0.0)**
estradiol	1	(0.4)	0	(0.0)
gonadotropin, chorionic	1	(0.4)	0	(0.0)
menotropins	1	(0.4)	0	(0.0)
urologicals	**5**	**(2.1)**	**12**	**(4.9)**
alfuzosin hydrochloride	0	(0.0)	2	(0.8)
dutasteride	0	(0.0)	1	(0.4)
finasteride	1	(0.4)	3	(1.2)
sildenafil citrate	0	(0.0)	1	(0.4)
tamsulosin hydrochloride	4	(1.7)	6	(2.4)
tolterodine tartrate	0	(0.0)	1	(0.4)
musculoskeletal system				
antigout preparations	**13**	**(5.5)**	**6**	**(2.4)**
allopurinol	11	(4.6)	2	(0.8)
benzbromarone	0	(0.0)	1	(0.4)
colchicine	2	(0.8)	2	(0.8)
febuxostat	1	(0.4)	1	(0.4)
antiinflammatory and antirheumatic products	**51**	**(21.5)**	**66**	**(26.9)**
aceclofenac	1	(0.4)	0	(0.0)
acemetacin	1	(0.4)	4	(1.6)
celecoxib	3	(1.3)	3	(1.2)
dexketoprofen tromethamine	3	(1.3)	6	(2.4)
diclofenac	1	(0.4)	3	(1.2)
diclofenac diethylamine	1	(0.4)	0	(0.0)
diclofenac epolamine	0	(0.0)	1	(0.4)
diclofenac potassium	3	(1.3)	2	(0.8)
diclofenac sodium	0	(0.0)	4	(1.6)
diclofenac sodium (+) misoprostol	1	(0.4)	0	(0.0)
etodolac	1	(0.4)	0	(0.0)
etoricoxib	0	(0.0)	1	(0.4)
ibuprofen	18	(7.6)	18	(7.3)
ibuprofen (+) pseudoephedrine hydrochloride	1	(0.4)	0	(0.0)
indomethacin	3	(1.3)	2	(0.8)
ketoprofen	2	(0.8)	3	(1.2)
ketoprofen lysine	1	(0.4)	0	(0.0)
ketorolac tromethamine	6	(2.5)	3	(1.2)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
loxoprofen	0	(0.0)	1	(0.4)
loxoprofen sodium	3	(1.3)	4	(1.6)
mefenamic acid	0	(0.0)	2	(0.8)
meloxicam	1	(0.4)	0	(0.0)
mucopolysaccharide polysulfate	0	(0.0)	7	(2.9)
naproxen	4	(1.7)	4	(1.6)
naproxen sodium	2	(0.8)	2	(0.8)
nimesulide	1	(0.4)	2	(0.8)
parecoxib	0	(0.0)	1	(0.4)
drugs for treatment of bone diseases	**5**	**(2.1)**	**6**	**(2.4)**
alendronate sodium (+) calcium (unspecified) (+) cholecalciferol	0	(0.0)	1	(0.4)
denosumab	1	(0.4)	1	(0.4)
pamidronate disodium	0	(0.0)	2	(0.8)
zoledronic acid	4	(1.7)	2	(0.8)
muscle relaxants	**4**	**(1.7)**	**10**	**(4.1)**
acetaminophen (+) caffeine (+) carisoprodol (+) diclofenac sodium	1	(0.4)	0	(0.0)
acetaminophen (+) methocarbamol	0	(0.0)	1	(0.4)
baclofen	0	(0.0)	1	(0.4)
caffeine (+) dipyrone (+) orphenadrine citrate	1	(0.4)	0	(0.0)
carisoprodol	0	(0.0)	2	(0.8)
chlorzoxazone	1	(0.4)	1	(0.4)
cyclobenzaprine hydrochloride	1	(0.4)	0	(0.0)
methocarbamol	0	(0.0)	1	(0.4)
onabotulinumtoxinA	0	(0.0)	1	(0.4)
rocuronium bromide	0	(0.0)	1	(0.4)
tizanidine hydrochloride	0	(0.0)	2	(0.8)
nervous system				
analgesics	**159**	**(67.1)**	**162**	**(66.1)**
acetaminophen	62	(26.2)	72	(29.4)
acetaminophen (+) caffeine	1	(0.4)	0	(0.0)
acetaminophen (+) caffeine (+) codeine phosphate (+) doxylamine succinate	1	(0.4)	0	(0.0)
acetaminophen (+) caffeine (+) codeine phosphate (+) meprobamate	1	(0.4)	0	(0.0)
acetaminophen (+) chlorpheniramine maleate (+) phenylephrine hydrochloride	0	(0.0)	1	(0.4)
acetaminophen (+) ciclonium bromide (+) codeine phosphate	0	(0.0)	1	(0.4)
acetaminophen (+) codeine	1	(0.4)	2	(0.8)
acetaminophen (+) codeine phosphate	15	(6.3)	6	(2.4)
acetaminophen (+) codeine phosphate (+) ibuprofen	0	(0.0)	1	(0.4)
acetaminophen (+) dextromethorphan hydrobromide (+) doxylamine succinate (+) ephedrine sulfate	0	(0.0)	1	(0.4)
acetaminophen (+) hydrocodone bitartrate	3	(1.3)	4	(1.6)
acetaminophen (+) oxycodone hydrochloride	9	(3.8)	2	(0.8)
acetaminophen (+) tramadol hydrochloride	10	(4.2)	11	(4.5)
adiphenine hydrochloride (+) dipyrone sodium (+) promethazine hydrochloride	0	(0.0)	1	(0.4)
anise oil (+) benzoic acid (+) camphor (+) glycerin (+) opium	0	(0.0)	1	(0.4)
ascorbic acid (+) aspirin (+) chlorpheniramine maleate (+) moroxydine hydrochloride (+) phenylephrine hydrochloride	0	(0.0)	1	(0.4)
aspirin	20	(8.4)	30	(12.2)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
aspirin (+) caffeine	1	(0.4)	0	(0.0)
aspirin (+) magnesium oxide	3	(1.3)	1	(0.4)
buprenorphine	3	(1.3)	4	(1.6)
codeine phosphate (+) naproxen sodium	1	(0.4)	0	(0.0)
cyclizine tartrate (+) morphine tartrate	0	(0.0)	1	(0.4)
dipyrone	21	(8.9)	18	(7.3)
dipyrone (+) pitofenone hydrochloride	0	(0.0)	1	(0.4)
dipyrone magnesium	0	(0.0)	1	(0.4)
fentanyl	33	(13.9)	24	(9.8)
fentanyl citrate	8	(3.4)	10	(4.1)
hydromorphone	5	(2.1)	0	(0.0)
hydromorphone hydrochloride	4	(1.7)	6	(2.4)
meperidine hydrochloride	1	(0.4)	0	(0.0)
morphine	11	(4.6)	11	(4.5)
morphine hydrochloride	9	(3.8)	6	(2.4)
morphine sulfate	28	(11.8)	17	(6.9)
naloxone hydrochloride (+) oxycodone hydrochloride	4	(1.7)	5	(2.0)
oxycodone	8	(3.4)	11	(4.5)
oxycodone hydrochloride	19	(8.0)	18	(7.3)
pentazocine	3	(1.3)	0	(0.0)
tramadol hydrochloride	27	(11.4)	30	(12.2)
anesthetics	**20**	**(8.4)**	**17**	**(6.9)**
bupivacaine hydrochloride	0	(0.0)	1	(0.4)
cocaine	1	(0.4)	0	(0.0)
epinephrine (+) lidocaine hydrochloride	0	(0.0)	3	(1.2)
lidocaine	7	(3.0)	5	(2.0)
lidocaine (+) prilocaine	4	(1.7)	2	(0.8)
lidocaine (+) sodium bicarbonate	0	(0.0)	2	(0.8)
lidocaine hydrochloride	8	(3.4)	7	(2.9)
mepivacaine hydrochloride	1	(0.4)	0	(0.0)
nitrous oxide	1	(0.4)	0	(0.0)
propofol	1	(0.4)	5	(2.0)
remifentanil hydrochloride	0	(0.0)	1	(0.4)
ropivacaine	2	(0.8)	0	(0.0)
ropivacaine hydrochloride	2	(0.8)	0	(0.0)
sevoflurane	0	(0.0)	1	(0.4)
sufentanil citrate	1	(0.4)	0	(0.0)
anti-Parkinson drugs	**1**	**(0.4)**	**1**	**(0.4)**
pramipexole dihydrochloride	1	(0.4)	0	(0.0)
rotigotine	0	(0.0)	1	(0.4)
antiepileptics	**41**	**(17.3)**	**31**	**(12.7)**
carbamazepine	3	(1.3)	3	(1.2)
clonazepam	6	(2.5)	4	(1.6)
gabapentin	19	(8.0)	9	(3.7)
levetiracetam	0	(0.0)	1	(0.4)
phenobarbital	0	(0.0)	1	(0.4)
phenytoin	0	(0.0)	2	(0.8)
pregabalin	17	(7.2)	13	(5.3)
other nervous system drugs	**7**	**(3.0)**	**5**	**(2.0)**
betahistine hydrochloride	1	(0.4)	0	(0.0)
disulfiram	1	(0.4)	1	(0.4)
methadone hydrochloride	4	(1.7)	4	(1.6)
nicotine	1	(0.4)	0	(0.0)
psychoanaleptics	**33**	**(13.9)**	**28**	**(11.4)**
amitriptyline hydrochloride	6	(2.5)	5	(2.0)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
atomoxetine hydrochloride	0	(0.0)	1	(0.4)
bupropion	1	(0.4)	0	(0.0)
bupropion hydrochloride	1	(0.4)	1	(0.4)
caffeine	0	(0.0)	1	(0.4)
citalopram	4	(1.7)	3	(1.2)
citalopram hydrobromide	1	(0.4)	0	(0.0)
duloxetine hydrochloride	4	(1.7)	3	(1.2)
escitalopram	0	(0.0)	1	(0.4)
escitalopram oxalate	1	(0.4)	1	(0.4)
fluoxetine hydrochloride	1	(0.4)	0	(0.0)
imipramine	0	(0.0)	1	(0.4)
mianserin hydrochloride	1	(0.4)	0	(0.0)
mirtazapine	7	(3.0)	6	(2.4)
nortriptyline	2	(0.8)	0	(0.0)
nortriptyline hydrochloride	1	(0.4)	1	(0.4)
paroxetine	1	(0.4)	0	(0.0)
piracetam	1	(0.4)	1	(0.4)
sertraline hydrochloride	2	(0.8)	5	(2.0)
trazodone hydrochloride	3	(1.3)	1	(0.4)
venlafaxine hydrochloride	2	(0.8)	2	(0.8)
psycholeptics	**78**	**(32.9)**	**72**	**(29.4)**
alprazolam	4	(1.7)	12	(4.9)
aripiprazole	0	(0.0)	1	(0.4)
bromazepam	3	(1.3)	1	(0.4)
brotizolam	3	(1.3)	3	(1.2)
diazepam	7	(3.0)	3	(1.2)
droperidol	1	(0.4)	0	(0.0)
estazolam	0	(0.0)	3	(1.2)
ethyl loflazepate	1	(0.4)	0	(0.0)
etizolam	1	(0.4)	0	(0.0)
flunitrazepam	1	(0.4)	1	(0.4)
haloperidol	2	(0.8)	0	(0.0)
hydroxyzine	1	(0.4)	0	(0.0)
hydroxyzine hydrochloride	2	(0.8)	0	(0.0)
hydroxyzine pamoate	1	(0.4)	0	(0.0)
levomepromazine	2	(0.8)	0	(0.0)
lorazepam	18	(7.6)	27	(11.0)
lormetazepam	0	(0.0)	2	(0.8)
melatonin	0	(0.0)	1	(0.4)
mephenoxalone	1	(0.4)	0	(0.0)
midazolam	13	(5.5)	3	(1.2)
midazolam hydrochloride	1	(0.4)	3	(1.2)
nitrazepam	0	(0.0)	1	(0.4)
olanzapine	0	(0.0)	1	(0.4)
oxazepam	3	(1.3)	1	(0.4)
prochlorperazine	5	(2.1)	4	(1.6)
prochlorperazine maleate	5	(2.1)	4	(1.6)
prochlorperazine mesylate	1	(0.4)	0	(0.0)
quetiapine fumarate	3	(1.3)	1	(0.4)
ramelteon	1	(0.4)	0	(0.0)
risperidone	0	(0.0)	1	(0.4)
sulpiride	0	(0.0)	2	(0.8)
temazepam	3	(1.3)	0	(0.0)
triazolam	0	(0.0)	3	(1.2)
zolpidem	3	(1.3)	4	(1.6)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
zolpidem tartrate	7	(3.0)	7	(2.9)
zopiclone	8	(3.4)	6	(2.4)
respiratory system				
antihistamines for systemic use	**43**	**(18.1)**	**147**	**(60.0)**
bisulepin hydrochloride	4	(1.7)	6	(2.4)
cetirizine hydrochloride	4	(1.7)	3	(1.2)
chloropyramine hydrochloride	3	(1.3)	7	(2.9)
chlorpheniramine	4	(1.7)	1	(0.4)
chlorpheniramine maleate	6	(2.5)	15	(6.1)
clemastine	1	(0.4)	10	(4.1)
clemastine fumarate	0	(0.0)	5	(2.0)
cyclizine	1	(0.4)	1	(0.4)
cyproheptadine hydrochloride	0	(0.0)	1	(0.4)
desloratadine	1	(0.4)	0	(0.0)
dexchlorpheniramine maleate	1	(0.4)	14	(5.7)
dimenhydrinate	1	(0.4)	1	(0.4)
dimethindene maleate	2	(0.8)	6	(2.4)
diphenhydramine	9	(3.8)	33	(13.5)
diphenhydramine hydrochloride	5	(2.1)	39	(15.9)
doxylamine succinate	1	(0.4)	0	(0.0)
fexofenadine hydrochloride	1	(0.4)	3	(1.2)
levocetirizine	1	(0.4)	0	(0.0)
levocetirizine dihydrochloride	1	(0.4)	3	(1.2)
loratadine	1	(0.4)	4	(1.6)
pheniramine maleate	0	(0.0)	2	(0.8)
promethazine	1	(0.4)	0	(0.0)
thiethylperazine maleate	1	(0.4)	0	(0.0)
cough and cold preparations	**19**	**(8.0)**	**23**	**(9.4)**
acetylcysteine	7	(3.0)	8	(3.3)
ambroxol	0	(0.0)	1	(0.4)
ambroxol hydrochloride	0	(0.0)	3	(1.2)
benzonatate	1	(0.4)	0	(0.0)
bromhexine hydrochloride	2	(0.8)	0	(0.0)
carbocysteine	2	(0.8)	1	(0.4)
codeine	4	(1.7)	7	(2.9)
codeine phosphate	2	(0.8)	2	(0.8)
codeine phosphate (+) guaifenesin	1	(0.4)	0	(0.0)
codeine phosphate (+) promethazine hydrochloride	1	(0.4)	0	(0.0)
cough, cold, and flu therapies (unspecified)	1	(0.4)	1	(0.4)
dextromethorphan	1	(0.4)	1	(0.4)
dextromethorphan hydrobromide	4	(1.7)	1	(0.4)
dextromethorphan hydrobromide (+) ephedrine hydrochloride	1	(0.4)	1	(0.4)
guaifenesin	0	(0.0)	1	(0.4)
hydrocodone	1	(0.4)	1	(0.4)
drugs for obstructive airway diseases	**26**	**(11.0)**	**22**	**(9.0)**
albuterol	4	(1.7)	6	(2.4)
albuterol (+) ipratropium bromide	0	(0.0)	2	(0.8)
albuterol sulfate	6	(2.5)	4	(1.6)
albuterol sulfate (+) ipratropium bromide	1	(0.4)	1	(0.4)
beclomethasone dipropionate	1	(0.4)	0	(0.0)
budesonide	0	(0.0)	2	(0.8)
budesonide (+) formoterol fumarate	0	(0.0)	1	(0.4)
ephedrine	1	(0.4)	0	(0.0)
epinephrine	4	(1.7)	3	(1.2)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
epinephrine hydrochloride	1	(0.4)	0	(0.0)
fenoterol hydrobromide (+) ipratropium bromide	0	(0.0)	1	(0.4)
fluticasone furoate	1	(0.4)	1	(0.4)
fluticasone furoate (+) vilanterol trifenatate	1	(0.4)	0	(0.0)
fluticasone propionate	3	(1.3)	1	(0.4)
fluticasone propionate (+) formoterol fumarate	0	(0.0)	1	(0.4)
fluticasone propionate (+) salmeterol xinafoate	2	(0.8)	3	(1.2)
formoterol fumarate (+) mometasone furoate	1	(0.4)	0	(0.0)
ipratropium bromide	5	(2.1)	3	(1.2)
montelukast sodium	1	(0.4)	0	(0.0)
theophylline	0	(0.0)	1	(0.4)
tiotropium bromide	2	(0.8)	4	(1.6)
nasal preparations	**1**	**(0.4)**	**2**	**(0.8)**
hydrocortisone (+) oxytetracycline calcium (+) polymyxin B sulfate	0	(0.0)	1	(0.4)
phenylpropanolamine hydrochloride	1	(0.4)	0	(0.0)
sea water	0	(0.0)	1	(0.4)
throat preparations	**1**	**(0.4)**	**0**	**(0.0)**
benzethonium chloride	1	(0.4)	0	(0.0)
sensory organs				
ophthalmologicals	**8**	**(3.4)**	**4**	**(1.6)**
bimatoprost	0	(0.0)	1	(0.4)
bimatoprost (+) timolol maleate	1	(0.4)	0	(0.0)
carbomer	1	(0.4)	0	(0.0)
carboxymethylcellulose sodium	0	(0.0)	1	(0.4)
dorzolamide hydrochloride (+) timolol maleate	1	(0.4)	0	(0.0)
ectoine (+) hyaluronate sodium	0	(0.0)	1	(0.4)
hypromellose	1	(0.4)	0	(0.0)
latanoprost	2	(0.8)	0	(0.0)
perfluorohexyloctane	0	(0.0)	1	(0.4)
pilocarpine	1	(0.4)	0	(0.0)
pilocarpine hydrochloride	0	(0.0)	1	(0.4)
pirenoxine	1	(0.4)	0	(0.0)
pranoprofen	1	(0.4)	0	(0.0)
tafluprost	1	(0.4)	0	(0.0)
timolol	0	(0.0)	1	(0.4)
timolol maleate	1	(0.4)	0	(0.0)
systemic hormonal preparations, excl. sex hormones and insulins				
calcium homeostasis	**2**	**(0.8)**	**0**	**(0.0)**
salcatonin	2	(0.8)	0	(0.0)
corticosteroids for systemic use	**105**	**(44.3)**	**150**	**(61.2)**
betamethasone (+) sodium chloride	1	(0.4)	0	(0.0)
betamethasone sodium phosphate	2	(0.8)	4	(1.6)
dexamethasone	82	(34.6)	100	(40.8)
dexamethasone phosphate	0	(0.0)	2	(0.8)
dexamethasone sodium phosphate	9	(3.8)	32	(13.1)
dexamethasone sodium phosphate (+) sodium chloride	4	(1.7)	1	(0.4)
hydrocortisone	4	(1.7)	2	(0.8)
hydrocortisone sodium succinate	1	(0.4)	4	(1.6)
methylprednisolone	2	(0.8)	5	(2.0)
methylprednisolone sodium succinate	0	(0.0)	3	(1.2)
prednisolone	2	(0.8)	3	(1.2)
prednisolone valerate acetate	0	(0.0)	1	(0.4)
prednisone	4	(1.7)	3	(1.2)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
triamcinolone acetonide	1	(0.4)	0	(0.0)
pituitary and hypothalamic hormones and analogues	**1**	**(0.4)**	**0**	**(0.0)**
ganirelix acetate	1	(0.4)	0	(0.0)
thyroid therapy	**48**	**(20.3)**	**45**	**(18.4)**
Thyroxine	2	(0.8)	1	(0.4)
levothyroxine sodium	46	(19.4)	43	(17.6)
liothyronine sodium	1	(0.4)	0	(0.0)
methimazole	0	(0.0)	1	(0.4)
various				
all other therapeutic products	**21**	**(8.9)**	**12**	**(4.9)**
Asian ginseng	1	(0.4)	0	(0.0)
Asian ginseng (+) ginger (+) Sichuan pepper	1	(0.4)	0	(0.0)
Chinese licorice (+) Chinese peony	1	(0.4)	0	(0.0)
Chinese peony	1	(0.4)	0	(0.0)
Enterococcus faecalis	1	(0.4)	1	(0.4)
[composition unspecified]	3	(1.3)	1	(0.4)
acetyl tyrosine (+) caffeine (+) citicoline (+) cyanocobalamin (+) folic acid (+) glucurolactone (+) malic acid (+) niacinamide (+) phenylalanine (+) pyridoxine hydrochloride (+) taurine	0	(0.0)	1	(0.4)
alcohol (+) alum, potassium (+) benzoin (+) camphor (+) cinnamon oil (+) eucalyptol (+) menthol (+) methyl salicylate (+) pine oil (+) potassium chlorate (+) sodium bicarbonate (+) sodium chloride (+) spearmint oil (+) thymol	0	(0.0)	1	(0.4)
ammonium glycyrrhizate (+) glycine (+) racemethionine	1	(0.4)	0	(0.0)
artichoke	1	(0.4)	0	(0.0)
bee pollen	1	(0.4)	0	(0.0)
calcium polystyrene sulfonate	0	(0.0)	1	(0.4)
caraway oil	1	(0.4)	0	(0.0)
cassia	1	(0.4)	0	(0.0)
cholecalciferol (+) lycopene (+) pygeum (+) saw palmetto (+) selenomethionine (+) stinging nettle (+) zinc gluconate	1	(0.4)	0	(0.0)
choline bitartrate (+) cyanocobalamin (+) cysteine hydrochloride (+) inositol (+) lecithin (+) liver extract	0	(0.0)	1	(0.4)
chondroitin sulfate sodium	1	(0.4)	0	(0.0)
chondroitin sulfate sodium (+) glucosamine sulfate	1	(0.4)	0	(0.0)
cordyceps (+) reishi (+) shiitake (+) tremella (+) turkey tails	1	(0.4)	0	(0.0)
cranberry	0	(0.0)	1	(0.4)
flumazenil	2	(0.8)	0	(0.0)
folinic acid	1	(0.4)	0	(0.0)
frankincense	1	(0.4)	0	(0.0)
ginger (+) greater galangal (+) turmeric	1	(0.4)	0	(0.0)
ginkgo	0	(0.0)	1	(0.4)
glucosamine	0	(0.0)	1	(0.4)
hemp	2	(0.8)	2	(0.8)
meglumine thioctate	0	(0.0)	1	(0.4)
milk thistle	2	(0.8)	0	(0.0)
oxygen	1	(0.4)	1	(0.4)
platycodon	1	(0.4)	0	(0.0)
rasburicase	0	(0.0)	1	(0.4)
saw palmetto	1	(0.4)	0	(0.0)
slippery elm	1	(0.4)	0	(0.0)

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
sodium thiosulfate	1	(0.4)	0	(0.0)
sugammadex sodium	0	(0.0)	1	(0.4)
turkey tails	1	(0.4)	0	(0.0)
turmeric	3	(1.3)	0	(0.0)
contrast media	**3**	**(1.3)**	**1**	**(0.4)**
diatrizoate meglumine (+) diatrizoate sodium	2	(0.8)	0	(0.0)
iohexol	1	(0.4)	0	(0.0)
iopamidol	2	(0.8)	1	(0.4)
diagnostic agents	**2**	**(0.8)**	**0**	**(0.0)**
edrophonium chloride	1	(0.4)	0	(0.0)
indigotindisulfonate sodium	1	(0.4)	0	(0.0)
diagnostic radiopharmaceuticals	**2**	**(0.8)**	**0**	**(0.0)**
fludeoxyglucose F 18	2	(0.8)	0	(0.0)
general nutrients	**19**	**(8.0)**	**23**	**(9.4)**
amino acids (unspecified) (+) carbohydrates (unspecified) (+) fat (unspecified) (+) fructooligosaccharides (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
amino acids (unspecified) (+) carbohydrates (unspecified) (+) fat (unspecified) (+) lecithin (+) medium-chain triglycerides (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	0	(0.0)	1	(0.4)
amino acids (unspecified) (+) carbohydrates (unspecified) (+) fat (unspecified) (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	0	(0.0)	1	(0.4)
amino acids (unspecified) (+) fat (unspecified) (+) fructooligosaccharides (+) inulin (+) lecithin (+) medium-chain triglycerides (+) minerals (unspecified) (+) pea (+) protein (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
beta-hydroxyisovaleric acid (+) carbohydrates (unspecified) (+) fat (unspecified) (+) fructooligosaccharides (+) levocarnitine (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	0	(0.0)	1	(0.4)
carbohydrates (unspecified) (+) fat (unspecified) (+) fiber (unspecified) (+) minerals (unspecified) (+) omega-3 marine triglycerides (+) protein (unspecified) (+) vitamins (unspecified)	5	(2.1)	0	(0.0)
carbohydrates (unspecified) (+) fat (unspecified) (+) fiber (unspecified) (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	1	(0.4)	2	(0.8)
carbohydrates (unspecified) (+) fat (unspecified) (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	9	(3.8)	12	(4.9)
carbohydrates (unspecified) (+) minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	1	(0.4)	0	(0.0)
dextrose	4	(1.7)	5	(2.0)
lecithin (+) protein (unspecified)	1	(0.4)	0	(0.0)
minerals (unspecified) (+) protein (unspecified) (+) vitamins (unspecified)	0	(0.0)	3	(1.2)
nutritional supplements	2	(0.8)	1	(0.4)
therapeutic radiopharmaceuticals	**1**	**(0.4)**	**0**	**(0.0)**
therapeutic radiopharmaceutical (unspecified)	1	(0.4)	0	(0.0)

Every subject is counted a single time for each applicable specific prior medication. A subject with multiple prior medications within a medication category is counted a single time for that category.

A medication class or specific medication 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.

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)

Appendix 2

Separate file

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Supplementary Document:

Additional material for responses to clarification questions

July 2019

File name	Version	Contains confidential information	Date
ID1140 Pembrolizumab ERG clarification letter – Supplementary Document v1.0	1.0	Yes	22-JUL-2019

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B.2 Clinical effectiveness

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Pembrolizumab monotherapy in patients with CPS≥1

Extent of exposure

The median duration of exposure was [redacted] days for pembrolizumab monotherapy, and 148 days for cetuximab plus chemotherapy (Table 1). The mean number of cycles was [redacted] for patients treated with pembrolizumab monotherapy, and 8.80 cycles (range: 1.00 to 57.0) for patients treated with cetuximab plus chemotherapy (Table 1). More participants in the pembrolizumab monotherapy group received treatment for ≥12 months than those in the cetuximab plus chemotherapy group (Table 2).

Table 1 Extent of exposure, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ASaT population CPS≥1 population

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Subjects in population	256		245	
Number of administrations[†]				
1 Cycle	[redacted]	[redacted]	20	(8.2)
2 Cycles	[redacted]	[redacted]	9	(3.7)
3 Cycles	[redacted]	[redacted]	30	(12.2)
4 Cycles	[redacted]	[redacted]	18	(7.3)
5 Cycles	[redacted]	[redacted]	18	(7.3)
6 Cycles	[redacted]	[redacted]	22	(9.0)
>=7 Cycles	[redacted]	[redacted]	128	(52.2)
Mean	[redacted]	[redacted]	8.80	
Median	[redacted]	[redacted]	7.00	
SD	[redacted]	[redacted]	9.17	
Range	[redacted]	[redacted]	1.00 to 57.0	
Number of days on therapy (days)				
Mean	[redacted]		186.77	
Median	[redacted]		148.00	
SD	[redacted]		202.68	
Range	[redacted]		1.00 to 1240.0	

[†] For Control arm, if any drug was administered during a cycle, it is counted as one administration.
For subjects who received second course treatment, doses administered in second course are excluded.
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Table 2 Exposure by duration, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ASaT population, CPS≥1

	Pembrolizumab (N=256)		Cetuximab + Chemotherapy (N=245)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	[redacted]	[redacted]	245	125
≥ 1 m	[redacted]	[redacted]	221	125
≥ 3 m	[redacted]	[redacted]	173	116
≥ 6 m	[redacted]	[redacted]	90	85
≥ 12 m	[redacted]	[redacted]	17	37

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.
For subjects who received second course treatment, doses administered in second course are excluded.
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Overall survival

The results from each overall survival analysis including both two-sided and one-sided p-values are summarised in Table 3.

Table 3 Summary of results of OS analyses – pembrolizumab monotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, PD-L1 CPS≥1 population

Analysis Method	Hazard Ratio	95% CI	P-value (2-sided)	P-value (1-sided)
ITT	0.74	(0.61; 0.90)	0.0027	0.0014
Simplified two-stage	0.71	(0.57; 0.89)	0.0027*	0.0014*
RPSFT	0.71	(0.57; 0.89)	0.0027*	0.0014*
IPCW	0.83	(0.67; 1.02)	0.0850§	0.0425§

* P-value retained from the ITT analysis (log-rank test) based on distribution of the test statistic under the null hypothesis of no treatment effect.

§ P-value based on bootstrap percentiles.

IPCW: inverse probability of censoring weighting method; ITT: intention-to-treat (no adjustment for crossover); RPSFT: rank preserving structural failure time method.

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Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

Comparing pembrolizumab monotherapy with cetuximab plus chemotherapy in participants whose tumours express PD-L1 CPS ≥1, pembrolizumab monotherapy demonstrated a statistically significant and clinically meaningful OS benefit compared with standard treatment (HR 0.74 [0.61, 0.90], p=0.00133) (Table 4). Median OS was 12.3 months (95% CI: 10.8, 14.3 months) versus 10.3 months (95% CI: 9.0, 11.5 months) (Table 4). By Kaplan-Meier (KM) estimation, OS rate at 18 months was 38.7% versus 26.6%, and at 24 months was 28.9% versus 17.4% (Table 15), the extended tail of the KM curve suggests long-term survival benefits from pembrolizumab monotherapy treatment (Figure 1).

Table 4 OS, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab	257	197 (76.7)	4068.2	4.8	12.3 (10.8, 14.3)	50.4 (44.1, 56.4)
Cetuximab + Chemotherapy	255	229 (89.8)	3403.6	6.7	10.3 (9.0, 11.5)	43.6 (37.4, 49.6)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab vs. Cetuximab + Chemotherapy					0.74 (0.61, 0.90)	0.00133§

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

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Table 5 OS rate, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
OS rate at 6 Months in (95% CI)†	71.1 (65.2, 76.3)	78.7 (73.2, 83.3)
OS rate at 12 Months in (95% CI)†	50.4 (44.1, 56.4)	43.6 (37.4, 49.6)
OS rate at 18 Months in (95% CI)†	38.7 (32.7, 44.6)	26.6 (21.3, 32.1)
OS rate at 24 Months in (95% CI)†	28.9 (23.5, 34.5)	17.4 (13.0, 22.4)

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

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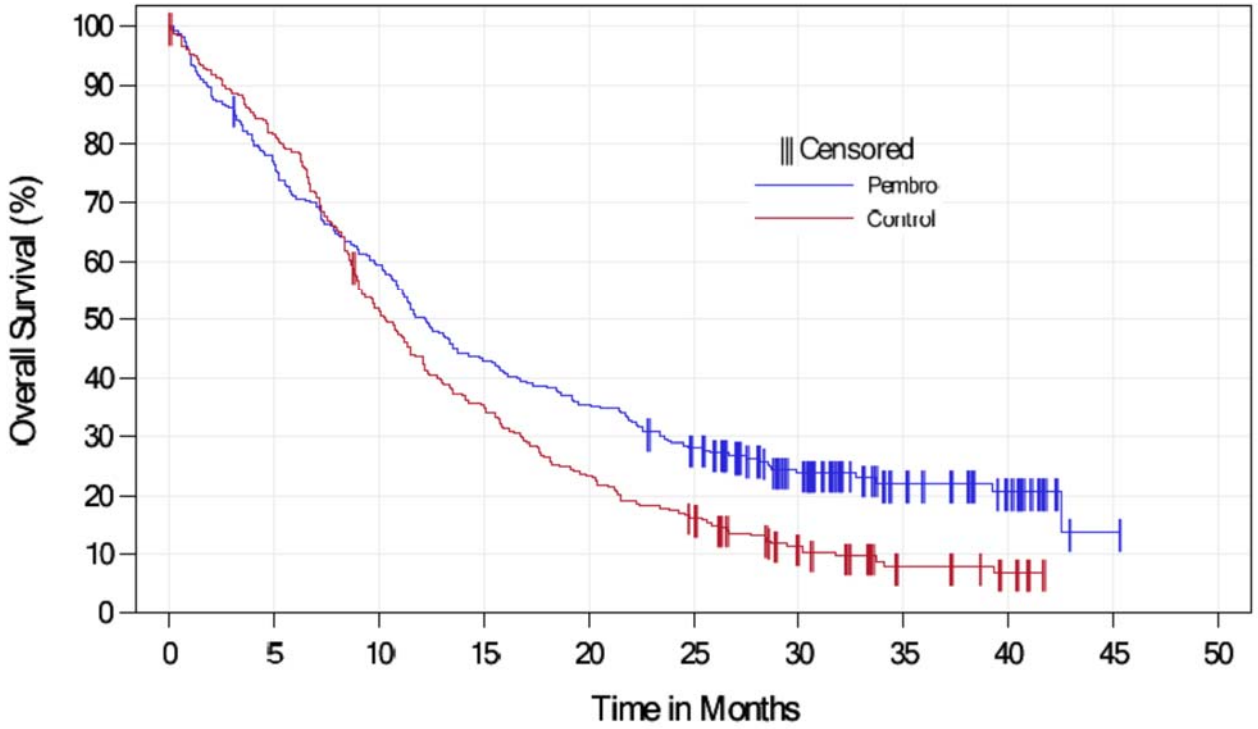
Figure 1 Kaplan-Meier estimates of OS, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup



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Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

Table 6 and Figure 2 present the results of the analysis of OS adjusting for treatment post-study switch from control arm to immune checkpoint inhibitors including Kaplan-Meier estimates of OS and estimation of treatment effect (without re-censoring procedure applied). The number of events in control arm is the same in the adjusted analysis as in the unadjusted ITT analysis (255 events). The adjusted HR for OS is 0.71 (95% CI: 0.57; 0.89) with a two-sided p-value of 0.0027 in the pembrolizumab monotherapy arm versus the control arm. Details of the 2-stage methodology for this analysis are provided in Appendix L.

Table 6 Analysis of overall survival, without recensoring, pembrolizumab vs, cetuximab + chemotherapy, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population with CPS≥1

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)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶¶]	p-Value[‖]
Cetuximab + Chemotherapy	255	229 (89.8)	3403.6	6.7	10.3 (9.0, 11.5)	43.6 (37.4, 49.6)	---	---	---
Cetuximab + Chemotherapy, 2-stage adjusted[¶]	255	229 (89.8)	3223.3	7.1	10.1 (9.0, 11.5)	43.1 (37.0, 49.1)	---	---	---
Pembrolizumab	257	197 (76.7)	4068.2	4.8	12.3 (10.8, 14.3)	50.4 (44.1, 56.4)	0.71 (0.57, 0.89)	0.0027	0.0027
Stage 1 model[††]							Acceleration factor[‡‡]		
[§] Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching							1.544 (1.152, 2.069)		

[¶] Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

[†] 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5. The 95% CI is derived by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[¶¶] Two sided p-value based on stratified Cox model, ITT population, analysis not adjusted for treatment switch.

[‖] Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for treatment switch.

[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), hemoglobin at secondary baseline and tumor size at secondary baseline.

[§] Patients were eligible to switch if they had documented progression.

[‡‡] Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

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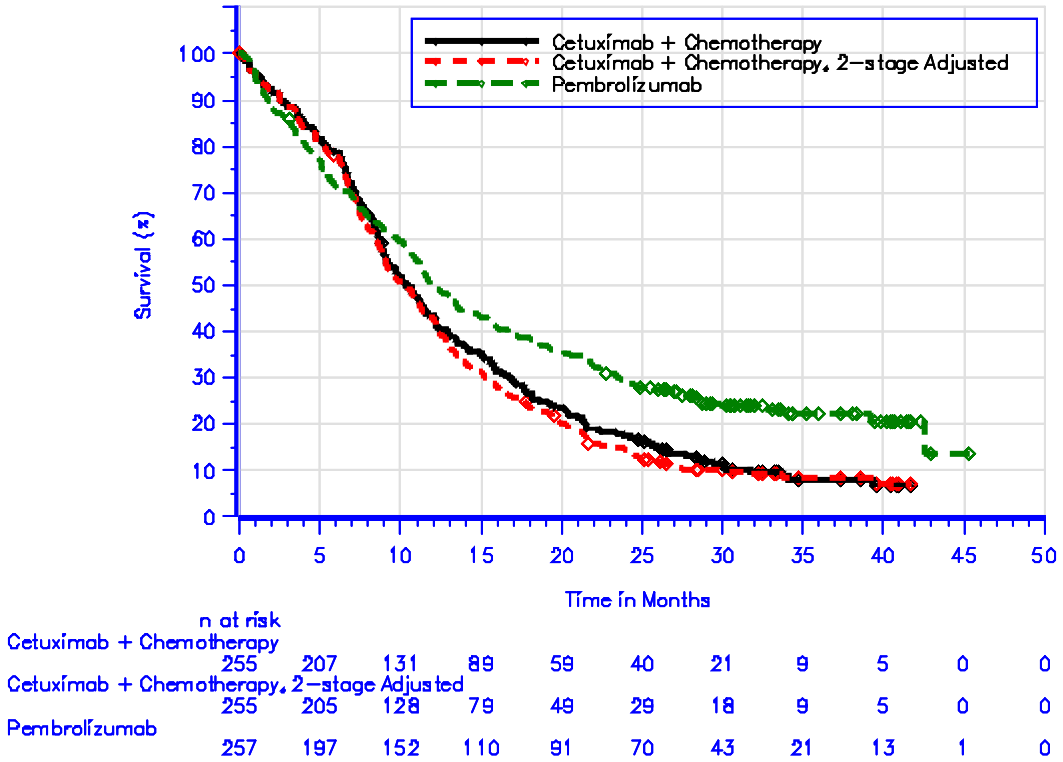
Figure 2 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, without recensoring, pembrolizumab vs. cetuximab + chemotherapy, ITT population with CPS≥1



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Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the rank preserving structural failure (RPSFT) method

Table 7 and Figure 3 present the results of the OS analysis adjusting for receiving subsequent immune checkpoint inhibitors after discontinuation of protocol treatment for the control arm using the RPSFT model without re-censoring. A total of 68/255 (26.7%) of control patients switched to an immune checkpoint inhibitor after discontinuation of the protocol treatment. The RPSFT-adjusted HR for OS is 0.71 (95% CI: 0.57; 0.89) with a two-sided ITT log-rank p-value of 0.0027 for the comparison between pembrolizumab monotherapy versus cetuximab plus chemotherapy.

Table 7 Analysis of overall survival, without recensoring, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, ITT population with CPS≥1, pembrolizumab monotherapy vs. cetuximab + chemotherapy

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	Survival Rate at Month 12[†] (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[§]	p-Value[‖]	p-Value[¶]
Cetuximab + Chemotherapy	255	229 (89.8)	3403.6	6.7	10.3 (9.0, 11.5)	43.6 (37.4, 49.6)			
Cetuximab + Chemotherapy, RPSFT adjusted	255	229 (89.8)	3245.4	7.1	10.1 (9.0, 11.5)	43.1 (37.0, 49.1)			
Pembrolizumab	257	197 (76.7)	4068.2	4.8	12.3 (10.8, 14.3)	50.4 (44.1, 56.4)	0.71 (0.57, 0.89)	0.0027	0.0027

Rank-preserving structural failure time (RPSFT) model is used to adjust for the effect in overall survival analysis for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors.

[†] From product-limit (Kaplan-Meier) method.

[‡] Based on Cox regression model with Efron′s method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

[§] Obtained by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[‖] Two sided p-value based on stratified Cox model, analysis not adjusted for treatment switch.

[¶] Two-sided p-value based on stratified log-rank test, analysis not adjusted for treatment switch.

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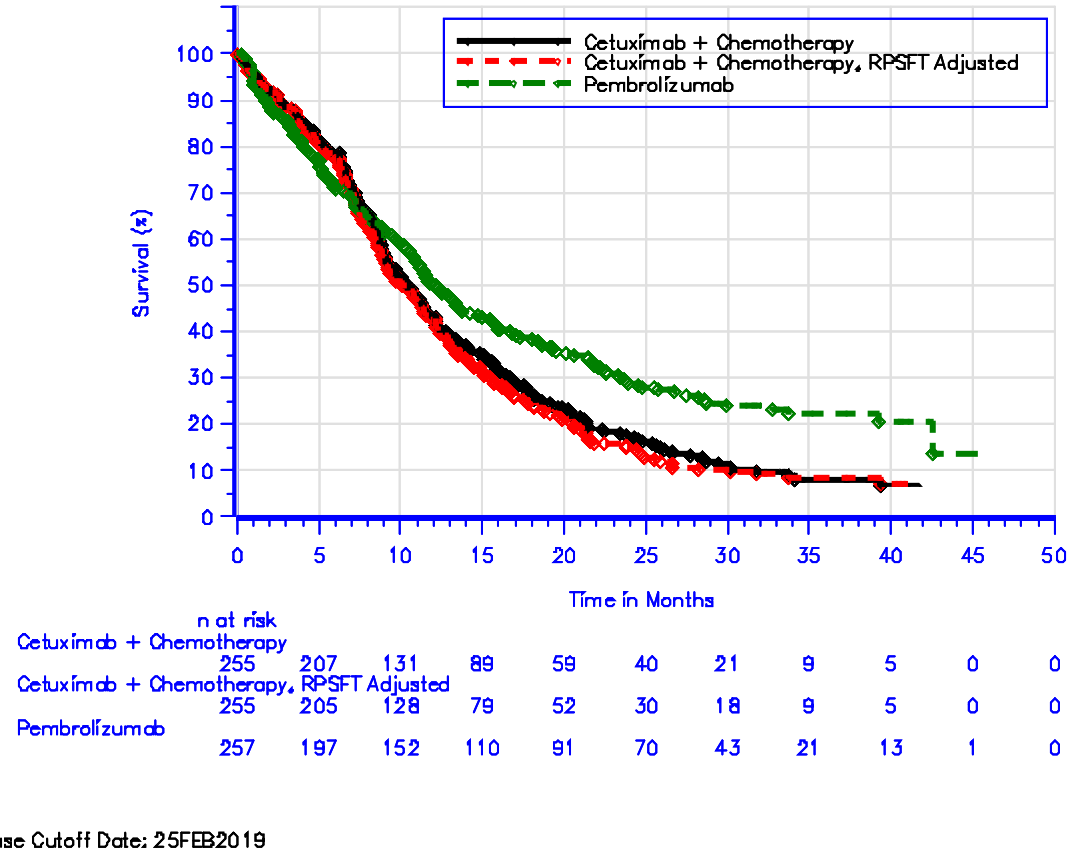
Figure 3 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, without recensoring, ITT population with CPS≥1, pembrolizumab vs. cetuximab + chemotherapy



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Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the inverse probability censored weighting (IPCW) method

Of those who switched in the control arm, 61/68 (89.7%) subjects died after switching, and therefore 61/229 (26.6%) observed events in the control arm were lost due to censoring at the time of switch. Among those who did not switch in the control arm, 168/187 (89.8%) deaths were observed, and included in the analysis. Table 8 summarises the results from the weighted Cox proportional hazard regression. The IPCW-adjusted hazard ratio of pembrolizumab versus control is 0.83, with 95% bootstrap percentile confidence interval of 0.67 to 1.02 (bootstrap two-sided p-value = 0.0850). Figure 4 shows the survival curves for the ITT-unadjusted and the IPCW-adjusted control arm compared to the pembrolizumab arm.

Table 8 Analysis of overall survival adjusting for treatment switch to immune checkpoint inhibitors in standard treatment arm using IPCW model comparison pembrolizumab versus cetuximab + chemotherapy, intention-to-treat population with CPS≥1

Treatment	N	Number of Events (%)	Person-Month	Event Rate/ 100 Person-Month (%)	Median OS† (Month) (95% CI)	Pembrolizumab vs. Cetuximab + Chemotherapy		
						Hazard Ratio†† (95% CI)	p-Value§	p-Value§§
Cetuximab + Chemotherapy	255	229 (89.8)	3403.6	6.7	10.3 (9.0 , 11.5)			
Cetuximab + Chemotherapy, IPCW Adjusted	255	168 (65.9)	2818.0	6.0	10.9 (9.7 , 12.2)			
Pembrolizumab	257	197 (76.7)	4068.2	4.8	12.3 (10.8 , 14.3)	0.83 (0.67, 1.02)	0.0788	0.0850

† From product-limit (Kaplan-Meier) method for censored data, if the median OS is reached

†† HR based on Cox regression model with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status, and bootstrap 95% CI. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ Two-sided p-value based on the IPCW log-rank test

§§ Two-sided p-value based on bootstrap percentiles

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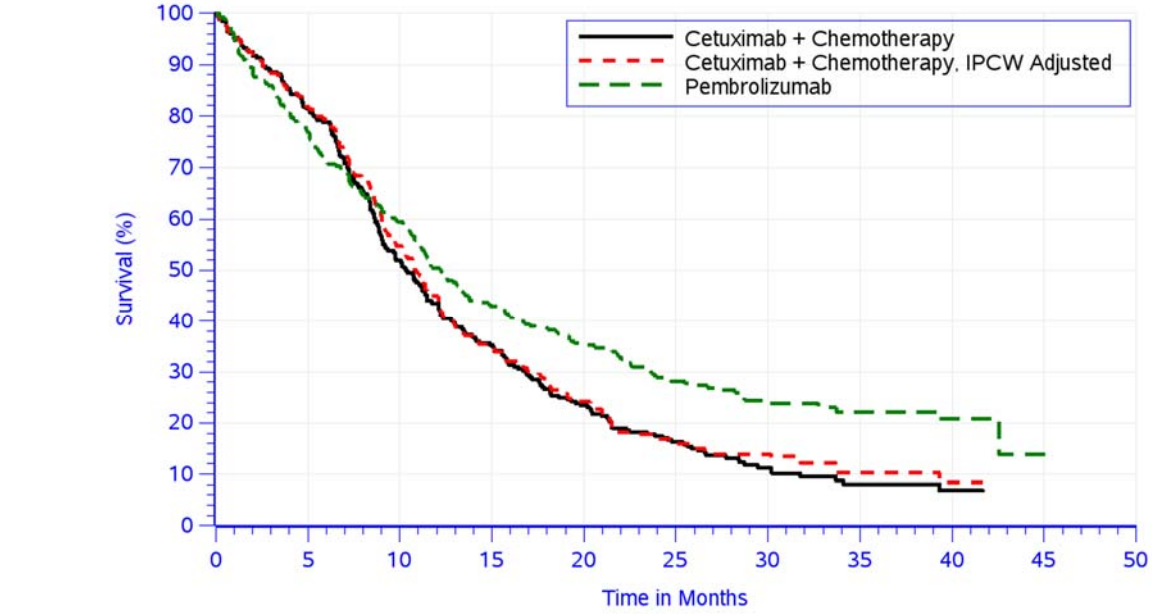
Figure 4 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received immune checkpoint inhibitors using IPCW comparison pembrolizumab versus cetuximab + chemotherapy, intention-to-treat population with CPS≥1



n at risk

Cetuximab + Chemotherapy	255	207	131	89	59	40	21	9	5	0	0
Cetuximab + Chemotherapy, IPCW Adjusted	255	195	110	64	38	25	18	9	5	0	0
Pembrolizumab	257	197	152	110	91	70	43	21	13	1	0

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Progression-free survival

Comparing the populations of participants with PD-L1 CPS≥1 in the pembrolizumab monotherapy group with the cetuximab plus chemotherapy group, median PFS was 3.2 months (95% CI: 2.2, 3.4) versus 5.0 months (95% CI: 4.8, 6.0) (Table 9). By KM estimation, PFS rates were higher at 12 months (20.6% vs 13.6%) (Table 10 and Figure 5).

Table 9 PFS based on BICR assessment per RECIST 1.1, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 6 in % † (95% CI)
Pembrolizumab	257	228 (88.7)	1897.4	12.0	3.2 (2.2, 3.4)	28.7 (23.3, 34.4)
Cetuximab + Chemotherapy	255	237 (92.9)	1791.7	13.2	5.0 (4.8, 6.0)	43.9 (37.6, 49.9)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab vs. Cetuximab + Chemotherapy					1.13 (0.94, 1.36)	0.89580§

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

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Table 10 Summary of PFS rate over time based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

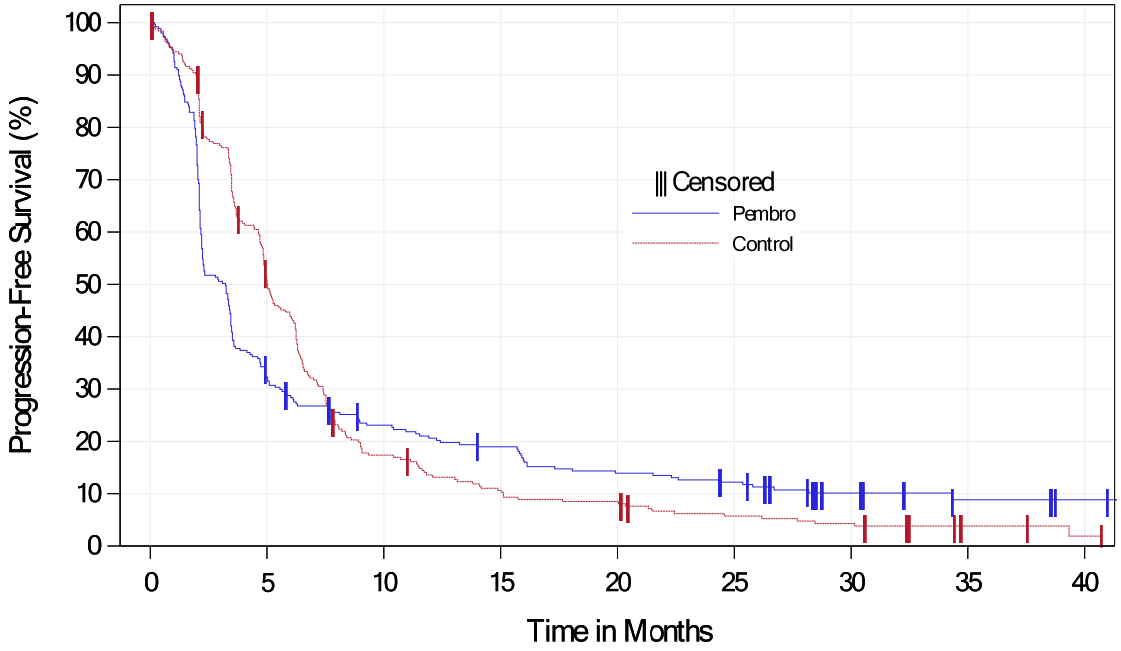
	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
PFS rate at 6 Months in (95% CI)†	28.7 (23.3, 34.4)	43.9 (37.6, 49.9)
PFS rate at 9 Months in (95% CI)†	23.5 (18.5, 28.9)	19.8 (15.1, 25.0)
PFS rate at 12 Months in (95% CI)†	20.6 (15.9, 25.8)	13.6 (9.6, 18.2)

BICR = Blinded Independent Central Review

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

(Database Cutoff Date: 25FEB2019).

Figure 5 Kaplan-Meier estimates of PFS based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup



At Risk

Pembro	257	82	56	45	33	27	12	6	3
Control	255	123	42	25	20	12	9	3	1

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Response rate

Comparing the populations of participants with PD-L1 CPS ≥1 in the pembrolizumab monotherapy group with the standard treatment group, the ORR was 19.1% (95% CI: 14.5, 24.4) versus 34.9% (95% CI: 29.1, 41.1) (Table 11). The best objective response (BOR) summary showed that a smaller proportion of participants treated with pembrolizumab achieved an objective response compared to participants treated with standard treatment. However, more participants achieved a complete response in the pembrolizumab monotherapy group than the standard treatment group (Table 12).

Table 11 Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab	257	49	19.1 (14.5,24.4)	-15.9 (-23.4,-8.3)	1.0000
Cetuximab + Chemotherapy	255	89	34.9 (29.1,41.1)		

BICR = Blinded Independent Central Review

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

[†] Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive); in case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is >=5; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

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Table 12 Summary of best objective response with confirmation based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	257		255	
Complete Response (CR)	15	(5.8)	11	(4.3)
Partial Response (PR)	43	(16.7)	103	(40.4)
Objective Response (CR+PR)	**58**	**(22.6)**	**114**	**(44.7)**
Stable Disease (SD)	64	(24.9)	62	(24.3)
Progressive Disease (PD)	100	(38.9)	32	(12.5)
Non-CR/Non-PD (NN)	11	(4.3)	10	(3.9)
Not Evaluable (NE)	4	(1.6)	1	(0.4)
No Assessment	20	(7.8)	36	(14.1)

	Pembrolizumab		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
BICR = Blinded Independent Central Review Responses are based on BICR assessments per RECIST 1.1. Database Cutoff Date: 25FEB2019				

Duration of response

Comparing the populations of all participants in the pembrolizumab monotherapy group with the cetuximab plus chemotherapy group:

- The median time to response [redacted] (Table 13).
- Median response duration [redacted] (Table 13).
- There was [redacted] of responders with an estimated response duration ≥6 months [redacted] (Table 13 and Figure 6).

A summary of the reasons that participants with a response based on RECIST 1.1 per BICR were censored from the DOR analysis is provided in (Table 14).

Table 13 Summary of time to response and duration of response based on BICR per RECIST 1.1 in subjects with confirmed response, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
Number of subjects with response[†]	[redacted]	[redacted]
Time to Response[†] (months)		
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
Response Duration[‡] (months)		
Median (Range)	[redacted]	[redacted]
Number (%[‡]) of Subjects with Extended Response Duration:		
≥6 months	[redacted]	[redacted]

[†] Response: Best objective response as confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
Database Cutoff Date: 25FEB2019.

Figure 6 Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

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Table 14 Summary of response outcome in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
Number of Subjects with Response[†]	[redacted]	[redacted]
Subjects Who Progressed or Died[‡] (%)	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]
Censored Subjects (%)	[redacted]	[redacted]
Subjects who missed 2 or more consecutive disease assessments	[redacted]	[redacted]
Subjects who started new anti-cancer treatment	[redacted]	[redacted]
Subjects who were lost to follow-up	[redacted]	[redacted]
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	[redacted]	[redacted]
Ongoing response[§]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]

[†] Includes subjects with a confirmed complete response or partial response.
[‡] Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
[§] Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

	Pembrolizumab (N=257)	Cetuximab + Chemotherapy (N=255)
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest. '+' indicates there was no progressive disease by the time of last disease assessment. Database Cutoff Date: 25FEB2019		

Health-related quality of life

EORTC QLQ-C30

The baseline global health status/QoL scores were [redacted] between the pembrolizumab monotherapy and cetuximab plus chemotherapy groups (Table 15). At Week 15 [redacted] were observed between groups, the mean change from baseline in the global health status/QOL score [redacted] in both the pembrolizumab monotherapy group ([redacted]) and the cetuximab plus chemotherapy group ([redacted]). The difference in LS means between pembrolizumab monotherapy and cetuximab plus chemotherapy at Week 15 was [redacted] (Table 15). A summary of the empirical mean change from baseline over time for the EORTC QLQ-C30 global health status/QoL scores is displayed in Figure 7. Global health status/QoL scores [redacted] over time in both treatment groups through Week 51.

Time to deterioration in the EORTC QLQ-C30 global health status/QoL score for pembrolizumab monotherapy was [redacted] when compared with cetuximab plus chemotherapy ([redacted]) (Table 16 and Figure 8). Similarly, time to deterioration in the in the EORTC QLQ-H&N35 pain score ([redacted]) (Table 17 and Figure 9) and swallowing score ([redacted]) (Table 18 and Figure 10) for pembrolizumab monotherapy were [redacted] when compared with cetuximab in combination with chemotherapy, respectively.

Table 15 Analysis of change from baseline of EORTC QLQ-C30 Global Health Status/QoL Scales at Week 15, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

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Figure 7 Empirical mean change from baseline in EORTC QLQ-C30 Global Health Status/QoL across time, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

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Table 16 Analysis of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

	Pembrolizumab (N=252)	Cetuximab + Chemotherapy (N=238)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)[†]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy	[redacted]	[redacted]
Hazard Ratio (95% CI)[‡]	[redacted]	[redacted]
p-value[§]	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
[§] One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).
Database cutoff date: 25FEB2019

Figure 8 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

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Table 17 Analysis of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

	Pembrolizumab (N=253)	Cetuximab + Chemotherapy (N=238)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)[†]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy	[redacted]	[redacted]
Hazard Ratio (95% CI)[‡]	[redacted]	[redacted]
p-value[§]	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
[§] One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).
Database cutoff date: 25FEB2019

Figure 9 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

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Table 18 Analysis of time to true deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab monotherapy vs. control, FAS population, CPS≥1 subgroup

	Pembrolizumab (N=253)	Cetuximab + Chemotherapy (N=238)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)[†]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy	[redacted]	[redacted]
Hazard Ratio (95% CI)[‡]	[redacted]	[redacted]
p-value[§]	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
[§] One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).
Database cutoff date: 25FEB2019

Figure 10 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

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EQ-5D

Analyses of the mean change from baseline to Week 15 in the EQ-5D utility scores and visual analog scale in the PRO FAS population are provided in Table 19 and Table 20. In the PRO FAS population, participants in both the pembrolizumab monotherapy and standard treatment groups exhibited [redacted] in the EQ-5D visual analog scale and utility scores up to Week 15.

Table 19 Analysis of change from baseline of EQ-5D Utility Score (using European Algorithm) at Week 15, pembrolizumab monotherapy versus cetuximab plus chemotherapy, FAS population, CPS≥1 population

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

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Table 20 Analysis of change from baseline of EQ-5D VAS at Week 15, pembrolizumab monotherapy versus cetuximab plus chemotherapy, FAS population, CPS≥1 population

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

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B.2.6.2 Pembrolizumab + chemotherapy combination therapy in patients with CPS≥1

Extent of exposure

The median duration of exposure was [redacted] days for pembrolizumab in combination with platinum and 5-FU chemotherapy and 148 days for cetuximab plus chemotherapy (Table 21). The mean number of cycles was [redacted] for patients treated with pembrolizumab in combination with platinum and 5-FU chemotherapy and 8.80 cycles (range: 1.00 to 57.0) for participants treated with cetuximab plus chemotherapy (Table 21). The mean number of chemotherapy cycles was also similar in the pembrolizumab in combination with platinum and 5-FU chemotherapy and cetuximab plus chemotherapy groups (Table 22). More participants in the pembrolizumab in combination with platinum and 5-FU chemotherapy group received treatment for ≥6 months and ≥12 months than those in the cetuximab plus chemotherapy group (Table 23).

Table 21 Extent of exposure, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ASaT population CPS≥1 population

	Pembrolizumab + Chemotherapy n	(%)	Cetuximab + Chemotherapy n	(%)
Subjects in population	237		245	
Number of administrations[†]				
1 Cycle	[redacted]	[redacted]	20	(8.2)
2 Cycles	[redacted]	[redacted]	9	(3.7)
3 Cycles	[redacted]	[redacted]	30	(12.2)
4 Cycles	[redacted]	[redacted]	18	(7.3)
5 Cycles	[redacted]	[redacted]	18	(7.3)
6 Cycles	[redacted]	[redacted]	22	(9.0)
>=7 Cycles	[redacted]	[redacted]	128	(52.2)
Mean	[redacted]	[redacted]	8.80	
Median	[redacted]	[redacted]	7.00	
SD	[redacted]	[redacted]	9.17	
Range	[redacted]	[redacted]	1.00 to 57.0	
Number of days on therapy (days)				
Mean	[redacted]		186.77	
Median	[redacted]		148.00	
SD	[redacted]		202.68	
Range	[redacted]		1.00 to 1240.0	

[†] For Pembro Combo and Control arms, if any drug was administered during a cycle, it is counted as one administration.

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
For subjects who received second course treatment, doses administered in second course are excluded. Database Cut-off Date: 25FEB2019				

Table 22 Summary of drug administration, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ASaT population CPS≥1 population

Number of Cycles	Pembrolizumab + Chemotherapy (N = 237)			Cetuximab + Chemotherapy (N = 245)		
	Pembrolizumab n (%)	Platinum n (%)	5-FU n (%)	Cetuximab n (%)	Platinum n (%)	5-FU n (%)
1	[redacted]	[redacted]	[redacted]	24 (9.8)	20 (8.2)	22 (9.0)
2	[redacted]	[redacted]	[redacted]	9 (3.7)	14 (5.7)	17 (6.9)
3	[redacted]	[redacted]	[redacted]	30 (12.2)	32 (13.1)	31 (12.7)
4	[redacted]	[redacted]	[redacted]	18 (7.3)	25 (10.2)	26 (10.6)
5	[redacted]	[redacted]	[redacted]	19 (7.8)	20 (8.2)	17 (6.9)
6	[redacted]	[redacted]	[redacted]	18 (7.3)	132 (53.9)	130 (53.1)
>=7	[redacted]	[redacted]	[redacted]	127 (51.8)	0 (0.00)	0 (0.00)
Mean	[redacted]	[redacted]	[redacted]	8.7	4.7	4.6
SD	[redacted]	[redacted]	[redacted]	9.2	1.7	1.8
Median	[redacted]	[redacted]	[redacted]	7.0	6.0	6.0
Range	[redacted]	[redacted]	[redacted]	1 to 57	1 to 6	1 to 6

For subjects who received second course treatment, doses administered in second course are excluded.
Database Cutoff Date: 25FEB2019

Table 23 Exposure by duration, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ASaT population CPS≥1 population

	Pembrolizumab + Chemotherapy (N=237)		Cetuximab + Chemotherapy (N=245)	
	n	Person-years	n	Person-years
Duration of Exposure				
> 0 m	[redacted]	[redacted]	245	125
≥ 1 m	[redacted]	[redacted]	221	125
≥ 3 m	[redacted]	[redacted]	173	116
≥ 6 m	[redacted]	[redacted]	90	85
≥ 12 m	[redacted]	[redacted]	17	37

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.
For subjects who received second course treatment, doses administered in second course are excluded.
Database Cutoff Date: 25FEB2019

Overall survival

The results from each overall survival analysis including both two-sided and one-sided p-values are summarised in Table 24.

Table 24 Summary of results of OS analyses – pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab in combination with platinum and 5-FU chemotherapy, PD-L1 CPS≥1 population

Analysis Method	Hazard Ratio	95% CI	P-value (2-sided)	P-value (1-sided)
ITT	0.65	(0.53; 0.80)	<0.0001	<0.0001
Simplified two-stage (no re-censoring)	0.62	(0.50; 0.78)	<0.0001*	<0.0001*
RPSFT (no re-censoring)	0.62	(0.50; 0.78)	<0.0001*	0.0001*
IPCW	0.72	(0.58; 0.91)	0.0050§	0.0025§

* P-value retained from the ITT analysis (log-rank test) based on distribution of the test statistic under the null hypothesis of no treatment effect.

§ P-value based on bootstrap percentiles.

IPCW: inverse probability of censoring weighting method; ITT: intention-to-treat (no adjustment for crossover); RPSFT: rank preserving structural failure time method

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Overall survival – results not adjusted for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor

The comparison between pembrolizumab plus chemotherapy group with the standard treatment group results in a HR for OS of 0.65 (95% CI: 0.53, 0.80), a clinically meaningful benefit that was not tested statistically, and a median OS of 13.6 months (95% CI: 10.7, 15.5 months) versus 10.4 months (95% CI: 9.1, 11.7 months) (Table 25). By KM estimation, OS rate at 18 months was 39.1% versus 26.7%, and at 24 months was 30.8% versus 16.8% (Table 26 and Figure 11).The extended tail of the KM curve suggests long-term survival benefits from combination treatment (Figure 11).

Table 25 Analysis of OS, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS † (Months) (95% CI)	OS Rate at Months 12 in % † (95% CI)
Pembrolizumab + Chemotherapy	242	177 (73.1)	4020.9	4.4	13.6 (10.7, 15.5)	55.0 (48.5, 61.0)
Cetuximab + Chemotherapy	235	213 (90.6)	3084.0	6.9	10.4 (9.1, 11.7)	43.5 (37.0, 49.7)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					0.65 (0.53, 0.80)	0.00002§

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

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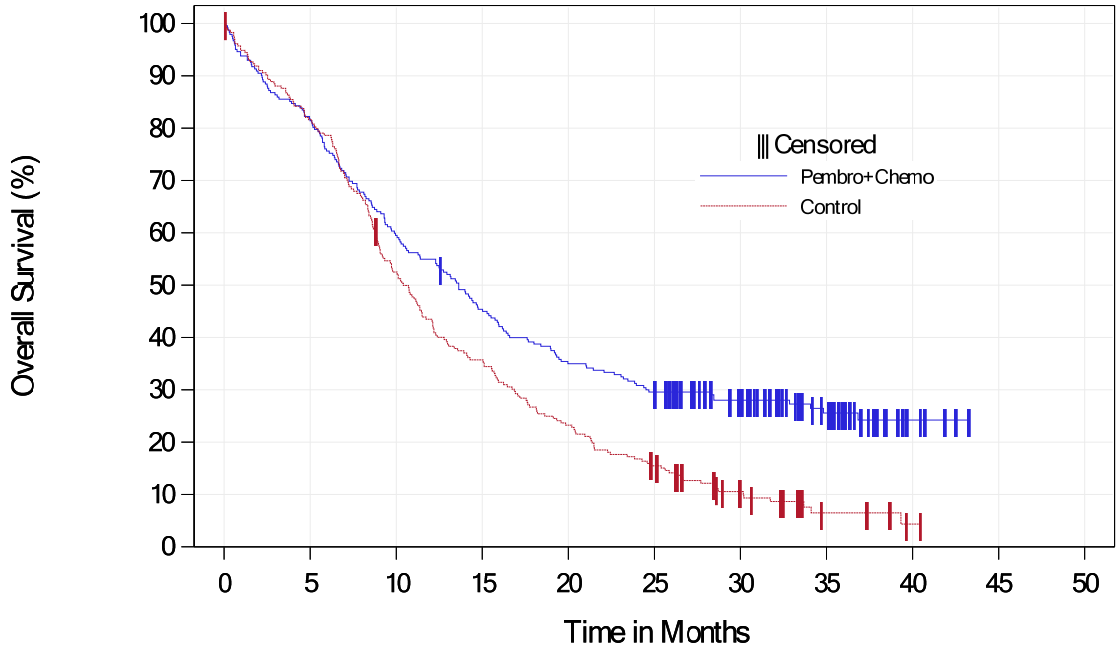
Table 26 OS rate, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
OS rate at 6 Months in (95% CI)†	75.6 (69.7, 80.5)	78.6 (72.8, 83.4)
OS rate at 12 Months in (95% CI)†	55.0 (48.5, 61.0)	43.5 (37.0, 49.7)
OS rate at 18 Months in (95% CI)†	39.1 (33.0, 45.2)	26.7 (21.2, 32.5)
OS rate at 24 Months in (95% CI)†	30.8 (25.1, 36.7)	16.8 (12.3, 21.9)

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

(Database Cutoff Date: 25FEB2019).

Figure 11 Kaplan-Meier estimates of OS, pembrolizumab combination therapy vs. control, ITT population, CPS≥1 subgroup



At Risk

Pembro+Chemo	242	197	144	109	84	70	52	29	5	0	0
Control	235	191	122	83	54	35	17	5	1	0	0

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Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

Table 27 and Figure 12 present the results of the analysis of OS adjusting for post-study treatment switch from control arm to immune checkpoint inhibitors including Kaplan-Meier estimates of OS and estimation of treatment effect (without re-censoring procedure applied). The number of events in control arm is the same in the adjusted analysis as in the unadjusted ITT analysis (213 events). The adjusted HR for OS is 0.62 (95% CI: 0.50; 0.78) with a two-sided p-value of <0.0001 in the pembrolizumab plus chemotherapy arm vs. the control arm. Details of the 2-stage methodology for this analysis are provided in Appendix L.

Table 27 Analysis of overall survival, without recensoring, pembrolizumab + chemotherapy vs, cetuximab + chemotherapy, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, ITT population with CPS≥1

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)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[‡]	p-Value[¶¶]	p-Value[‖]
Cetuximab + Chemotherapy	235	213 (90.6)	3084.0	6.9	10.4 (9.1, 11.7)	43.5 (37.0, 49.7)	---	---	---
Cetuximab + Chemotherapy, 2-stage adjusted[¶]	235	213 (90.6)	2917.4	7.3	10.3 (9.0, 11.5)	43.0 (36.6, 49.2)	---	---	---
Pembrolizumab + Chemotherapy	242	177 (73.1)	4020.9	4.4	13.6 (10.7, 15.5)	55.0 (48.5, 61.0)	0.62 (0.50, 0.78)	<.0001	<.0001
Stage 1 model[††]							Acceleration factor[‡‡]		
[§] Controls eligible to cross-over to immune checkpoint inhibitors, patients switching vs patients not switching							1.504 (1.111, 2.036)		

[¶] Survival times shrunk for the patients who actually crossed-over to immune checkpoint inhibitors.

[†] 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5. The 95% CI is derived by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[¶¶] Two sided p-value based on stratified Cox model, ITT population, analysis not adjusted for treatment switch.

[‖] Two sided p-value based on stratified log-rank test, ITT population, analysis not adjusted for treatment switch.

[††] Lognormal survival model for the control group using secondary baseline in time-to-event calculations and including following covariates: PD-L1 Status at Baseline (CPS < 20% vs. CPS ≥ 20%), HPV status (positive vs. negative), chemotherapy (Cisplatin vs. Carboplatin), ECOG at secondary baseline, race (White vs. All others), hemoglobin at secondary baseline and tumor size at secondary baseline.

[§] Patients were eligible to switch if they had documented progression.

[‡‡] Acceleration factor used to shrink the survival time of standard treatment patients who actually received subsequent immune checkpoint inhibitors. Its estimate and the 95% CI are derived from Stage 1 Lognormal model.

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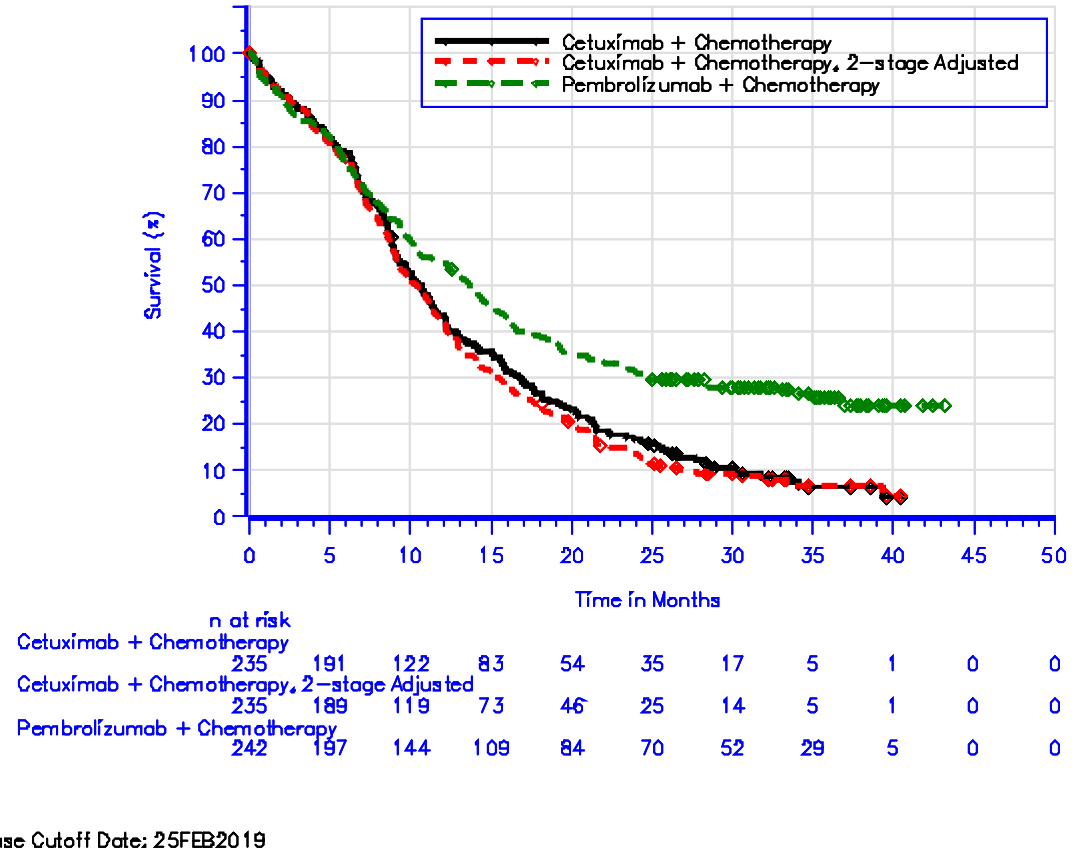
Figure 12 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using 2-stage analysis, without recensoring, pembrolizumab + chemotherapy vs. cetuximab + chemotherapy, ITT population with CPS≥1



Database Cutoff Date: 25FEB2019

Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the rank preserving structural failure (RPSFT) method

Table 28 and Figure 13 present the results of the OS analysis adjusting for receiving subsequent immune checkpoint inhibitors after discontinuation of protocol treatment for the control arm using RPSFT model without re-censoring. A total of 63/235 (26.8%) of control patients switched to an immune checkpoint inhibitor after discontinuation of the protocol treatment. The RPSFT-adjusted HR for OS is 0.62 (95% CI: 0.50; 0.78) with a two-sided ITT log-rank p-value <0.0001 in the pembrolizumab plus chemotherapy vs. cetuximab plus chemotherapy.

Table 28 Analysis of overall survival, without recensoring, adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, ITT population with CPS≥1, pembrolizumab + chemotherapy vs. cetuximab + chemotherapy

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median OS[†] (Months) (95% CI)	Survival Rate at Month 12[†] (95% CI)	Treatment vs. Cetuximab + Chemotherapy		
							Hazard Ratio[‡] (95% CI)[§]	p-Value[‖]	p-Value[¶]
Cetuximab + Chemotherapy	235	213 (90.6)	3084.0	6.9	10.4 (9.1, 11.7)	43.5 (37.0, 49.7)			
Cetuximab + Chemotherapy, RPSFT adjusted	235	213 (90.6)	2937.3	7.3	10.3 (9.0, 11.5)	43.0 (36.6, 49.2)			
Pembrolizumab + Chemotherapy	242	177 (73.1)	4020.9	4.4	13.6 (10.7, 15.5)	55.0 (48.5, 61.0)	0.62 (0.50, 0.78)	<.0001	<.0001

Rank-preserving structural failure time (RPSFT) model is used to adjust for the effect in overall survival analysis for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors.

[†] From product-limit (Kaplan-Meier) method.

[‡] Based on Cox regression model with Efron′s method of tie handling with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

[§] Obtained by inflating the standard error of the log-hazard ratio to preserve the ITT p-value from the Cox model.

[‖] Two sided p-value based on stratified Cox model, analysis not adjusted for treatment switch.

[¶] Two-sided p-value based on stratified log-rank test, analysis not adjusted for treatment switch.

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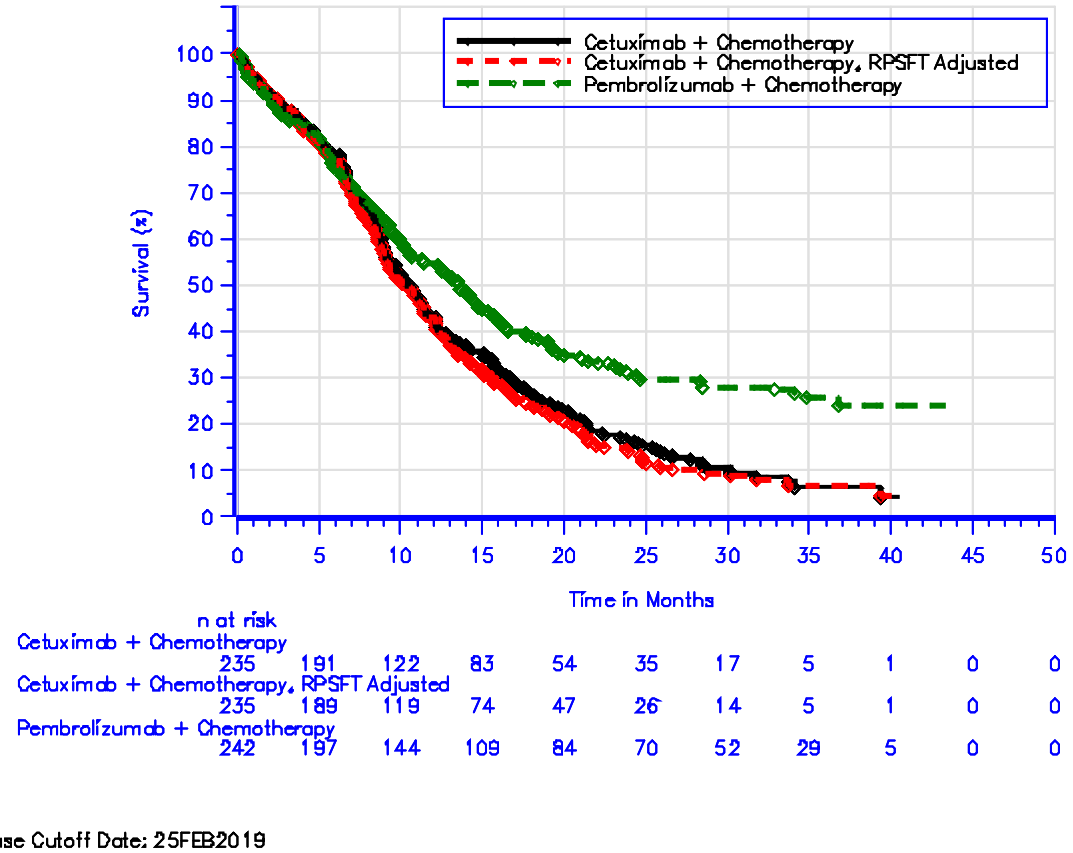
Figure 13 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received subsequent immune checkpoint inhibitors using RPSFT model, without recensoring, ITT population with CPS≥1, pembrolizumab + chemotherapy vs. cetuximab + chemotherapy



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Overall survival - adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the inverse probability censored weighting (IPCW) method

Of those who switched in the control arm, 57/63 (90.5%) subjects died after switching, and therefore 57/213 (26.8%) observed events in the control arm were lost due to censoring at the time of switch. Among those who did not switch in the control arm, 156/172 (90.7%) deaths were observed, and included in the analysis. Table 29 summarises the results from the weighted Cox proportional hazard regression. The IPCW-adjusted hazard ratio of pembrolizumab versus control is 0.72, with 95% bootstrap percentile confidence interval of 0.58 to 0.91 (bootstrap two-sided p-value = 0.0050). Figure 14 shows the survival curves for the ITT-unadjusted and the IPCW-adjusted control arm compared to the pembrolizumab plus chemotherapy arm.

Table 29 Analysis of overall survival adjusting for treatment switch to immune checkpoint inhibitors in standard treatment arm using IPCW model comparison, pembrolizumab + chemotherapy versus cetuximab + chemotherapy, intention-to-treat population with CPS≥1

Treatment	N	Number of Events (%)	Person-Month	Event Rate/ 100 Person-Month (%)	Median OS† (Month) (95% CI)	Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy		
						Hazard Ratio†† (95% CI)	p-Value§	p-Value§§
Cetuximab + Chemotherapy	235	213 (90.6)	3084.0	6.9	10.4 (9.1 , 11.7)			
Cetuximab + Chemotherapy, IPCW Adjusted	235	156 (66.4)	2516.1	6.2	10.8 (9.7 , 12.1)			
Pembrolizumab + Chemotherapy	242	177 (73.1)	4020.9	4.4	13.6 (10.7 , 15.5)	0.72 (0.58, 0.91)	0.0031	0.0050

† From product-limit (Kaplan-Meier) method for censored data, if the median OS is reached

†† HR based on Cox regression model with treatment as a covariate stratified by ECOG, HPV status and PD-L1 status, and bootstrap 95% CI. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ Two-sided p-value based on the IPCW log-rank test

§§ Two-sided p-value based on bootstrap percentiles

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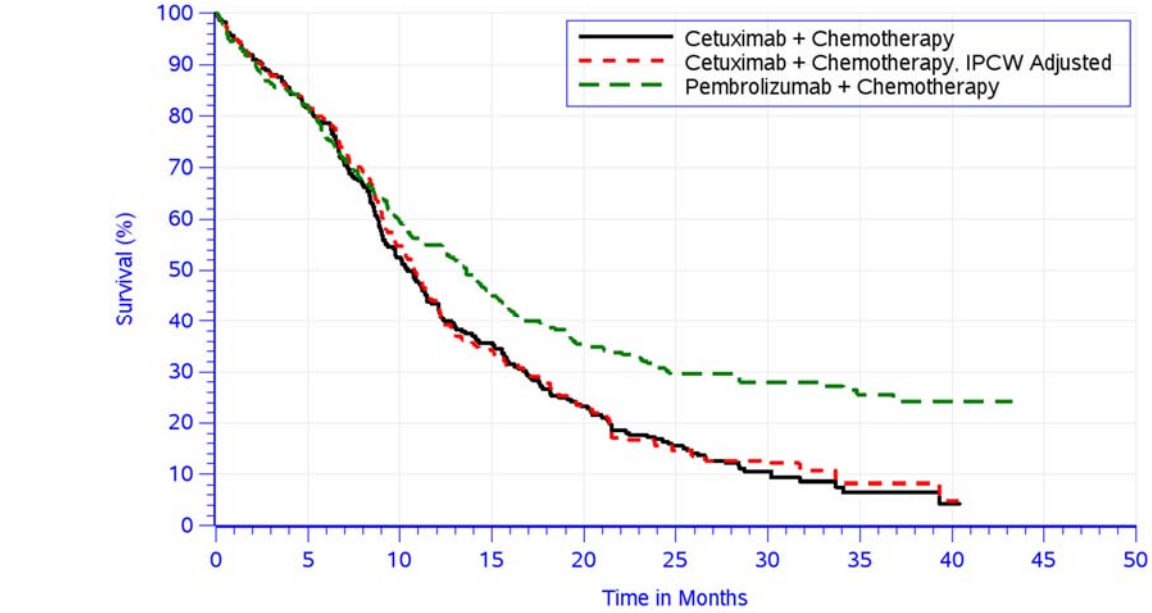
Figure 14 Kaplan-Meier curves of overall survival adjusting for subjects in standard treatment arm who received immune checkpoint inhibitors using IPCW comparison, pembrolizumab + chemotherapy versus cetuximab + chemotherapy, intention-to-treat population with CPS≥1



n at risk

Cetuximab + Chemotherapy	235	191	122	83	54	35	17	5	1	0	0
Cetuximab + Chemotherapy, IPCW Adjusted	235	179	101	58	33	21	14	5	1	0	0
Pembrolizumab + Chemotherapy	242	197	144	109	84	70	52	29	5	0	0

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Progression-free survival

The comparison between the pembrolizumab in combination with platinum and 5-FU chemotherapy group and the cetuximab plus chemotherapy group shows a median PFS of 5.1 months for the pembrolizumab in combination with platinum and 5-FU chemotherapy group (95% CI: 4.7, 6.2) and 5.0 months for the cetuximab plus chemotherapy group (95% CI: 4.8, 6.0) and a HR of 0.84 (95% CI: 0.69, 1.02) (Table 30). By KM estimation, PFS rates which were higher at 9 and 12 months (Table 31 and Figure 15).

Table 30 PFS based on BICR assessment per RECIST 1.1, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

Treatment	N	Number of Events (%)	Person-Months	Event Rate/ 100 Person-Months (%)	Median PFS † (Months) (95% CI)	PFS Rate at Months 6 in % † (95% CI)
Pembrolizumab + Chemotherapy	242	212 (87.6)	1982.4	10.7	5.1 (4.7, 6.2)	44.9 (38.5, 51.1)
Cetuximab + Chemotherapy	235	221 (94.0)	1582.8	14.0	5.0 (4.8, 6.0)	43.3 (36.9, 49.6)
Pairwise Comparisons					Hazard Ratio‡ (95% CI)‡	p-Value
Primary Pembrolizumab + Chemotherapy vs. Cetuximab + Chemotherapy					0.84 (0.69, 1.02)	0.03697§

† 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 ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

§ One-sided p-value based on log-rank test stratified by ECOG, HPV status and PD-L1 status. In case the event count in any stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is ≥5.

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Table 31 Summary of PFS rate over time based on BICR per RECIST 1.1, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

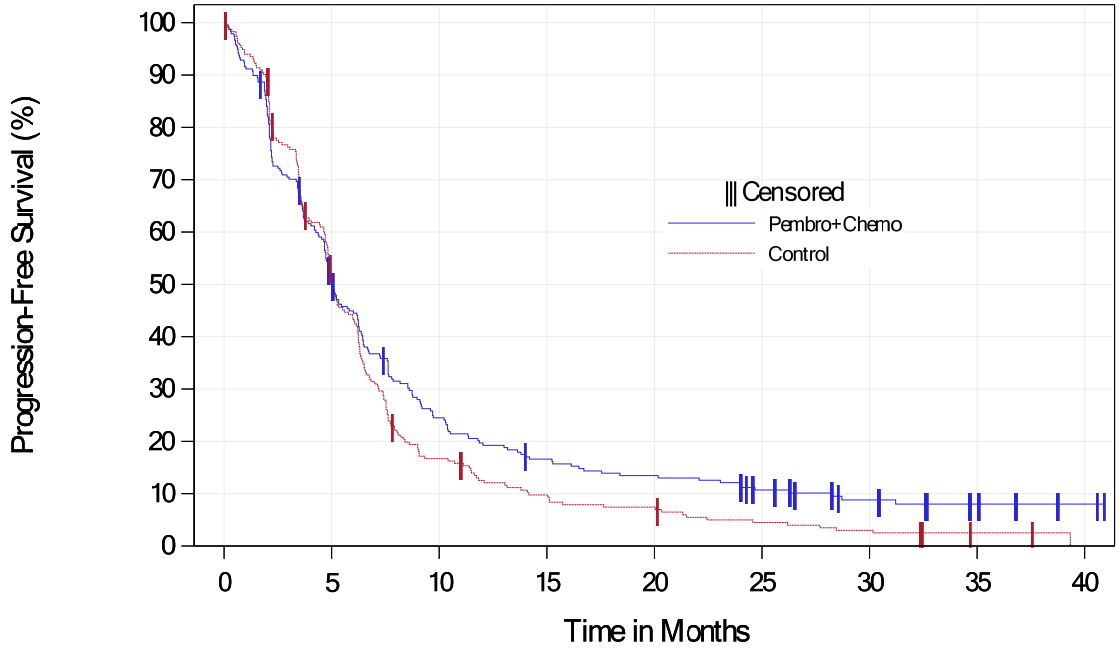
	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
PFS rate at 6 Months in (95% CI)†	44.9 (38.5, 51.1)	43.3 (36.9, 49.6)
PFS rate at 9 Months in (95% CI)†	28.0 (22.4, 33.9)	19.4 (14.5, 24.8)
PFS rate at 12 Months in (95% CI)†	19.7 (14.8, 25.0)	12.5 (8.6, 17.3)

BICR = Blinded Independent Central Review

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

(Database Cutoff Date: 25FEB2019).

Figure 15 Kaplan-Meier estimates of PFS based on BICR assessment per RECIST 1.1, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, CPS≥1 subgroup



At Risk

Pembro+Chemo	242	118	56	37	30	21	13	6	2
Control	235	113	37	21	16	9	6	2	0

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Response rate

Comparing the populations of participants with PD-L1 CPS≥1 in the pembrolizumab in combination with platinum and 5-FU chemotherapy group versus the cetuximab plus chemotherapy group, the (confirmed) ORR was similar: (36.4 % [95% CI: 30.3, 42.8] vs 35.7% [95% CI: 29.6, 42.2]) (Table 32). The best objective response (BOR) summary showed that a higher proportion of participants whose tumours express PD L1 CPS≥1 treated with pembrolizumab in combination with platinum and 5-FU chemotherapy also achieved a complete response (Table 33).

Table 32 Analysis of objective response (confirmed) based on BICR assessment per RECIST 1.1, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

Treatment	N	Number of Objective Responses	Objective Response Rate (%) (95% CI)	Difference in % vs. Control	
				Estimate (95% CI)[†]	p-Value[††]
Pembrolizumab + Chemotherapy	242	88	36.4 (30.3,42.8)	0.5 (-8.2,9.1)	0.4586
Cetuximab + Chemotherapy	235	84	35.7 (29.6,42.2)		

BICR = Blinded Independent Central Review

Responses are based on BICR assessments per RECIST 1.1 with confirmation.

[†] Based on Miettinen & Nurminen method stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive); in case the event count in on stratum is <5, stratification factors will be eliminated in the order of ECOG->HPV status->PD-L1 status until event count in every stratum is >=5; if no subjects are in one of the treatment groups involved in a comparison for a particular stratum, then that stratum is excluded from the treatment comparison.

[††] One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0.

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Table 33 Summary of best objective response with confirmation based on BICR per RECIST 1.1, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Number of Subjects in Population	242		235	
Complete Response (CR)	18	(7.4)	11	(4.7)
Partial Response (PR)	85	(35.1)	94	(40.0)
Objective Response (CR+PR)	**103**	**(42.6)**	**105**	**(44.7)**
Stable Disease (SD)	52	(21.5)	59	(25.1)
Progressive Disease (PD)	41	(16.9)	28	(11.9)
Non-CR/Non-PD (NN)	11	(4.5)	8	(3.4)
Not Evaluable (NE)	2	(0.8)	1	(0.4)
No Assessment	33	(13.6)	34	(14.5)

BICR = Blinded Independent Central Review

	Pembrolizumab + Chemotherapy		Cetuximab + Chemotherapy	
	n	(%)	n	(%)
Responses are based on BICR assessments per RECIST 1.1. Database Cutoff Date: 25FEB2019				

Duration of response

Comparing the populations of participants with PD-L1 CPS≥1 in the pembrolizumab in combination with platinum and 5-FU chemotherapy group with the cetuximab plus chemotherapy group, the median time to response [redacted], and the median response duration [redacted] (Table 34). There was [redacted] of responders with an estimated response duration ≥6 months [redacted] (Table 34 and Figure 16). A summary of the reasons that participants with a response based on RECIST 1.1 per BICR were censored from the duration of response analysis is provided in Database Cut-off Date: 25FEB2019

Table 35.

Table 34 Summary of time to response and duration of response based on BICR per RECIST 1.1 in subjects with confirmed response, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
Number of subjects with response[†]	[redacted]	[redacted]
Time to Response[†] (months)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
Response Duration[‡] (months)	[redacted]	[redacted]
Median (Range)	[redacted]	[redacted]
Number (%[‡]) of Subjects with Extended Response Duration:	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]

[†] Response: Best objective response as confirmed complete response or partial response.
[‡] From product-limit (Kaplan-Meier) method for censored data.
"+" indicates there is no progressive disease by the time of last disease assessment.
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Figure 16 Kaplan-Meier estimates of duration of response in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

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Table 35 Summary of response outcome in subjects with confirmed response based on BICR per RECIST 1.1, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ITT population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
Number of Subjects with Response[†]	[redacted]	[redacted]
Subjects Who Progressed or Died[‡] (%)	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]
Censored Subjects (%)	[redacted]	[redacted]
Subjects who missed 2 or more consecutive disease assessments	[redacted]	[redacted]
Subjects who started new anti-cancer treatment	[redacted]	[redacted]
Subjects who were lost to follow-up	[redacted]	[redacted]
Subjects whose last adequate assessment was ≥ 5 months prior to data cutoff date	[redacted]	[redacted]
Ongoing response[§]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]
Range of DOR (months)	[redacted]	[redacted]

[†] Includes subjects with a confirmed complete response or partial response.
[‡] Includes subjects who progressed or died without previously missing 2 or more consecutive disease assessments.
[§] Includes subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up, and whose last disease assessment was <5 months prior to data cutoff date.

	Pembrolizumab + Chemotherapy (N=242)	Cetuximab + Chemotherapy (N=235)
For censored subjects who met multiple criteria for censoring and do not have ongoing response, subjects are included in the censoring criterion that occurred earliest. '+' indicates there was no progressive disease by the time of last disease assessment. Database Cutoff Date: 25FEB2019		

Health-related quality of life

EORTC QLQ-C30

Over 15 weeks of follow up, participants receiving pembrolizumab in combination with platinum and 5-FU chemotherapy and cetuximab plus chemotherapy had [redacted] global health status/QoL. The mean change from baseline in the global health status/QOL score [redacted] in both the pembrolizumab in combination with platinum and 5-FU chemotherapy group ([redacted]) and the cetuximab plus chemotherapy group ([redacted]). The difference in LS means between pembrolizumab in combination with platinum and 5-FU chemotherapy and cetuximab plus chemotherapy at Week 15 was [redacted] (Table 36). A summary of the empirical mean change from baseline over time for the EORTC QLQ-C30 global health status/QoL scores is displayed in Figure 17, global health status/QoL scores [redacted] over time in both treatment groups through Week 51.

Time to deterioration in the EORTC QLQ-C30 global health status/QoL score for pembrolizumab plus chemotherapy was [redacted] when compared with standard treatment ([redacted]) (Table 37 and Figure 18). Similarly, time to deterioration in the EORTC QLQ H&N35 pain score (HR = 1.30; 95% CI: 0.84, 2.00; Table 38 and Figure 19) and swallowing score (HR = 0.94; 95% CI: 0.59, 1.50; Table 39 and Figure 20) for pembrolizumab plus chemotherapy were [redacted] when compared with standard treatment.

Table 36 Analysis of change from baseline of EORTC QLQ-C30 Global Health Status/QoL Scales at Week 15, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[†]
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

[†] Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive , Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

Database Cutoff: 25FEB2019

Figure 17 Empirical mean change from baseline in EORTC QLQ-C30 Global Health Status/QoL across time, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

Database Cut-off Date: 25FEB2019

Table 37 Analysis of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=231)	Cetuximab + Chemotherapy (N=220)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)[†]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy	[redacted]	[redacted]
Hazard Ratio (95% CI)[‡]	[redacted]	[redacted]
p-value[§]	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
[§] One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).
Database cutoff date: 25FEB2019

Figure 18 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-C30 Global Health Status/QoL, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

Database Cut-off Date: 25FEB2019

Table 38 Analysis of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=230)	Cetuximab + Chemotherapy (N=220)
Number of Events (%)		
Number of Censored (%)		
Kaplan-Meier Estimates (Months)[†]		
Median (95% CI)		
Q1, Q3		
vs Cetuximab + Chemotherapy		
Hazard Ratio (95% CI)[‡]		
p-value[§]		

[†] 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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
[§] One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).
Database cutoff date: 25FEB2019

Figure 19 Kaplan-Meier plot of time to true deterioration for EORTC QLQ-H&N35 Pain, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

Database Cut-off Date: 25FEB2019

Table 39 Analysis of time to true deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

	Pembrolizumab + Chemotherapy (N=230)	Cetuximab + Chemotherapy (N=220)
Number of Events (%)	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (Months)†	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
Q1, Q3	[redacted]	[redacted]
vs Cetuximab + Chemotherapy	[redacted]	[redacted]
Hazard Ratio (95% CI)‡	[redacted]	[redacted]
p-value§	[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 ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
§ One-sided p-value based on log-rank test stratified by ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive).
Time to true deterioration (event) is defined as time to first onset of 10 points or more worsening from baseline with confirmation under right-censoring rule (the last observation).
Database cutoff date: 25FEB2019

Figure 20 Kaplan-Meier Plot of Time to True Deterioration for EORTC QLQ-H&N35 Swallowing, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 subgroup

Database Cut-off Date: 25FEB2019

EQ-5D

Analyses of the mean change from baseline to Week 15 in the EQ-5D utility scores and visual analog scale in the PRO FAS population are provided in Table 40 and Table 41. In the PRO FAS population, participants in both the pembrolizumab in combination with platinum and 5-FU chemotherapy and cetuximab plus chemotherapy groups exhibited [redacted] scores in the EQ-5D utility scores and visual analog scale scores up to Week 15.

Table 40 Analysis of change from baseline of EQ-5D Utility Score (using European Algorithm) at Week 15, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 population

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

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Table 41 Analysis of change from baseline of EQ-5D VAS at Week 15, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, FAS population, CPS≥1 population

	Baseline		Week 15		Change from Baseline at Week 15	
Treatment	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)†
Pembrolizumab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab + Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

† Based on cLDA model with the PRO scores as the response variable, and treatment by study visit interaction, stratification factors (ECOG (0 vs. 1), HPV status (Positive vs. Negative) and PD-L1 status (Strongly Positive, Not Strongly Positive)) as covariates.

For baseline and Week 15, 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.

Database Cutoff: 25FEB2019

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Pembrolizumab monotherapy

Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

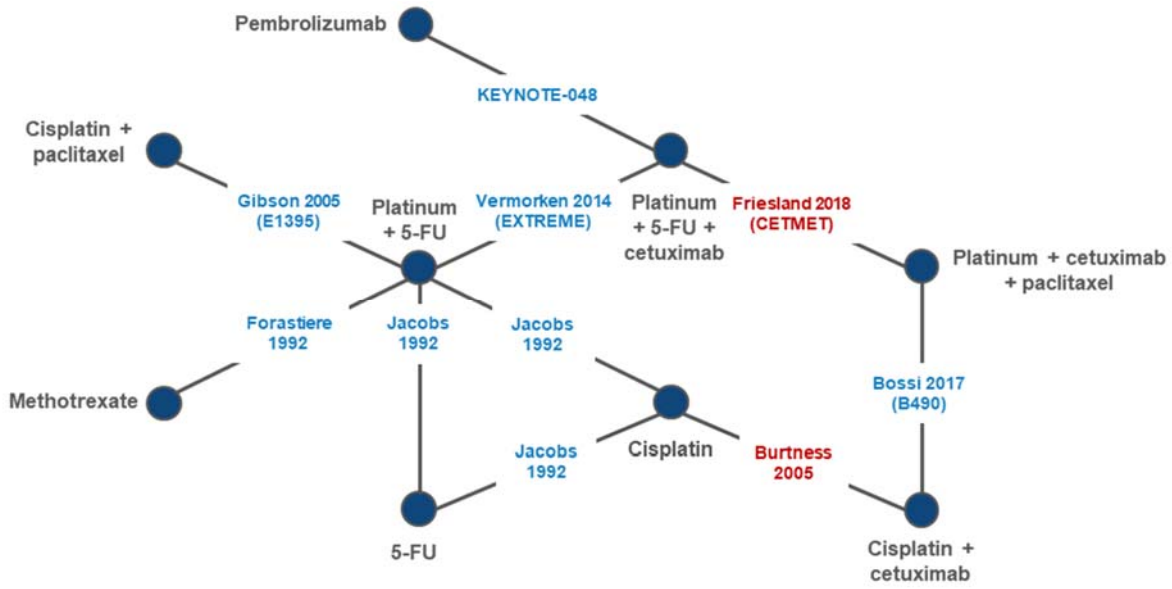
For OS, KM curves were presented in all of the eight included trials. All studies were included in the CPS≥1 population analyses. The NMA comparison network is presented in Figure 21. DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D section D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=0 and p2=0.5 for the CPS≥1 subgroup analysis. The results of time-varying OS HRs for pembrolizumab monotherapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 42.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment arms) in order to generate the OS proportions over time, which are summarised for each intervention in Figure 22.

Amongst patients in the CPS≥1 subgroup, and consistent with the results of the KEYNOTE-048 trial, OS NMA results showed a statistically meaningful improvement in OS with pembrolizumab monotherapy in comparison with the EXTREME regimen; the OS HRs and 95% CrIs were less than 1 for the majority of time points with OS benefit increasing steadily from month 6 ([redacted]) through month 36 ([redacted]) in the CPS≥1 subgroup. Similarly, pembrolizumab monotherapy was consistently associated with a statistically meaningful improvement in OS in comparison with platinum + 5-FU, with the magnitude of OS benefit increasing over time from month 6 (HR = 0.67; 95% CrI: 0.50, 0.90) through month 36 (HR = 0.44; 95% CrI: 0.26, 0.74) in the CPS ≥1 subgroup. Additional indirect comparisons of pembrolizumab monotherapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying

patient sample sizes to form the basis of the network connections. Among these comparisons in the CPS ≥1 subgroup, pembrolizumab monotherapy consistently showed a statistically meaningful improvement in OS in comparison with cisplatin, 5-FU, and methotrexate for the majority of time points, and showed a trend in OS benefit in comparison with cetuximab + cisplatin, cisplatin + paclitaxel, and platinum + paclitaxel + cetuximab comparators, although the 95% credible intervals were wide and did not exclude 1.

Figure 21 Full network of all randomised controlled trials for overall survival (pembrolizumab monotherapy)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 42 Estimated overall survival hazard ratios for pembrolizumab monotherapy versus comparators from fixed-effects network meta-analysis (P1=0, P2=0.5); PD-L1 CPS≥1 subgroup, crossover adjustment via the 2-stage method

Time point (month)	Platinum+ 5-FU+ Cetuximab	Cetuximab+ Cisplatin	Platinum+ 5-FU	Cisplatin+ Paclitaxel	Platinum+ Paclitaxel+ Cetuximab	Cisplatin	5-FU	Methotrexate
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab monotherapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 22 Estimated overall survival from fixed-effects network meta-analysis (P0=1, P2=0.5); pembrolizumab monotherapy versus comparators, PD-L1 CPS≥1 subgroup, crossover adjustment via the 2-stage method

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

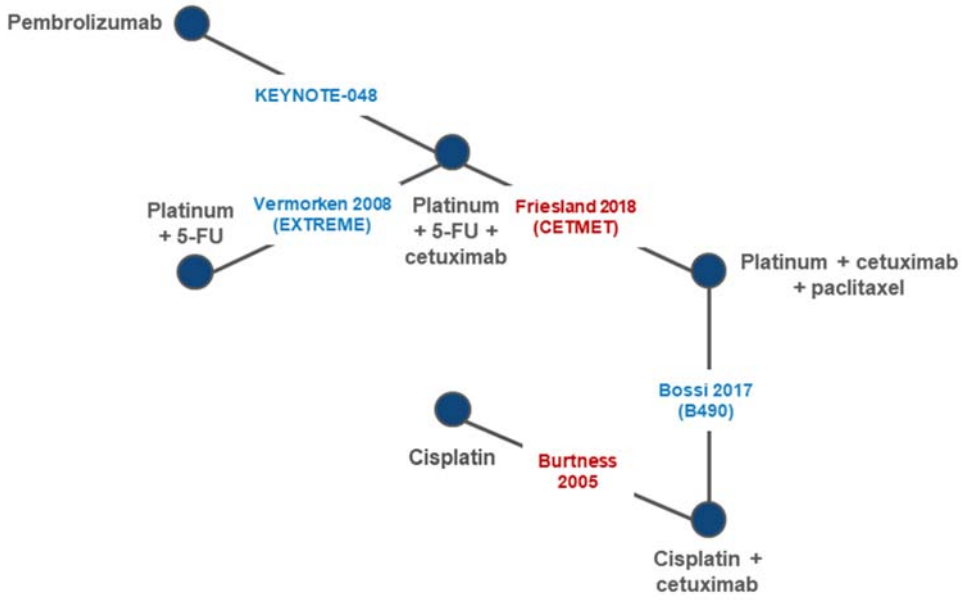
Progression-free survival

For PFS, KM curves were presented in five trials included in the SLR and after NMA feasibility assessment, all of which were included in the CPS≥1 population analysis, the network of trials is presented in Figure 23. DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=0 and p2=-1 for the CPS≥1 analysis. The results of time-varying PFS HRs for pembrolizumab monotherapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 43.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment arms) in order to generate the PFS proportions over time, which are summarised for each intervention in Figure 24.

Amongst patients in in CPS≥1 subgroup, and consistent with the results of the KEYNOTE-048, the NMA showed that the PFS benefit associated with pembrolizumab monotherapy compared with cetuximab in combination with platinum and 5-FU chemotherapy is generally only seen at later time points, with a statistically meaningful PFS benefit observed from month 9 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. In addition, pembrolizumab monotherapy demonstrated a statistically meaningful PFS improvement compared with platinum + 5-FU for the majority of time points starting from month 6 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. Additional indirect comparisons of pembrolizumab monotherapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying patient sample sizes to form the basis of the network connections. PFS was comparable for pembrolizumab versus the remaining regimens (cisplatin, platinum + paclitaxel + cetuximab, and cetuximab + cisplatin) at all time points.

Figure 23 Full network of all randomised controlled trials for progression-free survival (pembrolizumab monotherapy)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 43 Estimated progression-free survival hazard ratios for pembrolizumab monotherapy versus comparators from fixed-effects network meta-analysis (P1=0, P2=-1); PD-L1 CPS≥1 subgroup

Time point (month)	Platinum+ 5-FU+ Cetuximab	Cetuximab+ Cisplatin	Platinum+5-FU	Platinum+ Paclitaxel+ Cetuximab	Cisplatin
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab monotherapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.
Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 24 Estimated progression-free survival from fixed-effects network meta-analysis (P1=0, P2=-1); pembrolizumab monotherapy versus comparators, PD-L1 CPS≥1 subgroup

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

B.2.9.2 Pembrolizumab + chemotherapy combination therapy

Overall survival – adjustment for the post-study treatment switch-over of control arm patients to another immune checkpoint inhibitor via the simplified 2-stage method

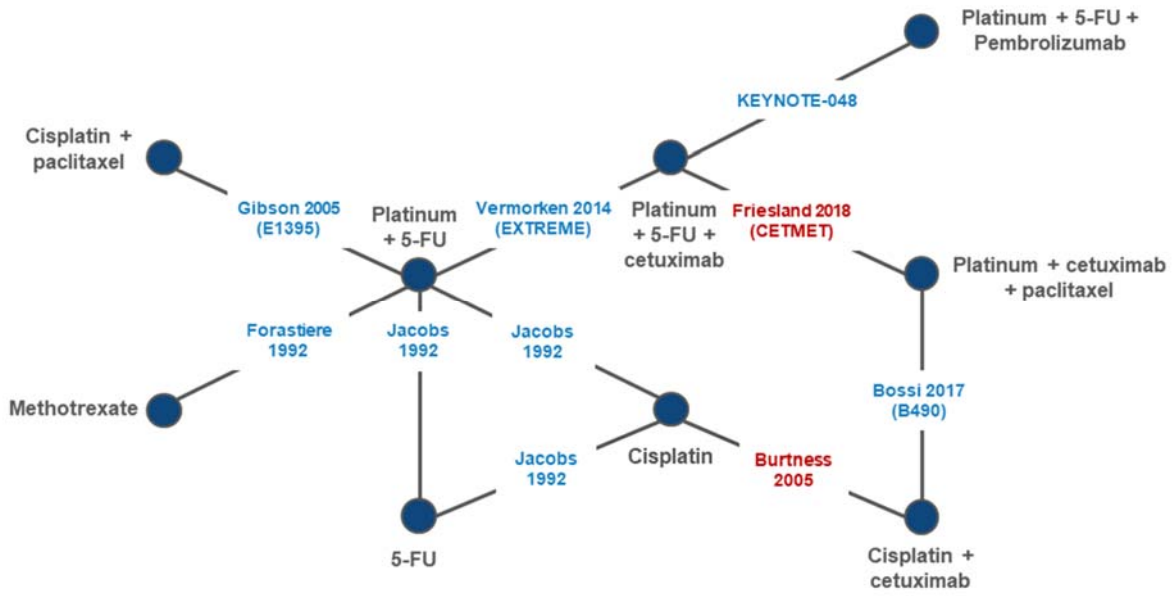
Network of the included trials for the OS outcome for the PD-L1 CPS≥1 population was the same as that of the overall population (Figure 25). DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D section D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=1 and p2=0. The results of time-

varying OS HRs for pembrolizumab monotherapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 44.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment arms) in order to generate the OS proportions over time, which are summarised for each intervention in Figure 26.

In the CPS≥1 subgroup, and consistent with the results of the KEYNOTE-048 trial, OS NMA results showed a statistically meaningful improvement in OS with pembrolizumab combination therapy in comparison with the EXTREME regimen; the OS HRs and 95% CrI bounds were less than 1 for the majority of time points with OS benefit increasing steadily from month 9 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. Similarly, pembrolizumab combination therapy was consistently associated with a statistically meaningful improvement in OS in comparison with platinum + 5-FU, with the magnitude of OS benefit increasing over time from month 6 ([redacted]) through month 36 ([redacted]) in the CPS≥1 subgroup. Additional indirect comparisons of pembrolizumab combination therapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying patient sample sizes to form the basis of the network connections. Among these comparisons in the CPS≥1 subgroup, pembrolizumab combination therapy consistently showed a statistically meaningful improvement in OS in comparison with 5-FU and methotrexate for the majority of time points, and showed a trend in OS benefit in comparison with cisplatin + paclitaxel, and cisplatin comparators, although the 95% credible intervals were wide and did not exclude 1.

Figure 25 Full network of all randomised controlled trials for overall survival (pembrolizumab combination therapy)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 44 Estimated overall survival hazard ratios for pembrolizumab combination therapy versus comparators from fixed-effects network meta-analysis (P1=1, P2=0); PD-L1 CPS≥1 subgroup, crossover adjustment via the 2-stage method

Time point (month)	Platinum+ 5-FU+ Cetuximab	Cetuximab+ Cisplatin	Platinum+ 5-FU	Cisplatin+ Paclitaxel	Platinum+ Paclitaxel+ Cetuximab	Cisplatin	5-FU	Methotrexate
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab + chemotherapy combination therapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 26 Estimated overall survival from fixed-effects network meta-analysis (P0=1, P2=0); pembrolizumab combination therapy versus comparators, PD-L1 CPS≥1 subgroup, crossover adjustment via the 2-stage method

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

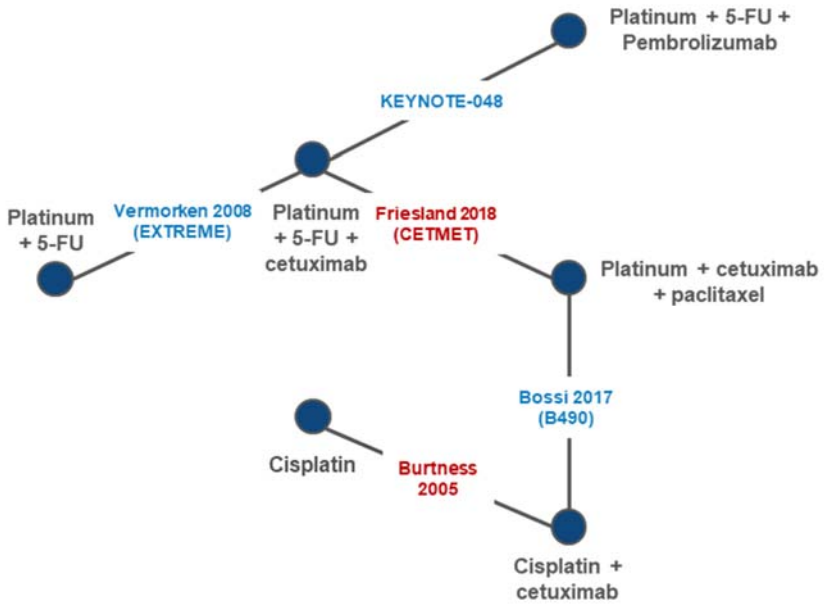
Progression-free survival

The network of the included trials for the PFS outcome for the PD-L1 CPS≥1 population is shown in Figure 27. DIC values for all the alternative fractional polynomial models that were fitted are presented in Appendix D.1.4. According to the model selection process, the best fitting model was the second-order fractional polynomial with p1=0 and p2=0.5. The results of time-varying PFS HRs for pembrolizumab in combination with platinum and 5-FU chemotherapy versus competing interventions, estimated from a fixed-effects model, are summarised in Table 45.

The estimated time-varying HRs were applied to a reference modelled survival function (platinum + 5-FU as the comparator with the largest number of treatment arms) in order to generate the PFS proportions over time, which are summarised for each intervention in Figure 28.

The pembrolizumab in combination with platinum and 5-FU chemotherapy versus cetuximab in combination with platinum and 5-FU chemotherapy PFS HRs and 95% CrI bounds were less than 1 for the majority of time points with PFS benefit increasing steadily from month 6 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. Similarly, pembrolizumab in combination with platinum and 5-FU chemotherapy was consistently associated with a statistically meaningful improvement in PFS in comparison with platinum + 5-FU, with the magnitude of PFS benefit increasing over time from month 3 ([redacted]) through month 36 ([redacted]) in the CPS ≥1 subgroup. Additional indirect comparisons of pembrolizumab in combination with platinum and 5-FU chemotherapy with the remaining treatment regimens were limited by the relatively smaller number of trials and underlying patient sample sizes to form the basis of the network connections. PFS was comparable for pembrolizumab in combination with platinum and 5-FU chemotherapy versus the remaining regimens (cetuximab + cisplatin, platinum + paclitaxel + cetuximab, and cisplatin) at all time points.

Figure 27 Full network of all randomised controlled trials for progression-free survival (pembrolizumab in combination with platinum and 5-FU chemotherapy versus comparators)



Notes: Trials in blue are in populations meeting the Tier 1 definition. Trials in red are in populations meeting the Tier 2 definition. Abbreviations: 1L, first-line; 5-FU, fluorouracil.

Table 45 Estimated progression-free survival hazard ratios for pembrolizumab in combination with platinum and 5-FU chemotherapy versus comparators from fixed-effects network meta-analysis (P1=0, P2=0.5); PD-L1 CPS≥1 subgroup

Time point (month)	Platinum+ 5-FU+ Cetuximab	Cetuximab+Cisplatin	Platinum+5-FU	Platinum+ Paclitaxel+ Cetuximab	Cisplatin
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals. Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab + chemotherapy combination therapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point.
Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

Figure 28 Estimated progression-free survival from fixed-effects network meta-analysis (P1=0, P2=0.5); pembrolizumab in combination with platinum and 5-FU chemotherapy versus comparators, PD-L1 CPS≥1 subgroup

Abbreviations: 5-FU, 5-fluorouracil; CPS, combined positive score; PD-L1, programmed death ligand 1.

B.2.10 Adverse reactions

Summaries of the AE data from the KEYNOTE-048 trial are provided in this section. Data tables showing the details of the adverse events from this trial are provided in Appendix F. Data for the (larger) overall population of the KEYNOTE-048 trial (including data from all patients, not just those in the CPS≥1 subgroups) are described; however, the overall summaries of adverse events between the CPS≥1 population versus the overall population are also compared to demonstrate that the AE profile in this subgroup does not differ substantially from that in the overall population.

B.2.10.1 Pembrolizumab monotherapy

The safety results from KEYNOTE-048 demonstrate that pembrolizumab monotherapy:

- Has a favourable adverse event profile compared with standard treatment.

- Is well tolerated with low rates of treatment discontinuation.
- The incidences and types of AEOSIs were generally consistent with the known safety profile of pembrolizumab monotherapy use in R/M HNSCC.

Summary of adverse events

In the overall population, a total of 290 participants (96.7%) in the pembrolizumab monotherapy group experienced at least 1 AE compared with 286 participants (99.7%) in the standard treatment group (Table 46). The favourable AE profile of pembrolizumab monotherapy compared with standard treatment was further demonstrated by the lower incidence of AEs for all of the AE categories in (Table 46). It can also be seen from Table 46 that the AE profile of pembrolizumab monotherapy in all of the AE categories, both considered on its own in and in terms of the difference between it and cetuximab + chemotherapy, in the CPS≥1 population does not differ substantially to that in the overall population.

Table 46 Adverse event summary, pembrolizumab monotherapy vs. cetuximab plus chemotherapy, ASaT population, comparison between the overall population and CPS≥1 subgroup

	Overall population				CPS≥1 subgroup				
	Pembrolizumab monotherapy		Cetuximab + chemotherapy		Pembrolizumab monotherapy		Cetuximab + chemotherapy		Difference in % vs control arm†
	n	(%)	n	(%)	n	(%)	n	(%)	Estimate (95% CI)
Subjects in population	300		287		256		245		
with one or more adverse events	290	(96.7)	286	(99.7)	248	(96.9)	244	(99.6)	-2.7(-5.7,-0.5)
with no adverse event	10	(3.3)	1	(0.3)	8	(3.1)	1	(0.4)	2.7(0.5,5.7)
with drug-related‡ adverse events	175	(58.3)	278	(96.9)	152	(59.4)	236	(96.3)	-37.0(-43.4,-30.5)
with toxicity grade 3-5 adverse events	164	(54.7)	239	(83.3)	140	(54.7)	203	(82.9)	-28.2(-35.7,-20.3)
with toxicity grade 3-5 drug-related adverse events	51	(17.0)	199	(69.3)	46	(18.0)	167	(68.2)	-50.2(-57.3,-42.4)
with serious adverse events	123	(41.0)	141	(49.1)	106	(41.4)	121	(49.4)	-8.0(-16.6,0.7)
with serious drug-related adverse events	28	(9.3)	72	(25.1)	28	(10.9)	59	(24.1)	-13.1(-19.8,-6.6)
with dose modification§ due to an adverse event	116	(38.7)	240	(83.6)	100	(39.1)	206	(84.1)	-45.0(-52.2,-37.2)
who died	25	(8.3)	28	(9.8)	18	(7.0)	28	(11.4)	-4.4(-9.7,0.7)
who died due to a drug-related adverse event	3	(1.0)	8	(2.8)	3	(1.2)	8	(3.3)	-2.1(-5.3,0.6)
discontinued drug due to an adverse event	36	(12.0)	79	(27.5)	30	(11.7)	67	(27.3)	-15.6(-22.5,-8.8)
discontinued drug due to a drug-related adverse event	15	(5.0)	59	(20.6)	15	(5.9)	48	(19.6)	-13.7(-19.7,-8.1)
discontinued drug due to a serious adverse event	29	(9.7)	48	(16.7)	23	(9.0)	45	(18.4)	-9.4(-15.5,-3.4)
discontinued drug due to a serious drug-related adverse event	9	(3.0)	28	(9.8)	9	(3.5)	25	(10.2)	-6.7(-11.5,-2.4)

†Based on Miettinen & Nurminen method.

‡Determined by the investigator to be related to the drug.
§Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.
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.
Database Cut-off Date: 25FEB2019

Adverse events by decreasing incidence

With the exception of hypothyroidism and dyspnoea, all other AEs were reported in a similar or lower proportion of participants receiving pembrolizumab monotherapy compared to standard treatment. The most common AEs reported in the pembrolizumab monotherapy group (>20% incidence) were fatigue and anaemia, whereas nausea, anaemia, hypomagnesemia, rash, fatigue, diarrhoea, constipation, and neutropenia were the most common AEs reported (>30% incidence) in the standard treatment group.

Drug-related adverse events

The proportion of participants with at least 1 drug-related AE (incidence ≥5%) was lower in the pembrolizumab monotherapy group (58.3% compared to 96.9% in the standard treatment group). With the exception of hypothyroidism (which were Grade 1 or 2), all other drug-related AEs (incidence ≥10%) were less frequently reported in the pembrolizumab monotherapy group.

Grade 3-5 adverse events

The proportion of participants with 1 or more Grade 3 to 5 AEs was lower in the pembrolizumab monotherapy group (54.7% compared with 83.3% in the standard treatment group). The main differences included a lower rate of neutropenia, neutrophil count decrease, anaemia, WBC decrease, thrombocytopenia, nausea, leukopenia, rash, febrile neutropenia, hypokalaemia, and mucosal inflammation events in the pembrolizumab monotherapy group. The most common Grade 3 to 5 AEs (>4% incidence) in the pembrolizumab monotherapy group were hyponatremia, pneumonia, and anaemia; whereas neutropenia, anaemia, and neutrophil count decrease were the most common Grade 3 to 5 AEs in the standard treatment group (>10% incidence).

Drug-related grade 3-5 adverse events

The proportion of participants with Grade 3 to 5 AEs considered to be drug-related was lower in the pembrolizumab monotherapy group (17.0% compared with 69.3% in the standard treatment group). The most common drug-related Grade 3 to 5 AEs in the pembrolizumab monotherapy group were hyponatremia and pneumonitis (>1% incidence), whereas neutropenia, anaemia, and neutrophil count decrease were events most commonly reported in the standard treatment group (>10% incidence).

Serious adverse events

The proportion of participants with 1 or more SAE was lower in the pembrolizumab monotherapy group compared with the standard treatment group (41.0% versus 49.1%). The most frequently (≥2% incidence) reported SAEs in the pembrolizumab monotherapy group were pneumonia, tumour haemorrhage, dyspnoea, and sepsis, whereas pneumonia, febrile neutropenia, nausea, anaemia, and pulmonary embolism were commonly reported in the standard treatment group.

Drug-related serious adverse events

The proportion of participants with 1 or more drug-related SAE was lower in the pembrolizumab monotherapy group (9.3% compared to 25.1% in the standard treatment group). The most frequently reported drug-related SAEs by decreasing incidence was pneumonitis (which is a known AEOSI of pembrolizumab) in the pembrolizumab monotherapy group (≥1% incidence), whereas febrile neutropenia, anaemia, pneumonia, and nausea were commonly reported in the standard treatment group (>2% incidence).

Adverse events resulting in death

The proportion of participants with AEs resulting in death was similar in the 2 treatment groups. The most common reason for death in participants treated with pembrolizumab monotherapy was sepsis (3 participants [1.0%]). In the standard treatment group the most common reason for death was pneumonia (6 participants [2.1%]) and tumour haemorrhage (3 participants [1.0%]). Drug-related deaths were reported in 3 (1.0%) and 8 (2.8%) participants in the pembrolizumab monotherapy and standard treatment groups, respectively.

Drug-related adverse events resulting in discontinuation

Drug-related AEs resulting in discontinuation of study intervention were lower in the pembrolizumab monotherapy group (5.0% compared to 20.6% in the standard treatment group). The most common drug-related AE resulting in the discontinuation of study treatment was autoimmune hepatitis, adrenal insufficiency, and pneumonitis in the pembrolizumab monotherapy group. The most common drug-related AE resulting in the discontinuation of study treatment was infusion related reaction and rash and anaemia in the standard treatment group.

Adverse events special interest

The overall incidence of AEOSI was similar in the pembrolizumab monotherapy group and the standard treatment group (31.0% and 23.7%, respectively) with the exception of a lower proportion of participants in the pembrolizumab monotherapy group discontinuing study intervention due to an AEOSI (including those considered to be drug-related).

The incidence rate of AEOSIs were similar between the two groups, except that pembrolizumab monotherapy group had a higher rate of hypothyroidism, pneumonitis and hyperthyroidism; whereas, the standard treatment group had a higher rate of infusion reactions and severe skin reactions. The majority of AEOSIs in the pembrolizumab monotherapy group were Grade 1 and 2, whereas in the standard treatment group AEOSIs were most commonly Grade 2 and 3.

B.2.10.2 Pembrolizumab + chemotherapy combination therapy in the overall population

The safety results from KEYNOTE-048 demonstrate that pembrolizumab plus chemotherapy:

- Has a comparable and tolerable safety profile compared with standard treatment. The results from the KEYNOTE-048 study are consistent with the known safety profiles of pembrolizumab monotherapy and platinum plus 5-FU chemotherapy, with no new safety issues identified.
- Per exposure-adjusted event rates, pembrolizumab plus chemotherapy does not result in an additive effect in terms of the frequency and severity of several important chemotherapy-related toxicities, including neutropenia, anaemia, and thrombocytopenia.
- The exposure-adjusted event rates of Grade 3 to 5 stomatitis and mucosal inflammation were higher in the pembrolizumab plus chemotherapy group than in the standard treatment group. A shorter time from prior radiation and more current smokers are identified as 2 risk factors that may contribute to the higher rate of these events in the pembrolizumab plus chemotherapy group.

- Higher rates of SAEs (including those considered to be related to study intervention) were reported in the pembrolizumab plus chemotherapy group compared to standard treatment group.
- The proportion of participants discontinuing study treatment due to an AE was similar between the pembrolizumab plus chemotherapy and the standard treatment groups.
- The incidences and types of AEOSIs were generally consistent with the known safety profile of pembrolizumab monotherapy use in R/M HNSCC.
- The AEs observed for pembrolizumab plus chemotherapy were effectively managed by standard clinical practice as applicable for pembrolizumab monotherapy or platinum plus 5-FU.

Summary of adverse events

The AE summary profile observed for participants treated with pembrolizumab plus chemotherapy was generally consistent with the known safety profiles of pembrolizumab monotherapy and of chemotherapy.

The frequency of AEs by category was similar in the pembrolizumab plus chemotherapy group and in the standard treatment group, including all AEs, drug-related AEs, Grade 3 to 5 AEs, dose modification due to AE, deaths due to AEs, and AEs leading to treatment discontinuation (Table 47). The pembrolizumab plus chemotherapy group experienced a higher frequency of SAEs and drug-related SAEs (59.8% and 37.3% compared with 49.1% and 25.1% in the standard treatment group, respectively) (Table 47). It can also be seen from Table 47 that the AE profile of pembrolizumab plus chemotherapy in all of the AE categories, both considered on its own in and in terms of the difference between it and cetuximab + chemotherapy, in the CPS≥1 population does not differ substantially to that in the overall population.

Table 47 Adverse event summary, pembrolizumab in combination with platinum and 5-FU chemotherapy vs. cetuximab plus chemotherapy, ASaT population, comparison between the overall population and CPS≥1 subgroup

	Overall population				CPS≥1 subgroup				
	Pembrolizumab + chemotherapy		Cetuximab + chemotherapy		Pembrolizumab + chemotherapy		Cetuximab + chemotherapy		Difference in % vs control arm†
	n	(%)	n	(%)	n	(%)	n	(%)	Estimate (95% CI)
Subjects in population	276		287		237		245		
with one or more adverse events	271	(98.2)	286	(99.7)	233	(98.3)	244	(99.6)	-1.3 (-3.9, 0.8)
with no adverse event	5	(1.8)	1	(0.3)	4	(1.7)	1	(0.4)	1.3 (-0.8, 3.9)
with drug-related‡ adverse events	264	(95.7)	278	(96.9)	227	(95.8)	236	(96.3)	-0.5 (-4.4, 3.2)
with toxicity grade 3-5 adverse events	235	(85.1)	239	(83.3)	203	(85.7)	203	(82.9)	2.8 (-3.8, 9.4)
with toxicity grade 3-5 drug-related adverse events	198	(71.7)	199	(69.3)	173	(73.0)	167	(68.2)	4.8 (-3.3, 12.9)
with serious adverse events	165	(59.8)	141	(49.1)	150	(63.3)	121	(49.4)	13.9 (5.0, 22.5)
with serious drug-related adverse events	103	(37.3)	72	(25.1)	96	(40.5)	59	(24.1)	16.4 (8.1, 24.6)
with dose modification§ due to an adverse event	233	(84.4)	240	(83.6)	203	(85.7)	206	(84.1)	1.6 (-4.9, 8.0)
who died	32	(11.6)	28	(9.8)	30	(12.7)	28	(11.4)	1.2 (-4.7, 7.2)
who died due to a drug-related adverse event	11	(4.0)	8	(2.8)	9	(3.8)	8	(3.3)	0.5 (-3.0, 4.2)
discontinued drug due to an adverse event	90	(32.6)	79	(27.5)	82	(34.6)	67	(27.3)	7.3 (-1.0, 15.5)
discontinued drug due to a drug-related adverse event	69	(25.0)	59	(20.6)	62	(26.2)	48	(19.6)	6.6 (-0.9, 14.1)
discontinued drug due to a serious adverse event	58	(21.0)	48	(16.7)	55	(23.2)	45	(18.4)	4.8 (-2.4, 12.1)
discontinued drug due to a serious drug-related adverse event	35	(12.7)	28	(9.8)	33	(13.9)	25	(10.2)	3.7 (-2.1, 9.7)

†Based on Miettinen & Nurminen method.

‡Determined by the investigator to be related to the drug.
§Defined as an action taken of dose reduced, drug interrupted or drug withdrawn.
Estimated differences and confidence intervals are provided in accordance with the statistical analysis plan.
For subjects who received second course treatment, adverse events which occurred in second course phase are excluded.
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.
Database Cut-off Date: 25FEB2019

Adverse events by decreasing incidence

The most frequently reported AEs (incidence >40%) in both treatment groups were anaemia and nausea, which are expected AEs of platinum and 5-FU chemotherapy, and additionally, in the standard treatment group, hypomagnesemia, which is consistent with the AE profiles of cetuximab.

Drug-related adverse events

The number of participants with at least 1 drug-related AE (incidence ≥5%) was comparable in both treatment groups. The most frequently reported drug-related AEs (incidence >40%) in participants in both treatment groups were anaemia and nausea, which are expected AEs of platinum and 5-FU chemotherapy. Treatment differences included a higher proportion of participants in the pembrolizumab plus chemotherapy group who had drug-related anaemia, thrombocytopenia, hypothyroidism, blood creatinine increase, peripheral sensory neuropathy, malaise, and acute kidney injury, and a higher proportion of participants in the standard treatment group who had various skin-related events, hypokalaemia, hypomagnesemia, hypophosphatemia, and infusion-related reactions.

Grade 3-5 adverse events

No substantial differences in the type and frequencies of Grade 3 to 5 AEs were reported between the 2 treatment groups, except for a higher rate of anaemia, stomatitis, and mucosal inflammation in the pembrolizumab plus chemotherapy group, and a higher rate of rash in the standard treatment group. The most frequently reported Grade 3 to 5 AEs (>10% incidence) by decreasing incidence were anaemia, neutropenia, and neutrophil count decrease in both treatment groups. The incidence of these most frequently reported Grade 3 or 5 events was comparable between the 2 treatment groups, with the exception of anaemia which was reported more frequently in the pembrolizumab plus chemotherapy group.

Drug-related grade 3-5 adverse events

The proportion of participants who experienced Grade 3 to 5 AEs considered to be drug-related were similar in both treatment groups. The most common drug-related Grade 3 to 5 AEs (>10% incidence) in both treatment groups were anaemia,

neutropenia, and neutrophil count decrease. The incidence of these events was comparable between the 2 treatment groups. The main difference was a higher rate of stomatitis, febrile neutropenia, and mucosal inflammation in the pembrolizumab plus chemotherapy group.

Serious adverse events

The proportion of participants with 1 or more SAE was higher in the pembrolizumab plus chemotherapy group (59.8% compared with 49.1% in the standard treatment group). The most frequently reported SAEs (>5% incidence in the pembrolizumab plus chemotherapy groups and >3% incidence in the standard treatment group) were febrile neutropenia, pneumonia, and anaemia in both treatment groups.

Drug-related serious adverse events

The number of participants with 1 or more drug-related SAE was higher in the pembrolizumab plus chemotherapy group (37.3% compared with 25.1% in the standard treatment group). The most frequently reported drug-related SAEs (≥3% incidence in the pembrolizumab plus chemotherapy group and >2.5% incidence in the standard treatment group), were febrile neutropenia and anaemia in both treatment groups.

Adverse events resulting in death

The proportion of participants with AEs resulting in death was similar in the 2 treatment groups (11.6% in the pembrolizumab plus chemotherapy group and 9.8% in the standard treatment group). The most common reason for death in participants treated with pembrolizumab plus chemotherapy was septic shock (5 participants [1.8%]). In the standard treatment group the most common reason for death was pneumonia (6 participants [2.1%]). The incidence of death due to infection was similar in both treatment groups.

Drug-related adverse events resulting in discontinuation

The proportion of participants discontinuing study treatment due to a drug-related AE was similar in the 2 treatment groups. The most common drug-related AEs resulting in the discontinuation of study treatment in the pembrolizumab plus chemotherapy

group were blood creatinine increase, neutropenia, mucosal inflammation, pneumonia, and septic shock. The most common drug-related AEs resulting in the discontinuation of study treatment in the standard treatment group were infusion related reaction, rash, and anaemia.

Adverse events special interest

The overall incidence of AEOSI was similar in the pembrolizumab plus chemotherapy group and the standard treatment group (26.4% and 23.7%, respectively). The incidence of drug-related AEOSIs was higher in the pembrolizumab plus chemotherapy group compared with the standard treatment group, whereas the incidence of Grade 3 to 5 AEOSIs (including those considered to be related to study intervention), AEOSIs resulting in dose modification (including all modifications and modifications due to cetuximab), and AEOSIs resulting in discontinuation of study intervention (including those considered to be related to study intervention) were lower in the pembrolizumab plus chemotherapy group.

The most common AEOSIs in pembrolizumab plus chemotherapy group were hypothyroidism, pneumonitis, hyperthyroidism, and colitis, which are currently known risks/AEOSI associated with pembrolizumab. Infusion reactions and severe skin reactions were the most common AEOSIs in the standard treatment group. The majority of AEOSIs in the pembrolizumab plus chemotherapy group were Grade 1 and 2, whereas in the standard treatment group AEOSIs were most commonly Grade 2 and 3.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

No changes made to the list of published studies.

B.3.2 Economic analysis

The patient population (baseline characteristics) are outlined below. The model structure remains the same. The intervention, comparators and treatment discontinuation rules remain as outlined in the original submission.

Table 48: Patient characteristics: monotherapy and combination therapy

Input	Monotherapy (mean)	Combination therapy (mean)
Age, years	60.77	60.72
Weight, kg	69.37	68.17
Body surface area, m²	1.60	1.74
% Females	16.7%	18.03%

Abbreviations: kg: kilograms

B.3.3 Clinical parameters and variables

Overall Method of Modelling Effectiveness

As outlined in the original submission, parametric models were fitted to the KEYNOTE-048 Kaplan–Meier (KM) data. The survival curve fitting was carried out in line with the NICE Decision Support Unit (DSU) guidelines outlined in Technical Support Document 14[1].

First however, the final analysis data was compared to the survival outcomes estimated from the original survival model assumptions used in the submission.

	Monotherapy				Combination therapy			
Treatment	**Pembrolizumab monotherapy**		**EXTREME**		**Pembrolizumab combination therapy**		**EXTREME**	
Timepoint	**2 year**	**3 year**	**2 year**	**3 year**	**2 year**	**3 year**	**2 year**	**3 year**
Original base case modelling: survival outcomes	30.8%	22.9%	17.0%	10.5%	32.3%	24.0%	16.2%	9.6%
KEYNOTE-048 Final Analysis	28.9%	22.1%	17.4%	8.0%	30.8%	24.5%	16.8%	6.5%

The updated data from KEYNOTE-048 shows that the survival modelling assumptions used in the submission (lognormal with a 45-week cut-point) are a good fit to the long-term data;

especially for the pembrolizumab monotherapy and combination therapy arms at three years of follow up. The lognormal with 45 week cut point is a good fit to the EXTREME arm at two years but provides an overestimate of survival at the later time point of three years by 2-3 percentage points.

A summary of the overall curve fitting exercise is provided below using the final analysis dataset.

Modelling overall survival

Monotherapy

Similar to the analysis of the IA2 data, when comparing the log cumulative hazards for OS observed in the pembrolizumab and EXTREME arms (Figure 29), the lines do not appear parallel and cross. The Grambsch and Therneau's test supports this interpretation since the result is statistically significant (p=0.0008), indicating a rejection of the proportional hazards assumption for OS. This is further validated in the analysis of the Schoenfeld residual plot reported in Figure 30.

Figure 29: Log cumulative hazards plot for OS (pembrolizumab monotherapy, CPS ≥1)

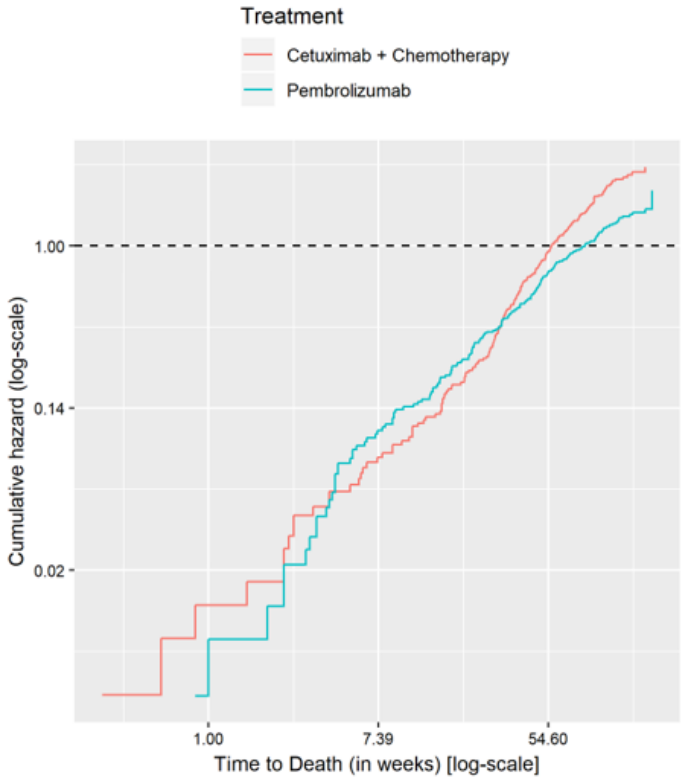
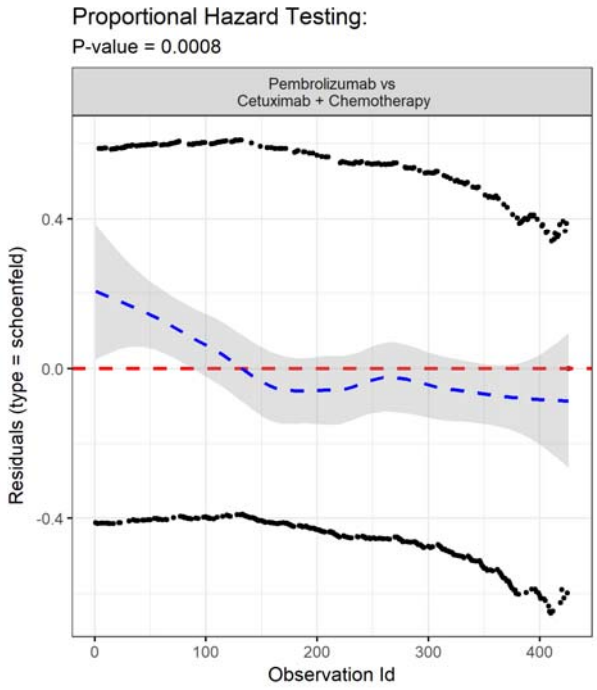


Figure 30: Schoenfeld residuals plot for OS (pembrolizumab monotherapy, CPS ≥1)



Based on the longer-term survival data, cut-off time points at 0, 45 and 80 weeks were explored. Given the maturity of the data, 80 weeks was chosen to allow for greater utilisation of the trial data whilst allowing enough data for which to conduct the extrapolation. The visual fit of the all six potential parametric curves is provided in Figure 31 and Figure 32. The goodness of fit statistics are provided in Table 49. The survival curves with cut-off time points at 0 and 45 weeks are presented in the appendix to this document.

For the comparison with platinum + 5-FU, the best fit time-varying hazard ratios, based on the lowest DIC value, was the p1=0, p2=0.5. Please refer to section B.2.9 for more information.

Table 49. Summary of goodness-of-fit qualities of OS survival models at 80-week cut-off point – pembrolizumab monotherapy and EXTREME (CPS≥ 1)

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	455.20	457.78	1	353.23	355.27	5
Weibull	454.27	459.44	4	354.40	358.48	6
Gompertz	454.20	459.37	3	351.13	355.22	3
Log-logistic	453.95	459.12	2	350.75	354.84	2
Log-normal	455.86	461.03	5	349.61	353.69	1
Generalised Gamma	-39870	-39863.	6	351.01	357.14	4

Figure 31: Plot of parametric fitting and extrapolation of long-term Overall Survival for the group treated with Pembrolizumab, with cut-point at Week 80 (monotherapy, CPS ≥1)

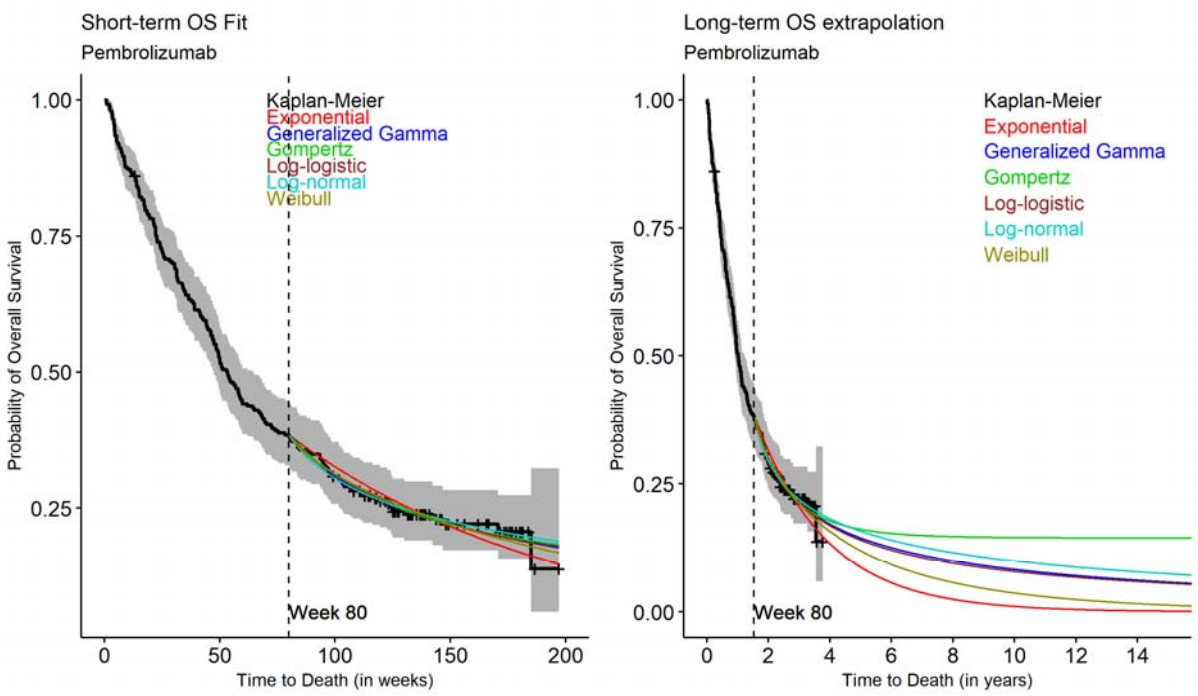
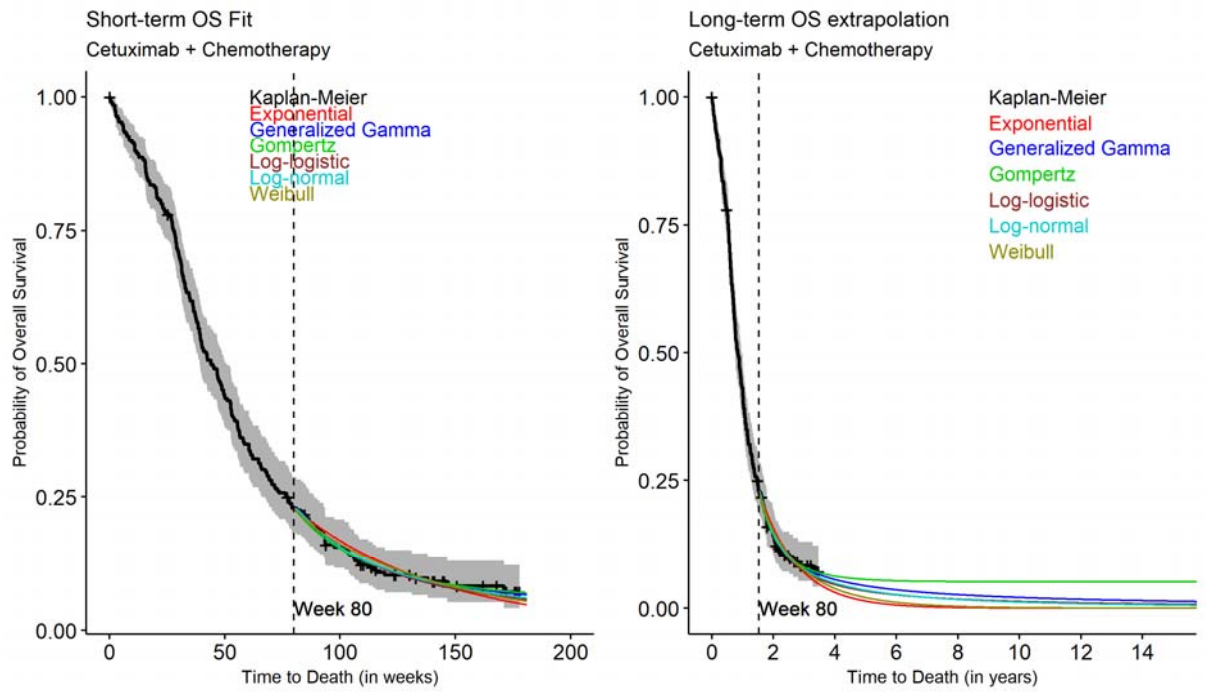


Figure 32: Plot of parametric fitting and extrapolation of long-term Overall Survival for the group treated with Cetuximab + platinum + 5-FU, with cut-point at Week 80 (monotherapy, CPS ≥1)



The goodness of fit statistics show similar AIC and BIC values (i.e. within a few points) for all distributions except for the generalised gamma. Across both arms the loglogistic is the best fit overall. Therefore, goodness of fit against longer term, external data sources was considered to select the base case distribution.

As used in the original submission, the clinical plausibility of the long-term extrapolations was compared to longer-term data from the previous technology appraisal for cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA473). The appraisal presented longer-term data from the relevant pivotal trial (EXTREME) to a time horizon of five years[2] presented in Table 50. Given this trial includes five-year data for both the EXTREME regimen and the platinum + 5-FU regimen, it provides a very useful validation of these longer-term survival estimates.

Table 50. Overall survival at random time points from the model and 5-year trial data *(replication of Table 7, page 36 from Submission template for the reconsideration of CDF drugs (TA473)[3]*

Treatment arm	% of patients alive at 28 months (1376 days)		% of patients alive at 36 months (1769 days)		% of patients alive at 42 months (2064 days)		% of patients alive at 59.5 months (2924 days)	
	Trial	Model	Trial	Model	Trial	Model	Trial	Model
Cetuximab	11.7	0.8	7.1	0.1	6.5	0.02	2.9	0
Standard of Care *(platinum +5-FU)*	8.3	0.08	4.4	0.01	4.4	0.002	1.7	0
Increment	**3.4**	**0.72**	**2.7**	**0.09**	**2.1**	**0.018**	**1.2**	**0**

To assess which of the distributions would provide a good projection of survival at longer term time points, the landmark time points of 3 and 5 years were summarised for each distribution to allow for comparison with the long-term EXTREME data. From this analysis, the exponential and Weibull distribution again provide an underestimate of the survival at 5 years for both the EXTREME regimen and platinum + 5-FU. The Gompertz provides an overestimate of survival for both the EXTREME regimen and platinum 5-FU; whilst the lognormal and loglogistic both provided similar estimates of long-term survival for EXTREME and platinum 5-FU. Notably, these curves now provide lower estimates of 5-year OS for the EXTREME regimen, which are more aligned with the long-term external data, reflected from the longer follow-up from KEYNOTE-048. The long-term extrapolation is slightly better matched with the external data for the loglogistic distribution compared to the lognormal (at 2% and 3% respectively versus an observed rate of 1.7% for platinum+5-FU). The loglogistic also provides a lower long-term estimate of survival for pembrolizumab monotherapy (14% compared to 16% for the lognormal distribution); and therefore, provides a more conservative estimate of the cost-effectiveness for pembrolizumab monotherapy versus EXTREME and platinum + 5-FU.

Table 51. Overall survival at landmark time points for all distributions for pembrolizumab monotherapy and comparators (CPS≥ 1)

	Distributions using 80 week cut-point											
Treatment	**Exponential**		**Weibull**		**Gompertz**		**Lognormal**		**Loglogistic**		**Generalised Gamma**	
	3 year	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**
Pembrolizumab monotherapy	0.21	0.09	0.21	0.12	0.21	0.16	0.22	0.16	**0.21**	**0.14**	0.21	0.14
EXTREME	0.07	0.01	0.07	0.02	0.08	0.06	0.08	0.03	**0.07**	**0.03**	0.08	0.04
Platinum + 5-FU	0.06	0.01	0.06	0.02	0.06	0.03	0.07	0.03	**0.06**	**0.02**	0.06	0.02

Base case model selection – monotherapy

Given all the considerations outlined above, the loglogistic distribution with 80-week cut off point was chosen as the base case survival model for the pembrolizumab monotherapy and comparator arms. The loglogistic was the best fitting distribution across both arms from a statistical perspective, and most importantly the long-term extrapolations provided a very good fit compared to the long-term data from the EXTREME trial, presented in TA473, for both the cetuximab + platinum + 5-FU (EXTREME) and the platinum + 5-FU arms.

The landmark survival rates are presented in Table 52 and the base case survival curves are presented in Figure 33 and Figure 34.

Table 52. Overall survival at landmark time points from the base case distribution for pembrolizumab monotherapy and comparators (CPS ≥1)

	Timepoints				
Treatment	**1 year**	**2 years**	**3 years**	**5 years**	**10 years**
Pembrolizumab monotherapy	0.50	0.30	0.21	0.14	0.08
EXTREME	0.42	0.14	0.07	0.03	0.01
Platinum + 5-FU	0.37	0.13	0.06	0.02	0.00

Figure 33. Base case overall survival modelling for pembrolizumab monotherapy and EXTREME: piecewise model using loglogistic distribution and 80 weeks cut off point (CPS ≥1)

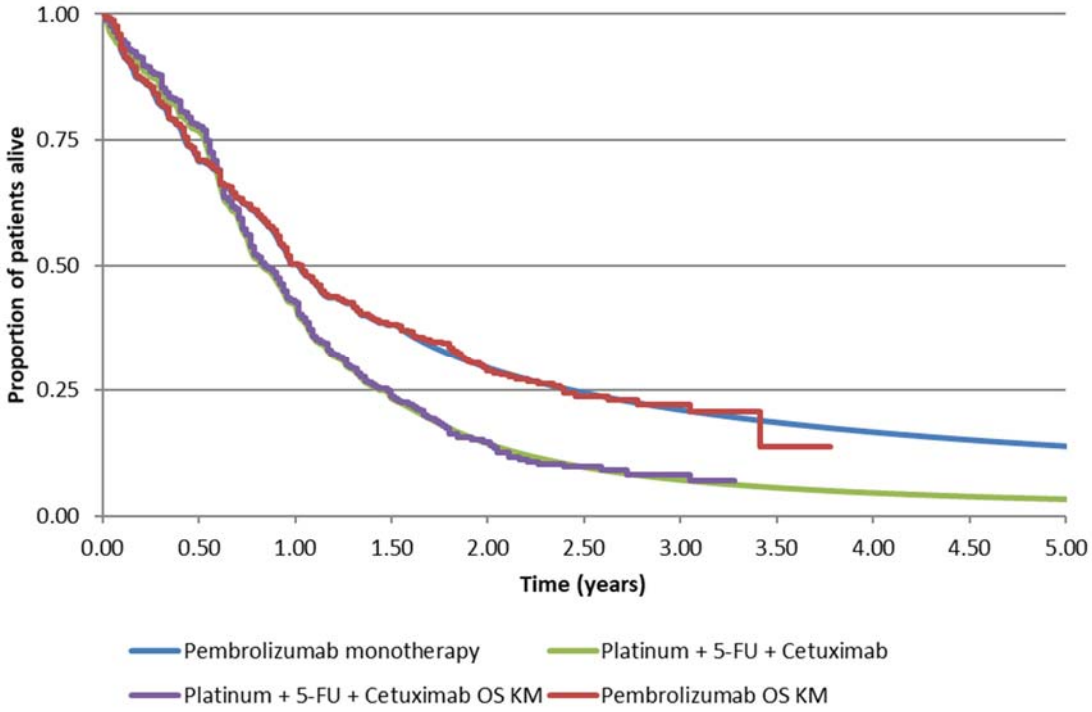
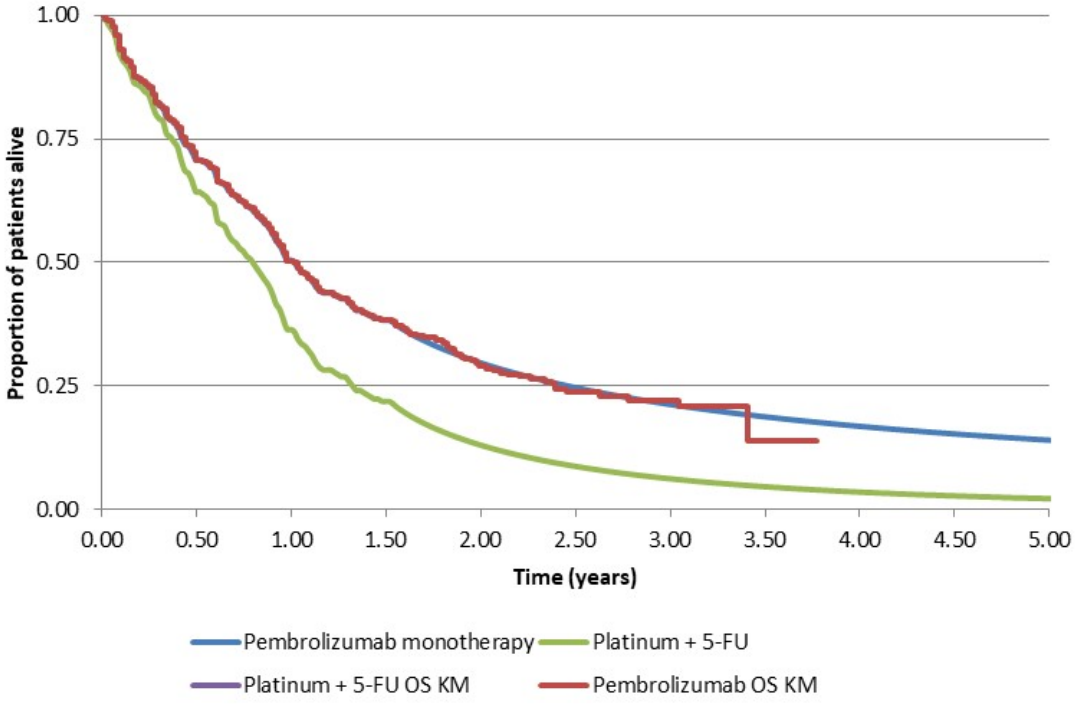


Figure 34. Base case overall survival modelling for pembrolizumab monotherapy and platinum + 5-FU: piecewise model using loglogistic distribution and 80 weeks cut off point (CPS ≥1)



Combination therapy

When comparing the log cumulative hazards for OS observed in the pembrolizumab combination therapy and EXTREME arms (Figure 35), the lines do not appear parallel and cross. The Grambsch and Therneau's test supports this interpretation since the result is statistically significant ($p < 0.05$), indicating a rejection of the proportional hazards assumption for OS. This is also validated in the analysis of the Schoenfeld residual plot reported in Figure 36.

Figure 35: Log cumulative hazards plot for OS (combination therapy, CPS ≥1)

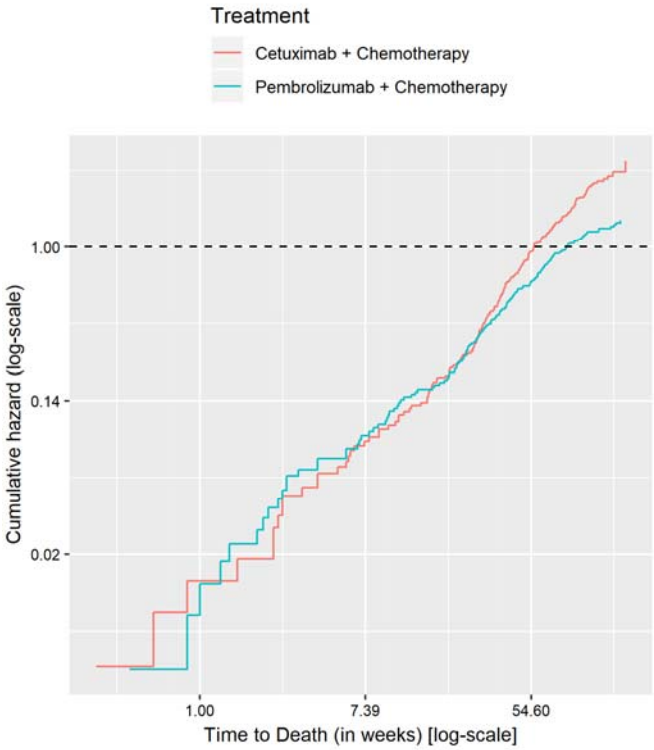
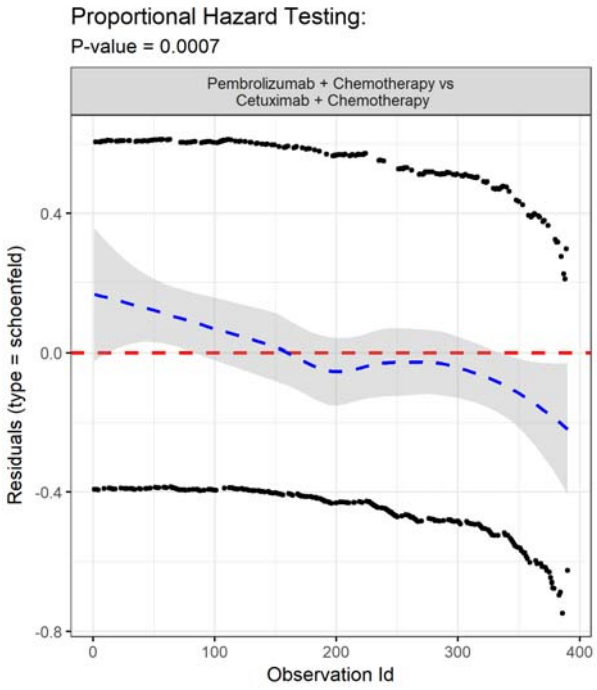


Figure 36: Schoenfeld residuals plot for OS (combination therapy, CPS ≥1)



This statistical and visual assessment suggests that a piecewise approach would be more appropriate for extrapolation. Based on the longer-term survival data, cut-off time points at 0, 45 and 80 weeks were explored. Given the maturity of the data, 80 weeks was chosen to allow for greater utilisation of the trial data whilst allowing enough data for which to conduct the extrapolation. The visual fit of the all six potential parametric curves is provided in Figure 37 and Figure 38. The goodness of fit statistics are provided in Table 53 .

For the comparison with platinum + 5-FU, the best fit time-varying hazard ratios, based on the lowest DIC value, was the p1=1, p2=0. Please refer to section B.2.9 for more information.

Table 53. Summary of goodness-of-fit qualities of OS survival models at 80-week cut-off point – pembrolizumab combination therapy and EXTREME (CPS≥ 1)

Fitted Function	Pembrolizumab Combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	346.95	349.48	5	331.15	333.10	3
Weibull	346.38	351.42	6	333.08	336.98	6
Gompertz	344.80	349.84	2	331.82	335.72	4
Log-logistic	345.59	350.63	4	330.17	334.07	2
Log-normal	343.75	348.79	1	329.49	333.40	1
Generalised Gamma	343.82	351.39	3	331.41	337.27	5

Figure 37: Plot of parametric fitting and extrapolation of long-term Overall Survival for the group treated with Pembrolizumab, with breaking point at Week 80 (combination therapy, CPS ≥1)

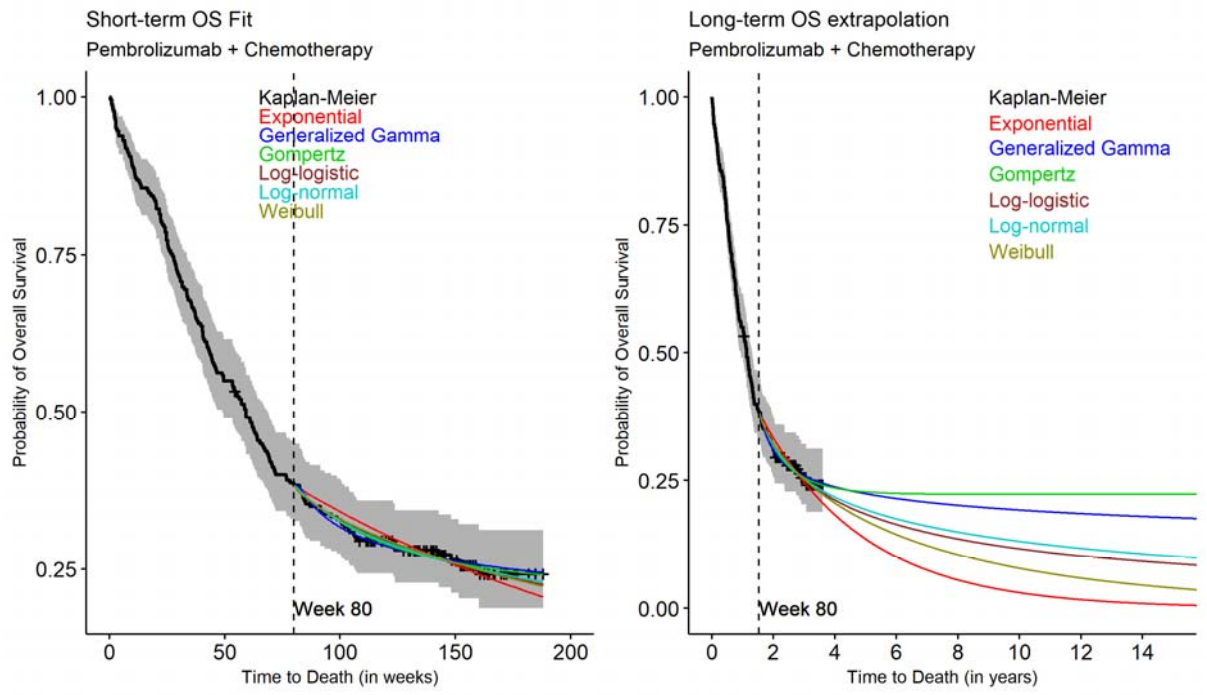
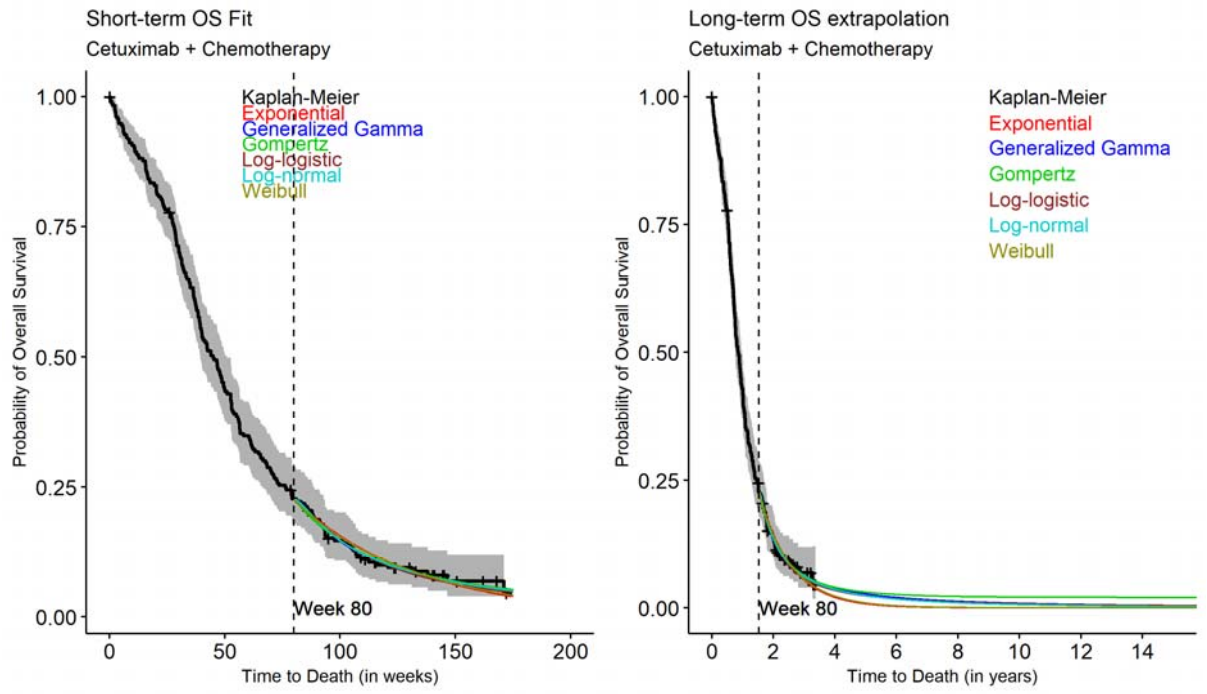


Figure 38: Plot of parametric fitting and extrapolation of long-term Overall Survival for the group treated with Cetuximab + platinum + 5-FU, with breaking point at Week 80 (combination therapy, CPS ≥1)



The goodness of fit statistics show similar AIC and BIC values (i.e. within 2-3 points) for all distributions, though the lognormal is the best fitting for both pembrolizumab combination therapy and the EXTREME regimen. Goodness of fit against longer term, external data sources was then considered to select the base case distribution.

As used in the original submission, the clinical plausibility of the long-term extrapolations was compared to longer-term data from the previous technology appraisal for cetuximab for treating recurrent or metastatic squamous cell cancer of the head and neck (TA473). The appraisal presented longer-term data from the relevant pivotal trial (EXTREME) to a time horizon of five years[2]. Given this trial includes five-year data for both the EXTREME regimen and the platinum + 5-FU regimen, it provides a very useful validation of these longer-term survival estimates. These results are presented in Table 50 above.

To assess which of the distributions would provide a good projection of survival at longer term time points, the landmark time points of 3 and 5 years were summarised for each distribution to allow for comparison with the long-term EXTREME data (see Table 54).

Table 54. Overall survival at landmark time points for all distributions for pembrolizumab combination therapy and comparators (CPS≥ 1)

	Distributions using 80 week cut-point											
Treatment	**Exponential**		**Weibull**		**Gompertz**		**Lognormal**		**Loglogistic**		**Generalised Gamma**	
	3 year	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**	**3 year**	**5 year**
Pembrolizumab combination therapy	0.25	0.14	0.25	0.17	0.26	0.23	**0.25**	**0.19**	0.25	0.18	0.26	0.22
EXTREME	0.05	0.01	0.06	0.01	0.06	0.03	**0.06**	**0.02**	0.06	0.02	0.06	0.03
Platinum + 5-FU	0.04	0.00	0.05	0.00	0.05	0.02	**0.05**	**0.01**	0.05	0.01	0.05	0.02

From this analysis, the exponential and Weibull distribution again provide an underestimate of the survival at 5 years for both the EXTREME regimen and platinum + 5-FU. The Gompertz, generalised gamma, lognormal and loglogistic all provide similar estimates of 5-year OS for the EXTREME regimen and platinum + 5-FU but the proportions alive with the Gompertz and generalised gamma most closely match the external data. However, the Gompertz and generalised gamma distribution provide higher estimates of OS for pembrolizumab at 5-years compared to the lognormal and loglogistic (23 and 22 percent compared to 19 and 18 percent respectively.)

Base case model selection – combination therapy

In order to be conservative, the lognormal distribution with 80-week cut off point was chosen as the base case survival model for the pembrolizumab combination therapy and comparator arms. The lognormal was the best fitting distribution across both arms from a statistical perspective, and most importantly the long-term extrapolations are a good match to the long-term data from the EXTREME trial, presented in TA473, for both the cetuximab + platinum + 5-FU (EXTREME) and the platinum + 5-FU arms.

The landmark survival rates are presented in Table 55 and the base case survival curves are presented in Figure 39 and Figure 40.

Table 55. Overall survival at landmark time points from the base case distribution for pembrolizumab combination therapy and comparators (CPS ≥1)

	Timepoints				
Treatment	**1 year**	**2 years**	**3 years**	**5 years**	**10 years**
Pembrolizumab combination therapy	0.54	0.32	0.25	0.19	0.13
EXTREME	0.42	0.13	0.06	0.02	0.01
Platinum + 5-FU	0.37	0.11	0.05	0.01	0.00

Figure 39. Base case overall survival modelling for pembrolizumab combination therapy and EXTREME: piecewise model using lognormal distribution and 80 weeks cut off point (CPS ≥1)

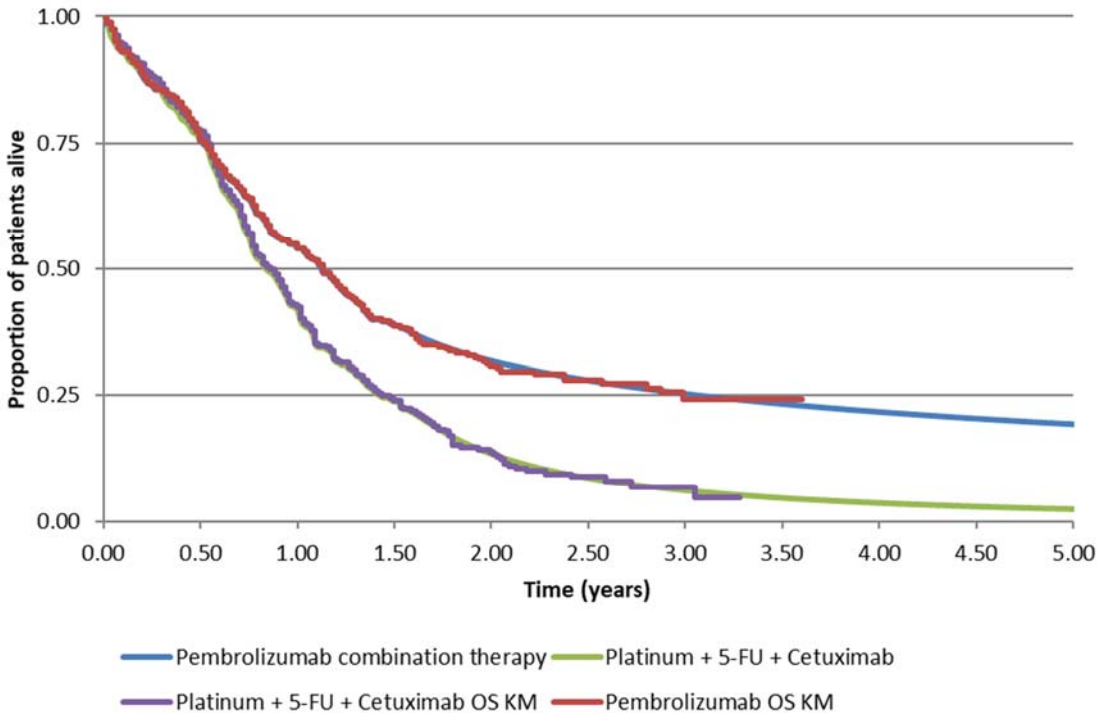
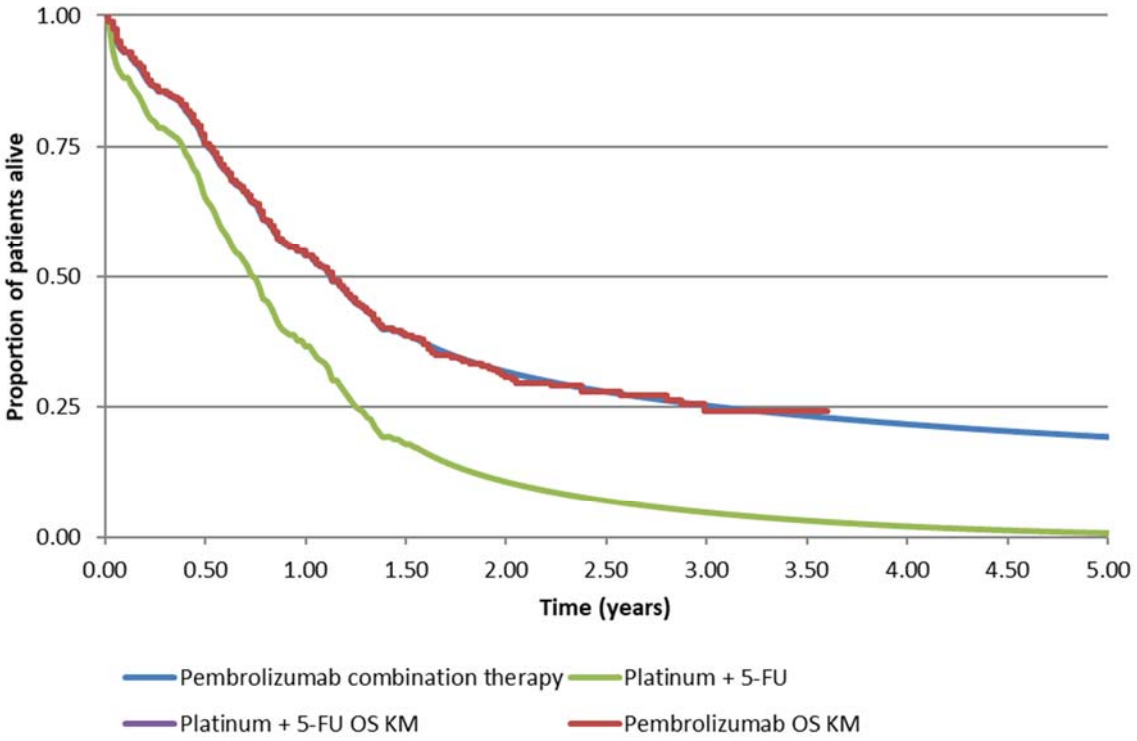


Figure 40. Base case overall survival modelling for pembrolizumab combination therapy and platinum + 5-FU: piecewise model using lognormal distribution and 80 weeks cut off point (CPS ≥1)



Modelling Progression-free Survival

Monotherapy

To identify the most plausible PFS curves among the standard parametric curves, the guidance from the NICE DSU was followed[1]. The definition of PFS used for the economic modelling was based on the central assessment by independent review committee. Based on the trial protocol of KEYNOTE-048, the first tumour assessment was performed at week 9 and then every 6 weeks thereafter. This resulted in a sharp drop of PFS between weeks 0 and 9. The parametric model proportional hazards (PH) assumption was assessed visually using the log-cumulative hazards plot, and additionally, assessed using the Grambsch-Therneau correlation test. Visual assessment of the log-cumulative hazards plot (Figure 41), and results of the Grambsch and Therneau's test ($p < 0.05$), indicate a rejection of the proportional hazards assumption for PFS. This is also validated in the analysis of the Schoenfeld residual plot reported in

Figure **42**.

Figure 41. Log cumulative hazards plot for PFS (monotherapy, CPS ≥1)

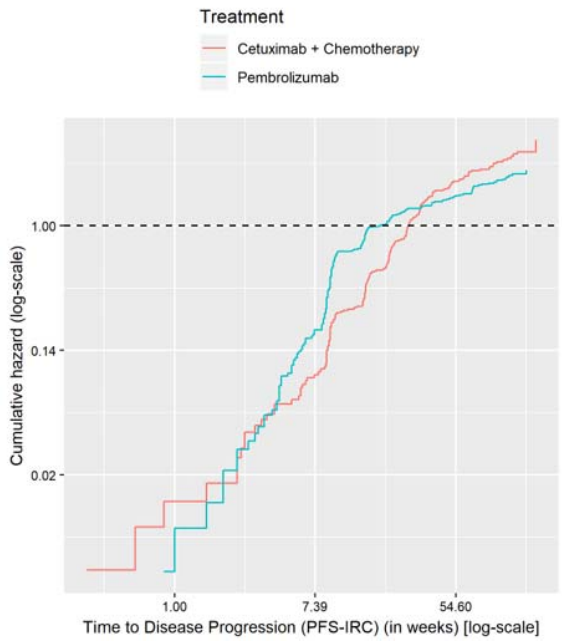
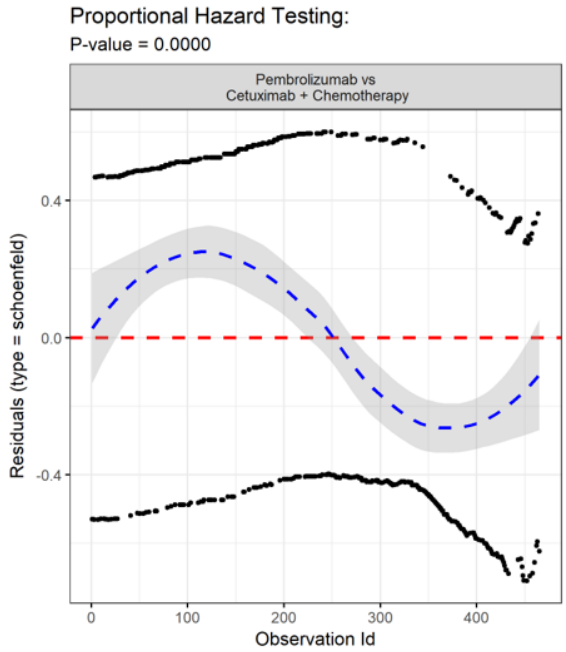


Figure 42: Schoenfeld residuals plot for PFS (monotherapy, CPS ≥1)



Given the shape of the curves, the direct use of KM data up until a point with fitted parametric functions was implemented. Based on the change in the hazard observed in the log-cumulative hazard plot the time periods of 25 and 52 weeks were explored as potential cut points. To allow the use of the most trial data, but with enough datapoints for extrapolation, the 52-week timepoint was selected. Scenario analysis is also presented for weeks 0 and 25 in the appendix.

Table 56 reports the AIC/BIC statistics for the second part of the PFS two-piece fit for pembrolizumab monotherapy and the EXTREME regimen based on KEYNOTE-048 PFS data from the 52-week cut-off point.

Table 56. Summary of goodness-of-fit measures of PFS as defined per RECIST v1.1 as assessed by BICR at a 52-week cut-off point – pembrolizumab monotherapy and EXTREME (CPS≥1)

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	288.39	290.30	1	241.66	243.13	1
Weibull	289.77	293.59	5	243.27	246.20	4
Gompertz	288.31	292.14	3	243.16	246.09	2
Log-logistic	288.49	292.31	4	243.21	246.15	3
Log-normal	288.26	292.08	2	243.76	246.69	5
Generalised Gamma	290.25	295.99	6	244.97	249.36	6

Figure 43: Plot of parametric fitting and extrapolation of long-term BIRC-assessed Progression-free Survival for the group treated with Pembrolizumab, with breaking point at Week 52 (monotherapy, CPS ≥1)

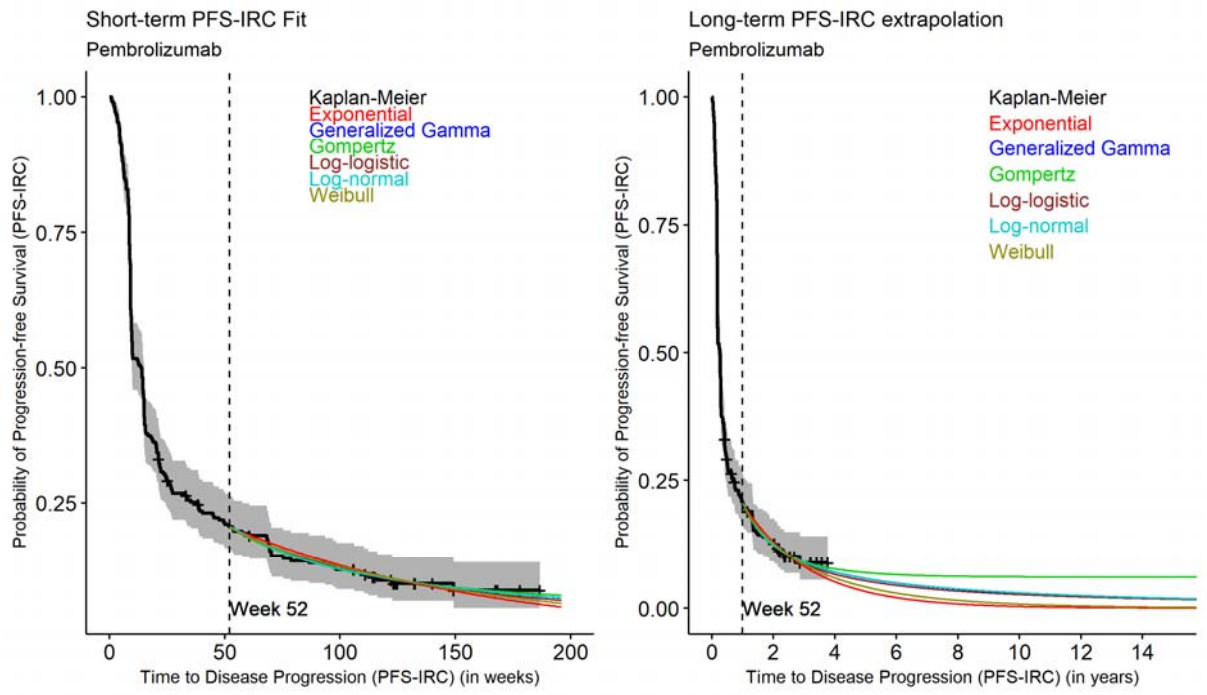
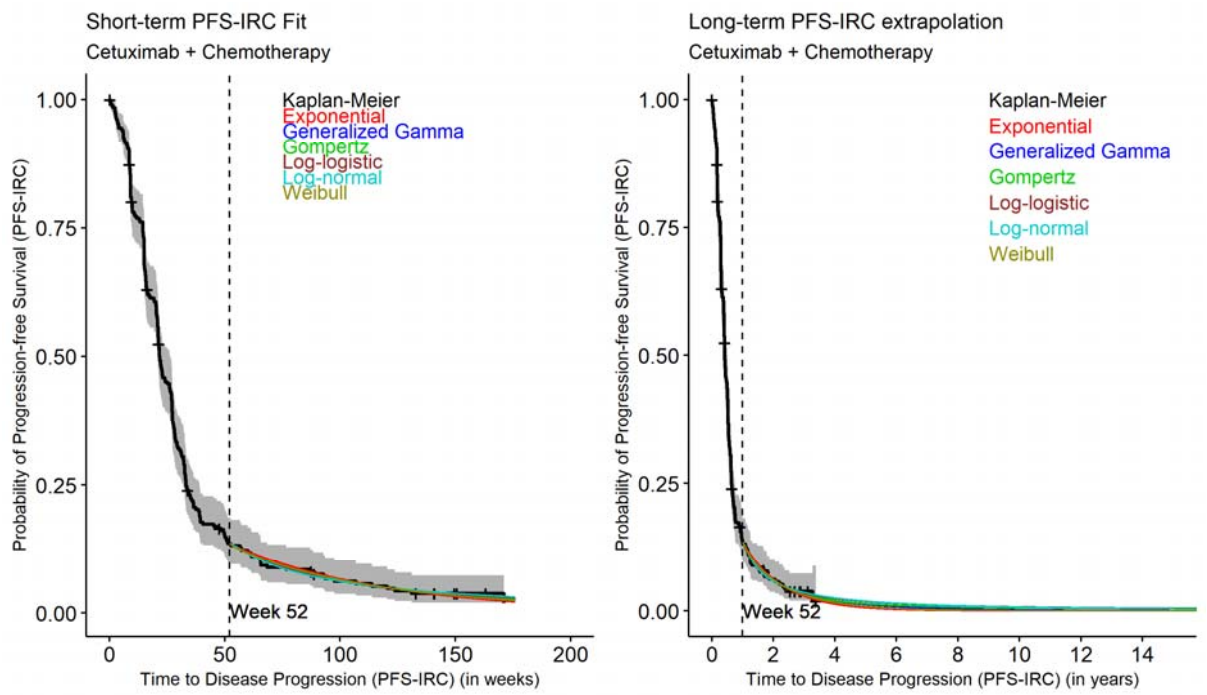
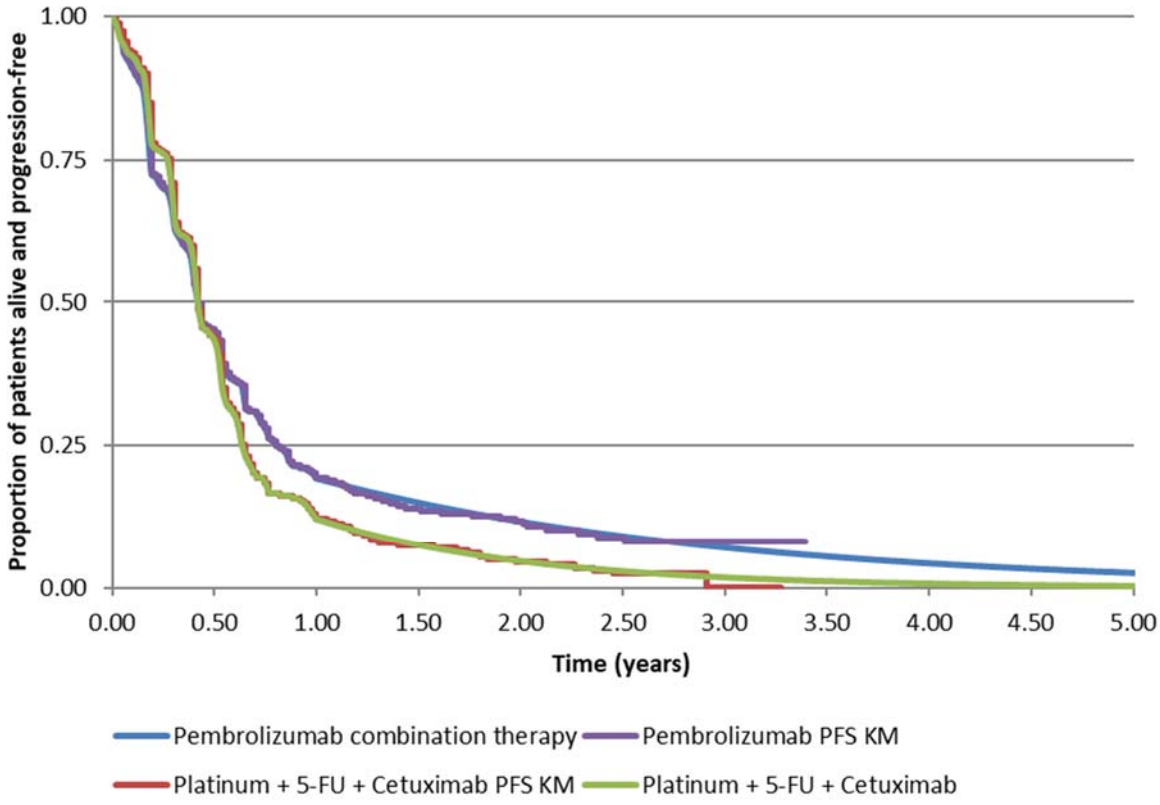


Figure 44: Plot of parametric fitting and extrapolation of long-term BIRC-assessed Progression-free Survival for the group treated with Cetuximab + platinum + 5-FU, with breaking point at Week 52 (monotherapy, CPS ≥1)



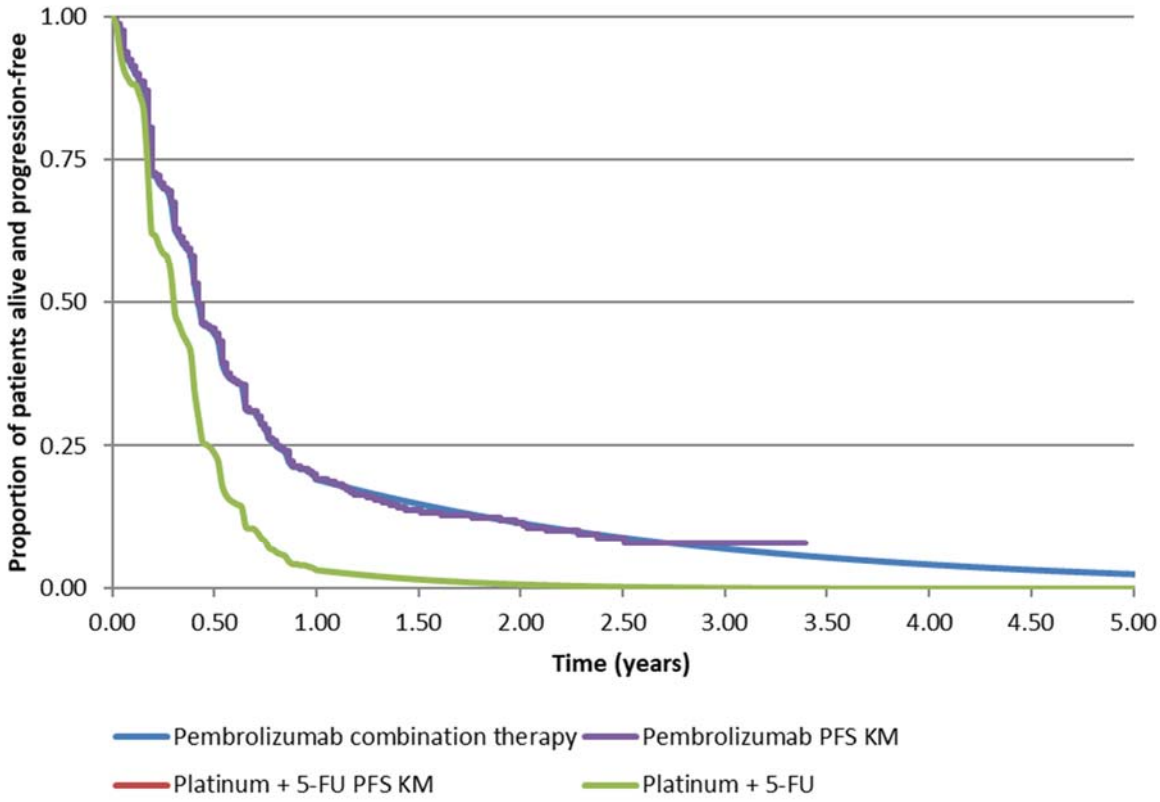
Considering the statistical and visual goodness of fit across both arms, the exponential distribution with 52 week cut point was selected as the base case distribution. Alternative distributions are considered in scenario analyses which may help better characterize the survival plateau associated with immunotherapy.

Figure 45. Base case progression-free survival extrapolations for pembrolizumab vs. platinum + 5 FU + cetuximab (exponential with 52 week cut-off point) (monotherapy, CPS ≥1)



For the comparison with platinum/5-FU, progression-free survival is modelled by applying time-varying HRs. The model allows up for a fractional polynomial up to the second order to be used to express the logarithm of the instantaneous hazard ratios. The best fit time-varying hazard ratios, based on the lowest DIC value, were the p1=0, p2=-1. Please refer to section B.2.9 for more information.

Figure 46. Base case progression-free survival extrapolations for pembrolizumab vs. platinum + 5 FU (exponential with 52 week cut-off point) (monotherapy, CPS ≥1)



Pembrolizumab Combination Therapy

When comparing the PFS outcomes observed in the pembrolizumab combination therapy and the EXTREME arm, the PH assumption does not appear to hold based on the visual assessment of the log-cumulative hazards plot in Figure 47, since the curves do not appear parallel. The Grambsch and Therneau's test supports this interpretation since the result is statistically significant ($p < 0.05$), indicating a rejection of the proportional hazards assumption for PFS. This is also validated in the analysis of the Schoenfeld residual plot reported in Figure 48.

Figure 47: Log cumulative hazards plot for PFS (combination therapy, CPS ≥1)

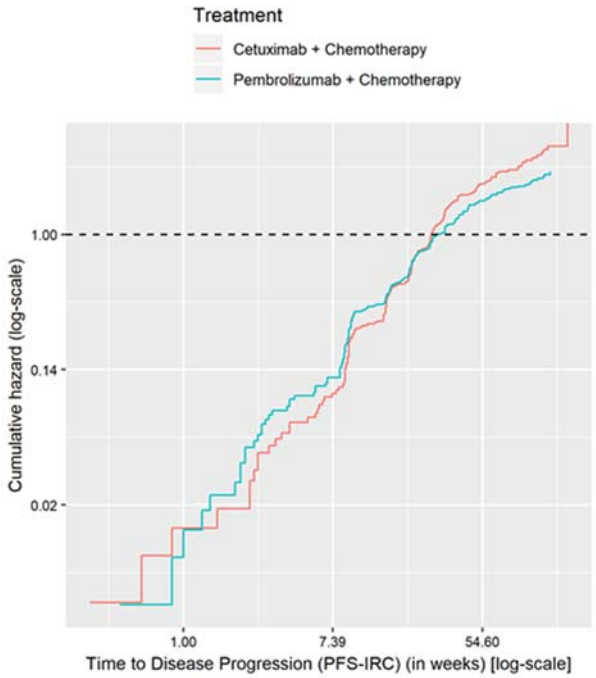
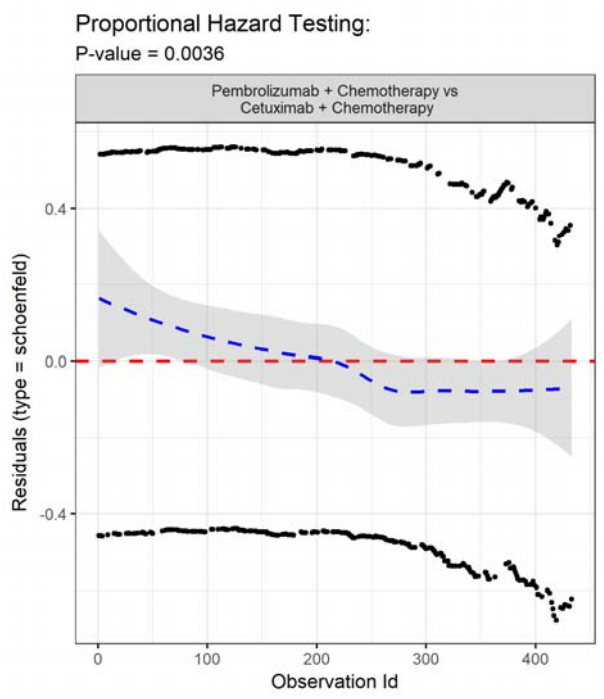


Figure 48: Schoenfeld residuals plot for PFS (combination therapy, CPS ≥1)



Again, given the shape of the curves, the direct use of KM data up until a point with fitted parametric functions was implemented. Based on the change in the hazard observed in the cumulative and log-cumulative hazard plots (see Figure 47), the time periods of 25 and 52 weeks were explored as potential cut points. To allow the use of the most trial data, but with

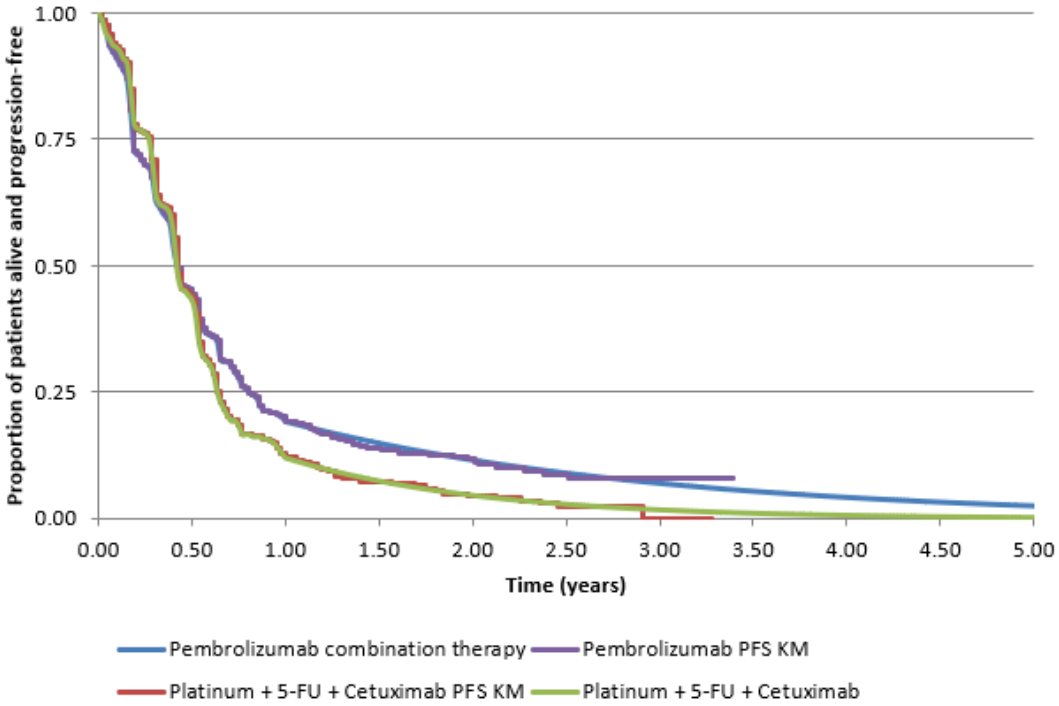
enough datapoints for extrapolating, the 52-week timepoint was selected. Scenario analysis is also presented for weeks 0 and 25 in the appendix. Table 57 reports the AIC/BIC statistics for the pembrolizumab combination therapy and EXTREME regimen.

Table 57. Summary of goodness-of-fit measures of PFS as defined per RECIST v1.1 as assessed by BICR at a 52-week cut-off point – pembrolizumab combination therapy and EXTREME

Fitted Function	Pembrolizumab combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	272.57	274.37	1	221.83	223.13	1
Weibull	273.30	276.92	4	223.77	226.36	2
Gompertz	272.70	276.31	2	223.82	226.41	3
Log-logistic	272.80	276.41	3	224.83	227.42	4
Log-normal	273.76	277.37	5	225.64	228.23	5
Generalised Gamma	274.98	280.40	6	225.76	229.65	6

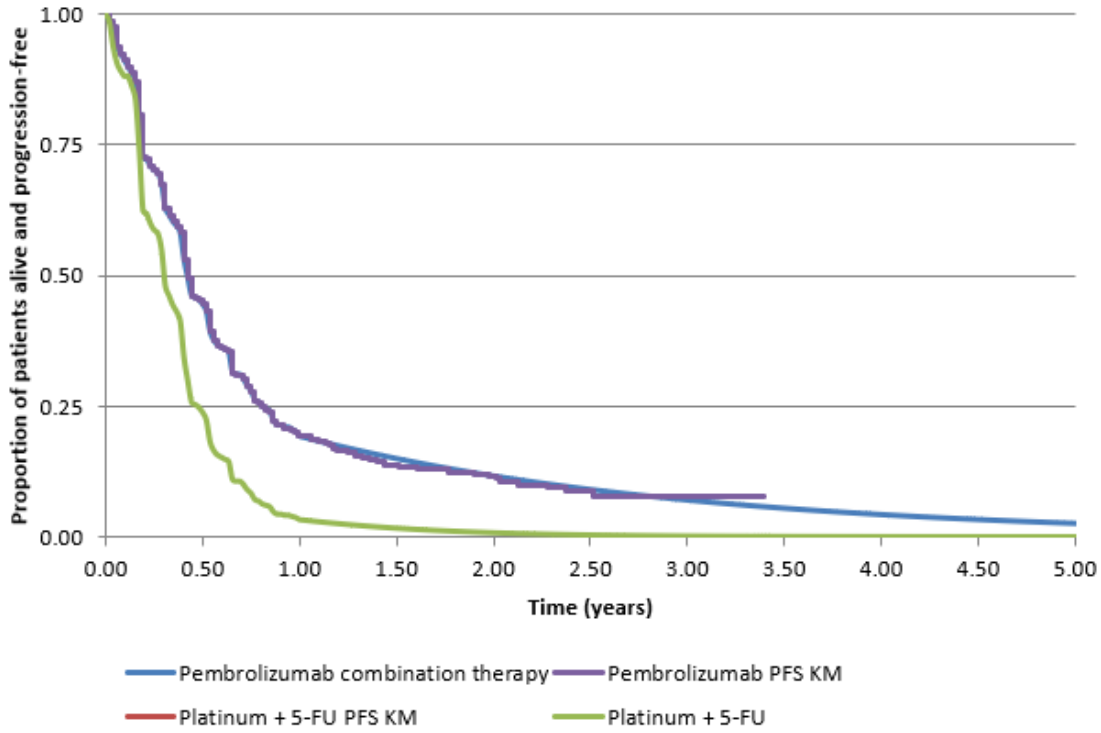
Considering the statistical and visual goodness of fit across both arms, the exponential distribution with 52 week cut point was selected as the base case distribution. Alternative distributions are considered in scenario analyses which may help better characterize the survival plateau associated with immunotherapy.

Figure 49: Progression-free survival extrapolations for pembrolizumab combination therapy vs. cetuximab + platinum + 5-FU (52 week cut-off point) (combination therapy, CPS ≥1)



For the comparison with platinum/5-FU, progression-free survival is modelled by applying time-varying HRs. The model allows up for a fractional polynomial up to the second order to be used to express the logarithm of the instantaneous hazard ratios. The best fit time-varying hazard ratios, based on the lowest DIC value, were the p1=0, p2=0.5. Please refer to section B.2.9 for more information.

Figure 50: Progression-free survival extrapolations for pembrolizumab combination therapy vs. platinum + 5 FU (52 week cut-off point) (combination therapy, CPS ≥1)



Adverse events

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients in any treatment arm. Treatment related adverse event costs (TRAE) were ascribed in each model cycle by applying the weekly incidence of these AEs, multiplied by the respective costs, to the time on treatment curve in each treatment arm. AE data for non-trial comparators were obtained from the published literature used in the NMA. The unit cost and the disutility associated with the individual AEs were assumed to be the same for all treatment arms, therefore the difference in terms of AE costs and disutilities were driven by the AE rates presented in Table 58. This was consistent with the methods used in previous oncology submissions and ensures the full cost and HRQoL impact associated with AEs are captured for both treatment arms without discounting[4, 5].

Table 58: AEs incidence - grade ≥3 5%+ incidence TRAEs per week of treatment exposure

Treatment	KN-048 Monotherapy arm				KN-048 Combination therapy arm				External comparator
	Pembrolizumab		Cetuximab + platinum + 5-FU		Pembrolizumab + platinum + 5-FU		Cetuximab + platinum + 5-FU		Platinum + 5-FU[6]
	Incidence	SE	Incidence	SE	Incidence	SE	Incidence	SE	Incidence
ALT/AST increase	NR	NR	NR	NR	NR	NR	NR	NR	NR
Anaemia	0.0018	0.0005	0.0075	0.0010	0.0078	0.0010	0.0075	0.0009	0.004
Asthenia	0.0004	0.0002	0.0014	0.0004	0.0010	0.0003	0.0014	0.0004	0.0006
Cardiac event	NR	NR	NR	NR	NR	NR	NR	NR	NR
Decreased appetite	0.0004	0.0002	0.0015	0.0004	0.0014	0.0004	0.0015	0.0004	NR
Dehydration	0.0003	0.0002	0.0012	0.0004	0.0008	0.0003	0.0012	0.0004	0.0006
Diarrhoea	NR	NR	NR	NR	NR	NR	0.0012	0.0004	0.0003
Dyspnoea	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fatigue	0.0012	0.0004	0.0021	0.0005	0.0022	0.0005	0.0021	0.0005	NR
Febrile Neutropenia	NR	NR	0.0026	0.0006	0.0027	0.0006	0.0026	0.0006	0.0014
Granulocytopenia	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hypokalaemia (low potassium)	0.0008	0.0003	0.0026	0.0006	0.0020	0.0005	NR	NR	0.0019
Hypomagnesemia (low magnesium)	NR	NR	0.0021	0.0005	0.0006	0.0002	0.0021	0.0005	0.0010
Hyponatraemia	0.0024	0.0005	0.0026	0.0006	0.0024	0.0005	0.0026	0.0006	NR
Hypotension	NR	NR	NR	NR	NR	NR	NR	NR	NR

Infection	NR	NR	NR	NR	NR	NR	NR	NR	NR
Leukopenia	NR	NR	0.0024	0.0005	0.0010	0.0003	0.0024	0.0005	NR
Lymphopenia	NR	NR	NR	NR	NR	NR	0.0014	0.0004	NR
Dysphagia/Mucositis	0.0005	0.0003	0.0023	0.0005	0.0030	0.0006	0.0023	0.0006	NR
Nausea/Vomiting	0.0001	0.0000	0.0038	0.0009	0.0029	0.0008	0.0038	0.0006	NR
Neutropenia	0.0001	0.0001	0.0093	0.0011	0.0054	0.0007	0.0093	0.0011	0.0101
Neutrophil count decreased	NR	NR	0.0057	0.0009	0.0033	0.0006	0.0057	0.0009	NR
White blood cell count decreased	NR	NR	0.0040	0.0008	0.0017	0.0004	0.0040	0.0008	NR
Phlebitis	NR	NR	NR	NR	NR	NR	NR	NR	0.0010
Platelet count decrease	NR	NR	NR	NR	0.0017	0.0004	0.0015	0.0004	NR
Pneumonia	0.0022	0.0005	0.0031	0.0006	0.0017	0.0004	0.0031	0.0007	NR
Pneumonia aspiration	NR	NR	NR	NR	0.0010	0.0003	0.0005	0.0003	NR
Skin reaction	0.0003	0.0002	0.0026	0.0006	0.0001	0.0001	0.0026	0.0006	0.0005
Stomatitis	NR	NR	NR	NR	0.0026	0.0005	0.0015	0.0005	0.0023
Thrombocytopenia	0.0001	0.0001	0.0040	0.0008	0.0028	0.0006	0.0040	0.0008	0.0021

KN-048; KEYNOTE-048; NR: not reported; SE: standard error; 5-FU – 5- Fluorouracil

Subsequent treatment

The distribution of second line treatments is taken from the final analysis of KEYNOTE-048. The five most commonly used subsequent treatments were taken from the trial but any treatments not available in the UK (i.e. cetuximab or cetuximab containing regimens) were excluded. For nivolumab, as it is funded in the Cancer Drugs Fund currently, it is also removed as a possible subsequent treatment and its percentage usage is split equally between the remaining subsequent therapies, as outlined in Table 59 and Table 60.

Table 59. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab monotherapy) – base case assumptions

Primary treatment	Subsequent treatment			
	Docetaxel	Paclitaxel	Carboplatin + Paclitaxel	Methotrexate
Pembrolizumab	8.40%	13.09%	16.21%	10.74%
EXTREME regimen	25.75%	27.24%	16.79%	14.55%
Platinum + 5-FU	25.75%	27.24%	16.79%	14.55%
Mean duration (months)	2.89	4.06	2.80	3.45
Weekly cost (£)	80.35	90.68	94.33	59.78
AE costs associated (£)	9.85	31.02	31.02	0.30

Table 60. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab combination therapy) – base case assumptions

Primary treatment	Subsequent treatment		
	Docetaxel	Paclitaxel	Methotrexate
Pembrolizumab + chemotherapy	22.12%	24.78%	22.12%
EXTREME regimen	31.97%	29.35%	20.77%
Platinum + 5-FU	31.97%	29.35%	20.77%
Mean duration (months)	2.66	2.69	1.77
Weekly cost (£)	80.35	90.68	59.78
AE costs associated (£)	9.85	31.02	0.30

A scenario is presented which includes post-platinum nivolumab usage, in line with the subsequent treatments administered in KEYNOTE-048 and current clinical practice in England.

Table 61 and Table 62 below show the subsequent treatments received in KEYNOTE-048 following combination and monotherapy which includes nivolumab usage as it was received in the trial.

Table 61. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab monotherapy) – nivolumab scenario analysis

Primary treatment	Subsequent treatment				
	Docetaxel	Nivolumab	Paclitaxel	Carboplatin + Paclitaxel	Methotrexate
Pembrolizumab	7.03%	5.47%	11.72%	14.84%	9.38%
EXTREME regimen	19.40%	25.37%	20.90%	10.45%	8.21%
Platinum + 5-FU	7.03%	5.47%	11.72%	14.84%	9.38%
Mean duration (months)	2.89	2.56	4.06	2.80	3.45
Weekly cost (£)	80.35	1,403.70	90.68	94.33	59.78
AE costs associated (£)	9.85	1.04	31.02	31.02	0.30

Table 62. Distribution of subsequent treatments following discontinuation of initial therapy (pembrolizumab combination therapy) – nivolumab scenario analysis

Primary treatment	Subsequent treatment			
	Docetaxel	Nivolumab	Paclitaxel	Methotrexate
Pembrolizumab + chemotherapy	20.35%	5.31%	23.01%	20.35%
EXTREME regimen	23.51%	25.37%	20.90%	12.31%
Platinum + 5-FU	23.51%	25.37%	20.90%	12.31%
Mean duration (months)	2.66	4.05	2.69	1.77
Weekly cost (£)	80.35	1,403.70	90.68	59.78
AE costs associated (£)	9.85	1.04	31.02	0.30

B.3.4 Measurement and valuation of health effects

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

The collection of health-related quality-of-life (HRQoL) data in the KEYNOTE-048 trial has been described in the original manufacturer's submission. The methodology of analysis is also as described in the original submission. The updated utility results are presented below for the final analysis dataset.

Mixed regression model – updated results

The coefficient for Grade ≥3 TRAEs derived from the regression analysis is -0.02519, adjusted for the weekly model cycle length and ascribed to those patients experiencing events in each cycle. The time-to-death coefficients were estimated for discrete time intervals prior to death, however only 0-30 days and 90-180 were found to be statistically significant at the 95% confidence interval; all other time intervals have a coefficient of 0. The respective disutilities are ascribed in the respective time period for those patients who die in the model simulation, adjusted for the weekly cycle length.

Table 63. Fixed effects utility model with time-to-death, no age, no interactions (UK algorithm)

Coefficient	Estimate	SE
Intercept (PFS)	0.8200	0.0109
Disease progression	0.7050	0.0155
ECOG score: 1	-0.09115	-0.0136
TRAEs: grade 3-5	-0.02519	0.0076
Time prior to death: 180-365 days	-0.0000	0.0000
Time prior to death: 90-180 days	0.0495	0.0106
Time prior to death: 60-90 days	0.1608	0.0137
Time prior to death: 30-60 days	0.1608	0.0137
Time prior to death: 0-30 days	0.3235	0.0217

Estimation of mean utility values for monotherapy and combination therapy – updated results

Table 64: Mean utility values - monotherapy subgroup

Utility	Mean	SE
PFS	0.771	0.005
PD	0.686	0.011
TRAEs: grade 3-5	0.132	0.015
Time prior to death: 180-365 days	0.0280	0.0112
Time prior to death: 90-180 days	0.0910	0.0285
Time prior to death: 60-90 days	0.2060	0.0294
Time prior to death: 30-60 days	0.2450	0.0334
Time prior to death: 0-30 days	0.3730	0.0562

HSUVs and the event-specific utility decrements are mean values of the combination therapy sample, presented below.

Table 65: Mean utility values - combination subgroup

Utility	Mean	SE
PFS	0.769	0.005
PD	0.673	0.012
TRAEs: grade 3-5	0.130	0.020
Time prior to death: 180-365 days	0.028	0.011
Time prior to death: 90-180 days	0.090	0.028
Time prior to death: 60-90 days	0.210	0.031
Time prior to death: 30-60 days	0.254	0.035
Time prior to death: 0-30 days	0.345	0.058

Adverse reactions

The coefficient for Grade ≥3 TRAEs derived from the regression analysis is -0.02519, adjusted for the weekly model cycle length and ascribed to those patients experiencing events in each cycle. For the mean utility values, the coefficient for ≥3 TRAEs is 0.132 for both the monotherapy and combination therapy regimens. The disutility used in the model is dependent on the utility method selected; in the base case, this is the mix regression model.

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

EQ-5D analyses based on the final analysis data from KEYNOTE-048 data showed that patients who had progressive disease experienced a lower HRQoL than those in the pre-

progression health state. A constant value for HRQoL is applied in each cycle, with a age-related utility decrement applied as outlined in the original submission and taken from Ara and Brazier [7].

Table 66. Summary of utility values for base case cost-effectiveness analysis

	Utilities		Reference in submission (section and page number)	Justification
	Mean	Standard Error		
Progression-free survival	0.7644	0.0137	Page 36	NICE Reference Case
Progressed disease	0.7041	0.0156		
TRAEs: grade 3-5	-0.0252	0.0076		
Time prior to death: 180-365 days	-0.0000	0.0000		
Time prior to death: 90-180 days	0.0495	0.0106		
Time prior to death: 60-90 days	0.1608	0.0137		
Time prior to death: 30-60 days	0.1608	0.0137		
Time prior to death: 0-30 days	0.3186	0.0217		

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

Intervention

There is no change to the expected dose or unit cost of pembrolizumab compared to the original manufacturer submission.

Comparators

There is not change to the expected dose or unit cost of the comparators compared to the original manufacturer submission.

Treatment duration

Treatment duration has been updated using the final analysis dataset. As previously outlined, given the maturity of the data, no further extrapolation was required, and the direct KM data were used in the economic model. In line with the KEYNOTE-048 protocol, a stopping rule has been implemented in the model whereby patients do not receive therapy beyond 24 months.

For the EXTREME regimen a maximum treatment duration of 18 weeks (i.e. 6 cycles administered every 3 weeks) was used for the platinum compounds (i.e. cisplatin and carboplatin) and 5-FU to reflect the clinical practice in England.

The time on treatment duration for platinum+5-FU is assumed to be equal to the PFS curve in the absence of alternative data. PFS was estimated as outlined in Section 3.3 using the output of the NMA described in Section 2.9.

Pembrolizumab monotherapy

Figure 51. Time on treatment (ToT) data for monotherapy (CPS ≥1)

Pembrolizumab combination therapy

Figure 52.Time on treatment (ToT) for combination therapy (CPS ≥1)

Administration Costs

Administration costs remain as outlined in the original manufacturer's submission.

Health-state unit costs and resource use

The inclusion of health state costs remains as outlined in the original manufacturer's submission.

Adverse reaction unit costs and resource use

Adverse reaction costs are included as outlined in the original submission. The adverse event rates have been updated based on the final analysis dataset and are presented in Table 58.

Miscellaneous unit costs and resource use

Subsequent Treatment Costs

Drug and administration costs

The inclusion of drug and administration costs for subsequent treatment is identical to the methodology outlined in the original manufacturer's submission. The rates of subsequent treatments based on the final analysis dataset is outlined in Table 59 and Table 60.

Terminal Care Costs

Terminal care costs remain as outlined in the original manufacturer's submission.

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

Summary of base-case analysis inputs

The full list of variables used in the cost-effectiveness analysis is presented in Table 67 below.

Table 67. Summary of variables applied in the economic model for pembrolizumab monotherapy

Variable	Base case value	Lower bound	Upper bound	Reference to section in submission
Discount rate (costs)	3.50%	0.00%	6.00%	Section 3.2 Original document B
Discount rate (outcomes)	3.50%	0.00%	6.00%	
Age (years)	60.77	41.25	80.29	
Weight (kg)	69.37	40.34	98.40	
Body surface area (m^2)	1.60	1.12	2.08	
PFS utility score	0.77	0.74	0.79	Section 3.4 Page 142-144
PD utility score	0.71	0.67	0.74	
TTD disutilities: 180-365 days prior to death	0	0	0	
TTD disutilities: 90-180 days prior to death	0.04945	0.0287524	0.0701476	
TTD disutilities: 60-90 days prior to death	0.1608	0.1338696	0.1877304	
TTD disutilities: 30-60 days prior to death	0.1608	0.1338696	0.1877304	
TTD disutilities: 0-30 days prior to death	0.3235	0.2809484	0.3660516	
PF health state costs	123.26	98.61	147.91	Section 3.5 Original document B
PD health state costs	64.31	51.45	77.18	
Terminal care health state costs	7797.92	6238.34	9357.51	
Pembrolizumab Overall survival parameters: alpha	0.102237652649452	-0.38	0.18	Section 3.3 Page 113-136
Pembrolizumab Overall survival parameters: beta	4.59869207533424	4.11	5.09	

Pembrolizumab Overall survival parameters: Q	x	x	x	
Pembrolizumab Progression-free survival parameters: alpha	-4.72784283494884	-5.12	-4.34	
Pembrolizumab Progression-free survival parameters: beta	x	x	x	
Pembrolizumab Progression-free survival parameters: Q	x	x	x	
Pembrolizumab Time on treatment parameters: alpha	-3.38950353027192	-3.51	-3.27	
Pembrolizumab Time on treatment parameters: beta	x	x	x	
Pembrolizumab Time on treatment parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Overall survival parameters: alpha	0.144121381120858	-0.14	0.43	
Platinum + 5-FU + Cetuximab Overall survival parameters: beta	3.6634115891292	3.24	4.08	
Platinum + 5-FU + Cetuximab Overall survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: alpha	-4.21005505806597	-4.62	-3.80	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: beta	x	x	x	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment parameters: alpha	-3.28397541299462	-3.41	-3.16	
Platinum + 5-FU + Cetuximab Time on treatment parameters: beta	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment parameters: Q	x	x	x	
Platinum + 5-FU Overall survival parameters: alpha	-0.102237652649452	-0.38	0.18	
Platinum + 5-FU Overall survival parameters: beta	4.59869207533424	4.11	5.09	
Platinum + 5-FU Overall survival parameters: Q	x	x	x	
Platinum + 5-FU Progression-free survival parameters: alpha	-4.72784283494884	-5.12	-4.34	
Platinum + 5-FU Progression-free survival parameters: beta	x	x	x	
Platinum + 5-FU Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU Time on treatment parameters: alpha	-3.28397541299462	-3.41	-3.16	
Platinum + 5-FU Time on treatment parameters: beta	x	x	x	
Platinum + 5-FU Time on treatment parameters: Q	x	x	x	
Pembrolizumab Time on treatment HR	1.00	0.80	1.20	
Platinum + 5-FU + Cetuximab Time on treatment HR	1.00	0.80	1.20	

Platinum + 5-FU Time on treatment HR	1.00	0.80	1.20	
ALT/AST increase weekly incidence rate, pembrolizumab	0	0	0	Section 3.3. Page 137-139
Anaemia weekly incidence rate, pembrolizumab	0.001844	0.00090712	0.00278088	
Asthenia weekly incidence rate, pembrolizumab	0.000395	-0.0000362	0.0008262	
Cardiac event weekly incidence rate, pembrolizumab	0	0	0	
Decreased appetite weekly incidence rate, pembrolizumab	0.000395	-0.00003424	0.00082424	
Dehydration weekly incidence rate, pembrolizumab	0.000263	-0.00006824	0.00059424	
Diarrhoea weekly incidence rate, pembrolizumab	0	0	0	
Dyspnoea weekly incidence rate, pembrolizumab	0	0	0	
Fatigue weekly incidence rate, pembrolizumab	0.001186	0.00044512	0.00192688	
Febrile Neutropenia weekly incidence rate, pembrolizumab	0	0	0	
Granulocytopenia weekly incidence rate, pembrolizumab	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, pembrolizumab	0.00079	0.00014124	0.00143876	
Hypomagnesemia (low magnesium) weekly incidence rate, pembrolizumab	0	0	0	
Hyponatraemia weekly incidence rate, pembrolizumab	0.002371	0.0013028	0.0034392	
Hypotension weekly incidence rate, pembrolizumab	0	0	0	
Infection weekly incidence rate, pembrolizumab	0	0	0	
Leukopenia weekly incidence rate, pembrolizumab	0	0	0	
Lymphopenia weekly incidence rate, pembrolizumab	0	0	0	
Dysphagia/Mucositis weekly incidence rate, pembrolizumab	0.000527	0.00001152	0.00104248	
Nausea/Vomiting weekly incidence rate, pembrolizumab	0.000132	0.000132	0.000132	
Neutropenia weekly incidence rate, pembrolizumab	0.000132	-0.00009928	0.00036328	
Neutrophil count decreased weekly incidence rate, pembrolizumab	0	0	0	
White bloodcell count decreased weekly incidence rate, pembrolizumab	0	0	0	
Phlebitis weekly incidence rate, pembrolizumab	0	0	0	
Platelet count decrease weekly incidence rate, pembrolizumab	0	0	0	
Pneumonia weekly incidence rate, pembrolizumab	0.00224	0.00122668	0.00325332	

Pneumonia aspiration weekly incidence rate, pembrolizumab	0	0	0	
Skin reaction weekly incidence rate, pembrolizumab	0.000263	-0.00006236	0.00058836	
Stomatitis weekly incidence rate, pembrolizumab	0	0	0	
Thrombocytopenia weekly incidence rate, pembrolizumab	0.000132	-0.00008752	0.00035152	
ALT/AST increase weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Anaemia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.007496	0.0055458	0.0094462	
Asthenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.001377	0.00059496	0.00215904	
Cardiac event weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Decreased appetite weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00153	0.00069896	0.00236104	
Dehydration weekly incidence rate, Platinum + 5-FU + Cetuximab	0.001224	0.00045764	0.00199036	
Diarrhoea weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Dyspnoea weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Fatigue weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002142	0.0010836	0.0032004	
Febrile Neutropenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002601	0.00137012	0.00383188	
Granulocytopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002601	0.00146224	0.00373976	
Hypomagnesemia (low magnesium) weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002142	0.0011914	0.0030926	
Hyponatraemia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002601	0.00150732	0.00369468	
Hypotension weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Infection weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Leukopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002448	0.00138176	0.00351424	
Lymphopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Dysphagia/Mucositis weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002295	0.0012562	0.0033338	
Nausea/Vomiting weekly incidence rate, Platinum + 5-FU + Cetuximab	0.003825	0.00215312	0.00549688	
Neutropenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.009331	0.0072632	0.0113988	

Neutrophil count decreased weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00566	0.00387052	0.00744948	
White bloodcell count decreased weekly incidence rate, Platinum + 5-FU + Cetuximab	0.003977	0.00250504	0.00544896	
Phlebitis weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Platelet count decrease weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Pneumonia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00306	0.00179384	0.00432616	
Pneumonia aspiration weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Skin reaction weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002601	0.00140736	0.00379464	
Stomatitis weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Thrombocytopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.003977	0.00240312	0.00555088	
ALT/AST increase weekly incidence rate, Platinum + 5-FU	0	0	0	
Anaemia weekly incidence rate, Platinum + 5-FU	4.0052325292077E-03	4.0052325292077E-03	4.0052325292077E-03	
Asthenia weekly incidence rate, Platinum + 5-FU	6.39061755191201E-04	6.39061755191201E-04	6.39061755191201E-04	
Cardiac event weekly incidence rate, Platinum + 5-FU	0	0	0	
Decreased appetite weekly incidence rate, Platinum + 5-FU	0	0	0	
Dehydration weekly incidence rate, Platinum + 5-FU	5.58302552552836E-04	5.58302552552836E-04	5.58302552552836E-04	
Diarrhoea weekly incidence rate, Platinum + 5-FU	3.17539979480043E-04	3.17539979480043E-04	3.17539979480043E-04	
Dyspnoea weekly incidence rate, Platinum + 5-FU	0	0	0	
Fatigue weekly incidence rate, Platinum + 5-FU	0	0	0	
Febrile Neutropenia weekly incidence rate, Platinum + 5-FU	1.37757434246572E-03	1.37757434246572E-03	1.37757434246572E-03	
Granulocytopenia weekly incidence rate, Platinum + 5-FU	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, Platinum + 5-FU	0.001882004229612	0.001882004229612	0.001882004229612	
Hypomagnesemia (low magnesium) weekly incidence rate, Platinum + 5-FU	9.64666456143187E-04	9.64666456143187E-04	9.64666456143187E-04	
Hyponatraemia weekly incidence rate, Platinum + 5-FU	0	0	0	
Hypotension weekly incidence rate, Platinum + 5-FU	0	0	0	

Infection weekly incidence rate, Platinum + 5-FU	0	0	0	
Leukopenia weekly incidence rate, Platinum + 5-FU	0	0	0	
Lymphopenia weekly incidence rate, Platinum + 5-FU	0	0	0	
Dysphagia/Mucositis weekly incidence rate, Platinum + 5-FU	0	0	0	
Nausea/Vomiting weekly incidence rate, Platinum + 5-FU	0	0	0	
Neutropenia weekly incidence rate, Platinum + 5-FU	1.01218833977753E-02	1.01218833977753E-02	1.01218833977753E-02	
Neutrophil count decreased weekly incidence rate, Platinum + 5-FU	0	0	0	
White bloodcell count decreased weekly incidence rate, Platinum + 5-FU	0	0	0	
Phlebitis weekly incidence rate, Platinum + 5-FU	9.64666456143187E-04	9.64666456143187E-04	9.64666456143187E-04	
Platelet count decrease weekly incidence rate, Platinum + 5-FU	0	0	0	
Pneumonia weekly incidence rate, Platinum + 5-FU	0	0	0	
Pneumonia aspiration weekly incidence rate, Platinum + 5-FU	0	0	0	
Skin reaction weekly incidence rate, Platinum + 5-FU	4.77796911407509E-04	4.77796911407509E-04	4.77796911407509E-04	
Stomatitis weekly incidence rate, Platinum + 5-FU	2.31007803915482E-03	2.31007803915482E-03	2.31007803915482E-03	
Thrombocytopenia weekly incidence rate, Platinum + 5-FU	2.05237711983427E-03	2.05237711983427E-03	2.05237711983427E-03	
ALT/AST increase disutility	0.02519	0.0101274	0.0402526	Section 3.4. Page 142
Anaemia disutility	0.02519	0.0101274	0.0402526	
Asthenia disutility	0.02519	0.0101274	0.0402526	
Cardiac event disutility	0.02519	0.0101274	0.0402526	
Decreased appetite disutility	0.02519	0.0101274	0.0402526	
Dehydration disutility	0.02519	0.0101274	0.0402526	
Diarrhoea disutility	0.02519	0.0101274	0.0402526	
Dyspnoea disutility	0.02519	0.0101274	0.0402526	
Fatigue disutility	0.02519	0.0101274	0.0402526	
Febrile Neutropenia disutility	0.02519	0.0101274	0.0402526	
Granulocytopenia disutility	0.02519	0.0101274	0.0402526	

Hypokalemia (low potassium) disutility	0.02519	0.0101274	0.0402526	
Hypomagnesemia (low magnesium) disutility	0.02519	0.0101274	0.0402526	
Hyponatraemia disutility	0.02519	0.0101274	0.0402526	
Hypotension disutility	0.02519	0.0101274	0.0402526	
Infection disutility	0.02519	0.0101274	0.0402526	
Leukopenia disutility	0.02519	0.0101274	0.0402526	
Lymphopenia disutility	0.02519	0.0101274	0.0402526	
Dysphagia/Mucositis disutility	0.02519	0.0101274	0.0402526	
Nausea/Vomiting disutility	0.02519	0.0101274	0.0402526	
Neutropenia disutility	0.02519	0.0101274	0.0402526	
Neutrophil count decreased disutility	0.02519	0.0101274	0.0402526	
White bloodcell count decreased disutility	0.02519	0.0101274	0.0402526	
Phlebitis disutility	0.02519	0.0101274	0.0402526	
Platelet count decrease disutility	0.02519	0.0101274	0.0402526	
Pneumonia disutility	0.02519	0.0101274	0.0402526	
Pneumonia aspiration disutility	0.02519	0.0101274	0.0402526	
Skin reaction disutility	0.02519	0.0101274	0.0402526	
Stomatitis disutility	0.02519	0.0101274	0.0402526	
Thrombocytopenia disutility	0.02519	0.0101274	0.0402526	

Table 68. Summary of variables applied in the economic model for pembrolizumab combination therapy

Variable	Base case value	Lower bound	Upper bound	Reference to section in submission
Discount rate (costs)	3.50%	0.00%	6.00%	Section 3.2 Original document B
Discount rate (outcomes)	3.50%	0.00%	6.00%	
Age (years)	60.72	40.94	80.50	
Weight (kg)	68.17	40.04	96.30	
Body surface area (m²)	1.74	1.28	2.19	
PFS utility score	0.76	0.74	0.79	Section 3.4 Page 142-144
PD utility score	0.70	0.67	0.73	
TTD disutilities: 180-365 days prior to death	0	0	0	
TTD disutilities: 90-180 days prior to death	0.04945	0.0287524	0.0701476	
TTD disutilities: 60-90 days prior to death	0.1608	0.1338696	0.1877304	
TTD disutilities: 30-60 days prior to death	0.1608	0.1338696	0.1877304	
TTD disutilities: 0-30 days prior to death	0.3186	0.2760484	0.3611516	
PF health state costs	123.26	98.61	147.91	Section 3.5 Original document B
PD health state costs	64.31	51.45	77.18	
Terminal care health state costs	7797.92	6238.34	9357.51	
Pembrolizumab Overall survival parameters: alpha	5.21882933969347	4.48	5.96	Section 3.3 Page 113-136
Pembrolizumab Overall survival parameters: beta	0.75312853311965	0.45	1.06	
Pembrolizumab Overall survival parameters: Q	x	x	x	
Pembrolizumab Progression-free survival parameters: alpha	-4.63680727010592	-5.04	-4.24	
Pembrolizumab Progression-free survival parameters: beta	x	x	x	
Pembrolizumab Progression-free survival parameters: Q	x	x	x	
Pembrolizumab Time on treatment parameters: alpha	-3.51396260141123	-3.64	-3.39	
Pembrolizumab Time on treatment parameters: beta	x	x	x	
Pembrolizumab Time on treatment parameters: Q	x	x	x	

Platinum + 5-FU + Cetuximab Overall survival parameters: alpha	3.51979334575272	3.12	3.92	
Platinum + 5-FU + Cetuximab Overall survival parameters: beta	0.293686857639755	0.04	0.55	
Platinum + 5-FU + Cetuximab Overall survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: alpha	-3.9961731499771	-4.41	-3.58	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: beta	x	x	x	
Platinum + 5-FU + Cetuximab Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment parameters: alpha	-3.28397541299462	-3.41	-3.16	
Platinum + 5-FU + Cetuximab Time on treatment parameters: beta	x	x	x	
Platinum + 5-FU + Cetuximab Time on treatment parameters: Q	x	x	x	
Platinum + 5-FU Overall survival parameters: alpha	5.21882933969347	4.48	5.96	
Platinum + 5-FU Overall survival parameters: beta	0.75312853311965	0.45	1.06	
Platinum + 5-FU Overall survival parameters: Q	x	x	x	
Platinum + 5-FU Progression-free survival parameters: alpha	-4.63680727010592	-5.04	-4.24	
Platinum + 5-FU Progression-free survival parameters: beta	x	x	x	
Platinum + 5-FU Progression-free survival parameters: Q	x	x	x	
Platinum + 5-FU Time on treatment parameters: alpha	-3.28397541299462	-3.41	-3.16	
Platinum + 5-FU Time on treatment parameters: beta	x	x	x	
Platinum + 5-FU Time on treatment parameters: Q	x	x	x	
Pembrolizumab Time on treatment HR	1.00	0.80	1.20	
Platinum + 5-FU + Cetuximab Time on treatment HR	1.00	0.80	1.20	
Platinum + 5-FU Time on treatment HR	1.00	0.80	1.20	
ALT/AST increase weekly incidence rate, pembrolizumab	0	0	0	Section 3.3. Page 137-139
Anaemia weekly incidence rate, pembrolizumab	0.007773	0.00589924	0.00964676	
Asthenia weekly incidence rate, pembrolizumab	0.000999	0.00036788	0.00163012	
Cardiac event weekly incidence rate, pembrolizumab	0	0	0	
Decreased appetite weekly incidence rate, pembrolizumab	0.001444	0.00066784	0.00222016	
Dehydration weekly incidence rate, pembrolizumab	0.000777	0.00017136	0.00138264	

Diarrhoea weekly incidence rate, pembrolizumab	0	0	0	
Dyspnoea weekly incidence rate, pembrolizumab	0	0	0	
Fatigue weekly incidence rate, pembrolizumab	0.002221	0.00121748	0.00322452	
Febrile Neutropenia weekly incidence rate, pembrolizumab	0.002665	0.00156152	0.00376848	
Granulocytopenia weekly incidence rate, pembrolizumab	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, pembrolizumab	0.001999	0.00103076	0.00296724	
Hypomagnesemia (low magnesium) weekly incidence rate, pembrolizumab	0.000555	0.00008656	0.00102344	
Hyponatraemia weekly incidence rate, pembrolizumab	0.002443	0.00140028	0.00348572	
Hypotension weekly incidence rate, pembrolizumab	0	0	0	
Infection weekly incidence rate, pembrolizumab	0	0	0	
Leukopenia weekly incidence rate, pembrolizumab	0.000999	0.00035024	0.00164776	
Lymphopenia weekly incidence rate, pembrolizumab	0	0	0	
Dysphagia/Mucositis weekly incidence rate, pembrolizumab	0.002998	0.00186904	0.00412696	
Nausea/Vomiting weekly incidence rate, pembrolizumab	0.002887	0.00129548	0.00447852	
Neutropenia weekly incidence rate, pembrolizumab	0.005441	0.00402	0.006862	
Neutrophil count decreased weekly incidence rate, pembrolizumab	0.003331	0.00218048	0.00448152	
White bloodcell count decreased weekly incidence rate, pembrolizumab	0.001666	0.00084672	0.00248528	
Phlebitis weekly incidence rate, pembrolizumab	0	0	0	
Platelet count decrease weekly incidence rate, pembrolizumab	0.001666	0.00081144	0.00252056	
Pneumonia weekly incidence rate, pembrolizumab	0.001666	0.00082124	0.00251076	
Pneumonia aspiration weekly incidence rate, pembrolizumab	0.000999	0.00035416	0.00164384	
Skin reaction weekly incidence rate, pembrolizumab	0.000111	-0.00005756	0.00027956	
Stomatitis weekly incidence rate, pembrolizumab	0.002554	0.00156028	0.00354772	
Thrombocytopenia weekly incidence rate, pembrolizumab	0.002776	0.00169604	0.00385596	
ALT/AST increase weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Anaemia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.007496	0.00565556	0.00933644	
Asthenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.001377	0.00058516	0.00216884	

Cardiac event weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Decreased appetite weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00153	0.00071464	0.00234536	
Dehydration weekly incidence rate, Platinum + 5-FU + Cetuximab	0.001224	0.00045176	0.00199624	
Diarrhoea weekly incidence rate, Platinum + 5-FU + Cetuximab	0.001224	0.00047332	0.00197468	
Dyspnoea weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Fatigue weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002142	0.00107968	0.00320432	
Febrile Neutropenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002601	0.00139756	0.00380444	
Granulocytopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Hypomagnesemia (low magnesium) weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002142	0.00119532	0.00308868	
Hyponatraemia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002601	0.00150928	0.00369272	
Hypotension weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Infection weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Leukopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002448	0.00138372	0.00351228	
Lymphopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.001377	0.00057928	0.00217472	
Dysphagia/Mucositis weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002295	0.00119936	0.00339064	
Nausea/Vomiting weekly incidence rate, Platinum + 5-FU + Cetuximab	0.003825	2.61619949569832E-03	5.03380050430168E-03	
Neutropenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.009331	0.00724948	0.01141252	
Neutrophil count decreased weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00566	0.00380192	0.00751808	
White bloodcell count decreased weekly incidence rate, Platinum + 5-FU + Cetuximab	0.003977	0.00246388	0.00549012	
Phlebitis weekly incidence rate, Platinum + 5-FU + Cetuximab	0	0	0	
Platelet count decrease weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00153	0.00066956	0.00239044	
Pneumonia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00306	0.00176248	0.00435752	
Pneumonia aspiration weekly incidence rate, Platinum + 5-FU + Cetuximab	0.000459	-0.0000408	0.0009588	

Skin reaction weekly incidence rate, Platinum + 5-FU + Cetuximab	0.002601	0.0014544	0.0037476	
Stomatitis weekly incidence rate, Platinum + 5-FU + Cetuximab	0.00153	0.00061076	0.00244924	
Thrombocytopenia weekly incidence rate, Platinum + 5-FU + Cetuximab	0.003977	0.00244428	0.00550972	
ALT/AST increase weekly incidence rate, Platinum + 5-FU	0	0	0	
Anaemia weekly incidence rate, Platinum + 5-FU	4.0052325292077E-03	4.0052325292077E-03	4.0052325292077E-03	
Asthenia weekly incidence rate, Platinum + 5-FU	6.39061755191201E-04	6.39061755191201E-04	6.39061755191201E-04	
Cardiac event weekly incidence rate, Platinum + 5-FU	0	0	0	
Decreased appetite weekly incidence rate, Platinum + 5-FU	0	0	0	
Dehydration weekly incidence rate, Platinum + 5-FU	5.58302552552836E-04	5.58302552552836E-04	5.58302552552836E-04	
Diarrhoea weekly incidence rate, Platinum + 5-FU	3.17539979480043E-04	3.17539979480043E-04	3.17539979480043E-04	
Dyspnoea weekly incidence rate, Platinum + 5-FU	0	0	0	
Fatigue weekly incidence rate, Platinum + 5-FU	0	0	0	
Febrile Neutropenia weekly incidence rate, Platinum + 5-FU	1.37757434246572E-03	1.37757434246572E-03	1.37757434246572E-03	
Granulocytopenia weekly incidence rate, Platinum + 5-FU	0	0	0	
Hypokalemia (low potassium) weekly incidence rate, Platinum + 5-FU	0.001882004229612	0.001882004229612	0.001882004229612	
Hypomagnesemia (low magnesium) weekly incidence rate, Platinum + 5-FU	9.64666456143187E-04	9.64666456143187E-04	9.64666456143187E-04	
Hyponatraemia weekly incidence rate, Platinum + 5-FU	0	0	0	
Hypotension weekly incidence rate, Platinum + 5-FU	0	0	0	
Infection weekly incidence rate, Platinum + 5-FU	0	0	0	
Leukopenia weekly incidence rate, Platinum + 5-FU	0	0	0	
Lymphopenia weekly incidence rate, Platinum + 5-FU	0	0	0	
Dysphagia/Mucositis weekly incidence rate, Platinum + 5-FU	0	0	0	
Nausea/Vomiting weekly incidence rate, Platinum + 5-FU	0	0	0	
Neutropenia weekly incidence rate, Platinum + 5-FU	1.01218833977753E-02	1.01218833977753E-02	1.01218833977753E-02	
Neutrophil count decreased weekly incidence rate, Platinum + 5-FU	0	0	0	

White bloodcell count decreased weekly incidence rate, Platinum + 5-FU	0	0	0	
Phlebitis weekly incidence rate, Platinum + 5-FU	9.64666456143187E-04	9.64666456143187E-04	9.64666456143187E-04	
Platelet count decrease weekly incidence rate, Platinum + 5-FU	0	0	0	
Pneumonia weekly incidence rate, Platinum + 5-FU	0	0	0	
Pneumonia aspiration weekly incidence rate, Platinum + 5-FU	0	0	0	
Skin reaction weekly incidence rate, Platinum + 5-FU	4.77796911407509E-04	4.77796911407509E-04	4.77796911407509E-04	
Stomatitis weekly incidence rate, Platinum + 5-FU	2.31007803915482E-03	2.31007803915482E-03	2.31007803915482E-03	
Thrombocytopenia weekly incidence rate, Platinum + 5-FU	2.05237711983427E-03	2.05237711983427E-03	2.05237711983427E-03	
ALT/AST increase disutility	0.02519	0.0101274	0.0402526	Section 3.4. Page 142
Anaemia disutility	0.02519	0.0101274	0.0402526	
Asthenia disutility	0.02519	0.0101274	0.0402526	
Cardiac event disutility	0.02519	0.0101274	0.0402526	
Decreased appetite disutility	0.02519	0.0101274	0.0402526	
Dehydration disutility	0.02519	0.0101274	0.0402526	
Diarrhoea disutility	0.02519	0.0101274	0.0402526	
Dyspnoea disutility	0.02519	0.0101274	0.0402526	
Fatigue disutility	0.02519	0.0101274	0.0402526	
Febrile Neutropenia disutility	0.02519	0.0101274	0.0402526	
Granulocytopenia disutility	0.02519	0.0101274	0.0402526	
Hypokalemia (low potassium) disutility	0.02519	0.0101274	0.0402526	
Hypomagnesemia (low magnesium) disutility	0.02519	0.0101274	0.0402526	
Hyponatraemia disutility	0.02519	0.0101274	0.0402526	
Hypotension disutility	0.02519	0.0101274	0.0402526	
Infection disutility	0.02519	0.0101274	0.0402526	
Leukopenia disutility	0.02519	0.0101274	0.0402526	
Lymphopenia disutility	0.02519	0.0101274	0.0402526	

Dysphagia/Mucositis disutility	0.02519	0.0101274	0.0402526	
Nausea/Vomiting disutility	0.02519	0.0101274	0.0402526	
Neutropenia disutility	0.02519	0.0101274	0.0402526	
Neutrophil count decreased disutility	0.02519	0.0101274	0.0402526	
White bloodcell count decreased disutility	0.02519	0.0101274	0.0402526	
Phlebitis disutility	0.02519	0.0101274	0.0402526	
Platelet count decrease disutility	0.02519	0.0101274	0.0402526	
Pneumonia disutility	0.02519	0.0101274	0.0402526	
Pneumonia aspiration disutility	0.02519	0.0101274	0.0402526	
Skin reaction disutility	0.02519	0.0101274	0.0402526	
Stomatitis disutility	0.02519	0.0101274	0.0402526	
Thrombocytopenia disutility	0.02519	0.0101274	0.0402526	

Assumptions

Table 69 summarises the assumptions used in the economic model.

Table 69: List of assumptions used in the economic model

Assumption	Justification
Use KM data for the first 52 weeks from KEYNOTE-048 trial to model PFS for pembrolizumab and EXTREME, then extrapolate	Based on the shape of the survival curves, 2-phases piecewise approach was considered appropriate. Given the data maturity and hazards over time, 52 weeks was considered an appropriate point to begin the extrapolation.
Use KM data for the first 80 weeks from KEYNOTE-048 trial to model OS for pembrolizumab and EXTREME, then extrapolate	Based on the shape of the survival curves, 2-phases piecewise approach was considered appropriate. For the first 80 weeks OS KM data provides robust and reliable estimate and at that point patient numbers are sufficient to implement parametric fitting based on KEYNOTE-048 data.
Use KM data for the time-to-treatment discontinuation curves	The KM data from KN-048 are fully mature for time to treatment continuation, therefore extrapolation via parametric models is not required.
The incidence of AEs from KEYNOTE-048 and published trials was assumed to reflect that observed in practice	Assumption based on the results of the KEYNOTE-048 trial and the published trials for platinum plus 5-FU for the indication under consideration. The same method and criteria were applied in a recent NICE oncology appraisals of pembrolizumab.[4, 5]
The quality of life of patients is appropriately captured by considering time to death utilities	Previous studies have suggested there is a decline in HRQoL in the final months of life of patients which may not appropriately be captured solely through the use of progression-based health state[8, 9]. 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.
Utilities were adjusted by UK general population utility where utility deceases with age	Based on the Ara and Brazier study suggesting the impact of age on HRQoL.[7]
Resource use is assumed to be equal between pembrolizumab and EXTREME/platinum plus 5-FU arms	Due to paucity of data, resource use was assumed to be equal per treatment arm in the pre- and post- progression health states.
Pembrolizumab will be administered for a maximum of 35 cycles (24 months).	This assumption is in line with KEYNOTE-048 clinical trial
Platinum plus 5-FU will be administered for up to 6 cycles	This assumption was implemented to reflect UK clinical practice.
Cetuximab is assumed to be administered with an	This is the assumption used in the appraisal TA472 for cetuximab.[3]

initial loading dose of and then subsequent doses every week. No vial sharing is assumed.	
No use of nivolumab as a subsequent therapy despite its use in KEYNOTE-048.	NICE position statement requests the exclusion as comparators or subsequent treatments, any drugs currently available in the Cancer Drugs Fund.[10] Therefore, a cross-over adjustment was conducted to remove its effect on the overall survival curve and its cost was not included in the economic model. A scenario including the efficacy and cost of nivolumab was presented, given the use of nivolumab in current NHS practice.
Comparison with EXTREME regimen is based on full KEYNOTE-048 population.	KEYNOTE-048 was not designed to analyse subgroups by cancer origin, such as the oral cavity. Therefore, the comparison to the EXTREME regimen was based on all cancer subgroups to maintain randomisation and powering.

B.3.7 Base-case results

The results of the economic model for the CPS ≥1 population are presented below. In the base case analysis, the estimated mean overall survival was 2.40 years with pembrolizumab monotherapy, 1.27 years for EXTREME and 1.10 years for platinum + 5-FU. Patients treated with pembrolizumab monotherapy accrued 1.69 QALYs compared to 0.91 QALYs for the EXTREME regimen and 0.78 QALYs for platinum + 5-FU.

The estimated mean overall survival was 3.05 years with pembrolizumab combination therapy, 1.18 years with the EXTREME regimen and 0.96 years with platinum + 5-FU. Patients treated with pembrolizumab combination therapy accrued 2.12 QALYs compared to 0.85 QALYs for EXTREME and 0.68 QALYs for platinum + 5-FU.

Base-case incremental cost-effectiveness analysis results

Table 70 below presents the base case incremental cost-effectiveness results for pembrolizumab monotherapy in the CPS ≥1 population, incorporating the discount of the CAA. The results show pembrolizumab monotherapy to be cost-effective compared to both the EXTREME regimen and platinum + 5-FU when considering a willingness to pay threshold of £50,000 per QALY. When pembrolizumab monotherapy is compared to EXTREME, pembrolizumab dominates the EXTREME regimen; the incremental-cost-effectiveness ratio (ICER) for pembrolizumab monotherapy is £31,212 when compared to platinum + 5-FU.

Table 70. Base-case results – monotherapy (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	48,945	2.40	1.69	-	-	-	-
EXTREME regimen	51,832	1.27	0.91	-2,886	1.13	0.78	Dominant
Platinum + 5-FU	20,616	1.10	0.78	28,329	1.30	0.91	31,212
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 71 below presents the base case incremental cost-effectiveness results for pembrolizumab combination therapy in the CPS ≥1 population, incorporating the discount of the CAA. The results show pembrolizumab combination therapy to be cost-effective compared to both the EXTREME regimen and platinum + 5-FU when considering a willingness to pay threshold of £50,000 per QALY. The corresponding incremental-cost-effectiveness ratio (ICER) when pembrolizumab combination therapy is compared to EXTREME is £9,255 and £31,070 when compared to platinum + 5-FU. These ICERs should be considered in the context of pembrolizumab being an innovative new treatment option for patients at the end of their life.

Table 71. Base-case results - combination therapy (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	64,414	3.05	2.12	-	-	-	-
EXTREME regimen	52,597	1.18	0.85	11,817	1.88	1.28	9,255
Platinum + 5-FU	19,652	0.96	0.68	44,762	2.10	1.44	31,070
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

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 Table 67.

Monotherapy

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis for pembrolizumab monotherapy are presented in Table 72 and Table 73 and the corresponding scatterplots and cost-effectiveness acceptability curves (CEAC) are presented in Figure 53 to Figure 56.

The cost-effectiveness acceptability curve shows that there is an approximately 100% probability that pembrolizumab monotherapy therapy is cost-effective when compared to the EXTREME regimen and a 99.2% probability that it is cost-effective compared to platinum + 5-FU at the £50,000 per QALY gained threshold.

Table 72. Probabilistic sensitivity analyses for pembrolizumab monotherapy vs EXTREME (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	49,019	2.39	1.68	-	-	-	-
EXTREME regimen	51,864	1.27	0.91	-2,845	1.12	0.77	Dominant
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 53. CEAC for pembrolizumab monotherapy vs EXTREME

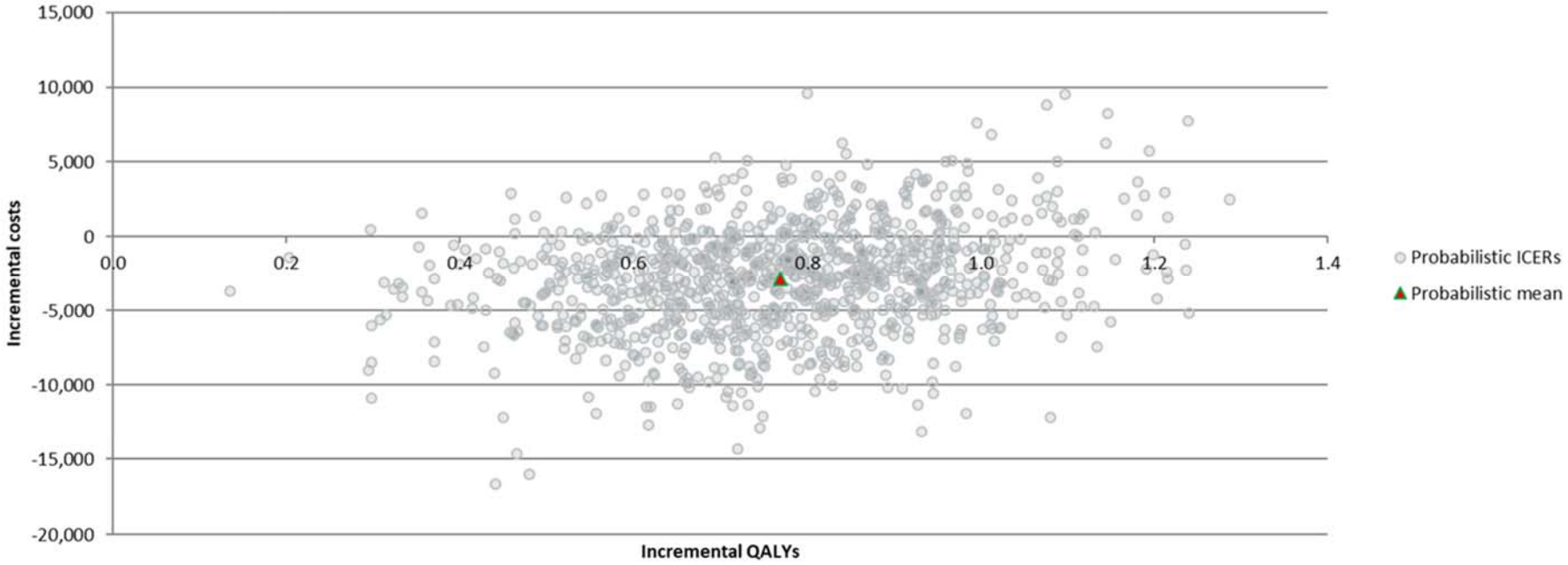


Figure 54. Scatterplot for pembrolizumab monotherapy vs EXTREME (CPS ≥1)

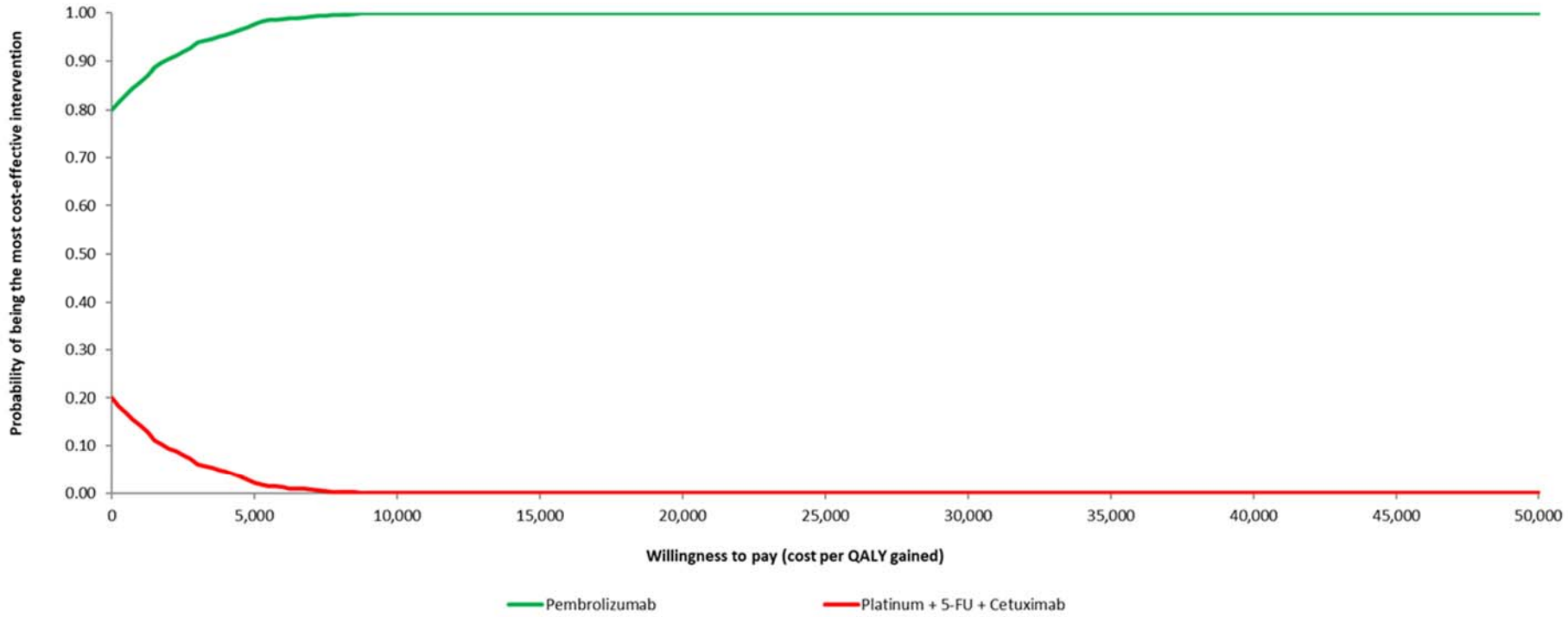


Table 73. Probabilistic sensitivity analyses for pembrolizumab monotherapy vs platinum +5-FU (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	48,876	2.37	1.67	-	-	-	-
Platinum + 5-FU	20,622	1.10	0.78	28,254	1.27	0.89	31,832
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 55. CEAC for pembrolizumab monotherapy vs platinum + 5-FU (CPS ≥1)

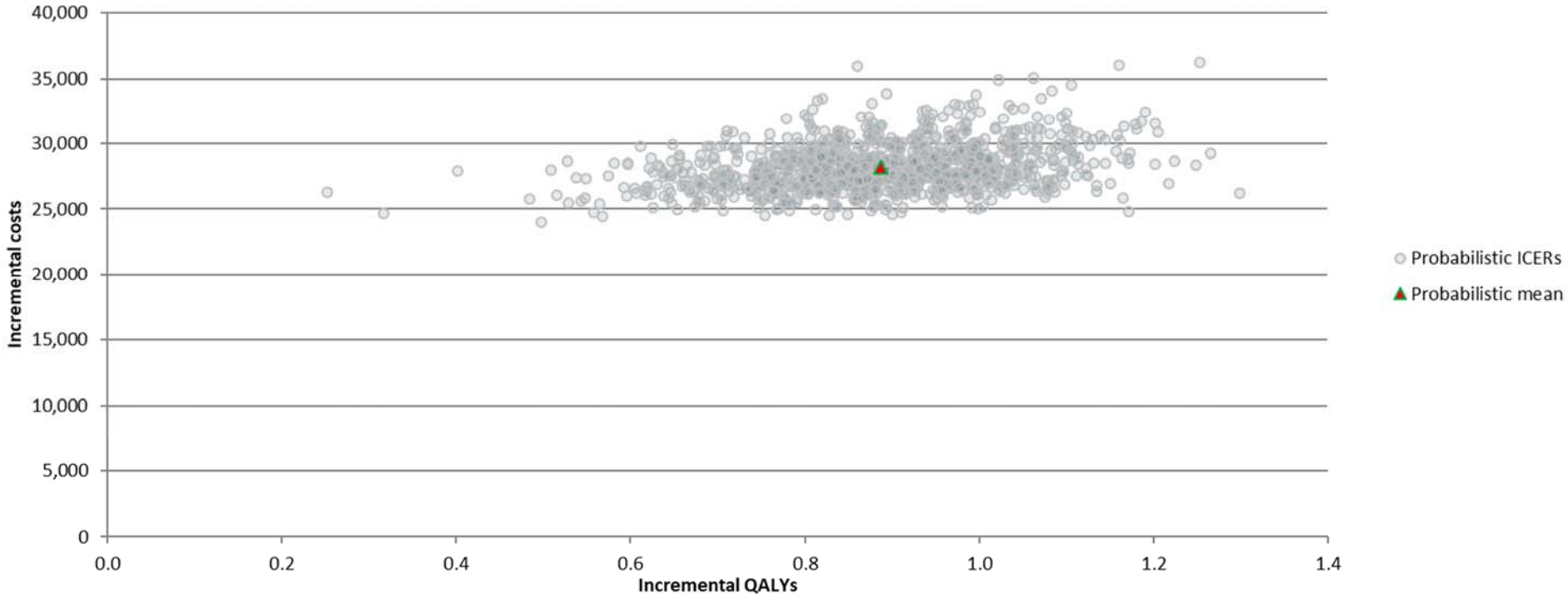
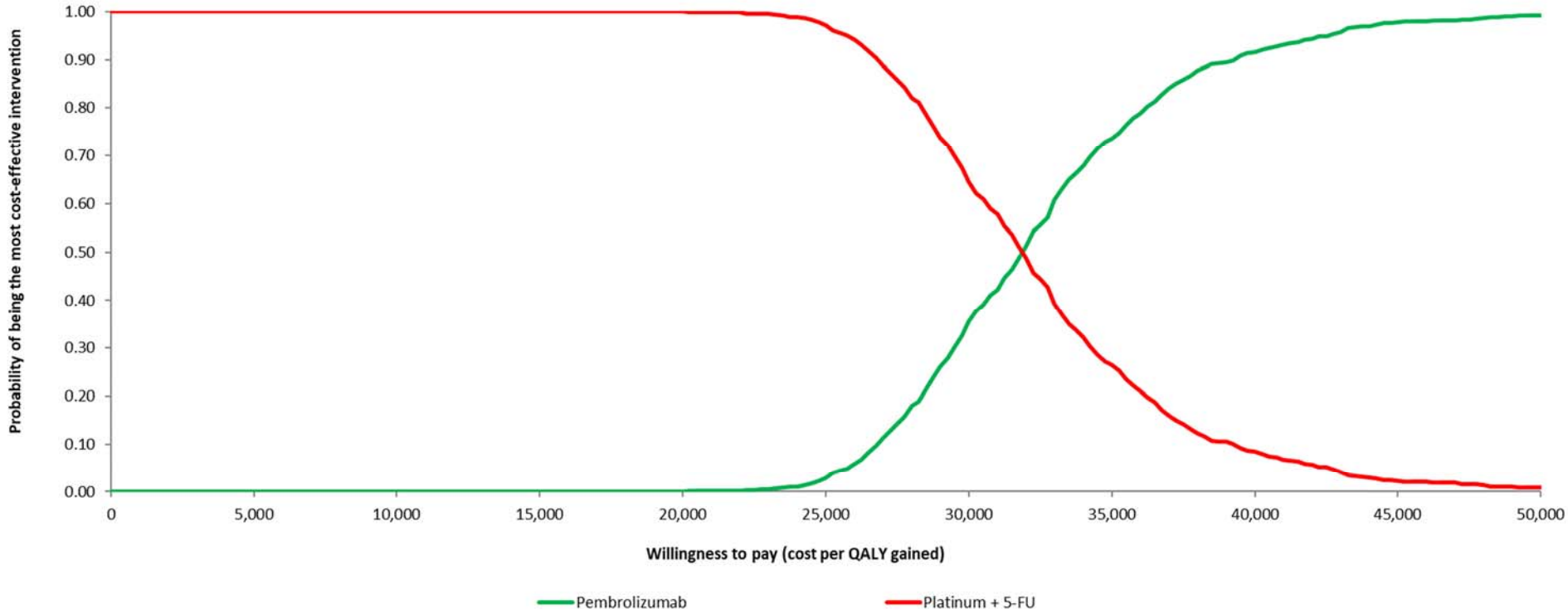


Figure 56. Scatterplot for pembrolizumab monotherapy vs platinum + 5-FU (CPS ≥1)



Combination therapy

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis for pembrolizumab combination therapy are presented in Table 74 to Table 75. The corresponding scatterplot and cost-effectiveness acceptability curves (CEAC) are presented in Figure 57 and Figure 58.

The cost-effectiveness acceptability curve shows that there is an approximately 100% probability that pembrolizumab combination therapy is cost-effective when compared to the EXTREME regimen and a 98.8% probability that it is cost-effective compared to platinum + 5-FU at the £50,000 per QALY gained threshold.

Table 74. Probabilistic sensitivity analyses for pembrolizumab combination therapy vs EXTREME (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	64,258	2.07	2.98	-	-	-	-
EXTREME regimen	52,610	1.19	0.85	11,649	1.79	1.22	9,552
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 57. Scatterplot for pembrolizumab combination therapy vs EXTREME (CPS ≥1)

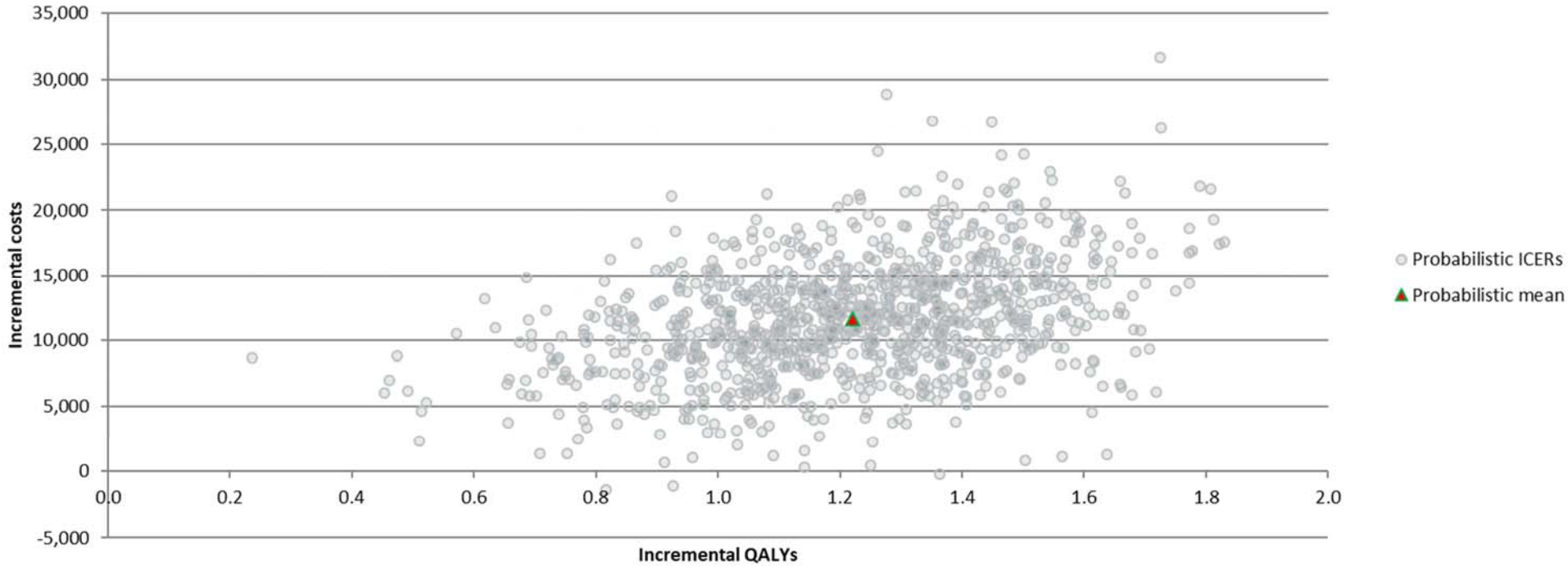


Figure 58. CEAC for pembrolizumab combination therapy vs EXTREME (CPS ≥1)

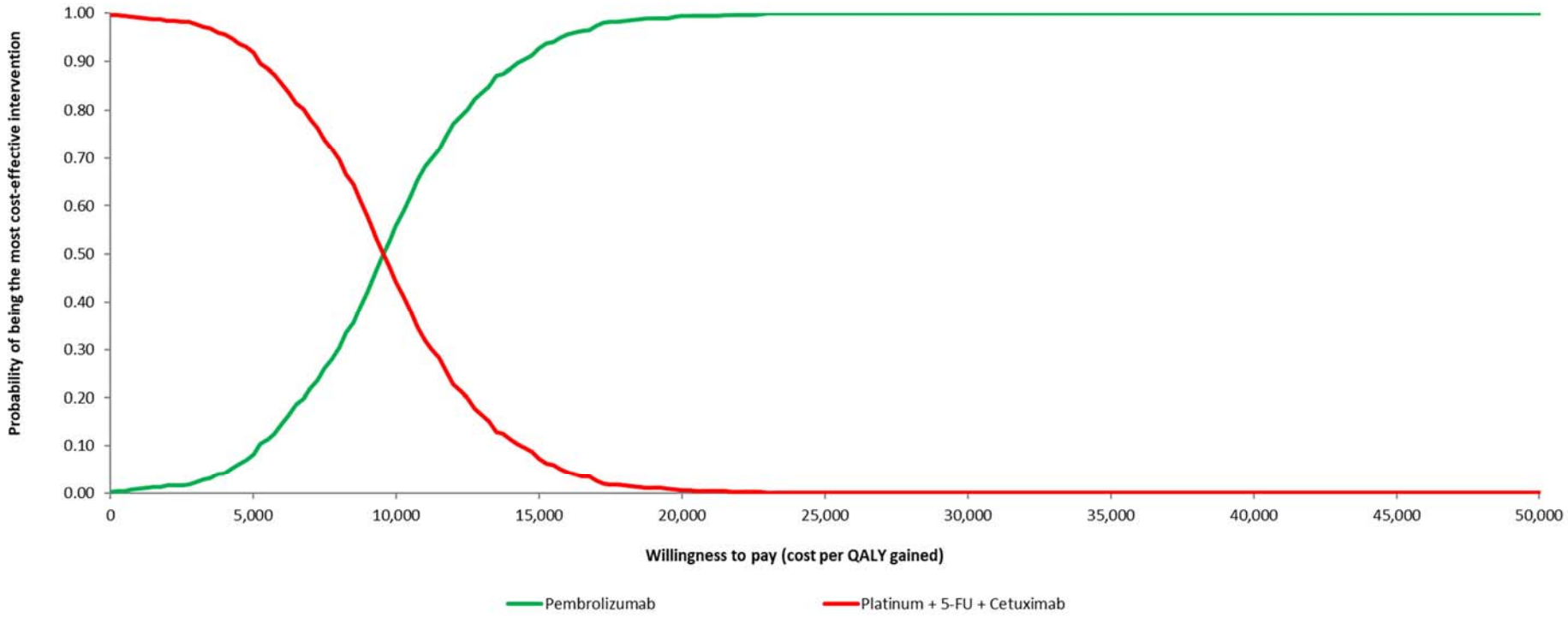


Table 75. Probabilistic sensitivity analyses for pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	64,081	2.97	2.07	-	-	-	-
Platinum + 5-FU	19,654	0.96	0.68	44,427	1.39	2.01	32,043
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Figure 59. Scatterplot for pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)

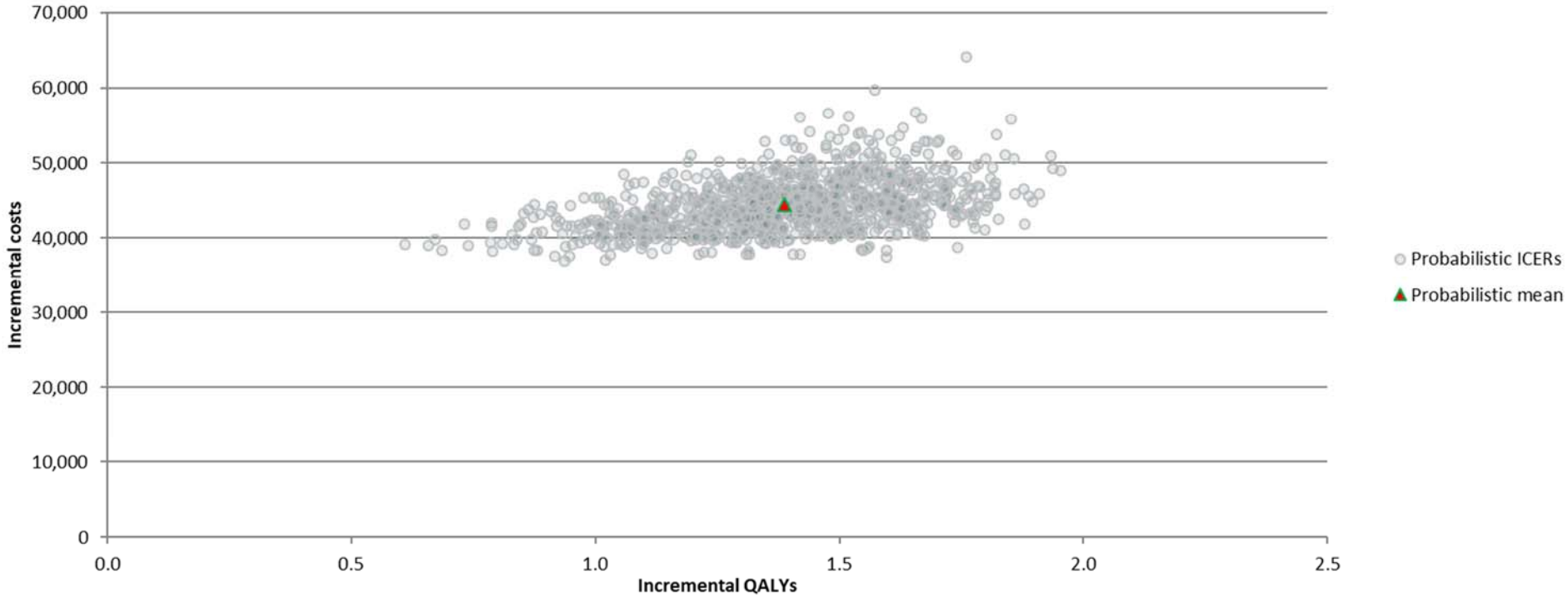
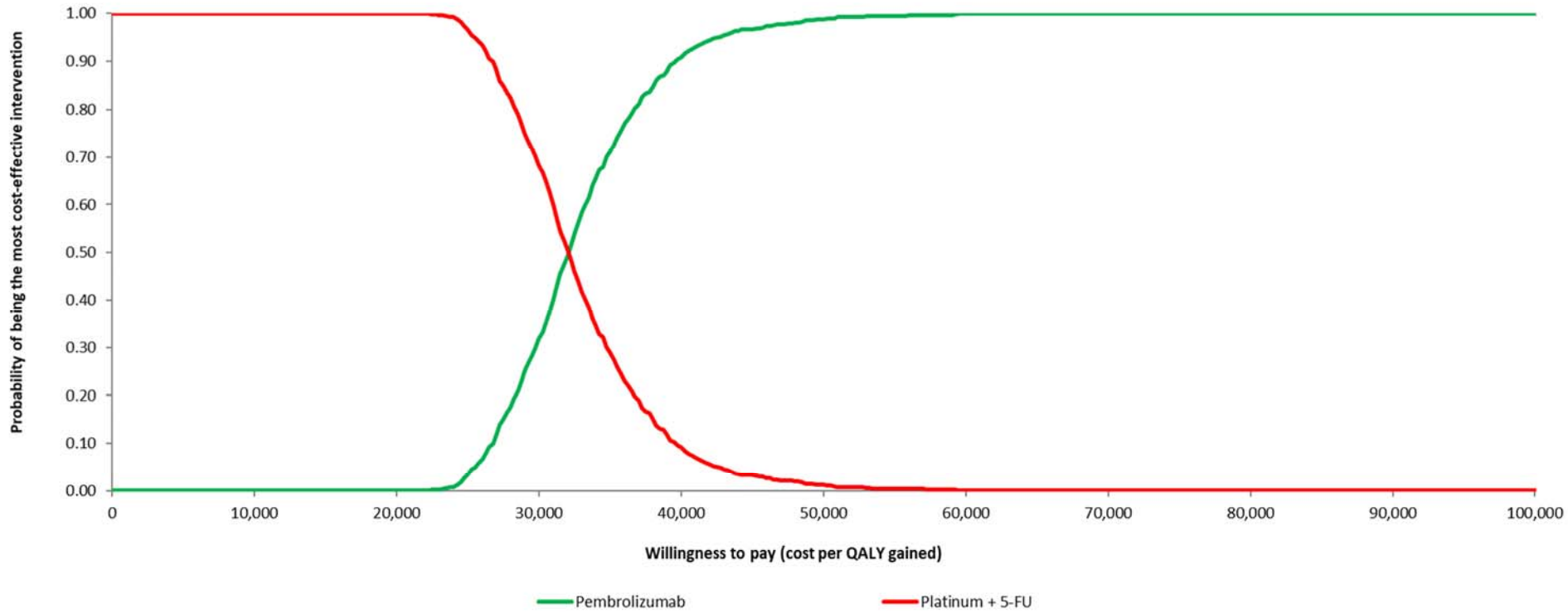


Figure 60. CEAC for pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)



Deterministic sensitivity analysis

Extensive sensitivity analyses were conducted to explore the uncertainty associated with the estimates of cost-effectiveness. One-way deterministic sensitivity analysis (DSA) was conducted using the parameters outlined in Table 67 and Table 68, and the associated lower and upper bound. The tornado diagrams of these one-way DSA are presented in Figure 61 to

Figure **64** and the full table of results are presented in Appendix Q.

Figure 61. Tornado diagram presenting one-way DSA results: pembrolizumab monotherapy vs EXTREME (CPS ≥1)

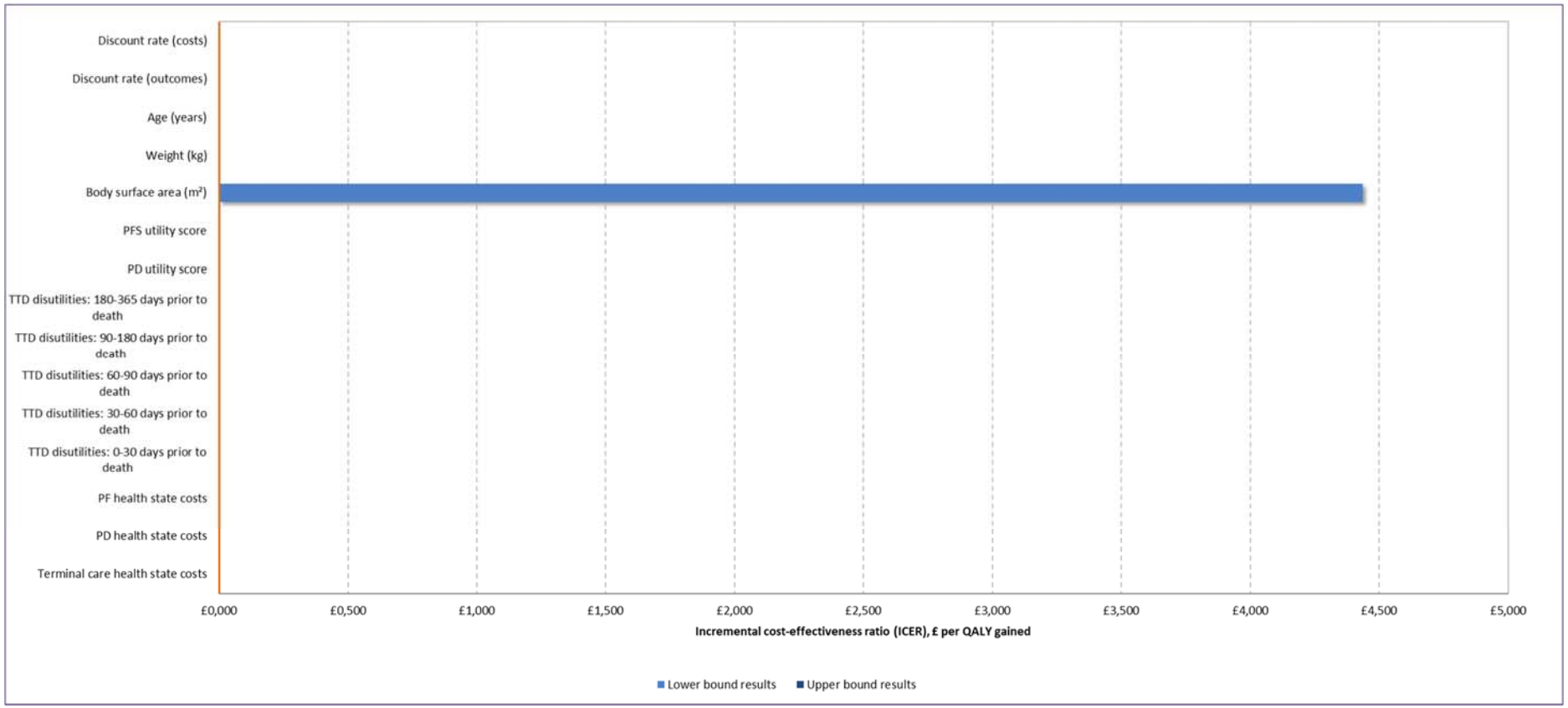


Figure 62. Tornado diagram presenting one-way DSA results: pembrolizumab monotherapy vs platinum + 5-FU (CPS ≥1)

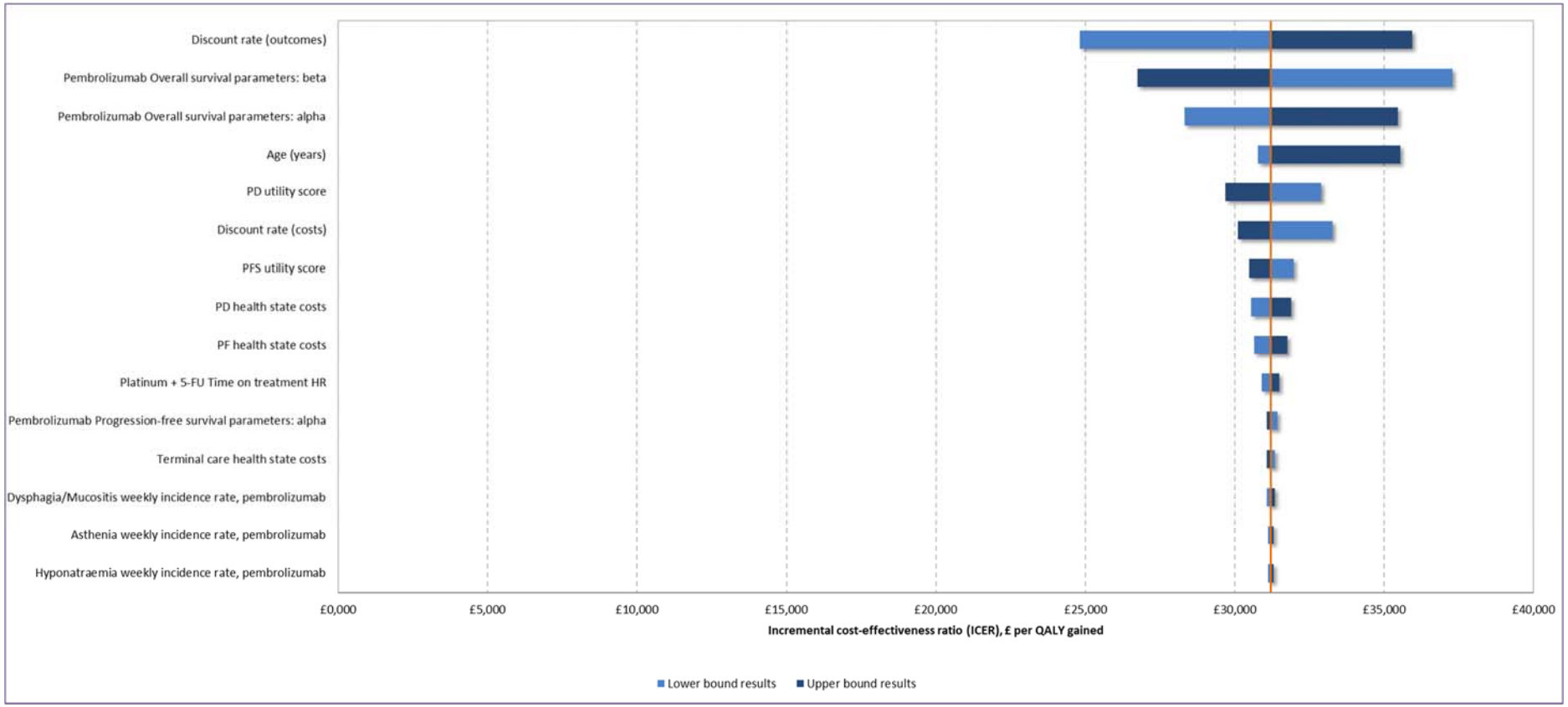


Figure 63. Tornado diagram presenting one-way DSA results: pembrolizumab combination therapy vs EXTREME (CPS ≥1)

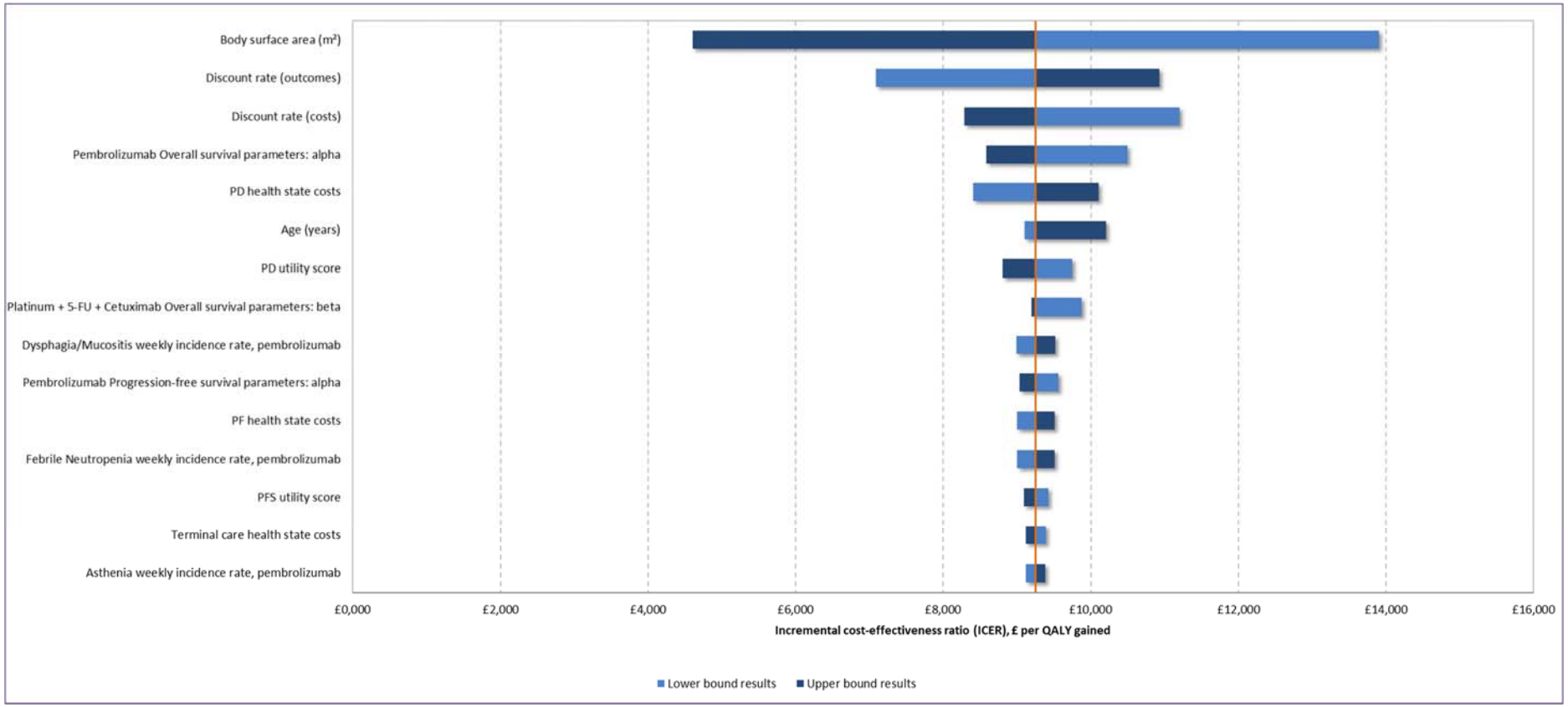
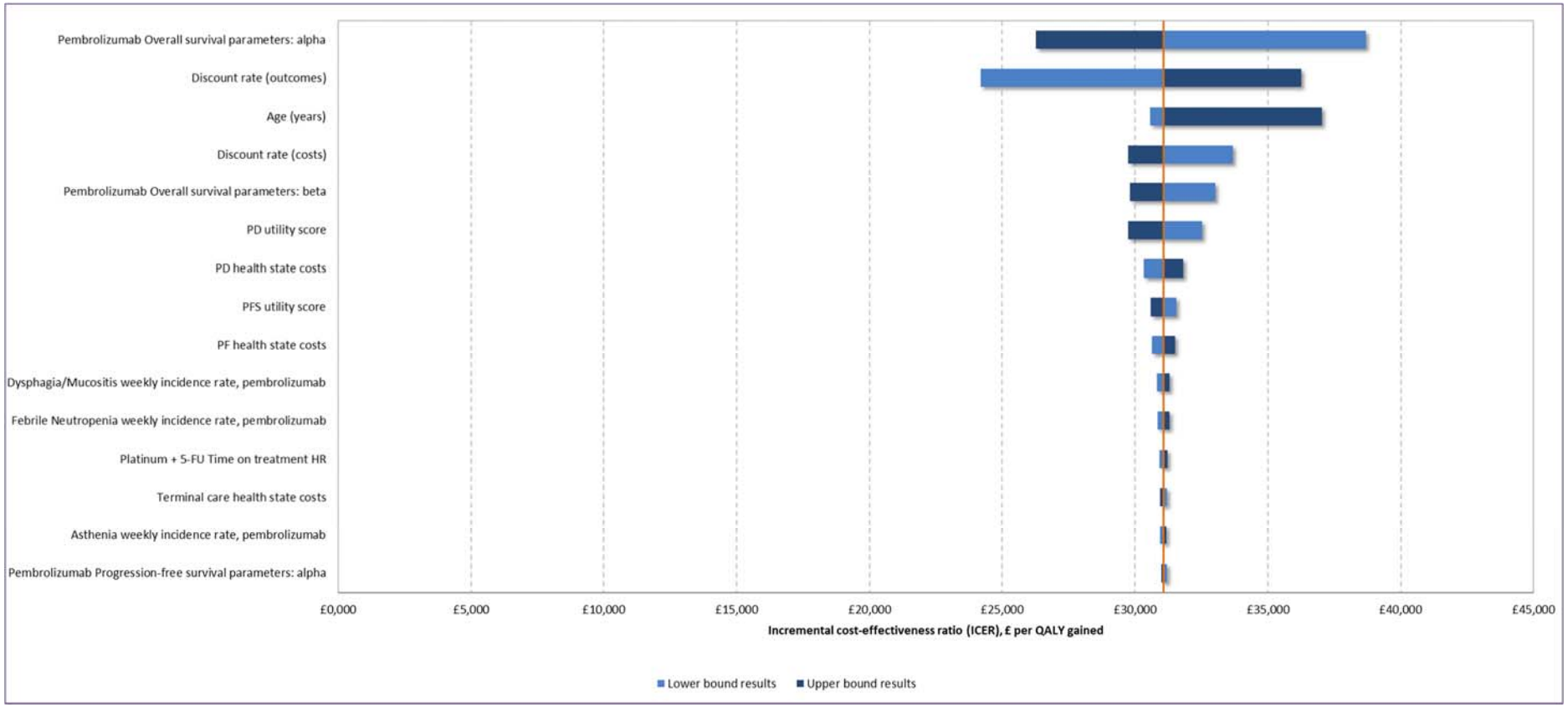


Figure 64. Tornado diagram presenting one-way DSA results: pembrolizumab combination therapy vs platinum + 5-FU (CPS ≥1)



The one-way DSA shows the economic model is robust to a wide range of variables explored for uncertainty. In all comparisons the ICER remained below the range considered cost-effective for an end of life treatment.

Scenario analysis

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

The parameters explored are summarized below.

Model structure

- Time horizon (reduced to 10 years)

Efficacy estimates

- Overall survival
    - Pembrolizumab monotherapy: 80 weeks with lognormal distribution (alternative good statistical fit)
    - Pembrolizumab monotherapy: 80 weeks with Weibull distribution (conservative extrapolation)
    - Pembrolizumab monotherapy: 45 weeks with lognormal distribution (aligned with interim analysis)
    - Pembrolizumab monotherapy: full parametric with loglogistic (best statistical fit)
    - Pembrolizumab combination therapy: 80 weeks with generalised gamma distribution (good fit to observed data)
    - Pembrolizumab combination therapy: 80 weeks with Weibull distribution (conservative extrapolation)
    - Pembrolizumab combination therapy: 45 weeks with lognormal distribution (aligned with interim analysis)
    - Pembrolizumab combination therapy: full parametric with Gompertz (best statistical fit)

- Progression free survival
    - Pembrolizumab monotherapy: 52 weeks with gompertz distribution (second best fit)
    - Pembrolizumab monotherapy: fully parametric with generalized gamma (best statistical fit)
    - Pembrolizumab combination therapy: 52 weeks with gompertz distribution (second best fit)
    - Pembrolizumab combination therapy: fully parametric with loglogistic (best statistical fit)
- Treatment effect waning
    - Three and five years

Scenario for subsequent therapies

- Including the cost and efficacy of nivolumab

Utilities

- Use mean health state utilities

Treatment Costs

- Q6W dosing (monotherapy only)
- Allow vial sharing
- Time to treatment discontinuation
    - Pembrolizumab monotherapy: fully parametric with Weibull (best statistical fit)
    - Pembrolizumab combination therapy: fully parametric with exponential (best statistical fit)

Scenario analyses results

The scenario analysis results are all presented in the tables below.

Table 76. Scenarios analysis results: pembrolizumab monotherapy vs EXTREME

Pembrolizumab monotherapy vs platinum + 5-fu + cetuximab	Pembrolizumab		EXTREME		Cost differential	QALY differential	ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs				
Pembrolizumab Monotherapy Versus Extreme base case	£48,945	1.69	£51,832	0.91	-£2,886	0.78	Dominant	N/A
Time horizon (reduced to 10 years)	£47,400	1.46	£50,219	0.88	-£2,820	0.58	Dominant	N/A
Pembrolizumab monotherapy: 80 weeks with lognormal distribution (alternative good statistical fit)	£49,633	1.83	£51,815	0.91	-£2,182	0.92	Dominant	N/A
Pembrolizumab monotherapy: 80 weeks with Weibull distribution (conservative extrapolation)	£47,644	1.42	£50,025	0.84	-£2,381	0.58	Dominant	N/A
Pembrolizumab monotherapy: 45 weeks with Lognormal distribution (Align with interim analysis)	£48,851	1.67	£51,807	0.92	-£2,956	0.75	Dominant	N/A
Pembrolizumab monotherapy: full parametric with loglogistic (best statistical fit)	£48,161	1.55	£52,125	0.97	-£3,964	0.59	Dominant	N/A
PFS - Pembrolizumab monotherapy: 52 weeks with gompertz distribution (second best fit)	£50,658	1.72	£52,023	0.92	-£1,364	0.80	Dominant	N/A
PFS -Pembrolizumab monotherapy: fully parametric with generalised gamma (best statistical fit)	£49,317	1.70	£51,767	0.91	-£2,450	0.78	Dominant	N/A
Treatment Waning 3 years	£48,942	1.69	£51,832	0.91	-£2,890	0.78	Dominant	N/A
Treatment Waning 5 years	£48,943	1.69	£51,832	0.91	-£2,888	0.78	Dominant	N/A
Subsequent treatment: Including the cost and efficacy of nivolumab	£49,481	1.69	£54,383	0.91	-£4,902	0.78	Dominant	N/A
Use mean health state utilities	£48,945	1.66	£51,832	0.90	-£2,886	0.76	Dominant	N/A
Q6W dosing (monotherapy only)	£49,742	1.69	£51,832	0.91	-£2,090	0.78	Dominant	N/A
Allow vial sharing	£48,937	1.69	£49,345	0.91	-£409	0.78	Dominant	N/A
TTD Fully parametric distribution with best statistical fit	£46,673	1.69	£49,159	0.91	-£2,486	0.78	Dominant	N/A

Table 77. Scenarios analysis results: pembrolizumab monotherapy vs platinum + 5-FU

Pembrolizumab monotherapy vs platinum + 5-FU	Pembrolizumab		Platinum + 5-FU		Cost differential	QALY differential	ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs				
Pembrolizumab Monotherapy Versus Platinum + 5-FU	£48,945	1.69	£20,616	0.78	£28,329	0.91	£31,212	
Time horizon (reduced to 10 years)	£47,400	1.46	£20,551	0.77	£26,849	0.69	£39,141	£7,928
Pembrolizumab monotherapy: 80 weeks with lognormal distribution (alternative good statistical fit)	£49,633	1.83	£20,759	0.81	£28,874	1.02	£28,391	-£2,821
Pembrolizumab monotherapy: 80 weeks with Weibull distribution (conservative extrapolation)	£47,644	1.42	£20,472	0.75	£27,172	0.67	£40,546	£9,333
Pembrolizumab monotherapy: 45 weeks with Lognormal distribution (Align with interim analysis)	£48,851	1.67	£20,595	0.78	£28,256	0.89	£31,721	£508
Pembrolizumab monotherapy: full parametric with loglogistic (best statistical fit)	£48,161	1.55	£20,349	0.76	£27,812	0.79	£35,225	£4,013
PFS - Pembrolizumab monotherapy: 52 weeks with gompertz distribution (second best fit)	£50,658	1.72	£20,607	0.78	£30,051	0.94	£31,984	£772
PFS -Pembrolizumab monotherapy: fully parametric with generalised gamma (best statistical fit)	£49,317	1.70	£20,582	0.78	£28,735	0.92	£31,397	£185
Treatment Waning 3 years	£48,934	1.69	£20,616	0.78	£28,318	0.90	£31,303	£91
Treatment Waning 5 years	£48,938	1.69	£20,616	0.78	£28,322	0.91	£31,265	£53
Subsequent treatment: Including the cost and efficacy of nivolumab	£49,481	1.69	£22,908	0.78	£26,573	0.91	£29,277	-£1,935
Use mean health state utilities	£48,945	1.66	£20,616	0.76	£28,329	0.89	£31,707	£494
Q6W dosing (monotherapy only)	£49,742	1.69	£20,616	0.78	£29,125	0.91	£32,089	£877
Allow vial sharing	£48,937	1.69	£20,592	0.78	£28,344	0.91	£31,229	£17
TTD Fully parametric distribution with best statistical fit	£46,673	1.69	£20,184	0.78	£26,489	0.91	£29,178	-£2,034

Table 78. Scenarios analysis results: pembrolizumab combination vs EXTREME

Pembrolizumab combination therapy vs	Pembrolizumab		Platinum + 5-FU		Cost differential	QALY differential	ICER	Difference in ICER
EXTREME	Total Costs	Total QALYs	Total Costs	Total QALYs				
Pembrolizumab Combination therapy Versus Extreme base case	£64,414	2.12	£52,597	0.85	£11,817	1.28	£9,255	
Time horizon (reduced to 10 years)	£60,758	1.71	£51,461	0.83	£9,297	0.88	£10,578	£1,323
Pembrolizumab combination therapy: 80 weeks with generalised gamma distribution (better observed fit to data)	£67,256	2.53	£52,989	0.86	£14,266	1.66	£8,575	-£680
Pembrolizumab combination therapy: 80 weeks with Weibull distribution (conservative extrapolation)	£61,956	1.77	£50,771	0.79	£11,185	0.98	£11,437	£2,182
Pembrolizumab combination therapy: 45 weeks with lognormal distribution (Align with interim analysis)	£62,622	1.87	£52,941	0.88	£9,680	0.99	£9,755	£500
Pembrolizumab combination therapy: full parametric with Gompertz (best statistical fit)	£63,673	2.02	£50,134	0.77	£13,539	1.25	£10,854	£1,598
PFS - Pembrolizumab combination therapy: 52 weeks with gompertz distribution (second best fit)	£65,964	2.15	£52,604	0.85	£13,361	1.31	£10,235	£980
PFS - Pembrolizumab combination therapy: fully parametric with loglogistic (best statistical fit)	£64,478	2.12	£52,690	0.85	£11,787	1.28	£9,238	-£18
Treatment Waning 3 years	£64,394	2.12	£52,597	0.85	£11,797	1.27	£9,270	£15
Treatment Waning 5 years	£64,399	2.12	£52,597	0.85	£11,802	1.27	£9,261	£6
Subsequent treatment: Including the cost and efficacy of nivolumab	£65,306	2.12	£56,827	0.85	£8,479	1.28	£6,641	-£2,615
Use mean health state utilities	£64,414	2.05	£52,597	0.82	£11,817	1.23	£9,645	£389
Allow vial sharing	£64,402	2.12	£50,056	0.85	£14,346	1.28	£11,236	£1,980
TTD Fully parametric distribution with best statistical fit	£60,345	2.12	£50,261	0.85	£10,084	1.28	£7,890	-£1,366

Table 79. Scenarios analysis results: pembrolizumab combination vs platinum + 5-FU

Pembrolizumab combination therapy vs Platinum + 5-FU	Pembrolizumab		Platinum + 5-FU		Cost differential	QALY differential	ICER	Difference in ICER
	Total Costs	Total QALYs	Total Costs	Total QALYs				
Pembrolizumab Combination therapy Versus Platinum + 5-FU	£64,414	2.12	£19,652	0.68	£44,762	1.44	£31,070	
Time horizon (reduced to 10 years)	£60,758	1.71	£19,652	0.68	£41,106	1.03	£39,895	£8,825
Pembrolizumab combination therapy: 80 weeks with generalised gamma distribution (better observed fit to data)	£67,256	2.53	£19,774	0.71	£47,482	1.82	£26,084	-£4,985
Pembrolizumab combination therapy: 80 weeks with Weibull distribution (conservative extrapolation)	£61,956	1.77	£19,615	0.68	£42,341	1.10	£38,639	£7,569
Pembrolizumab combination therapy: 45 weeks with lognormal distribution (Align with interim analysis)	£62,622	1.87	£19,550	0.67	£43,072	1.20	£35,951	£4,882
Pembrolizumab combination therapy: full parametric with gompertz (best statistical fit)	£63,673	2.02	£19,628	0.69	£44,045	1.33	£33,085	£2,016
PFS - Pembrolizumab combination therapy: 52 weeks with gompertz distribution (second best fit)	£65,964	2.15	£19,654	0.68	£46,311	1.47	£31,517	£447
PFS - Pembrolizumab combination therapy: fully parametric with loglogistic (best statistical fit)	£64,478	2.12	£19,651	0.68	£44,827	1.44	£31,088	£19
Treatment Waning 3 years	£63,153	1.92	£19,652	0.68	£43,501	1.24	£35,056	£3,987
Treatment Waning 5 years	£63,172	1.93	£19,652	0.68	£43,520	1.24	£34,959	£3,889
Subsequent treatment: Including the cost and efficacy of nivolumab	£65,306	2.12	£23,356	0.68	£41,949	1.44	£29,117	-£1,952
Use mean health state utilities	£64,414	2.05	£19,652	0.66	£44,762	1.39	£32,253	£1,183
Allow vial sharing	£64,402	2.12	£19,637	0.68	£44,765	1.44	£31,071	£2
TTD Fully parametric distribution with best statistical fit	£60,345	2.12	£19,141	0.68	£41,204	1.44	£28,572	-£2,497

The results show that pembrolizumab monotherapy and pembrolizumab combination remains a cost-effectiveness treatment option versus the EXTREME regimen and platinum + 5-FU in all of the scenarios explored. The results are robust to changes in the time horizon, estimation of treatment costs and utility values; and pembrolizumab becomes more cost-effective when second-line treatment with nivolumab is included, as is current NHS practice. Exploration of the efficacy assumptions is where the greatest variation in cost-effectiveness is observed – though pembrolizumab remains cost-effective in all scenarios explored. Most alternative survival distributions and cut-off points provide similar results of cost-effectiveness. The use of the conservative survival modelling with the Weibull distribution increase the ICER; but it remains below the £50,000 cost per QALY threshold for the comparison of pembrolizumab combination therapy and monotherapy versus platinum + 5-FU. However, these survival curves were shown to be a poor fit to real world data and are not considered plausible considering the evidence available.

The results are also robust to the exploration of a "treatment waning effect" which is implemented to explore the loss of treatment efficacy with pembrolizumab over longer time periods. It works by setting the hazard rate equal to the hazard in the comparator arm after the pre-specified time. Even when implemented after a very short time, such as three years, there is limited impact on the ICER. The reason for this is because after the initial 1-2 years, the condition survival between both arms is similar; therefore, setting the pembrolizumab arm equal to the comparator arm has minimal impact. This is supported by the 5-year data from the EXTREME trial which shows the EXTREME and platinum + 5-FU arms flattening out over the long-term.

B 3.8.3 Summary of sensitivity analyses results

We have conducted extensive sensitivity analyses to understand the key determinants of the cost-effectiveness of pembrolizumab monotherapy and combination therapy for r/m HNSCC. The results demonstrate that the model is robust to all scenarios explored, including some very pessimistic assumptions regarding the long-term survival of pembrolizumab monotherapy and combination therapy.

One of the key drivers of cost-effectiveness is the choice of survival extrapolation used for overall survival for the pembrolizumab monotherapy, pembrolizumab combination therapy and comparator arms. The choice of the model selection process for extrapolating overall survival was explored extensively in section B.3.3, where evidence to support the base case assumptions was provided. Alternative scenarios using a range of different distributions and

approaches were also explored, and these showed that pembrolizumab remains a cost-effective treatment option, either as a monotherapy or in combination with chemotherapy.

B.3.9 Subgroup analysis

Subgroup analysis for the CPS 20 population is presented below. The same survival modelling assumptions have been used as on the base case (summarized below). All other variables remain the same.

Table 80. Survival modelling used for CPS ≥20 subgroup analysis

Regimen name	Treatment arm	Overall Survival	Progression-free survival	Time to treatment discontinuation
Monotherapy	Pembrolizumab monotherapy	80-week cut-off with loglogistic	52-week cut-off with exponential	KM only
	EXTREME	80-week cut-off with loglogistic	52-week cut-off with exponential	KM only
	Platinum + 5-FU	80-week cut-off with loglogistic	52-week cut-off with exponential	PFS extrapolation
Combination therapy	Pembrolizumab combination therapy	80-week cut-off with lognormal	52-week cut-off with exponential	KM only
	EXTREME	80-week cut-off with lognormal	52-week cut-off with exponential	KM only
	Platinum + 5-FU	80-week cut-off with lognormal	52-week cut-off with exponential	PFS extrapolation

Table 81. Sub-group analysis results: Monotherapy (CPS ≥20)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab monotherapy	55,046	2.94	2.06	-	-	-	-
EXTREME regimen	55,357	1.38	0.99	-311	1.56	1.08	Dominant
Platinum + 5-FU	20,912	1.16	0.83	34,134	1.78	1.24	27,595
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 82. Sub-group analysis results: Combination therapy (CPS ≥20)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Pembrolizumab combination therapy	69,563	3.18	2.23	-	-	-	-
EXTREME regimen	56,385	1.38	0.98	13,178	1.81	1.25	10,585
Platinum + 5-FU	19,990	1.08	0.77	49,573	2.11	1.46	33,894
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

These results show that pembrolizumab remains a cost-effective treatment option for patients with r/m HNSCC at both CPS ≥1 and CPS 20 cut-off levels.

B.4 References

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10. NICE *Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product*. 2019.

B.5 Appendices

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix L: KEYNOTE-048 additional methodological details

Appendix M: KEYNOTE-048 overall population clinical effectiveness data

Appendix N: Additional NMA results for sensitivity analyses in the cost-effectiveness analysis

Appendix P: Survival modelling

Appendix Q: Deterministic Sensitivity Analysis

Appendix S: Data from the KEYNOTE-048 study specific to patients with PD-L1 CPS≥1 whose cancer originated in the oral cavity

Appendix T: Changes made to the economic model from Interim Analysis 2 to Final Analysis Dataset

NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

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.

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	The Swallows Head & Neck Cancer Support Group
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Our goal is to provide the best support and awareness, globally, for Head and Neck Cancer. We aim to inform and educate in order to enable early diagnosis thereby increasing survivorship rates to 100% over 10 years. The Swallows supports all people affected by head and neck cancers, patients, carers friends or relatives. The patient is the focus for support, help and signposting, however the role of carers and others is vital too, with their own support needs often overlooked. It is our intention for every person affected by head and neck cancer to have access to support at the point they need it and by the method off their choice on a 24/7 basis. This could be by telephone, email or social media. This is the key growth area for The Swallows as we move into 2020, namely that over a three-year period, we expand our global reach and provide resources to enable this 24/7 support to be freely available to all people affected by head and neck cancers.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	Talk with our members network

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Head & Neck Cancer has a massive impact o the person, carer and family due to many factors, isolation, ability to swallows, depression, reconstruction, side effects, financial and many more. Carers go on the same journey but on different tracks, they live the cancer without having a diagnosis. The carer normally becomes the one dealing with all the family, finance and work issues as well as caring for the patient 24/7.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients in most cases they think the treatment and care they receive from the NHS is excellent, With regard to the carer they believe the patient receives excellent treatment and care but the carer is not part of the pathway so receive very little support and care.
8. Is there an unmet need for patients with this condition?	Support from other patients & carers to help them understand the issues on living with the cancer from a patient/carers point of view. Lack of knowledge to help them make an informed decision regarding other treatment available.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Hopefully achieve complete responses and or progression free long term.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Possible side effects and the unknown – Quality of Life must be considered in survivorship - It is new and lack of awareness frightens them
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.	Patients with recurrent or metastatic head and neck cancer

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that I know
Other issues	
13. Are there any other issues that you would like the committee to consider?	
Key messages	
14. In up to 5 bullet points, please summarise the key messages of your submission: • Help improve survivorship • Survivorship is not survivorship without Quality of Life • Side Effects of the drug • Impact on the other areas of treatment the patient may be going through	

- Time taken and location of the treatment

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Thank you for agreeing to give us 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- 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 13 pages.

About you	
1. Your name	**ROBERT METCALF**
2. Name of organisation	**THE CHRISTIE NHS FT, MANCHESTER, M20 4BX**

3. Job title or position	**CONSULTANT HEAD AND NECK CANCER MEDICAL ONCOLOGIST**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition 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	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ I don't know if they submitted one/the contents of the submission

your nominating organisation's submission)	
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
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the treatment of patients with recurrent and metastatic head and neck cancer is to improve survival.
8. What do you consider a clinically significant treatment response? (For example, a	**Improvements in overall survival:** the most clinically significant survival measure is long term survival (rather than median survival). The 3 year survival as reported in the Keynote-048 study is clinically significant and has not been seen previously in any study or real world analysis in the same population. The 3 year survival seen in this patient population prior to this study was <10%. This was reported in the 2008 paper defining the standard of care chemotherapy (Vermorken, New England Journal of Medicine) in the same population. As a clinician routinely

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	treating this patient population, I would say that increasing the 3 year survival from 10% (as previously reported) to 20% would be considered clinically significant in view of both the relative change (doubling the proportion of patients surviving 3 years) and in absolute figures (increasing the longer term survivors by >10%). Having frequently discussed the risks and benefits of drug therapies in the setting of recurrent and metastatic disaease with the same patient population, patients are universally more impressed with the prospect of increasing the chances of long term survival versus an increase in average/median survival.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Prior to keynote048 study, there has only been a single clinical trial showing survival gain with any combination drug therapy for this same population (Vermorken, New England Journal of Medicine 2008). This has not been subsequently improved upon and itself provided a median survival of <12 months (meeting the criteria for a terminal illness) with almost all patients dying within 3 years.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The standard of care is chemotherapy with platinum 5FU and cetuximab as described in the Vermorken et al. paper (New England Journal of Medicine 2008). This was the comparator arm (also called the EXTREME regimen) in the keynote-048 study. The European (ESMO) guidelines (Gregoire, et al., Annals of Oncology 2010) describe that combination chemotherapy should be used as per the Vermorken paper.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	The pathway is well defined for patients fit to receive combination therapy. The only significant variance from the ESMO guidelines is that the guidelines include a proposal that single agent methotrexate or taxane chemotherapy (mono-chemotherapy) should be considered for patients in whom you would expect that they may not tolerate combination therapy (eg due to multiple co-morbidities or poor performance status). In practice, given there is no strong evidence for survival gain from mono-chemotherapy, this is not

across the NHS? (Please state if your experience is from outside England.)	universally offered and patients with significant co-morbidities or poor performance status are often offered best supportive care alone. Such patients would not be representing in clinical trials.
• What impact would the technology have on the current pathway of care?	This treatment would replace the current standard of care (platinum/5FU/cetuximab) for first line therapy in this patient population.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The current care is combination intravenous drug therapy delivered through specialist oncology units. The new technology is also combination intravenous drug therapy delivered through specialist oncology units. In that respect the technology is very similar in terms of healthcare resource.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary care/specialist oncology clinics.
• What investment is needed to introduce the technology? (For	Nil. The infrastructure to deliver combination intravenous drug therapy delivered through specialist oncology units to this patient population is already in place. These drugs are also being used in other oncology indications so there are teams within the NHS with experience of delivering and managing the toxicities of these different drug therapies.

example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes, significantly so given the current standard was the comparator arm in this study.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, significantly so given the prolonged tumour regressions seen with immunotherapy. From my own clinical practice I have regularly seen the quality of life benefit associated with tumour regression. For example, patients with locally recurrent disease typically are unable to swallow or breath normally and need to have a tracheostomy to enable them to keep breathing/prevent slow suffocation from tumour growth and a feeding tube to prevent them wasting away. Tumour regression within the head and neck region both removes the sense of suffocation associated with progressing airway compromise and improved the physical ability of patients enabling more normal day-to-day activities. The other clear example of quality of life gains seen with tumour regressions in the head and neck region is that this disease frequently causes fungating/disfiguring tumour growths over the face and neck and even if patients are physically able to go out of the house, there is a psychological barrier to going out in public due to the unsightly tumour growths. Patients with regression of locally recurrent growths on the face and neck often therefore report significant improvements in their enjoyment of life as they feel empowered to go out and enjoy life.whilst they can.

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	None specifically.
The use of the technology	
14. 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.)	In the context of this technology being a combination intravenous drug therapy delivered through specialist oncology units it is neither easier nor more difficult to use. The side effect profiles vary between the current standard and the technology under assessment (i.e. chemotherapy versus immunotherapy toxicities). However the management of chemotherapy related and immunotherapy related toxicities, although different have a similar level of complexity requiring oncology expertise. However, there is a significant amount of experience in the use of these agents in other settings and there are management guidelines for the monitoring and toxicity management.

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The treatment would be started when there is biopsy proven recurrent or metastatic disease and discontinued when there is evidence of disease progression or intolerable toxicity (the same rules for the current first line chemotherapy population).
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	There is a clear psychological and social benefits arising from response to therapy for recurrent head and neck cancers as summarised above in response to question 12.
17. 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. The improved 3 year survival is dramatic and unprecedented for this patient group and this is the first time an immune targeted therapy has shown activity in the first line setting.
• Does the use of the technology address any particular unmet need of the patient population?	The main unmet need which this study addresses is that these patients die of their disease despite the current therapy with most being dead within a year and almost all being dead within 3 years.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Given the current standard is EXTREME chemotherapy, the adverse events would not be expected to significantly differ in their deleterious impact on quality of life. However, given the significantly greater duration of response to therapy in the pembrolizumab treatment patients, I would expect the disease related adverse event profile to be significantly improved.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	As discussed above, overall survival is the most important outcome and this was measured in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	NA
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	NA
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NA
21. Are you aware of any new evidence for the comparator	The comparator treatment was published in 2008 and there is no new evidence for this treatment since.

treatment(s) since the publication of NICE technology appraisal guidance [TA473]?	
22. How do data on real-world experience compare with the trial data?	Real world data including those at our own institution are comparable with the standard treatment are (EXTREME) in the trial data.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	NA
23b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	
24. Would you expect pembrolizumab to be	NA

associated with a quality of life benefit beyond that achieved from any slowing of disease progression? If yes, is there any evidence to support this?	
25. In clinical practice, is vial sharing used for current treatment options? If yes, please provide details (i.e. is wastage a problem?).	UK

Key messages

26. In up to 5 bullet points, please summarise the key messages of your statement.

- Longer term survival gain is the most important end-point
- Pembrolizumab showed significantly improved longer term survival
- Toxicity compared with the current standard is different, although the management is broadly equally complex
- The infrastructure is in place to deliver these treatments
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

Thank you for agreeing to give us 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.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- 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 13 pages.

About you	
1. Your name	**Dr. Shanmugasundaram Ramkumar**
2. Name of organisation	**University Hospital Southampton NHS Foundation Trust** **Royal College of Radiologists**

3. Job title or position	**Consultant Clinical Oncologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition 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	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (I don't know if they submitted one

your nominating organisation's submission)	
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.)	☐
The aim of treatment for this condition	
7. 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 control progression of recurrent or metastatic head and neck squamous cell carcinoma and improve overall survival
8. What do you consider a clinically significant treatment response? (For example, a	1. Radiological evidence of reduction in tumour size by RECIST v1.1 criteria 2. Clinical improvement of symptoms

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there is a need for patients with recurrent or metastatic head and neck squamous cell carcinoma, but Nivolumab is approved via Cancer Drugs Fund for similar condition- i.e; progression after platinum-based chemotherapy in recurrent or metastatic head and neck squamous cell carcinoma
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Patients with recurrent/metastatic head and neck squamous cell carcinoma are being offered Nivolumab via Cancer Drugs Fund (CDF) after progression within 6 months of platinum-based chemotherapy , otherwise second line palliative chemotherapy is offered.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE recommendation via CDF (TA490)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals	The pathway of care for these group of patients in NHS is second line palliative chemotherapy (usually with docetaxel or methotrexate) are well defined until the publication of TA490 guidelines by NICE in November 2017, where Nivolumab is another option via CDF. There is not much of differences of opinion between professionals across NHS as far as I am aware.

across the NHS? (Please state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	Provide an alternative treatment option in second line setting for recurrent or metastatic head and neck squamous cell carcinoma progressing within 6 months on platinum-based palliative chemotherapy, ensure PD-L1 testing for all eligible patients and can be delivered in 3 weekly cycles.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, I presume so if recommended by NICE.
• How does healthcare resource use differ between the technology and current care?	Probably not much difference except the Cost of drug (technology) and frequency of delivery of drug when compared to Nivolumab.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist Head and Neck cancer clinics with experience in treating patient with Immunotherapy
• What investment is needed to introduce the technology? (For	Current facilities can support the introduction of this technology (Pembrolizumab) as most specialist NHS cancer centres are delivering immunotherapy to cancer patients.

example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Possibly offer similar clinical benefit compared to current care with Nivolumab, but if compared to second line palliative chemotherapy, then there might be more meaningful clinical benefits.
• Do you expect the technology to increase length of life more than current care?	May offer similar OS rates if compared to current care with Nivolumab, but can increase length of life if compared to second line palliative chemotherapy.
• Do you expect the technology to increase health-related quality of life more than current care?	Potentially, but there is no head to head comparison between Pembrolizumab and Nivolumab to confirm this, but if compared with second line palliative chemotherapy then there might be an increase in health-related quality of life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	<u>More effective:</u> Males PDL-1 TPS score>50 Smokers and p16 negative cancer patients

The use of the technology	
14. 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.)	Not difficult to use compared to current care with Nivolumab except delivered in 3 weekly cycles compared to Nivolumab which is delivered in 2 weekly cycles, but PD-L1 testing might be mandatory
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	PDL-1 testing as response rates better Start after progression on platinum based chemotherapy Stop after disease progression or after 2 years

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Cannot comment
17. 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?	Pembrolizumab if compared with second line palliative chemotherapy can be considered innovative and can have a substantial impact on health-related benefits particularly with relation to overall survival and safety profile, but Immunotherapy with Nivolumab has already been available for these groups of patients via CDF,
• Is the technology a 'step-change' in the management of the condition?	Yes when compared to second line palliative chemotherapy

• Does the use of the technology address any particular unmet need of the patient population?	No, as Nivolumab is currently offered to these patients via Cancer Drugs Fund and Pembrolizumab might be an alternative treatment option and can be given 3 weekly cycles rather than 2 weekly cycles of Nivolumab.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Immune related toxicities are similar to other immunotherapy drugs and can be managed.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Pembrolizumab is currently not in use for recurrent or metastatic head and neck squamous cell carcinoma in the NHS.
• If not, how could the results be extrapolated to the UK setting?	The results from Keynote -40 trials suggest benefit in terms of progression free survival and overall survival for recurrent or metastatic head and neck squamous cell carcinoma and can be used instead of palliative chemotherapy with durable responses and safety profile.
• What, in your view, are the most important	Overall survival - yes Progression free survival – yes

outcomes, and were they measured in the trials?	Overall response rate- yes Time to Progression – yes Duration of response – yes Safety and tolerability- yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PDL-1 TPS score>_50 seems to predict long term clinical outcomes
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA473]?	No
22. How do data on real-world experience compare with the trial data?	For cancer immunotherapy, there seems to be similar real-world experience compared with trial data according to my clinical experience
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	NA
23b. Consider whether these issues are different from issues with current care and why.	NA
Topic-specific questions	

24. Would you expect pembrolizumab to be associated with a quality of life benefit beyond that achieved from any slowing of disease progression? If yes, is there any evidence to support this?	Possibly as there was improved duration of response form Keynote-40 trial which could led to a quality of life benefit.
25. In clinical practice, is vial sharing used for current treatment options? If yes, please provide details (i.e. is wastage a problem?).	In Southampton, the dose for Nivolumab is capped at a standard 240mg, but I am not aware of any vial sharing-this is a question better answered by oncology pharmacists who mange the delivery of drugs.
Key messages	

26. In up to 5 bullet points, please summarise the key messages of your statement.

- Updated survival data from Keynote-040 trial suggest that Pembrolizumab improved OS in recurrent or Metastatic head and Neck Squamous cell carcinoma
- Effect of Pembrolizumab appears to be greater in patients with PD-L1 expressing tumours
- Pembrolizumab shows favourable safety profile
- Pembrolizumab appears to offer an alternative choice to Nivolumab in second line setting
- Pembrolizumab can be given in 3 weekly cycles.

Thank you for your time.

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ID1140 ERG REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Pembrolizumab for untreated recurrent or metastatic squamous cell carcinoma of the head and neck [ID1140]

ERG Final report

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 17/56/06

Completed 20th August 2019

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Pembrolizumab for untreated recurrent or metastatic squamous cell carcinoma of the head and neck [ID1140]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors

Janette Greenhalgh, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Marty Richardson, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Sarah Nevitt, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Angela Boland, Director, LR*i*G, University of Liverpool

Sophie Beale, Research Associate (Decision Analysis), LR*i*G, University of Liverpool

Tosin Lambe, Research Associate (Health Economics), LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Information Specialist), LR*i*G, University of Liverpool

Ashley Marsden, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Richard Shaw, Honorary Consultant in Oral & Maxillofacial/Head & Neck Surgery, Aintree University Hospitals NHS Foundation Trust. National Specialty Lead: Surgical Oncology NIHR Clinical Research Network (CRN)

Correspondence to: Janette Greenhalgh, Senior Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors:

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervision of the final report
James Mahon	Critical appraisal of the economic evidence
Marty Richardson	Critical appraisal of the statistical evidence
Sarah Nevitt	Critical appraisal of the statistical evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Tosin Lambe	Critical appraisal of the economic evidence
Yenal Dundar	Critical appraisal of the adverse event data and cross checking of the company search strategies
Ashley Marsden	Critical appraisal of the company submission
Richard Shaw	Clinical advice and critical appraisal of the clinical sections of the company submission

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LIST OF ABBREVIATIONS

AE	adverse event
AEOSI	adverse event of special interest
AIC	Akaike Information Criterion
AUC	area under the curve
BIC	Bayesian Information Criterion
BNF	British National Formulary
BICR	blinded independent central review
CAA	Commercial Access Agreement
CDF	Cancer Drugs fund
CEAC	cost effectiveness acceptability curve
PLAT+5-FU	platinum+fluorouracil
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CPS	combined positive score
CR	complete response
CS	company submission
CSR	clinical study report
CT	computed tomography
DIC	deviance information criteria
DOR	duration of response
ECOG	Eastern Co-Operative Group
EMA	European Medicines Agency
eMIT	electronic Marketing Information Tool
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck module
EQ-5D-3L	EuroQol-5 Dimensions-3 Levels
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EXTREME	Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer Trial
5-FU	fluorouracil
FP	fractional polynomials
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
HRQoL	health-related quality of life
HPV	human papillomavirus
IA	interim analysis
ICER	incremental cost effectiveness ratio
IV	Intravenous
IPCW	inverse probability of censoring weights
K-M	Kaplan-Meier
KEYNOTE-048	main trial discussed the company submission
KPS	Karnofsky performance status
LS	least squares
LYG	life year gained
NMA	network meta-analysis
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PAS	Patient Access Scheme
PD	progressive disease
PD-L1	programmed death ligand 1
PF	progression-free
PFS	progression-free survival

PH	proportional hazards
PLAT	platinum chemotherapy
PLAT+5-FU	platinum chemotherapy plus fluorouracil
PP	post-progression
PR	partial response
PS	performance status
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Resource Unit
QALY	quality adjusted life year
RCT	randomised controlled trial
R/M	recurrent or metastatic
RPSFTM	Rank Preserving Structural Failure Time Model
SAE	serious adverse event
SD	standard deviation
SoC	standard of care
SAE	serious adverse event
SLR	systematic literature review
STA	single technology appraisal
ToT	time on treatment
TSAP	trial statistical analysis plan
VAS	visual analogue scale
WTP	willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Merck, Sharp & Dohme Ltd in support of the use of pembrolizumab (Keytruda®) as a monotherapy and in combination with platinum-based chemotherapy, for recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC) previously untreated in the recurrent or metastatic setting.

1.2 Critique of the decision problem in the company submission

The company has presented data from the KEYNOTE-048 trial, a phase III, open label, randomised controlled trial (RCT) that enrolled 882 patients with HNSCC, untreated in the R/M setting. In the trial, patients were randomised to receive pembrolizumab monotherapy, pembrolizumab combined with platinum and fluorouracil (pembrolizumab+PLAT+5-FU) or cetuximab combined with platinum and fluorouracil (cetuximab+PLAT+5-FU). The platinum therapy used in all arms of the trial is cisplatin or carboplatin, determined according to pre-arranged physician's choice. At baseline, a pre-defined subgroup of 754 patients in the KEYNOTE-048 trial had tumours that tested positive for PD-L1 expression defined as a combined positive score (CPS) ≥1.

1.2.1 Population

The population discussed in the CS is a subset of the population described in the final scope issued by NICE, as it only relates to adults with R/M HNSCC previously untreated in the R/M setting whose tumours test positive for PD-L1 expression defined as a combined positive score (CPS) ≥1. The ERG highlights that no information has been provided by the company about patients whose tumours do not express PD-L1 CPS≥1.

The company has not discussed testing of PD-L1 status in the NHS for patients with R/M HNSCC; however, clinical advice to the ERG is that, as PD-L1 testing is routinely carried for other types of cancer tumour (e.g., lung cancer and melanoma) and that scaling up testing to include tumours from patients with R/M HNSCC should not be problematic. Clinical advice to the ERG is that CPS is a reasonably well-established measure of PD-L1 expression.

The population recruited to the KEYNOTE-048 trial is only representative of the fittest patients in the NHS with R/M HNSCC i.e., those patients who are fit enough to receive cetuximab+PLAT+5-FU.

1.2.2 Interventions

Two interventions are specified in the final scope issued by NICE and discussed in the CS, namely pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU. Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death-1 (PD-1) that prevents PD-1 from engaging with its ligands, PD-L1 and PD-L2. It is administered as an intravenous infusion. The platinum therapy discussed in the CS is either cisplatin or carboplatin, and this element of treatment is administered intravenously along with 5-FU. In the KEYNOTE-048 trial, treatment with pembrolizumab is restricted by a 2-year treatment stopping rule, although some patients may be re-challenged with pembrolizumab following disease progression.

The anticipated licensed indication for the use of pembrolizumab monotherapy is [redacted] and the anticipated licensed indication for the use of pembrolizumab+PLAT+5-FU is for [redacted]. The company expects to receive a positive opinion from the European Medicines Agency Committee for Human Medicinal Products for the use of pembrolizumab as a monotherapy and in combination with platinum+5-FU in September 2019. The ERG highlights that no evidence has been presented by the company for the population of patients whose tumours do **not** express [redacted].

The company states that the decision on whether to treat patients with pembrolizumab or pembrolizumab+PLAT+5-FU should be based on the judgement of the treating physician and patient wishes. However, the ERG highlights that, when considering use in the NHS, the relative cost effectiveness of the two interventions should be taken into account.

1.2.3 Comparators

Cetuximab+PLAT+5-FU

Recruitment to the pembrolizumab+PLAT+5-FU arm was pause for a period 3 months due to an external data monitoring committee recommendation. To avoid breaking randomisation, patients recruited to the cetuximab+PLAT+5-FU arm during this 3-month period were excluded from analyses relating to the comparison of the effectiveness of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. As a consequence, when carrying out clinical effectiveness calculations, the number of patients in the cetuximab+PLAT+5-FU arm differs depending on whether the comparison is versus pembrolizumab monotherapy (n=255) or pembrolizumab+PLAT+5-FU (n=235).

Cetuximab+PLAT+5-FU is only recommended by NICE as an option for treating adults with R/M HNSCC cancer that started in the oral cavity. Approximately 30% of patients recruited to the KEYNOTE-048 trial whose tumours expressed PD-L1 CPS≥1 had cancer that originated in the oral cavity. Clinical advice to the ERG is that in NHS practice cetuximab+PLAT+5-FU is rarely used to treat oral cavity patients as a minority of patients in this group are fit enough to tolerate the treatment.

In response to the ERG's clarification question, the company provided KEYNOTE-048 trial subgroup data for patients whose cancer started in the oral cavity. In their response, the company emphasised, and the ERG acknowledges, that the KEYNOTE-048 trial was not powered to detect statistically significant differences between treatments in the oral cavity subgroup.

Platinum-based chemotherapy regimens

There is no direct evidence available from the KEYNOTE-048 trial for the clinical effectiveness of pembrolizumab (monotherapy or in combination) versus any platinum-based chemotherapy regimen. The company has carried out network meta-analyses (NMAs) using the (fractional polynomial) method introduced by Jansen to generate effectiveness data for patients receiving different types of chemotherapy.

Clinical advice to the ERG is that PLAT+5-FU is commonly used to treat patients with R/M HNSCC in the NHS who are fit enough to tolerate chemotherapy. However, clinical advice to the ERG is that there is increasing use of single agent platinum as a first-line treatment followed by treatment with nivolumab in the second-line setting. The ERG notes that nivolumab is currently available only through the Cancer Drugs Fund.

1.2.4 Outcomes

The company has provided clinical evidence from the KEYNOTE-048 trial relating to treatment with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU for all five outcomes specified in the final scope issued by NICE: Overall survival (OS), progression-free survival (PFS), response rate (specifically objective response rate and duration of response), Adverse effects (AEs) of treatment and health-related quality of life (HRQoL).

1.2.5 Subgroups

In the final scope issued by NICE, it is stated that, if the evidence allows, subgroups based on tumour expression of PD-L1 status should be considered. All of the evidence presented in the CS relates to patients with tumours that express PD-L1 CPS≥1. Updated results for a number of other subgroups are presented in the Supplementary Document (July 2019). However, the

ERG highlights that whilst the company has provided evidence from the subgroup of patients in the KEYNOTE-048 trial whose cancer originated in the oral cavity, no evidence has been provided for the subgroup whose cancer did not originate in the oral cavity.

Other considerations

The company did not identify any equity or equality issues.

The ERG agrees with the company that pembrolizumab (as monotherapy or in combination) should be considered under NICE's End of Life criteria.

Pembrolizumab and cetuximab are both available to the NHS at discounted prices (via a Commercial Access Agreement [CAA] and a Patient Access Scheme [PAS], respectively). However, the discounted price of cetuximab is not known to the company.

1.3 Summary of the clinical evidence submitted by the company

1.3.1 Direct evidence (patients with CPS≥1)

Updated final analysis results for all outcomes (data cut-off date 25 February 2019) have been provided by the company in the Supplementary Document (July 2019).

KEYNOTE-048 trial OS results from the unadjusted analysis, from the 2-stage adjusted analysis (adjusted to take account of the effect of subsequent anti-PD-L1 treatment) and for the subgroup of patients whose cancer originated in the oral cavity are similar and, therefore, only results from the unadjusted analysis are presented in this summary:

I. median OS was longer for patients receiving pembrolizumab monotherapy (12.3 months [95% CI: 10.8 to 14.3]) than for patients receiving cetuximab+PLAT+5-FU (10.3 months [95% CI: 9.0 to 11.5])

II. median OS was longer for patients receiving pembrolizumab+PLAT+5-FU (13.6 months [95% CI: 10.7 to 15.5]) than for patients receiving cetuximab+PLAT+5-FU (10.4 months [95% CI: 9.1 to 11.7]).

Similarly, the KEYNOTE-048 trial PFS results for PD-L1 CPS≥1 population and for the subgroup of patients whose cancer originated in the oral cavity were similar and so only results for the PD-L1 CPS≥1 population are presented in this summary.

I. median PFS was shorter for patients receiving pembrolizumab monotherapy than for patients receiving cetuximab+PLAT+5-FU (3.2 months [95% CI: 2.2 to 3.4] and 5.0 months [95% CI: 4.8 to 6.0]).

II. median PFS was similar for patients receiving pembrolizumab+PLAT+5-FU ([redacted]) and for patients receiving cetuximab+PLAT+5-FU ([redacted]).

In the PD-L1 CPS≥1 population of the KEYNOTE-048 trial, patients in the pembrolizumab monotherapy arm reported similar rates of AEs compared with patients treated with cetuximab+PLAT+5-FU arm (96.9% versus 99.6%). Incidence rates across all categories of AEs were lower in the pembrolizumab monotherapy arm than in the cetuximab+PLAT+5-FU arm. Rates of Grade 3 to 5 drug-related AEs were lower in the pembrolizumab monotherapy arm compared with the cetuximab+PLAT+5-FU arm (18% versus 68.2%) as were drug-related serious AEs (10.9% versus 21.4%). Fewer patients in the pembrolizumab arm discontinued treatment due to a drug-related AE (5.9% versus 19.6%). In the overall trial population, rates of adverse event of special interest (AEOSI) were similar for patients treated with pembrolizumab monotherapy and patients treated with cetuximab+PLAT+5-FU (31.0% and 23.7% respectively).

In the PD-L1 CPS≥1 population of the KEYNOTE-048 trial, patients in the pembrolizumab+PLAT+5-FU arm and patients in the cetuximab+PLAT+5-FU arm reported similar rates of AEs (98.3% and 99.6% respectively). Incidence rates across most categories of AEs were higher in the pembrolizumab+PLAT+5-FU arm than in the cetuximab+PLAT+5-FU arm. Rates of Grade 3 to 5 drug-related AEs were slightly higher for patients treated with pembrolizumab+PLAT+5-FU compared with patients treated with cetuximab+PLAT+5-FU (73.0% versus 68.2%). More drug-related serious AEs were reported by patients in the pembrolizumab+PLAT+5-U arm than by patients in the cetuximab+PLAT+5-FU arm (40.5% versus 24.1%). Similar numbers of patients discontinued treatment due to a drug-related AE (26.2% and 19.6%). In the overall trial population, rates of AEOSIs were similar for patients treated with pembrolizumab+PLAT+5-FU and patients treated with cetuximab+PLAT+5-FU (26.4% and 23.7% respectively).

Health-related quality of life (HRQoL) as measured using the EuroQoL-5 dimensions–3 Levels (EQ-5D-3L) questionnaire and EuroQoL visual analogue scale (VAS) yielded results that were [redacted] over time (15 weeks) for patients treated with pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU. [redacted] were reported for HRQoL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 module (EORTC QLQ-30) with the EORTC-QLQ head and neck module (H&N35) when comparing patients treated with pembrolizumab

monotherapy versus those treated with cetuximab+PLAT+5-FU or when comparing patients treated with pembrolizumab+PLAT+5-FU versus those treated with cetuximab+PLAT+5-FU.

Indirect evidence

For the comparisons of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and PLAT+5-FU, the OS NMA included eight trials. Results from this NMA suggest that from month 6 onwards, treatment with pembrolizumab monotherapy statistically significantly improves OS in comparison to both cetuximab+PLAT+5-FU and PLAT+5-FU. The results also suggest that in the early stages of treatment (month 1 to month 6), pembrolizumab+PLAT+5-FU has little effect on OS in comparison to cetuximab+PLAT+5-FU. However, from 9 months onwards, the HRs demonstrate a statistically significant improvement in OS for pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. Similarly, for the comparison of pembrolizumab+PLAT+5-FU versus PLAT+5-FU, pembrolizumab monotherapy is shown to statistically significantly improve OS from month 6 onwards.

For PFS, results from the company NMA, which included five trials, suggest that in the early stages of treatment (month 1 to month 3), pembrolizumab monotherapy is statistically significantly less efficacious than cetuximab+PLAT+5-FU in terms of PFS. However, the trend changes over time, with HRs favouring pembrolizumab monotherapy from 6 months (and shows statistically significant results from 9 months onwards). For the comparison of pembrolizumab monotherapy versus PLAT+5-FU, no differences are observed between the two treatments until month 6, when pembrolizumab monotherapy is shown to statistically significantly improve PFS from this time-point onwards.

In addition, the results indicate that, in the early stages of treatment (month 1 to month 3), pembrolizumab+PLAT+5-FU has little effect on PFS in comparison to cetuximab+PLAT+5-FU. However, from month 6 onwards, the HRs demonstrate a statistically significant improvement in PFS for pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. Similarly, for the comparison of pembrolizumab+PLAT+5-FU versus PLAT+5-FU, pembrolizumab+PLAT+5-FU is shown to statistically significantly improve OS from month 3 onwards.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

The ERG considers that the KEYNOTE-048 trial is a good quality and well conducted phase III, open label, RCT with an appropriate, pre-defined, statistical approach to the analysis of efficacy, safety and patient reported outcomes.

The ERG notes that when interpreting results from the analyses in the oral cavity cancer patient subgroup, no adjustment for multiple testing was performed, and the KEYNOTE-048 trial was not powered to detect statistically significant differences between treatments for this subgroup. It is, therefore, difficult to draw firm conclusions about the relative effectiveness of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU or for pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU for this subgroup.

The ERG agrees with the company that the simplified 2-stage method was the most appropriate method to use to adjust KEYNOTE-048 trial OS Kaplan-Meier (K-M) data to take account of the effect of subsequent anti-PD-L1 treatment; however, the ERG highlights that the adjustment had a negligible effect on the data. The ERG also agrees with the company that, for all patients whose tumours expressed PD-L1 CPS≥1, the proportional hazards assumption is violated for both OS and PFS data from the KEYNOTE-048 trial for both the comparisons of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and for pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. The ERG, therefore, considers that the HRs calculated using KEYNOTE-048 trial data are not appropriate measures to use to compare KEYNOTE-048 trial OS or PFS results.

The ERG agrees with the company that AEs reported in the overall KEYNOTE-048 trial population appear to be consistent with the known safety profiles of pembrolizumab and cetuximab+PLAT+5-FU with no new AEs identified. However, clinical advice to the ERG is that AEs arising from treatment with pembrolizumab and other immunotherapies require careful monitoring by a specialist clinical team with the experience to provide early recognition and management of immunotherapy-related AEs and that this can place a high burden on NHS staff and systems.

Indirect evidence

The ERG agrees with the company that KEYNOTE-048 trial OS K-M data adjusted using the simplified 2-stage method was the most appropriate data to use in the OS NMA.

Overall, the ERG considers that despite some heterogeneity in terms of patient characteristics and reported outcomes, it was reasonable to synthesise data from the studies that provided the data used in the company's NMAs and that, generally, the company's approach to performing the NMAs was appropriate. However, the ERG has some reservations about the methods employed to select the most appropriate fractional polynomial model due to a lack of information being provided by the company. The ERG also has concerns about possible heterogeneity due to only data from the KEYNOTE-048 trial being restricted to patients whose tumours expressed PD-L1 CPS≥1, and that data used in the NMAs were not stratified by origin

of cancer (oral cavity and non-oral cavity). However, the ERG considers that these reservations are of minor importance in this STA as evidence for the comparisons of interest may be obtained without resort to NMAs.

Summary of ERG rationale for using KEYNOTE-048 trial evidence rather than NMA results in the economic critique

The ERG stresses that the company has only submitted trial evidence that relates to patients who **are** fit enough to receive cetuximab+PLAT+5-FU and, therefore, all statistical (and economic) evidence presented in the CS and in this ERG report only relates to these patients.

The company has provided direct evidence of effectiveness (OS and PFS), for the interventions of interest versus cetuximab+PLAT+5-FU from the KEYNOTE-048 trial for the subgroup of patients whose cancer originated in the oral cavity. Cetuximab+PLAT+5-FU is currently the only treatment recommended by NICE for these patients.

Results from the EXTREME trial show that, for patients whose cancer did not originate in the oral cavity, the OS of patients treated with cetuximab+PLAT+5-FU was not statistically significantly different from that of patients treated with PLAT+5-FU. The ERG considers that this finding (i.e., the absence of a statistically significant difference between the effectiveness of the two treatments) can be applied to data from the KEYNOTE-048 trial. The effect of this is that the OS Kaplan-Meier (K-M) data from patients in the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial can be used to represent the experience of patients whose cancer did not originate in the oral cavity and who were treated with PLAT+5-FU.

For patients whose cancer did not originate in the oral cavity, results from the EXTREME trial showed that treatment with cetuximab+PLAT+5-FU may deliver a modest benefit compared with treatment with PLAT+5-FU. So, whilst using data from the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial to represent the effect of treatment with PLAT+5-FU, may over-estimate effectiveness, this approach still represents a reasonable proxy.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo partitioned survival model in Microsoft Excel to compare the cost effectiveness of treatment with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and PLAT+5-FU as first-line treatments for adults with R/M HNSCC whose tumours tested positive for PD-L1 expression where CPS≥1. The model comprises three mutually exclusive health states: progression-free (PF), post-progression (PP) and death. All patients enter the model in the PF health state. The model time horizon is set at 20 years with a 1-week cycle length and the perspective is that of

the UK NHS. Outcomes are measured in quality adjusted life years (QALYs), and both costs and QALYs are discounted at an annual rate of 3.5%, as recommended by NICE.

In the company model, OS K-M data from the KEYNOTE-048 trial were used up to week 80 followed by parametric extrapolation thereafter for the comparison of treatment with pembrolizumab monotherapy (log-logistic function) or pembrolizumab+PLAT+5-FU (log-normal function) versus cetuximab+PLAT+5-FU. Results from the company NMAs were applied to the pembrolizumab and pembrolizumab+PLAT+5-FU OS models to represent the experience of patients receiving PLAT+5-FU.

For pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU, the company modelled PFS by appending exponential functions to KEYNOTE-048 trial PFS K-M data from week 52. Results from the company NMAs were applied to the pembrolizumab and pembrolizumab+PLAT+5-FU OS models to represent the experience of patients receiving PLAT+5-FU.

The time on treatment (ToT) K-M data in the KEYNOTE-048 trial did not require extrapolation beyond the trial follow-up period. For patients receiving PLAT+5-FU, ToT was assumed to be the same as PFS (estimated by the company's NMA).

The company model includes AEs of Grade ≥3 occurring in >1% of patients in the KEYNOTE-048 trial. During the KEYNOTE-048 trial HRQoL data were collected using the EQ-5D-3L questionnaires. Responses from these questionnaires (stratified by progression status, baseline ECOG score and number of days to death) were converted to EQ-5D-3L utility values using a published algorithm and then used to represent the HRQoL of patients in the PF health state and those in the PP health state. Resource use and costs were estimated based on information from the KEYNOTE-048 trial, published sources and clinical experts.

Using the CAA discount for pembrolizumab and list prices for other drugs, results from the company's base case deterministic analysis showed that treatment with pembrolizumab monotherapy dominates cetuximab+PLAT+5-FU by being cheaper (£48,945 versus £51,832) and more effective (2.40 QALYs versus 1.27). The pairwise incremental cost effectiveness ratio (ICER) per quality adjusted life years (QALY) gained for the comparison of treatment with pembrolizumab monotherapy versus PLAT+5-FU is £31,212. The pairwise ICERs per QALY gained for the comparison of treatment with pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and versus PLAT+5-FU are £9,255 and £31,070 respectively.

The results from the company's probabilistic sensitivity analysis are consistent with the company's base case (deterministic) analysis. Using a willingness-to-pay threshold of £50,000

per QALY gained, the probability of treatment with pembrolizumab monotherapy being cost effective is 100% versus cetuximab+PLAT+5-FU and 99.2% versus PLAT+5-FU. The probabilities of treatment with pembrolizumab+PLAT+5-FU being cost effective are 100% and 98.8% compared with cetuximab+PLAT+5-FU and PLAT+5-FU respectively.

The company carried out a wide range of deterministic sensitivity analyses. The most influential parameters were body surface area of modelled patients (for pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU), discount rate of health outcomes (pembrolizumab monotherapy versus PLAT+5-FU) and choice of OS parametric function (for pembrolizumab+PLAT+5-FU versus PLAT+5-FU). None of the scenarios explored by the company produced an ICER that was higher than £50,000 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG is satisfied that the cost effectiveness results produced by the updated company model are likely to be an accurate reflection of the model structure and inputs described in the CS and the Supplementary Document (July 2019).

The ERG has made four revisions to the company model. The areas in which changes have been made are:

- using a single cetuximab+PLAT+5-FU arm
- using a Weibull distribution to extrapolate KEYNOTE-048 K-M OS data
- lifetime duration of treatment effect on OS (treatment waning)
- modelling time to treatment discontinuation.

In addition, the ERG considers that oral cavity and non-oral cavity patients should be considered separately in the economic model as the standard of care in the NHS for each group is different (cetuximab+PLAT+5-FU for oral cavity patients and PLAT+5-FU for non-oral cavity patients).

1.7 Summary of company's case for End of Life criteria being met

A technology meets NICE End of Life criteria if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months.

The company considers that pembrolizumab (monotherapy and in combination with PLAT+5-FU) should be considered as an end of life treatment as:

- Results from the KEYNOTE-048 trial show that median OS for patients treated with cetuximab+PLAT+5-FU is 10.3 months (95% CI: 9.0 to 11.5 months)

- Base case results from the company model show that, compared with treatment with cetuximab+PLAT+5-FU and PLAT+5-FU, treatment with pembrolizumab monotherapy offers life extensions of 1.06 and 1.44 years respectively
- Base case results from the company model show that, compared with treatment with cetuximab+PLAT+5-FU and PLAT+5-FU, treatment with pembrolizumab+PLAT+5-FU offers life extensions of 1.19 and 1.61 years respectively.

1.8 ERG commentary on End of Life criteria

After applying the ERG revisions to the company model, mean OS for oral cavity and non-oral cavity patients is around 12 months and, compared with standard of care, mean life expectancy gain for patients treated with pembrolizumab (monotherapy or in combination with PLAT+5-FU), even in the most pessimistic scenarios considered by the ERG, is over 3 months. The ERG is, therefore, satisfied that pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU meet both components of the NICE End of Life criteria for the populations under consideration when compared with treatment with either cetuximab+PLAT+5-FU (oral cavity patients) or PLAT+5-FU (non-oral cavity patients).

1.9 ERG commentary on the robustness of evidence submitted by the company

1.9.1 Strengths

Clinical evidence

- The KEYNOTE-048 trial is a good quality and well conducted phase III, open label, RCT
- An appropriate, pre-defined, statistical approach was used to analyse the efficacy, safety and patient reported outcome data from the KEYNOTE-048 trial
- Generally, the company's approach to performing the NMAs was appropriate.

Cost effectiveness evidence

- The economic model accurately incorporated the parameter values described in the CS and in the Supplementary Document (July 2019)
- Detailed descriptions relating to the parameters used to populate the model were provided in the CS and in the Supplementary Document (July 2019)
- A comprehensive range of scenario and sensitivity analyses were performed with all major areas of uncertainty addressed.

1.9.2 Weaknesses and areas of uncertainty

Clinical evidence

- The company has not provided any evidence for patients whose cancer did not express PD-L1 CPS≥1

- The population recruited to the KEYNOTE-048 trial is only representative of the fittest patients in the NHS with R/M HNSCC i.e., those patients who are fit enough to receive cetuximab+PLAT+5-FU
- Information relating to two interventions has been provided by the company. The company states that the choice between treatment with pembrolizumab or pembrolizumab+PLAT+5-FU should be based on the judgement of the treating physician and patient wishes
- Cetuximab+PLAT+5-FU is only recommended by NICE for patients whose cancer originated in the oral cavity. Approximately 30% of patients in in the KEYNOTE-048 trial had cancer that started in the oral cavity
- Approximately 70% of patients in the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial (non-oral cavity patients) received a standard of care that is not recommended by NICE
- The KEYNOTE-048 trial was not powered to detect statistically significant differences between treatments in the oral cavity subgroup
- There is no direct evidence available to compare the clinical effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus platinum-based chemotherapy regimens.

Cost effectiveness evidence

- The company model includes multiple hidden sheets and employs lengthy visual basic code to make changes each time the interventions and comparators are changed. This makes it difficult to check model algorithms
- The model had an algorithm error which meant that the results presented by the company that relate to the waning of effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU are incorrect
- Results for pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus PLAT+5-FU were based on NMAs which are flawed because the NMAs did not stratify patients by origin of cancer
- The company's chosen distributions for the long-term extrapolation of K-M OS data from the KEYNOTE-048 trial for all treatment arms are clinically implausible
- When considering ToT, it was not possible to separate out any of the combination treatments into their constituent parts; this means that the costs associated with any combination treatment are likely to be overestimated in the company model.

1.10 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG presented a preferred scenario using (i) data for all patients receiving cetuximab+PLAT+5-FU regardless of whether the intervention was pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU (R1) and (ii) a Weibull distribution to extrapolate OS K-M data in all treatment arms (R2).

For oral cavity patients, the comparison of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU, these amendments do not stop pembrolizumab monotherapy being

the dominant strategy; this strategy remained dominant when mortality rates for the intervention and comparator were equalised at 3 and 5 years.

For oral cavity patients, the comparison of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU, the ERG amendments increased the company's base ICER per QALY gained from £3,547 to £12,802. Compared with the company base case ICER per QALY gained, with 3-year waning, the revised ICER per QALY gained increased by £13,444 to £22,699 and with 5-year waning, the revised ICER per QALY gained increased by £7,298 to £16,553.

For non-oral cavity patients, the comparison of pembrolizumab monotherapy versus PLAT+5-FU, the ERG amendments increased the ICER per QALY gained by £12,644 to £43,856. Compared to the company base case ICER per QALY gained, with 3-year waning, the ICER per QALY gained increased by £41,367 to £72,579 per QALY gained and with 5-year waning, the ICER per QALY gained increased by £24,873 to £56,085.

For non-oral cavity patients, the comparison of pembrolizumab+PLAT+5-FU versus PLAT+5-FU, the ERG amendments increased the ICER per QALY gained by £11,720 to £42,790. Compared to the company base case ICER per QALY gained, with 3-year waning, the ICER per QALY gained increased by £59,958 to £91,028 and with 5-year waning, the ICER per QALY gained increased by £31,974 to £63,044.

1.11 Cost effectiveness conclusions

Oral cavity patients

Due to the price of cetuximab being confidential, the ERG is unable to comment on the cost effectiveness of pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU in this ERG report. Please see Confidential Appendix 1 where the ERG's conclusions are presented using the CAA price for pembrolizumab and the PAS price for cetuximab.

Non-oral cavity patients

The company's cost effectiveness results show that, at a willingness to pay threshold of £50,000 per QALY gained, treatment with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus PLAT+5-FU are likely to be cost effective. However, the ERG considers that, as there are two interventions, a fully incremental cost effectiveness analysis is required. Table 1 shows the results of a fully incremental cost effectiveness analysis using the ERG's preferred scenario (R1-R2).

Table 1 Fully incremental analysis for non-oral cavity patients

Treatment	Total costs	Total QALYS	Incremental costs	Incremental QALYs	ICER per QALY gained
PLAT+5-FU	£22,076	0.839	-	-	-
Pembrolizumab monotherapy	£47,644	1.422	£25,568	0.583	£43,856
Pembrolizumab+PLAT+5-FU	£61,956	1.771	£14,312	0.349	£41,009

ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years

Whilst noting that the results of any incremental analysis may change when the effect of treatment waning is taken into account, the results suggests that, at a willingness to pay threshold of £50,000 per QALY gained, treatment with pembrolizumab+PLAT+5-FU is the most cost effective option when compared with pembrolizumab monotherapy and PLAT+5-FU for non-oral cavity patients.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Section B1.3 of the company submission (CS). The Evidence Review Group (ERG) considers that the company's description presents an accurate summary of the underlying health problem. Key points made by the company and considered by the ERG to be of particular relevance to the current appraisal are presented in Box 1.

The ERG highlights that the patient population discussed in the CS is a subset of the patient population specified in the final scope issued by NICE.[1] The patient population discussed in the CS is adults with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) previously untreated in the R/M setting whose tumours test positive for programmed death ligand 1 (PD-L1) expression defined as combined positive score (CPS≥1). The population in the final scope issued by NICE[1] is a wider population, namely, adults with R/M HNSCC previously untreated in the R/M setting.

Box 1 Key points from the company's description of underlying health problem

Description of disease

- Head and neck cancers describe an anatomically heterogeneous group of cancers that arise most often from the oral cavity, oropharynx, hypopharynx, and larynx.[2] This submission will focus on malignancies of the oral cavity, oropharynx, hypopharynx and larynx, excluding other primary tumour sites.
- More than 90% of head and neck cancers are squamous cell carcinomas, originating from the epithelium of the mucosal lining of the upper aerodigestive tract.[3]
- These neoplasms are aggressive in their biologic behaviour, resulting in significant destructive disease above the clavicle, with the development of local (cervical) lymph node metastases and distant metastases even after effective local therapy.[3]
- Sites of metastases include lymph nodes, bone, liver and lung.[4]
- Historically, major risk factors for head and neck cancers include alcohol and tobacco use; however, in recent years the HPV has been shown to be a causative agent in the majority of oropharyngeal cancers.[2,4] Tobacco-related HNSCC disease has declined, whereas HPV-positive disease has increased.[4] HPV-positive and HPV-negative HNSCC represent two distinct biologies with different clinical presentations and prognosis.[4]

Staging

Head and neck cancer is staged according to the American Joint Committee on Cancer/Union for International Cancer Control TNM staging classification system.[5] HNSCC tumour staging is complex and based on the location of tumour, nodal involvement, and the degree of structural involvement at sub-sites. Classification considers local, regional, and distant characteristics of the disease; local disease includes the primary tumour (T 1-4); regional disease indicates the involvement of cervical lymph nodes (N 0-3); and distant metastasis (M 0-1) assesses spread of the primary tumour to sites beyond the cervical lymphatic system.

Epidemiology

- Head and neck cancer is the eighth most common cancer in the UK. In 2015, 12,061 new cases of head and neck cancer were reported accounting for 3% of all new cancer cases.[6]
- HNSCC is more prevalent in a male population, occurring at approximately a 2:1 male:female ratio.[6]
- Approximately 3% to 4% of all patients with HNSCC have distant metastases at diagnosis.[7]

Reported recurrence rates vary widely depending on tumour localisation, primary tumour stage, and treatment modality. Significantly, 10% to 30% of patients with cancer of the lip or oral cavity subsequently develop second primary neoplasms of the upper aerodigestive tract.[3] Studies generally report recurrence rates of approximately 40% to 50% for head and neck carcinomas.

Burden of disease

- The challenges of R/M HNSCC include pain, altered speech, and difficulties with swallowing, breathing, and social function.[8] Patients with R/M disease have a poor prognosis, with a median survival time of 6 to 9 months.[2] The challenges of R/M HNSCC include pain, altered speech, and difficulties with swallowing, breathing, and social function.[8] Patients with R/M disease have a poor prognosis, with a median survival time of 6 to 9 months.[2]
- R/M HNSCC is a devastating disease that severely impacts the daily life of patients.[8-10]

CPS= combined proportion score; PLAT+5-FU=chemotherapy; HNSCC=head and neck squamous cell carcinoma; HPV=human papillomavirus; R/M=recurrent or metastatic; TNM=tumour, node, metastases
Source: adapted from CS, Section B1.3

The ERG notes that the epidemiological information presented in Box 1 relates to all patients with R/M HNSCC and that, currently, there are no published epidemiological data specific to patients whose tumours test positive for PD-L1 expression defined as CPS≥1.

2.2 Company's overview of current service provision

The company's overview of current service provision is also presented in Section B1.3 of the CS. The ERG considers that the company's overview presents an accurate summary of current service provision and highlights the key points made by the company in Box 2.

Box 2 Key points from the company's overview of current service provision

Treatment options

- Treatments for HNSCC vary according to the specific tumour sites and typically treatment involves surgery and/or radiotherapy with curative intent, with systemic therapy in cases of locoregionally advanced disease. For R/M disease, patients typically receive chemotherapy after resection.
- The EXTREME regimen is also recommended for this population by the European Head & Neck Society, the European Society for Medical Oncology, and the European Society for Radiotherapy & Oncology joint clinical practice guidelines.[11] The US National Comprehensive Cancer Network guidelines[12] provide a comprehensive list of systemic therapy options for HNSCC and also includes the EXTREME regimen as one of only two Category 1 evidence supported combination regimens that they recommend as first-line treatments for patients with R/M HNSCC.

HNSCC=head and neck squamous cell carcinoma; R/M=recurrent or metastatic
Source: adapted from CS, Section B1.3

In the CS (Figure 3 [p24], reproduced as Figure 1 in this ERG report), the company provides a summary of the treatment pathway for patients with HNSCC in the NHS, indicating the proposed position of pembrolizumab monotherapy and pembrolizumab plus platinum chemotherapy plus fluorouracil (pembrolizumab+PLAT+5-FU). The company states (CS, p22) that the choice of treatment (either pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU) will be made by the treating clinician in accordance with patient preference.

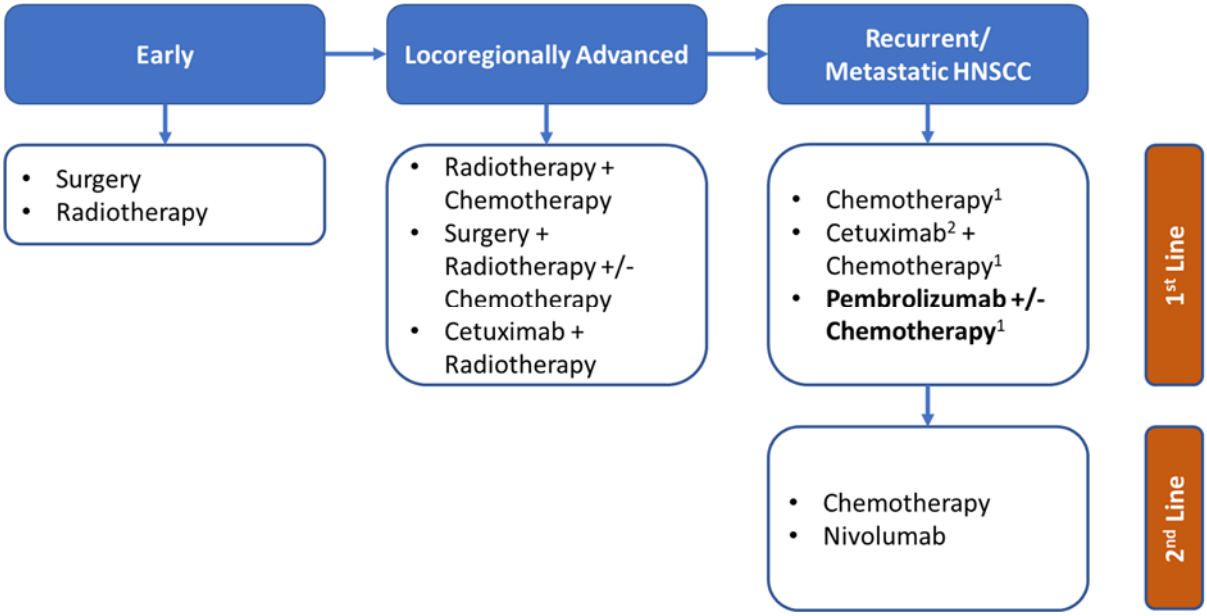

Figure 1 Proposed position of pembrolizumab in the clinical treatment pathway for HNSCC

Source: CS, Figure 3
HNSCC=head and neck squamous cell carcinoma
[1]Platinum-based chemotherapy regimens [2] If the cancer started in the oral cavity

2.3 Innovation

The company considers that treatments with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU are innovative for the reasons given in Box 3.

Box 3 Company's rationale for pembrolizumab as innovative treatment

- 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. This mode of action has been demonstrated for both pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU in the PD-L1 CPS≥1 population.
- Pembrolizumab offers a durable and well-tolerated treatment option for patients with R/M HNSCC and PD-L1 expression of CPS≥1.
- Currently, first line-treatment options for R/M HNSCC in routine UK clinical practice are limited to platinum-based chemotherapy regimens which are associated with significantly poorer efficacy in terms of OS and PFS compared to treatment with pembrolizumab (either as monotherapy or in combination with PLAT+5-FU) along with significantly worse AE rates compared to pembrolizumab monotherapy.
- Patients who have R/M HNSCC starting in the oral cavity may be treated with cetuximab+PLAT+5-FU regimens. The results from the KEYNOTE-048[13] show that treatment with pembrolizumab also results in significantly superior survival outcomes compared to this regimen, along with a more favourable safety profile (using pembrolizumab monotherapy, or a comparable safety profile using pembrolizumab+PLAT+5-FU).
- R/M HNSCC is a highly symptomatic disease that can exert a considerably negative effect on patients' HRQoL, in particular arising from pain, difficulties with swallowing and speech, breathing and social function. It is therefore notable that patients treated with pembrolizumab monotherapy or pembrolizumab in combination with platinum-based chemotherapy exhibited [redacted] HRQoL scores over 15 weeks of follow-up.

AE=adverse event; CPS= combined proportion score; PLAT+5-FU=chemotherapy; HNSCC=head and neck squamous cell carcinoma; HRQoL=health-related quality of life; OS=overall survival; PD-1=programmed death 1; PD-L1=programmed death ligand 1; PFS=progression-free survival; R/M=recurrent or metastatic.
Source: adapted from CS, Section B1.3

2.4 Number of patients eligible for treatment with pembrolizumab

The company estimates (Company's Budget Impact Analysis Submission, Table 10) that 958 patients with R/M HNSCC will be eligible for treatment with pembrolizumab in England and Wales in 2020, rising to 1,036 patients in 2024. The company's estimates are based on information from the Office for National Statistics,[14,15] Cancer Research UK,[16] European treatment guidelines[11] and TA490.[17] The proportion of patients with R/M HNSCC whose tumours test positive for PD-L1 expression defined as CPS≥1 was assumed to be 85%, based on data from the KEYNOTE-048 trial. The ERG considers that the company's estimates are reasonable.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE[1] and that addressed within the CS is presented in Table 2. Each parameter is discussed in more detail in the text following the table.

Table 2 Comparison between NICE scope and company decision problem

Final scope issued by NICE **Parameter and specification**	**Summary of a comparison between the decision problem stated in the NICE scope and addressed in the company submission**
Population Adults with recurrent or metastatic squamous cell carcinoma of the head and neck previously untreated in the recurrent or metastatic setting	The evidence presented in the CS is relevant to a subset of the population specified in the final scope issued by NICE The population discussed in the CS is adults with R/M HNSCC previously untreated in the R/M setting whose tumours test positive for PD-L1 expression defined as CPS≥1 CPS consists of the percentage of PD-L1+ tumour cells and infiltrating immune cells relative to the total number of tumour cells as determined by a central laboratory immunohistochemistry assay.
Intervention • Pembrolizumab alone • Pembrolizumab in combination with platinum-based chemotherapy	The company has provided evidence for two interventions: • Pembrolizumab monotherapy • Pembrolizumab+PLAT+5-FU Direct evidence for the clinical effectiveness of these two interventions has been derived from the KEYNOTE-048 trial. In this trial, the platinum-treatment was either cisplatin or carboplatin plus 5-FU (by investigator choice).
Comparators • Platinum-based chemotherapy • Cetuximab in combination with platinum-based chemotherapy (only if the cancer started in the oral cavity)	<u>Direct clinical evidence presented in the CS</u> KEYNOTE-048 trial data allow two treatment comparisons: 1. pembrolizumab monotherapy versus cetuximab+PLAT+5-FU 2. pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU The company has not provided any direct evidence to compare the effectiveness of pembrolizumab (monotherapy or combination) versus platinum-based chemotherapy. Platinum-based chemotherapy is the standard of care in the NHS for patients with non-oral cancer. Results from the comparison of treatment with pembrolizumab (monotherapy or combination) versus cetuximab+PLAT+5-FU have been presented for the subgroup of the KEYNOTE-048 trial whose tumours test positive for PD-L1 expression, regardless of site of disease. In response to the ERG's clarification request, the company provided subgroup analysis results for patients whose tumours started in the oral cavity. Cetuximab+PLAT+5-FU is the standard of care in the NHS for patients with oral cancer. <u>Indirect clinical evidence presented in the CS</u> Pembrolizumab (monotherapy or combination) is compared with a number of platinum-based chemotherapy treatments via the company's NMAs.
Outcomes • OS • PFS • Response rate • AEs	As per the final scope issued by NICE.

• HRQoL	
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 technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any PAS for the intervention or comparator technologies will be taken into account. The economic modelling for subgroups should include the costs associated with diagnostic testing for PD-L1 in people with R/M metastatic head and neck cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.	The company has provided ICERs per QALY gained for the comparisons of: • pembrolizumab monotherapy versus cetuximab+5-FU and versus PLAT+5-FU • pembrolizumab+PLAT+5-FU versus cetuximab+5-FU and versus PLAT+5-FU The costs have been calculated from the NHS perspective The time horizon considered is 20 years. The ERG considers this sufficiently long to reflect any differences in costs or outcomes between the technologies being compared The PAS price for pembrolizumab and list prices for the comparator drugs are used in the company calculations Company calculations include the costs associated with diagnostic testing for PD-L1 disease and a sensitivity analysis without these costs has been undertaken.
Other considerations If the evidence allows, subgroups based on tumour expression of PD-L1 status will be considered. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The evidence provided in the CS relates to patients with R/M HNSCC that is previously untreated in the R/M setting with PD-L1 expression defined as CPS≥1 determined by a central laboratory immunohistochemistry assay. Results for other subgroups including PD-L1 expression level defined by CPS (CPS≥20 versus not CPS≥20 and CPS≥ 1 versus not CPS≥1) are presented in Appendix E of the CS.

AE=adverse event; CPS=combined proportion score; CS=company submission; DH=department of Health; HNSCC=head and neck squamous cell carcinoma; HRQoL=health-related quality of life; OS=overall survival; PAS=Patient Access Scheme; NMA=network meta-analysis; PD-L1=programmed death ligand 1; PFS=progression-free survival; R/M=recurrent or metastatic; RR=response rate
Source: CS, adapted from Table 1

The company has presented data from the KEYNOTE-048[13] trial, a phase III, open label, randomised controlled trial (RCT) that enrolled patients with HNSCC, untreated in the R/M setting. In the trial, patients were randomised to receive pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU or cetuximab+PLAT+5-FU. The platinum therapy used in all arms of the trial is cisplatin or carboplatin.

The KEYNOTE-048 trial was conducted in 229 centres in 37 countries. Ten patients were treated at two centres in the UK. Unless otherwise stated, all other data presented in this ERG report relate to the CPS≥1 population of the KEYNOTE-048 trial.

Approximately one third (34.2%) of patients (CPS≥1) recruited to the KEYNOTE-048 trial were treated in centres in Europe (CS, p56). The median age of these patients was 61 years and approximately two-thirds had metastatic disease. The European Cooperative Oncology Group (ECOG) performance status (PS) of these patients was either 0 or 1. Clinical advice to the

ERG is that although patients recruited to the KEYNOTE-048 trial are representative of patients in the NHS who are treated with cetuximab+PLAT+5-FU, very few patients with R/M HNSCC are fit enough to be treated with the cetuximab+PLAT+5-FU.

3.1 Populations

The ERG has a number of concerns about the patient population discussed in the CS in relation to the final scope issued by NICE[1] and to clinical practice.

Population specified by NICE and the population discussed in the CS

In the final scope issued by NICE,[1] the patient population is specified as adults with R/M HNSCC previously untreated in the recurrent or metastatic setting. The population discussed in the CS is a subset of the population described in the final scope,[1] namely adults with R/M HNSCC previously untreated in the R/M setting with tumours having PD-L1 expression defined as CPS≥1. The company presents full details of all of the patients in the KEYNOTE-048 trial in Appendix M of the CS including the 128 patients with CPS<1.

Populations in the licensed indications

The interventions listed in the final scope issued by NICE[1] are pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU. The company expects to receive a positive opinion from the European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP) for the use of pembrolizumab in September 2019. The company expects the licensed indication for pembrolizumab monotherapy to be [redacted] and for pembrolizumab+PLAT+5-FU will be [redacted]

The ERG notes that the anticipated licensed indication for the use of pembrolizumab monotherapy is [redacted] and the anticipated licensed indication for the use of pembrolizumab+PLAT+5-FU is for [redacted]. This means that, within the current Single Technology Appraisal, two interventions are being appraised. The company anticipates (CS, p22) that, in clinical practice, the choice of pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU will be made by the treating clinician in consultation with the patient.

The ERG highlights that the clinical effectiveness evidence provided in the CS only relates to the population whose tumours express PD-L1 with a CPS≥1.

During the clarification telephone conference, the company explained that treatment with pembrolizumab+PLAT+5-FU would be most suitable for patients for whom a rapid response

is desirable. Clinical advice to the ERG, however, is that if patients are so unwell that an immediate response to treatment is necessary, then they may also be too ill to tolerate the level of AEs associated with receiving pembrolizumab+PLAT+5-FU.

Testing for PD-L1 expression

In the KEYNOTE-048 trial, PD-L1 status was determined from core needle or excisional biopsies or resected tissue using the PD-L1 immunohistochemistry 22C3 pharmDx assay. PD-L1 tumour expression in the trial was characterised as a combined positive score (CPS), that is, a measure of the percentage of PD-L1+ tumour cells and infiltrating immune cells relative to the total number of tumour cells present in the tumour biopsy. The company has not discussed testing of PD-L1 status in the NHS for patients with R/M HNSCC; however, clinical advice to the ERG is that as PD-L1 testing is routinely carried for other types of cancer tumour (e.g., lung cancer and melanoma), scaling up testing to include tumours from patients with R/M HNSCC should not be problematic. Clinical advice to the ERG is that CPS is a reasonably well established measure of PD-L1 expression.

3.2 Interventions

Two interventions are specified in the final scope issued by NICE[1] and discussed in the CS, pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU. Pembrolizumab is a highly selective, humanised monoclonal antibody against programmed death-1 (PD-1) that prevents PD-1 from engaging with its ligands, PD-L1 and PD-L2 (CS, p14). It is administered as an intravenous infusion. The platinum therapy discussed in the CS is either cisplatin or carboplatin, and this element of treatment is administered intravenously along with 5-FU.

The treatment regimens for pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU described in the CS are presented in Table 3. The company anticipates that the pembrolizumab monotherapy licence will include an option to administer pembrolizumab at a fixed dose of 400mg over 30 minutes every 6 weeks but no evidence of the effectiveness of this regimen has been provided in the CS. Clinical advice to the ERG is that, at some centres, patients receiving 5-FU must attend the hospital on four consecutive days and that this requirement is likely to cause logistical issues for the NHS.

Table 3 KEYNOTE-048 trial intervention treatment regimens

Drug	Dose	Frequency	Regimen	Limit
Pembrolizumab	200mg IV	Every 3 weeks	Day 1 of each cycle	2 years or until disease progression or toxicity
Cisplatin or Carboplatin	100mg/m^2 IV AUC 5 IV	Every 3 weeks	Day 1 of each cycle	6 cycles
5-FU	1000mg/m^2 IV	Every 3 weeks	Days 1 to 4 of each cycle	6 cycles

IV=intravenous
Source: adapted from CS, Table 6

3.3 Comparators

Cetuximab+PLAT+5-FU for patients whose cancer started in the oral cavity

Cetuximab+PLAT+5-FU is only recommended by NICE[18] as an option for treating adults with R/M HNSCC cancer that started in the oral cavity (oral-cavity patients). The NICE recommendation[18] to limit use of cetuximab+PLAT+5-FU to patients whose cancer started in the oral cavity was based on an evaluation of clinical effectiveness data (which informed cost effectiveness analyses) from a protocol-defined subgroup of patients in the EXTREME[19,20] trial whose cancer started in the oral cavity. The treatment regimen for cetuximab+PLAT+5-FU as described in the CS is shown in Table 4.

Table 4 KEYNOTE-048 trial comparator treatment regimen

Drug	Dose	Frequency	Regimen	Limit
Cetuximab	Initial dose on day 1 is 400 mg/m^2 IV followed by weekly doses of 250 mg/m^2	Every week	Days 1, 8, and 15 of each cycle (3 week cycles)	Until disease progression or unacceptable toxicity
Cisplatin or Carboplatin	100mg/m^2 IV AUC 5 IV	Every 3 weeks	Day 1 of each cycle	6 cycles
5-FU	1000mg/m^2 IV	Every 3 weeks	Days 1 to 4 of each cycle	6 cycles

IV=intravenous
Source: adapted from CS, Table 6

Only 31% of patients in the comparator arm of the KEYNOTE-048 trial had cancer that started in the oral cavity. This means that 69% of patients received treatment that is not standard of care in the NHS and is outside of the final scope issued by NICE.[1] The company considers (CS, p55) that treatment with cetuximab+PLAT+5-FU is at least as effective as any chemotherapy regimen used in the NHS. If this opinion is valid, comparisons of the effectiveness of pembrolizumab (monotherapy or combination) versus cetuximab+PLAT+5-FU may be conservative.

Clinical advice to the ERG is that, in line with the NICE recommendation,[18] cetuximab+PLAT+5-FU is used in the NHS to treat patients whose cancer started in the oral

cavity. However, it is rarely used as a minority of patients in this group are fit enough to tolerate the treatment.

In response to the ERG's clarification question A2, the company provided subgroup outcome data for patients whose cancer started in the oral cavity. The ERG acknowledges that the KEYNOTE-048 trial was not designed to analyse subgroup data based on site of cancer origin.

Platinum-based chemotherapy

In the final scope issued by NICE,[1] 'platinum-based chemotherapy regimens' are a stipulated comparator. The comparator in the KEYNOTE-048 trial is cetuximab+PLAT+5-FU. There is no direct evidence available from the KEYNOTE-048 trial for the clinical effectiveness of pembrolizumab (monotherapy or in combination) versus any platinum-based chemotherapy regimen. The company has carried out network meta-analyses (NMAs) to generate comparative effectiveness data.

Clinical advice to the ERG is that PLAT+5-FU is commonly used to treat patients with R/M HNSCC in the NHS who are fit enough to tolerate chemotherapy. However, clinical advice to the ERG is also that the use of single agent platinum as a first-line treatment is increasing, followed by treatment with nivolumab as a second-line treatment. The ERG notes that nivolumab is available to patients in the NHS only through the Cancer Drugs Fund (CDF).

Outcomes

The company has provided clinical evidence relating to treatment with pembrolizumab (monotherapy and combination) from the KEYNOTE-048 trial, for all five outcomes specified in the final scope issued by NICE[1]:

- Centrally assessed (RECIST v1.1) progression-free survival (PFS)
- Overall survival (OS) defined as the time from the date of randomisation to the date of death from any cause
- Response rate (RR), specifically objective response rate (ORR) and duration of response (DoR)
- Adverse effects (AEs) of treatment
- Health-related quality of life (HRQoL) using the European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaire, the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life-Core 30 (QLQ-C30) instrument, the EORTC QLQ-H&N35 pain and time to deterioration measures.

Results from the second interim analysis (IA2) of data from the KEYNOTE-048 trial were provided in the CS (data cut-off date 13 June 2018) and updated final analysis results for all outcomes (data cut-off date 25 February 2019) were provided by the company in a Supplementary Document (July 2019) during the post-clarification period.

3.4 Economic analysis

As specified in the final scope issued by NICE,[1] the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 20-year time horizon (considered by the company to be long enough to reflect all important differences in costs or outcomes between the technologies being compared) and costs were considered from an NHS perspective. When generating cost effectiveness estimates, the company used the expected Commercial Access Agreement (CAA) price for pembrolizumab and the list prices of cetuximab and the comparator drugs. In addition, in line with the final scope issued by NICE,[1] the company presented cost effectiveness estimates that included the costs associated with diagnostic testing for PD-L1 as well as results from a sensitivity analysis that did not include diagnostic testing costs.

3.5 Subgroups

In the final scope issued by NICE,[1] it is stated that if the evidence allows, subgroups based on tumour expression of PD-L1 status should be considered. All of the evidence presented in the CS relates to patients with tumours that express PD-L1 defined as CPS≥1. Updated results for other subgroups, including PD-L1 expression level defined by CPS (CPS≥20 versus not CPS≥20 and CPS≥ 1 versus not CPS≥1), are presented in Appendix E of the Supplementary Document (July 2019), provided by the company during the post-clarification period.

3.6 Other considerations

The company did not identify any equity or equality issues (CS, Section B.1.4).

The company has put forward a case for treatment with pembrolizumab (as monotherapy or in combination) to be considered under NICE's End of Life criteria (CS, Part A, Table 13).

Pembrolizumab and cetuximab are both available to the NHS at discounted prices (via a CAA and a Patient Access Scheme [PAS], respectively). The discounted price of cetuximab is not known to the company.

4 CLINICAL EFFECTIVENESS

4.1 Systematic review methods

Full details of the process and methods used by the company to identify and select the clinical evidence relevant to the technology being appraised are presented in Appendix D of the CS. The ERG assessed whether the review was conducted in accordance with the criteria listed in Table 5.

Table 5 ERG appraisal of systematic review methods

Review process	ERG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Were data extracted by two or more reviewers independently?	Not explicitly stated
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were appropriate methods used for data synthesis?	Yes

Overall, the ERG considers that the methods used by the company in their systematic review of clinical effectiveness evidence were satisfactory. The ERG has run its own searches and is confident that no relevant publications were missed.

4.1.1 Literature search

The company reports that the details relating to the KEYNOTE-048 trial, the main source of the company's clinical effectiveness evidence, were taken from the trial clinical study report (original and updated). The ERG notes that the details of the KEYNOTE-048 trial are not reported in a published paper.

4.1.2 Quality assessment methods

To assess the quality of the KEYNOTE-048 trial, the company has (appropriately) applied the criteria from the NICE User Guide For Company Evidence Submission template.[21]

To assess the quality of the trials included in the NMAs, the company has used the Cochrane Risk of Bias tool.[22]

4.1.3 Data synthesis

The company identified only one RCT (the KEYNOTE-048 trial) which reported clinical effectiveness outcomes for pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU in patients with R/M HNSCC who had been previously untreated in the R/M setting.

Cetuximab with cisplatin+5-FU for patients whose cancer started in the oral cavity is also a comparator listed in the final scope[1] issued by NICE; in response to the ERG's clarification request, the company provided evidence to allow a comparison of pembrolizumab or pembrolizumab+PLAT+5-FU with cetuximab+PLAT+5-FU for patients whose cancer started in the oral cavity.

To compare the clinical effectiveness of treatment with pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU with platinum-based chemotherapy (one of the comparators listed in the final scope[1] issued by NICE), the company conducted NMAs.

4.2 ERG critique of clinical effectiveness evidence

All information presented in this section of the ERG report has been taken directly from the CS or the Supplementary Document (July 2019) unless otherwise stated.

4.2.1 Studies of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU

The comparator in the KEYNOTE-048 trial is cetuximab+PLAT+5-FU. In the final scope,[1] cetuximab+PLAT+5-FU is listed as a comparator only for patients whose cancer started in the oral cavity. The ERG notes that approximately one third of the 754 patients in the PD-L1+ population of the KEYNOTE-048 trial had cancer that started in the oral cavity. This means that two thirds of the patients in the comparator arm of the KEYNOTE-048 trial received treatment that is not relevant to the final scope[1] issued by NICE. Clinical advice to the ERG is that cetuximab+ PLAT+5-FU is recognised internationally as standard of care (SoC) for all patients with R/M HNSCC who are fit enough to tolerate the regimen. However, in line with NICE guidance (TA473[18]), cetuximab+ PLAT+5-FU is only used in the NHS to treat patients with R/M HNSCC whose cancer started in the oral cavity and who are fit enough to tolerate the treatment regimen.

In response to the ERG's clarification request, the company provided outcome data for the patients in the KEYNOTE-048 trial with PD-L1 CPS≥1 R/M HNSCC whose cancer started in the oral cavity.

4.2.2 Studies of comparator treatments

The seven[20,23-28] trials included in the company's NMAs (in addition to the KEYNOTE-048 trial) are briefly described in Section 4.9.3 of this ERG report. The company used the NMAs to compare treatment with pembrolizumab (monotherapy and combination therapy) with treatment with platinum-based chemotherapy. Please see Section 4.9.6 of this ERG report for discussion and critique of the company's NMAs.

4.3 Characteristics of the KEYNOTE-048 trial

4.3.1 Trial characteristics

The patient population discussed in the CS is the 754 patients recruited to the KEYNOTE-048 trial whose tumours expressed PD-L1 CPS≥1.

The KEYNOTE-048 trial stratification factors were: PD-L1 subgroup (strongly positive versus not strongly positive, defined by tumour proportion score ≥50%); human papillomavirus (HPV) status (positive or negative) in patients with cancer in the oropharynx; and Eastern Cooperative Oncology Group performance status (ECOG PS) (0 or 1).

Clinical advice to the ERG is that the KEYNOTE-048 trial eligibility criteria are reasonable and that the participating treatment centres are representative of treatment centres in the UK. The ERG is satisfied that the KEYNOTE-048 trial was well designed and well conducted. However, the comparator treatment (cetuximab+PLAT+5-FU) is only recommended by NICE for treating patients with cancer that started in the oral cavity. Only one third of the patients in the PD-L1 subgroup of patients recruited to the KEYNOTE-048 trial had cancer that started in the oral cavity. Clinical advice to the ERG is that, in the NHS, only the fittest patients with R/M HNSCC whose cancer started in the oral cavity are treated with cetuximab+PLAT+5-FU. There is no comparator arm in the KEYNOTE-048 trial for platinum-based chemotherapy, the other comparator listed in the final scope issued by NICE.

4.3.2 Baseline characteristics of patients recruited to the KEYNOTE-048 trial

In the CS, baseline characteristics are reported separately for patients randomised to the pembrolizumab monotherapy arm (CS, Table 8) and to the pembrolizumab+PLAT+5-FU arm (CS, Table 9). Table 6 and Table 7 in this ERG report are abridged versions of the information presented in the CS.

Clinical advice to the ERG is that, overall, the patients recruited to the KEYNOTE-048 trial are representative of patients in the NHS who would be considered fit enough for treatment with

chemotherapy; however, very few patients with R/M HNSCC are fit enough to tolerate any treatment.

The ERG agrees with the company (CS, p34) that the baseline characteristics of patients randomised to treatment with pembrolizumab monotherapy and cetuximab+PLAT+5-FU were well balanced (Table 6). The ERG also agrees with the company (CS, p39) that the baseline characteristics of patients randomised to treatment with pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU were well generally well-balanced (Table 7).

The ERG notes that the patients recruited to the pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU arms of the trial appear to be very similar in terms of their baseline characteristics; how treatment decisions will be made in routine clinical practice by clinicians and patients is not clear in the CS.

The company has highlighted (CS, p34 and p39) that, compared with patients in the cetuximab+PLAT+5-FU arm of the trial, the times from the last platinum therapy and from prior systemic therapy were shorter for patients treated with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU.

Table 6 Baseline characteristics - patients treated with pembrolizumab monotherapy and cetuximab+PLAT+5-FU (patients with PD-L1 CPS≥1)

Characteristic	Pembrolizumab (n=257)	Cetuximab+PLAT+5-FU (n=255)	Total (n=512)
Mean age	60.8	60.8	60.8
Male n (%)	209 (81.3)	220 (86.3)	429 (83.8)
Race n (%)			
White	188 (73.2)	189 (74.1)	377 (73.6)
Asian	50 (19.5)	47 (18.4)	97 (18.9)
Multi-Racial	10 (3.9)	9 (3.5)	19 (3.7)
American Indian or Alaska Native	4 (1.6)	6 (2.4)	10 (2.0)
Missing	2 (0.8)	1 (0.4)	3 (0.6)
Region group n (%)			
North America	68 (26.5)	54 (21.2)	122 (23.8)
European Union	74 (28.8)	92 (36.1)	166 (32.4)
Rest of the World	115 (44.7)	109 (42.7)	224 (43.8)
Smoking status n (%)			
Never smoker	59 (23.0)	61 (23. 9)	120 (23.4)
Ex-smoker	154 (59.9)	156 (61.2)	310 (60.5)
Current smoker	44 (17.1)	36 (14.1)	80 (15.6)
Missing	0 (0)	2 (0.8)	2 (0.4)
HPV status n (%)			
Positive	54 (21.0)	55 (21.6)	109 (21.3)
Negative	203 (79.0)	200 (78.4)	403 (78.7)
PD-L1 CPS status (CPS>=20) n (%)			
CPS>=20	133 (51.8)	122 (47.8)	255 (49.8)
CPS<20	123 (47.9)	131 (51.4)	254 (49.6)
Missing	1 (0.4)	2 (0.8)	3 (0.6)
Disease status n (%)			
Metastatic	179 (69.6)	168 (65.9)	347 (67.8)
Recurrent	75 (29.2)	84 (32.9)	159 (31.1)
Neither	3 (1.2)	3 (1.2)	6 (1.2)
ECOG PS n (%)			
0	104 (40.5)	101 (39.6)	205 (40.0)
1	153 59.5)	154 (60.4)	307 (60.0)
Primary tumour location – oral cavity n (%)			
Yes	75 (29.2)	80 (31.4)	155 (30.3)
No	182 (70.8)	175 (68.6)	357 (69.7)
Time from latest platinum therapy (days)			
Number of patients with data	112	120	232
Mean (SD)	754.6 (676.3)	860.9 (864.3)	809.6 (779.4)
Time from prior systemic therapy (days)			
Number of patients with data	130	125	255
Mean (SD)	810.8 (1029.7)	847.0 (846.5)	828.5 (942.7)

CPS=combined positive score; ECOG PS=European Cooperative Oncology Group performance status; HPV=human papillomavirus; PD-L1=programmed death ligand; SD=standard deviation;
Source: adapted from CS, Table 8

Table 7 Baseline characteristics - patients treated with pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU (patients with PD-L1 CPS≥1)

Characteristic	Pembrolizumab+ PLAT+5-FU(n=242)	Cetuximab+ PLAT+5-FU (n=235)	Total (n=477)
Mean age	60.6	60.8	60.7
Male n (%)	188 (77.7)	203 (86.4)	391 (82.0)
Race n (%)			
White	178 (73.6)	173 (73.6)	351 (73.6)
Asian	48 (19.8)	43 (18.3)	91 (19.1)
Multi-Racial	4 (1.7)	9 (3.8)	13 (2.7)
American Indian or Alaska Native	2 (0.8)	6 (2.6)	8 (1.7)
Missing	0 (0)	1 (0.4)	1 (0.2)
Region group n (%)			
North America	53 (21.9)	51 (21.7)	104 (21.8)
European Union	76 (31.4)	82 (34.9)	158 (33.1)
Rest of the World	113 (46.7)	102 (43.4)	215 (45.1)
Smoking status n (%)			
Never smoker	50 (20.7)	58 (24.7)	108 (22.6)
Ex-smoker	143 (59.1)	142 (60.4)	285 (59.7)
Current smoker	49 (20.2)	33 (14.0)	82 (17.2)
Missing	0 (0.0)	2 (0.9)	2 (0.4)
HPV status n (%)			
Positive	53 (21.9)	50 (21.3)	103 (21.6)
Negative	189 (78.1)	185 (78.7)	374 (78.4)
PD-L1 CPS status (CPS>=20) n (%)			
CPS>=20	126 (52.1)	110 (46.8)	236 (49.5)
CPS<20	115 (47.5)	123 (52.3)	238 (49.9)
Missing	1 (0.4)	2 (0.9)	3 (0.6)
Disease Status n (%)			
Metastatic	173 (71.5)	154 (65.5)	327 (68.6)
Recurrent	65 (26.9)	78 (33.2)	143 (30.0)
Neither	4 (1.7)	3 (1.3)	7 (1.5)
ECOG PS n (%)			
0	92 (38.0)	94 (40.0)	186 (39.0)
1	150 (62.0)	141 (60.0)	291 (61.0)
Primary tumour location – oral cavity n (%)			
Yes	77 (31.8)	73 (31.1)	150 (31.4)
No	165 (68.2)	162 (68.9)	327 (68.6)
Time from latest platinum therapy (days)			
Number of patients with data	109	113	222
Mean (SD)	734.4 (939.9)	866.8 (883.0)	801.8 (911.7)
Time from prior systemic therapy (days)			
Number of patients with data	118	118	236
Mean (SD)	705.3 (905.8)	851.8 (863.8)	778.5 (886.2)

CPS=combined positive score; ECOG PS=European Cooperative Oncology Group performance status; HPV=human papillomavirus; PD-L1=programmed death-ligand; SD=standard deviation 1; Source: adapted from CS, Table 9

4.4 Risk of bias assessment for the KEYNOTE-048 trial

The company assessed the risk of bias of the KEYNOTE-048 trial using the minimum criteria set out in the NICE User Guide For Company Evidence Submission Template.[21] The ERG considers that the KEYNOTE-048 trial was generally well designed and conducted and the ERG agrees with the company's conclusion that the trial has a low risk of bias for all domains. While the open-label design provides the opportunity for subjective results and investigator-assessed outcomes to be biased, the primary outcome of PFS was based on independent radiology review, conducted in a blinded manner. The other co-primary outcome, OS, is an objective outcome.

Table 8 Assessment of risk of bias for the KEYNOTE-048 trial

Study question	Company assessment	Company rationale	ERG comment
Was randomisation carried out appropriately?	Yes	Randomisation was conducted centrally via an interactive voice response system/integrated web response system.	Agree
Was the concealment of treatment allocation adequate?	N/A	This was an open-label study in that study treatment assignment was not blinded to investigators or study participants.	Disagree. Randomisation was conducted centrally and therefore treatment allocation could not be predicted prior to randomisation.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	The three treatment groups were generally balanced for all baseline characteristics, for the population of all participants, and for the populations of participants with PD-L1 CPS≥1 and CPS≥20.	Agree
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	This was an open-label study in that that study treatment assignment was not blinded to investigators or study participants. However, the PD-L1 status of all participants was blinded to both investigators and the sponsor. Assessment of treatment response and disease progression were conducted via blinded independent central review.	Agree
Were there any unexpected imbalances in drop-outs between groups?	No	At the time of the second interim analysis, fewer patients in the pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU groups compared to the standard treatment group had (i) discontinued the study and discontinued study medication and (ii) had discontinued the study due to death. Furthermore, fewer patients in	Agree. The ERG notes that the number of patients who discontinued treatment and reasons for discontinuation were specified and accounted for.

		the pembrolizumab+PLAT+5FU group compared with the standard treatment group had discontinued study medication due to progressive disease.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes specified in the study protocol were measured and reported in the KEYNOTE-048 clinical study report.	Agree, the company made available the clinical study report, protocol and statistical analysis plan (and relevant updates) alongside its submission to the ERG.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Yes	The analyses of primary efficacy endpoints were based on the intention-to-treat population, i.e., patients were included in the treatment group to which they are randomised.	Agree
Were appropriate methods used to account for missing data?	Yes	Appropriate methods were used to account for missing data (see Document B section B.2.4).	Agree

CPS=combined positive score; PD-L1=programmed death ligand 1;
Source: CS Appendix D, Section D.1.3 (Table 26) and ERG comment

4.5 Statistical approach adopted for the KEYNOTE-048 trial

Information relevant to the statistical approach taken by the company has been extracted from the clinical study report (CSR),[29] the trial protocol (including the trial statistical analysis plan [TSAP]),[30] from the CS and the Supplementary Document (July 2019) provided during the clarification process.

A summary of checks made by the ERG to assess the statistical approach used to analyse data from the KEYNOTE-048 trial is provided in Table 9.

Table 9 ERG assessment of statistical approach used to analyse KEYNOTE-048 trial data

Review process	ERG judgement	ERG comment
Were all the methods used to calculate the sample size correct?	Yes	The company planned to randomise approximately 825 patients to the KEYNOTE-048 trial. The sample size calculation is provided in the protocol (pp100-102)
Were all primary and secondary efficacy outcomes presented in the CS pre-specified?	Yes	In the CS, results are presented for the co-primary efficacy outcomes of PFS by BICR and OS, and for the secondary efficacy outcomes of proportions progression-free at 6 months and 12 months, and ORR. These outcomes were pre-specified in the protocol (pp105-106)
Were all relevant outcomes defined and analysed appropriately?	Partial	Definitions for PFS, OS and ORR were pre-specified in the protocol (pp105-106). The company employed a multiplicity strategy to account for testing of multiple hypotheses at multiple time points; see Section 4.5.1 of this ERG report for more information. The company used a Cox PH model to analyse the outcomes of PFS and OS. The company considered the PH assumption to be violated for both OS and PFS data for both the comparisons of pembrolizumab monotherapy vs cetuximab+PLAT+5-FU and pembrolizumab+PLAT+5-FU vs cetuximab+PLAT+5-FU (CS, p119). The ERG agrees with the company's assessment of PH, and therefore considers that HRs are not an appropriate measure of treatment effect for PFS and OS data from the KEYNOTE-048 trial. See Section 4.5.2 of this ERG report for more information. The company employed three statistical methods to adjust for treatment switching. The company concluded, and the ERG agrees, that the simplified 2-stage method is the most appropriate method to adjust for treatment switching in the KEYNOTE-048 trial. See Section 4.5.3 of this ERG report for more information
Was appropriate rationale provided for all protocol amendments?	Yes	Protocol amendments, and the rationale for these changes are provided in the CSR (pp114-116). The ERG is satisfied with the rationale for the amendments and notes that most amendments were made before the data cut-off date for the first interim analysis (17th October 2017). The final protocol amendment was made on 9th November 2017; however, the ERG considers that no changes in this final protocol amendment were driven by trial results
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data was pre-specified in the protocol (p111). The ERG considers the company's approach to be appropriate
Were all subgroup analyses and sensitivity analyses presented in the CS pre-specified?	Yes	• The company presents results for the PD-L1 CPS≥1 patient population, as was pre-specified in the trial protocol (pp16-18) • The company presents results from subgroup analyses for PFS, OS and ORR for various demographic and baseline characteristics (Supplementary Document [July 2019], Appendix E). These subgroup analyses were pre-specified in the protocol (p118) • The company provided clinical effectiveness results for people with cancer that started in the oral cavity (PD-L1 CPS≥1 subgroup) following a request for this information by the ERG in the clarification letter; see Section 4.5.1 of this ERG report for more information • No sensitivity analyses were presented in the CS

BICR=blinded independent central review; CPS=combined positive score; CSR=clinical study report; HR=hazard ratio; IPCW=inverse probability of censoring weights; ORR=objective response rate; OS=overall survival; PD-L1= PFS=progression-free survival; PH=proportional hazards; RPSFTM=rank preserving structural failure time model
Source: CS, Supplementary Document (July 2019), CSR, trial protocol and ERG comment

Overall, the ERG considers that the company's statistical approach for the analysis of data from the KEYNOTE-048 trial was mostly appropriate. The ERG discusses the key issues relating to the statistical analyses of the KEYNOTE-048 trial in Sections 4.5.1 to 4.5.3.

4.5.1 Multiplicity strategy

The company investigated multiple PFS and OS hypotheses. The company planned to conduct two interim analyses (interim analysis 1 [IA1] and IA2), and a final analysis. It was, therefore, important that the company took multiple testing into consideration in the design of the KEYNOTE-048 trial.

Alpha was split between the PFS and OS hypotheses so that the overall type 1 error rate for the study was controlled at 2.5% (one-sided). The company used a group-sequential approach to allocate alpha for each OS and PFS hypothesis between the interim and final analyses. At each analysis, hypotheses were tested sequentially so that alpha could be re-allocated to other hypotheses in the case of a successful test. The full set of multiplicity rules was pre-specified in the trial protocol (pp114-115).

The company planned to test PFS at IA1, and to perform the final analysis of PFS at IA2 if superiority of PFS had not already been demonstrated at IA1 for the particular hypothesis of interest. The PFS hypotheses are listed within the CS (p46).

The company planned to test OS at IA1, IA2 and the final analysis. The OS hypotheses are listed within the CS (pp46-47).

In the clarification letter to the company, the ERG requested that the company provide clinical effectiveness results for people with cancer that started in the oral cavity (within the PD-L1 CPS≥1 subgroup), as, in the final scope listed by NICE[1], cetuximab+PLAT+5-FU was listed as a comparator only for people whose cancer started in the oral cavity. The ERG requested that all statistical tests be performed at the 5% significance level, as it would not have been possible for the company to incorporate these analyses in the multiple testing strategy. The company provided clinical effectiveness for this patient subgroup in accordance with the ERG's request. When interpreting results from the analyses in the oral cavity cancer patient subgroup, it is important to remember that no adjustment for multiple testing was performed, and also that the KEYNOTE-048 trial was not powered to detect statistically significant differences in the oral cavity cancer patient subgroup. It is therefore difficult to draw firm conclusions from the clinical effectiveness results provided for people with cancer that started in the oral cavity within the PD-L1 CPS≥1 subgroup.

4.5.2 Proportional hazards

The company used a Cox proportional hazards (PH) model to analyse the outcomes of PFS and OS and presented hazard ratios (HRs) to summarise treatment effect. This method of analysis is only appropriate if the PH assumption is valid, that is, if the event hazards

associated with the intervention and comparator data are proportional over time.[31] The company considered the PH assumption to be violated for both OS and PFS data from the KEYNOTE-048 trial for both the comparisons of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU due to crossing Kaplan-Meier (K-M) curves (CS, p119). The ERG performed its own assessment of PH by considering H-H plots (which show the relationship between the cumulative hazard for each trial event at common time points in two trial arms) and log-cumulative hazard plots (which show the relationship between log survival probability and log time in each treatment group). The ERG agrees with the company's assessment of PH and, therefore, considers that HRs calculated using KEYNOTE-048 trial data are not an appropriate measure of comparative OS or PFS. Reported HRs should be interpreted with caution as it is not known whether they overestimate or underestimate the treatment effect.

4.5.3 Adjusting for subsequent anti-PD-1 treatment

Following disease progression, patients in the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial could receive subsequent treatments, including the anti-PD-1 treatment, nivolumab. Nivolumab is currently available, via the CDF, as a treatment for HNSCC after platinum-based chemotherapy (TA490).[17] However, NICE has advised that treatments available via the CDF after 1st April 2016 (such as nivolumab) should not be considered as comparators, or be included in treatment sequences, in appraisals of new cancer products.[32] The company, therefore, adjusted for the effect of subsequent treatment with immune checkpoint inhibitors using statistical methods which adjust OS for treatment switching. It is not clear if, or how many patients, received subsequent treatment with immune checkpoint inhibitors other than nivolumab, or what these other immune checkpoint inhibitors were.

The company employed three statistical treatment switching adjustment methods: the simplified 2-stage method, the rank preserving structural failure time model (RPSFTM), and the inverse probability of censoring weights (IPCW) method. The company details how each of these methods were applied in Appendix L to the CS. In the company's base-case network meta-analyses (NMAs), the company uses OS data from the KEYNOTE-048 trial that have been adjusted for treatment switching using the simplified 2-stage method. The ERG agrees with the company that the simplified 2-stage method is the most appropriate method to adjust for treatment switching in the KEYNOTE-048 trial. Further ERG critique of the three statistical treatment switching adjustment methods are provided in Appendix 1.

4.5.4 Enrolment pause

The company highlights (CS, p39) that enrolment in the pembrolizumab+PLAT+5-FU group was paused for 3 months during 2015 due to an external Data Monitoring Committee (DMC)

recommendation. Following a review of safety data, the DMC recommended lifting the enrolment pause. To maintain randomisation, patients randomised to the cetuximab+PLAT+5-FU arm during the 3 month pause were excluded from demographic and efficacy analyses of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. So, in these analyses (for the PD-L1 CPS>1 population), the numbers of patients in the cetuximab+PLAT+5-FU group were 255 versus pembrolizumab monotherapy and 235 versus pembrolizumab+PLAT+5-FU. The ERG considers that this approach was appropriate. Data from all patients were included in the safety analyses.

4.5.5 KEYNOTE-048 trial stopping rule

It is stated in Section B.3.5 of the CS (p198) that, 'In line with the KEYNOTE-048 protocol, a stopping rule has been implemented in the model whereby patients do not receive therapy beyond 24 months.' There is no full discussion of the 'stopping rule' in the CS. In the CSR, July 2019[29] (Section 5.8, p2469), it is stated that, [redacted].

4.6 Efficacy results from the KEYNOTE-048 trial

All results presented in this section are from the final analysis of the KEYNOTE-048 trial (data cut-off date: 25 Feb 2019). In the clarification letter to the company, the ERG requested that the company provide clinical effectiveness results for people with cancer that started in the oral cavity (PD-L1 CPS≥1 subgroup) as this is one of the populations listed in the final scope issued by NICE.[1] The company provided clinical effectiveness results for this patient subgroup and highlighted that the KEYNOTE-048 trial was not powered to detect statistically significant differences between treatments in the oral cavity subgroup. The ERG agrees that this is an important limitation of the available direct evidence.

As discussed in Section 4.5.3, the company concluded, and the ERG agrees, that the simplified 2-stage method is the most appropriate method to adjust for subsequent therapy in the KEYNOTE-048 trial. Therefore, in this ERG report, results are only presented for unadjusted OS data, and OS data adjusted using the simplified 2-stage method.

4.6.1 Pembrolizumab monotherapy versus cetuximab+PLAT+5-FU

Overall survival

A summary of the OS results (unadjusted for subsequent anti-PD-1 treatment, and adjusted for subsequent anti-PD-1 treatment via the simplified 2-stage method, for all patients and for patients whose cancer originated in the oral cavity) is provided in Table 10.

Table 10 Summary of OS results: pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (CPS≥1)

Treatment	n	Number of events (%)	Median OS (months) (95% CI)	OS rate at month 12 in % (95% CI)	Pembrolizumab vs cetuximab++PLAT+5-FU	
					HR (95% CI)	p-value
Unadjusted for subsequent anti-PD-1 treatment, all patients						
Pembrolizumab	257	197 (76.7)	12.3 (10.8 to 14.3)	50.4 (44.1 to 56.4)	0.74 (0.61 to 0.90)	0.0013[§]
Cetuximab+ PLAT+5-FU	255	229 (89.8)	10.3 (9.0 to 11.5)	43.6 (37.4 to 49.6)		
Adjusted for subsequent anti-PD-1 treatment via simplified 2-stage method, all patients						
Pembrolizumab	257	197 (76.7)	12.3 (10.8 to 14.3)	50.4 (44.1 to 56.4)	0.71 (0.57 to 0.89)	Log-rank: 0.0027[¶] Cox model: 0.0027[‖]
Cetuximab+ PLAT+5-FU 2-stage adjusted	255	229 (89.8)	10.1 (9.0 to 11.5)	43.1 (37.0 to 49.1)		
Unadjusted for subsequent anti-PD-1 treatment, patients whose cancer originated in the oral cavity						
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]		
Adjusted for subsequent anti-PD-1 treatment via simplified 2-stage method, patients whose cancer originated in the oral cavity						
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+ PLAT+5-FU 2-stage adjusted	[redacted]	[redacted]	[redacted]	[redacted]		

[§] One-sided p-value based on log-rank test
[¶] Two-sided p-value based on Cox model, analysis not adjusted for treatment switch
[‖] Two-sided p-value based on log-rank test, analysis not adjusted for treatment switch
CI=confidence interval; CPS=combined positive score; HR=hazard ratio; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1
Source: Table 4 and Table 6 Supplementary Document (July 2019); Table 188 and Table 192, Appendix S to the Supplementary Document (July 2019)

The ERG considers that a HR is not an appropriate measure of effect to summarise OS data from the KEYNOTE-048 trial (Section 4.5.2). For all patients, results from both the unadjusted analysis and the 2-stage adjusted analysis suggest that median OS was longer for patients receiving pembrolizumab compared to patients receiving cetuximab+PLAT+5-FU. However, for patients whose cancer originated in the oral cavity, median OS from both unadjusted and adjusted analysis was longer for patients receiving cetuximab+PLAT+5-FU than for patients receiving pembrolizumab.

Progression-free survival by blinded independent central review

A summary of the PFS results is provided in Table 11.

Table 11 Summary of PFS results: pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (CPS≥1)

Treatment	n	Number of events (%)	Median PFS (months) (95% CI)	PFS rate at months 6 in % (95% CI)	Pembrolizumab vs cetuximab+PLAT+5-FU	
					HR (95% CI)	p-value
All patients						
Pembrolizumab	257	228 (88.7)	3.2 (2.2 to 3.4)	28.7 (23.3 to 34.4)	1.13 (0.94 to 1.36)	0.8958§
Cetuximab+ PLAT+5-FU	255	237 (92.9)	5.0 (4.8 to 6.0)	43.9 (37.6 to 49.9)		
Patients whose cancer originated in the oral cavity						
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]		

§ One-sided p-value based on log-rank test
CI=confidence interval; CPS=combined positive score; HR=hazard ratio; PD-L1=programmed death-ligand 1; PFS=progression-free survival
Source: Table 9, Supplementary Document (July 2019); Table 195, Appendix S to the Supplementary Document (July 2019)

The ERG considers that HRs are not an appropriate measure of effect to summarise PFS data from the KEYNOTE-048 trial (see Section 4.5.2). For all patients and for patients whose cancer originated in the oral cavity, median PFS was longer for patients receiving cetuximab+PLAT+5-FU than for patients receiving pembrolizumab.

Objective response rate by blinded independent central review

A summary of the ORR results is provided in Table 12, and a summary of best objective response is provided in Table 13.

Table 12 Summary of ORR results: pembrolizumab monotherapy versus cetuximab+ PLAT+5-FU (CPS≥1)

Treatment	n	Number of objective responses	ORR (%) (95% CI)	Pembrolizumab vs cetuximab+PLAT+5-FU	
				Difference in % (95% CI)	p-value†
All patients					
Pembrolizumab	257	49	19.1 (14.5 to 24.4)	-15.9 (-23.4 to -8.3)	1.0000
Cetuximab+ PLAT+5-FU	255	89	34.9 (29.1 to 41.1)		
Patients whose cancer originated in the oral cavity					
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]		

† One-sided p-value for testing. H0: difference in % = 0 versus H1: difference in % > 0
CI=confidence interval; CPS=combined positive score; PD-L1=programmed death-ligand 1; ORR=objective response rate
Source: Table 11, Supplementary Document (July 2019); Table 197, Appendix S to the Supplementary Document (July 2019)

Table 13 Summary of best objective response: pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (CPS≥1)

	Pembrolizumab		Cetuximab+PLAT+5-FU	
	All patients (n=257)	Patients whose cancer originated in the oral cavity [redacted]	All patients (n=255)	Patients whose cancer originated in the oral cavity [redacted]
	n (%)	**n (%)**	**n (%)**	**n (%)**
Complete response (CR)	15 (5.8)	[redacted]	11(4.3)	[redacted]
Partial response (PR)	43 (16.7)	[redacted]	103 (40.4)	[redacted]
Objective response (CR+PR)	58 (22.6)	[redacted]	114 (44.7)	[redacted]
Stable disease	64 (24.9)	[redacted]	62 (24.3)	[redacted]
Progressive Disease (PD)	100 (38.9)	[redacted]	32 (12.5)	[redacted]
Non-CR/Non-PD	11 (4.3)	[redacted]	10 (3.9)	[redacted]
Not evaluable	4 (1.6)	[redacted]	1 (0.4)	[redacted]
No assessment	20 (7.8)	[redacted]	36 (14.1)	[redacted]

CPS=combined positive score; PD-L1=programmed death-ligand 1
Source: Table 12, Supplementary Document (July 2019); Table 198, Appendix S to the Supplementary Document (July 2019)

ORR was considerably higher in the cetuximab+PLAT+5-FU arm in comparison to the pembrolizumab arm for all patients and for patients whose cancer originated in the oral cavity. It is important to note that the reported p-values are one-sided; it is therefore not possible for the p-value to demonstrate a statistically significant difference in favour of cetuximab+PLAT+5-FU. The ERG notes that the 95% confidence interval for the difference in ORR between the two treatment arms only includes values favouring cetuximab+PLAT+5-FU.

Duration of response by blinded independent central review

A summary of the DoR results is provided in Table 14.

Table 14 Summary of DoR: pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (CPS≥1)

	Pembrolizumab	Cetuximab+ PLAT+5-FU
All patients		
Number of subjects with response† (total patients)	[redacted]	[redacted]
Time to response† (months)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
DoR (months)		
Median (range)*	[redacted]	[redacted]
Number (%‡) of subjects with extended response duration (≥6 months)	[redacted]	[redacted]
Patients whose cancer originated in the oral cavity		
Number of subjects with response† (total patients)	[redacted]	[redacted]
Time to response† (months)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
DoR (months)		
Median (range)*	[redacted]	[redacted]
Number (%‡) of subjects with extended response duration (≥6 months)	[redacted]	[redacted]

† Response: best objective response as confirmed complete response or partial response
* "+" indicates there is no progressive disease by the time of last disease assessment
CPS=combined positive score; DoR=duration of response; PD-L1=programmed death-ligand 1; SD=standard deviation
Source: Table 13, Supplementary Document (July 2019); Table 199, Appendix S to the Supplementary Document (July 2019)

Among those who responded, for all patients and for patients whose cancer originated in the oral cavity, median DoR was considerably longer for patients in the pembrolizumab monotherapy arm than for patients in the cetuximab+PLAT+5-FU arm. The ERG highlights that these median DoR values are based on very small numbers of patients, particularly in the pembrolizumab monotherapy arm.

4.6.2 Pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU

Overall survival

A summary of the OS results (unadjusted for subsequent anti-PD-1 treatment and adjusted for subsequent anti-PD-1 treatment via the simplified 2-stage method) are provided in Table 15.

Table 15 Summary of OS results: pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (CPS≥1)

Treatment	n	Number of events (%)	Median OS (months) (95% CI)	OS rate at month 12 in % (95% CI)	Pembrolizumab+PLAT+5-FU vs cetuximab+PLAT+5-FU	
					HR (95% CI)	p-value
Unadjusted for subsequent anti-PD-1 treatment, all patients						
Pembrolizumab+ PLAT+5-FU	242	177 (73.1)	13.6 (10.7 to 15.5)	55.0 (48.5 to 61.0)	0.65 (0.53 to 0.80)	0.00002[§]
Cetuximab+ PLAT+5-FU	235	213 (90.6)	10.4 (9.1 to 11.7)	43.5 (37.0 to 49.7)		
Adjusted for subsequent anti-PD-1 treatment via simplified 2-stage method, all patients						
Pembrolizumab+ PLAT+5-FU	242	177 (73.1)	13.6 (10.7 to 15.5)	55.0 (48.5 to 61.0)	0.62 (0.50 to 0.78)	Cox model: <0.0001[¶] Log-rank: <0.0001[‖]
Cetuximab+PLAT+5-FU 2-stage adjusted	235	213 (90.6)	10.3 (9.0 to 11.5)	43.0 (36.6 to 49.2)		
Unadjusted for subsequent anti-PD-1 treatment, patients whose cancer originated in the oral cavity						
Pembrolizumab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]		
Adjusted for subsequent anti-PD-1 treatment via simplified 2-stage method, patients whose cancer originated in the oral cavity						
Pembrolizumab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+PLAT+5-FU 2-stage adjusted	[redacted]	[redacted]	[redacted]	[redacted]		

[§] One-sided p-value based on log-rank test
[¶] Two-sided p-value based on Cox model, analysis not adjusted for treatment switch
[‖] Two-sided p-value based on log-rank test, analysis not adjusted for treatment switch
CI=confidence interval; CPS=combined positive score; HR=hazard ratio; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1
Source: Table 25 and Table 27, Supplementary Document (July 2019); Table 215 and Table 219, Appendix S to the Supplementary Document (July 2019)

The ERG considers that a HR is not an appropriate measure of effect to summarise OS data from the KEYNOTE-048 trial (see Section 4.5.2). The ERG notes that results from both the unadjusted analysis and the 2-stage adjusted analysis, for all patients and for patients whose cancer originated in the oral cavity suggest that median OS was longer for patients receiving pembrolizumab+PLAT+5-FU than for patients receiving cetuximab+PLAT+5-FU.

Progression-free survival by blinded independent central review

A summary of the PFS results is provided in Table 16.

Table 16 Summary of PFS results: pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (CPS≥1)

Treatment	n	Number of events (%)	Median PFS (months) (95% CI)	PFS rate at months 6 in % (95% CI)	Pembrolizumab+ PLAT+5-FU vs cetuximab+ PLAT+5-FU	
					HR (95% CI)	p-value
All patients						
Pembrolizumab+ PLAT+5-FU	242	212 (87.6)	5.1 (4.7 to 6.2)	44.9 (38.5 to 51.1)	0.84 (0.69 to 1.02)	0.0370[§]
Cetuximab+ PLAT+5-FU	235	221 (94.0)	5.0 (4.8 to 6.0)	43.3 (36.9 to 49.6)		
Patients whose cancer originated in the oral cavity						
Pembrolizumab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]		

[§] One-sided p-value based on log-rank test
CI=confidence interval; CPS=combined positive score; HR=hazard ratio; PD-L1=programmed death-ligand 1; PFS=progression-free survival
Source: Table 30, Supplementary Document (July 2019); Table 222, Appendix S to the Supplementary Document (July 2019)

The ERG considers that a HR is not an appropriate measure of effect to summarise PFS data from the KEYNOTE-048 trial (Section 4.5.2). For all patients and for patients whose cancer originated in the oral cavity, median PFS was similar between the two treatment arms.

Objective response rate by blinded independent central review

A summary of the ORR results is provided in

Table 17 and a summary of best objective response is provided in Table 18.

Table 17 Summary of ORR results: pembrolizumab+PLAT+5-FU versus cetuximab+ PLAT+5-FU (CPS≥1)

Treatment	n	Number of objective responses	ORR (%) (95% CI)	Pembrolizumab+ PLAT+5-FU vs cetuximab+ PLAT+5-FU	
				Difference in % (95% CI)	p-value[†]
All patients					
Pembrolizumab+ PLAT+5-FU	242	88	36.4 (30.3 to 42.8)	0.5 (-8.2 to 9.1)	0.4586
Cetuximab+ PLAT+5-FU	235	84	35.7 (29.6 to 42.2)		
Patients whose cancer originated in the oral cavity					
Pembrolizumab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+ PLAT+5-FU	[redacted]	[redacted]	[redacted]		

[†] One-sided p-value for testing. H0: difference in %=0 versus H1: difference in %>0
CI=confidence interval; CPS=combined positive score; PD-L1=programmed death-ligand 1; ORR=objective response rate
Source: Table 32, Supplementary Document (July 2019); Table 224, Appendix S to the Supplementary Document (July 2019)

Table 18 Summary of best objective response: pembrolizumab+ PLAT+5-FU versus cetuximab+PLAT+5-FU (CPS≥1)

	Pembrolizumab + PLAT+5-FU		Cetuximab+PLAT+5-FU	
	All patients (n=242)	Oral cavity patients [redacted]	All patients (n=235)	Oral cavity patients [redacted]
	n (%)	n (%)	n (%)	n (%)
Complete response (CR)	18 (7.4)	[redacted]	11 (4.7)	[redacted]
Partial response (PR)	85 (35.1)	[redacted]	94 (40.0)	[redacted]
Objective response (CR+PR)	103 (42.6)	[redacted]	105 (44.7)	[redacted]
Stable disease	52 (21.5)	[redacted]	59 (25.1)	[redacted]
Progressive Disease (PD)	41 (16.9)	[redacted]	28 (11.9)	[redacted]
Non-CR/Non-PD	11 (4.5)	[redacted]	8 (3.4)	[redacted]
Not evaluable	2 (0.8)	[redacted]	1 (0.4)	[redacted]
No assessment	33 (13.6)	[redacted]	34 (14.5)	[redacted]

CPS=combined positive score; PD-L1=programmed death-ligand 1
Source: Table 33, Supplementary Document (July 2019); Table 225, Appendix S to the Supplementary Document (July 2019)

The results suggest that, for all patients and for patients whose cancer originated in the oral cavity, pembrolizumab+PLAT+5-FU has little effect on ORR in comparison to cetuximab+PLAT+5-FU There were no important differences in terms of best objective response between the two treatment arms.

Duration of response by blinded independent central review

A summary of the DoR results is provided in Table 19.

Table 19 Summary of DoR: pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (oral cavity patients, CPS≥1)

	Pembrolizumab+ PLAT+5-FU	Cetuximab+PLAT+5-FU
All patients		
Number of subjects with response† (total patients)	[redacted]	[redacted]
Time to response† (months)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
DoR (months)		
Median (range)*	[redacted]	[redacted]
Number (%‡) of subjects with extended response duration (≥6 months)	[redacted]	[redacted]
Patients whose cancer originated in the oral cavity		
Number of subjects with response† (total patients)	[redacted]	[redacted]
Time to response† (months)		
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
DoR (months)		
Median (range)*	[redacted]	[redacted]
Number (%‡) of subjects with extended response duration (≥6 months)	[redacted]	[redacted]

† Response: best objective response as confirmed complete response or partial response
* "+" indicates there is no progressive disease by the time of last disease assessmentCPS=combined positive score; DoR=duration of response; PD-L1=programmed death-ligand 1; SD=standard deviation
Source: Table 34, Supplementary Document (July 2019); Table 226, Appendix S to the Supplementary Document (July 2019)

Among those who responded, for all patients and for patients whose cancer originated in the oral cavity, median DoR was longer for patients in the pembrolizumab+ PLAT+5-FU arm than for patients in the cetuximab+ PLAT+5-FU arm. The ERG highlights that these median DoR values are based on relatively small numbers of patients who responded in both treatment arms.

4.7 Adverse events

The company provides an overview of safety data from the KEYNOTE-048 trial in Section B.2.10 of the Supplementary Document (July 2019). The company has reported summary AE data that are relevant to the CPS≥1 subgroup from the KEYNOTE-048 trial; however, data for the specific AEs experienced by patients in the CPS≥1 subgroup are not presented in the CS.

Full details of the specific AEs reported for the overall trial population are provided in Appendix F of the Supplementary Document (July 2019). Data relevant to the overall trial population for individual drug-related AEs, Grade 3 to Grade 5 drug-related AEs, drug-related serious adverse events (SAE) and adverse events of special interest (AEOSI) are discussed briefly in the text of this ERG report and supporting tables are presented in Appendix 2 and Appendix 3 of this ERG report.

4.7.1 Pembrolizumab monotherapy

For the comparison of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU, the ERG agrees with the company that the proportions of patients who reported AEs in the overall safety population (96.7% and 99.7% respectively) and in the CPS≥1 population (96.9% and 99.6% respectively) are similar in each treatment arm (Table 20).

The company reports that patients with CPS≥1 in the pembrolizumab monotherapy arm of the KEYNOTE-048 trial reported lower rates of all categories of AEs compared with patients with CPS≥1 treated with cetuximab+PLAT+5-FU. The ERG agrees with the company but notes that similar proportions of patients in both arms experienced serious AEs (41.4% and 49.4%), similar numbers of patients died (7% and 11.4%) and similar numbers of patients died due to a drug-related AE (1.2% and 3.3%). Additional AE data are presented for patients with CPS≥1 in Table 20.

Table 20 Summary of adverse events: pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (CPS≥1)

Adverse event category	CPS≥1 subgroup				
	Pembrolizumab monotherapy		Cetuximab +PLAT+5-FU		Difference in % vs control arm
	n	(%)	n	(%)	Estimate (95% CI)
Number of patients	256		245		
One or more adverse events	248	(96.9)	244	(99.6)	-2.7 (-5.7 to -0.5)
No adverse event	8	(3.1)	1	(0.4)	2.7 (0.5 to 5.7)
Drug-related adverse events	152	(59.4)	236	(96.3)	-37.0 (-43.4 to -30.5)
Grade 3 to 5 adverse events	140	(54.57)	203	(82.9)	-28.2 (-35.7 to -20.3)
Grade 3 to 5 drug-related adverse events	46	(18.0)	167	(68.2)	-50.2 (-57.3 to -42.4)
Serious adverse events	106	(41.4)	121	(49.4)	-8.0 (-16.6 to -0.7)
Serious drug-related adverse events	28	(10.9)	59	(24.1)	-13.1 (-19.8 to -6.6)
Dose modification due to an adverse event	100	(39.1)	206	(84.1)	-45.0 (-52.2 to -37.2)
Deaths	18	(7.0)	28	(11.4)	-4.4 (-9.7 to 0.7)
Death due to a drug-related adverse event	3	(1.2)	8	(3.3)	-2.1 (-5.3 to 0.6)
Drug discontinuation due to an adverse event	30	(11.7)	67	(27.3)	-15.6 (-22.5 to -8.8)
Drug discontinuation due to a drug-related adverse event	15	(5.9)	48	(19.6)	-13.7 (-19.7 to -8.1)
Drug discontinuation due to a serious adverse event	23	(9.0)	45	(18.4)	-9.4 (-15.5 to -3.4)
Drug discontinuation due to a serious drug-related adverse event	9	(3.5)	25	(10.2)	-6.7 (-11.5 to -2.4)

Source: Table 46, Supplementary Document (July 2019)

Specific adverse events (overall trial population: pembrolizumab monotherapy vs cetuximab+PLAT+5-FU)

Drug-related adverse events

The data in Table 58 (Appendix 2) show that in the overall trial population, the most frequently occurring drug-related AEs (incidence of ≥5%) in the pembrolizumab arm were fatigue (14.3%), hypothyroidism (13.0%), rash (8.3%), pruritis (7.3%), decreased appetite (5.3%) and diarrhoea (5.7%). The most frequently occurring AEs in the cetuximab+PLAT+5-FU arm were nausea (45.6%), anaemia (41.1%), hypomagnesaemia (33.1%), rash (35.2%) and neutropenia (31.4%). The ERG agrees with the company that, with the exception of hypothyroidism, all other types of drug-related AEs were more frequently reported in the cetuximab+PLAT+5-FU arm compared with pembrolizumab monotherapy.

Grade 3-5 drug-related adverse events

The data in Table 59 (Appendix 2) show that in the overall trial population, the most frequently occurring drug-related Grade 3 to Grade 5 AEs (incidence of ≥5%) in the pembrolizumab arm were hyponatraemia (2.0%), pneumonitis (1.3%), fatigue (1.0%), anaemia (0.7%), mucosal inflammation (0.7%) and rash (0.7%). The most frequently occurring AEs in the cetuximab+PLAT+5-FU arm were neutropenia (20.2%), anaemia (15%), neutrophil count decrease (12.2%), thrombocytopaenia (8.4%) and rash (5.9%). The ERG agrees with the company (Supplementary Document, Section B.2.10.1) that, compared with the pembrolizumab monotherapy arm, rates of all Grade 3 to Grade 5 drug-related AEs were greater in the cetuximab+PLAT+5-FU arm.

Drug-related serious adverse events

The data in Table 60 (Appendix 2) show that fewer patients in the pembrolizumab monotherapy arm experienced a SAE (incidence of ≥1%) compared with the cetuximab+PLAT+5-FU arm (9.3% vs 25.1%). The SAEs reported in the pembrolizumab arm were pneumonitis (1.0%), anaemia (0.3%), diarrhoea (0.3%), fatigue (0.3%) and pneumonia (0.3%). The most frequently reported SAEs in the cetuximab+PLAT+5-FU arm were febrile neutropenia (3.5%), anaemia (2.8%), pneumonia (2.4%) and nausea (2.4%).

Adverse events of special interest

Adverse events of special interest are defined in the updated CSR[29] (CSR, p8974) as AEs that are clinically consistent with the known safety profile of pembrolizumab and are likely to be of immune aetiology.

The ERG agrees with the company that:

- The rates of AEOSIs were similar in both arms of the trial (31.0% versus 23.7%)
- Patients in the pembrolizumab monotherapy arm had higher rates of hypothyroidism (18.0% versus 6.3%), pneumonitis (6.0% vs 1.0%) and hyperthyroidism (2.7% versus 1.0%) compared with patients in the cetuximab+PLAT+5-FU arm
- Patients in the cetuximab+PLAT+5-FU had higher rates of infusion reactions (9.4% versus 1.3%) and severe skin reactions (7.0% versus 2.7%) compared with patients in the pembrolizumab arm
- Fewer patients in the pembrolizumab arm discontinued treatment due to a drug-related AEOSI (2.7% versus 6.6%) compared with patients in the with cetuximab+PLAT+5-FU arm.

Summary of adverse events: pembrolizumab monotherapy versus cetuximab+PLAT+5-FU

The company states that in the CPS≥1 population, the AE profile of treatment with pembrolizumab monotherapy compares favourably with that of treatment with cetuximab+PLAT+5-FU and that, in the KEYNOTE-048 trial, pembrolizumab monotherapy was associated with lower rates of treatment discontinuation than cetuximab+PLAT+5-FU.

For the overall trial population, the company also notes that the incidences and types of AEOSIs reported during the KEYNOTE-048 trial were in line with those reported in other trials of pembrolizumab monotherapy.

4.7.2 Pembrolizumab+PLAT+5-FU

For the comparison of pemborolizumab+PLAT+5-FU versus cetuximab, the ERG agrees with the company that the proportions of patients who reported AEs in the overall trial safety population (98.2% and 99.7%) and in the CPS≥1 population (98.3% and 99.6% respectively) were similar in each treatment arm (Table 21).

The ERG notes that in the CPS≥1 population, patients in the pembrolizumab+PLAT+5-FU arm generally experienced higher rates of all categories of AEs when compared with patients treated with cetuximab+PLAT+5-FU (Table 21).

Table 21 Summary of adverse events: pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (CPS≥1)

Adverse event category	CPS≥1 subgroup				
	Pembrolizumab +PLAT+5-FU		Cetuximab +PLAT+5-FU		Difference in % vs control arm
	n	(%)	n	(%)	Estimate (95% CI)
Number of patients	237		245		
One or more adverse events	233	(98.3)	244	(99.6)	-1.3 (-3.9 to 0.8)
No adverse event	4	(1.7)	1	(0.4)	1.3 (-0.8 to 3.9)
Drug-related adverse events	227	(95.8)	236	(96.3)	-0.5 (-4.4 to 3.2)
Grade 3 to 5 adverse events	203	(85.7)	203	(82.9)	2.8 (-3.8 to 9.4)
Grade 3 to 5 drug-related adverse events	173	(73.0)	167	(68.2)	4.8 (-3.3 to 12.9)
Serious adverse events	150	(63.3)	121	(49.4)	13.9 (5.0 to 22.5)
Serious drug-related adverse events	96	(40.5)	59	(24.1)	16.4 (8.1 to 24.6)
Dose modification due to an adverse event	203	(85.7)	206	(84.1)	1.6 (-4.9 to 8.0)
Deaths	30	(12.7)	28	(11.4)	1.6 (-4.9 to 8.0)
Death due to a drug-related adverse event	9	(3.8)	8	(3.3)	0.5 (-3.0 to 4.2)
Drug discontinuation due to an adverse event	82	(34.6)	67	(27.3)	7.3 (-1.0 to 15.5)
Drug discontinuation due to a drug-related adverse event	62	(26.2)	48	(19.6)	6.6 (-0.9 to 14.1)
Drug discontinuation drug due to a serious adverse event	55	(23.2)	45	(18.4)	4.8 (-2.4 to 12.1)
Drug discontinuation due to a serious drug-related adverse event	33	(13.9)	25	(10.2)	3.7 (-2.1 to 9.7)

AE=adverse event
Source: Table 47, Supplementary Document (July 2019)

Specific adverse events (overall trial population: pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU)

Drug-related adverse events

The data in Table 61 (Appendix 3) show that in the overall trial population, the most frequently occurring drug-related AEs (incidence of ≥5%) in the pembrolizumab+PLAT+5-FU arm were anaemia (48.6%), nausea (45.3%), neutropenia (33.0%), fatigue (30.4%), mucosal inflammation (27.9%), thrombocytopenia (27.2%) and vomiting (27.2%). The most frequently occurring drug-related AEs in the cetuximab+PLAT+5-FU arm were nausea (45.6%), anaemia (41.1%), hypomagnesaemia (33.1%), neutropenia (31.0%) and fatigue (28.9%).

Grade 3-5 drug-related adverse events

The data in Table 62 (Appendix 3) show that in the overall trial population, the most frequently occurring drug-related Grade 3 to Grade 5 AEs (incidence of ≥1%) in the pembrolizumab+PLAT+5-FU arm were anaemia (19.6%), neutropenia (17.8%), decreased neutrophil count (9.8%), mucosal inflammation (9.4%), thrombocytopenia (8.7%). The most frequently occurring AEs in the cetuximab+PLAT+5-FU arm were neutropenia (20.2%), anaemia (15.0%), decreased neutrophil count (12.2%) and thrombocytopaenia (8.4%). The ERG agrees with the company that, compared with the pembrolizumab+PLAT+5-FU arm, rates of all Grade 3 to Grade 5 drug-related AEs were similar in the cetuximab+PLAT+5-FU arm.

Drug-related serious adverse events

The data in Table 63 (Appendix 3) show that more patients in the pembrolizumab+PLAT+5-FU arm experienced a SAE (incidence of ≥1%) compared with the cetuximab+PLAT+5-FU arm (37.0% versus 25.1%). The SAEs most frequently reported in the pembrolizumab+PLAT+5-FU arm were febrile neutropenia (5.4%), anaemia (4.0%), stomatitis (2.9%), neutropenia (2.2%), mucosal inflammation (2.2%), nausea (2.2%), septic shock (2.2%), and thrombocytopenia (2.2%). The most frequently reported SAEs in the cetuximab+PLAT+5-FU arm were febrile neutropenia (3.5%), anaemia (2.8%), nausea (2.4%) and pneumonia (2.4%).

Adverse events of special interest

The ERG agrees with the company that:

- The rates of AEOSIs were similar in both arms of the trial (26.4% versus 23.7%)
- Patients in the pembrolizumab+PLAT+5-FU arm had higher rates of hypothyroidism (15.9% versus 6.3%), pneumonitis (5.4% vs 1.0%), hyperthyroidism (4.3% versus 1.0%) and colitis compared with patients in the cetuximab+PLAT+5-FU arm
- Patients in the pembrolizumab+PLAT+5-FU arm had lower rates of infusion reactions (2.2% versus 9.4%) and severe skin reactions (0.7% versus 7.0%) compared with patients in the cetuximab+PLAT+5-FU arm
- Fewer patients in the pembrolizumab+PLAT+5-FU arm discontinued treatment due to a drug-related AEOSI (3.3% versus 6.6%) than patients in the cetuximab+PLAT+5-FU arm.
- Most of the AEOSIs in the pembrolizumab+PLAT+5-FU arm were Grade 1 and 2, whereas in the cetuximab+PLAT+5-FU arm, AEOSIs were generally Grade 2 and 3.

Summary of adverse events: pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU

The company reports that in the overall trial population, the AEs arising during treatment with pembrolizumab+PLAT+5-FU in the KEYNOTE-048 trial were consistent with AEs known to be associated with pembrolizumab and with platinum+5-FU. The company also reports that treatment with pembrolizumab+PLA+5-FU did not increase the frequency or severity of key chemotherapy-related AEs (neutropenia, anaemia and thrombocytopenia).

The ERG agrees with the company's summary that similar rates of AEs occurred in the pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU arms for most categories of AEs in the KEYNOTE-048 trial (all AEs, drug-related AEs, Grade 3 to 5 AEs, AEs leading to dose reduction, death due to AEs and AEs leading to treatment discontinuation); however, there were more SAEs and drug-related SAEs reported by patients in the pembrolizumab+PLAT+5-FU arm.

4.8 Health-related quality of life

The company reports (CS, p56) that HRQoL outcomes were measured during the KEYNOTE-048 trial using the European Quality of Life-5 Dimensions-3 level (EQ-5D-3L[33]) questionnaire and the European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life – Core 30 (QLQ-C30[34]) questionnaire with the QLQ-H&N35[35] head and neck cancer module.

The company states (CS, p191) that the data collection schedule for all questionnaires was Day 1 of cycle 1 (baseline), day 1 of each subsequent treatment cycle, at the treatment discontinuation visit and 30 days after the last dose of study medication (+/- 3 days).

4.8.1 EQ-5D-3L

Pembrolizumab monotherapy versus cetuximab+PLAT+5-FU

The company reports (Supplementary Document [July 2019], p46) that at Week 15, the utility and VAS results for patients treated with pembrolizumab monotherapy and patients treated with cetuximab+PLAT+5-FU were [redacted] (Table 22 and Table 23).

Table 22 Analysis of change from baseline of EQ-5D VAS at Week 15, pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (CPS≥1 population)

Treatment	Baseline		Week 15		Change from baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison				Difference in LS Means (95% CI)		p-value
Pembrolizumab vs cetuximab+PLAT+5-FU				[redacted]		[redacted]

CI=confidence interval; LS=least squares; SD=standard deviation
Source: Table 20, Supplementary Document (July 2019)

Table 23 Analysis of change from baseline of EQ-5D utility score (using European Algorithm) at Week 15, pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (CPS≥1 population)

Treatment	Baseline		Week 15		Change from baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison				Difference in LS Means (95% CI)		p-value
Pembrolizumab vs cetuximab+PLAT+5-FU				[redacted]		[redacted]

CI=confidence interval; LS=least squares; SD=standard deviation
Source: Table 19 Supplementary Document (July 2019)

Pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU

The company reports (CS, p114) that up to Week 15, the scores for patients treated with pembrolizumab+PLAT+5-FU and patients treated with cetuximab+PLAT+5-FU were [redacted] for both the VAS and utility measures (Table 24 and

Table 25).

Table 24 Analysis of change from baseline of EQ-5D VAS at Week 15, pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (CPS≥1 population)

Treatment	Baseline		Week 15		Change from baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
Pembrolizumab+PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison				Difference in LS Means (95% CI)		p-value
Pembrolizumab+PLAT+5-FU vs cetuximab+PLAT+5-FU				[redacted]		[redacted]

CI=confidence interval; LS=least squares; SD=standard deviation
Source: Table 41, Supplementary Document (July 2019)

Table 25 Analysis of change from baseline of EQ-5D utility score (using European Algorithm) at Week 15, pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (CPS≥1 population)

Treatment	Baseline		Week 15		Change from baseline at Week 15	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)
Pembrolizumab+PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cetuximab+PLAT+5-FU	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pairwise comparison			Difference in LS Means (95% CI)			p-value
Pembrolizumab+PLAT+5-FU vs cetuximab+PLAT+5-FU				[redacted]		[redacted]

CI=confidence interval; LS=least squares; SD=standard deviation
Source: Table 40, Supplementary Document (July 2019)

4.8.2 EORTC QLQ-C30 and QLQ-H&N35

Pembrolizumab monotherapy versus cetuximab+PLAT+5-FU

The company reports (Supplementary Document [July 2019], p35) that for patients treated with pembrolizumab monotherapy and cetuximab+PLAT+5-FU:

- the baseline scores for the EORTC QLQ-C30 questionnaire were similar between groups
- at Week 15, [redacted] were noted between the two treatment groups. The overall results for the EORTC QLQ-C30 [redacted] in the pembrolizumab monotherapy arm ([redacted](LS mean=[redacted])
- at week 15, the difference in LS means between the two treatment groups was [redacted]
- time to deterioration scores measured using the EORTC QLQ-C30 questionnaire were [redacted]
- EORTC QLQ-C30 scores [redacted] over time in both treatment groups (up to Week 51)
- time to deterioration scores measured by the EORTC QLQ-C30 were [redacted] between treatment arms ([redacted])
- time to deterioration scores measured by the QLQ-H&N35 pain score ([redacted]) and swallowing score ([redacted]) were [redacted] between treatment arms

Pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU

The company reports (Supplementary Document [July 2019], p74) that for patients treated with pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU:

- [redacted] scores were recorded over 15 weeks of follow up using the QLQ-C30 measure

- mean change from baseline as measured by the QLQ-C30 questionnaire [redacted] in the pembrolizumab+PLAT+5-FU arm (LS mean=[redacted] and the cetuximab+PLAT+5-FU arm (LS mean=[redacted])
- the difference in LS means (QLQ-C30) at Week 15 was [redacted])
- global health status scores (QLQ-C30) [redacted] over time in both treatment arms (up to Week 51)
- the comparison of time to deterioration scores (QLQ-C30) showed [redacted] in both treatment arms ([redacted])
- time to deterioration scores measured by the QLQ-H&N35 pain score ([redacted]) and swallowing score ([redacted]) were [redacted] between treatment arms.

4.9 ERG critique of the indirect evidence

Due to a lack of direct evidence for the comparison of treatment with pembrolizumab (monotherapy or combination therapy) with platinum-based chemotherapy regimens, the company conducted NMAs to obtain indirect estimates of clinical effectiveness for these comparisons.

4.9.1 Methodological approach to the network meta-analyses

The company's base case NMA for the outcome of OS incorporates data from the KEYNOTE-048 trial that were adjusted for subsequent therapy using the 2-stage method (see Section 4.5.3 of this ERG report). The company also performed sensitivity analyses that incorporated unadjusted OS data and data adjusted using the RPSFTM and the IPCW method. However, the ERG does not consider that either the RPSFTM or IPCW method are appropriate methods of adjusting for the effect of subsequent therapy in the KEYNOTE-048 trial (see Section 4.5.3 of this ERG report), and therefore does not consider the results of these sensitivity analyses in this ERG report.

The company performed NMAs for the outcomes of PFS and OS using methods that allowed for time-varying HRs. The company adopted this approach as performing NMAs that incorporate constant HRs relies on the assumption of PH within trials included in the network. The company highlights (CS, p119) that the PH assumption is violated for both OS data and PFS data from the KEYNOTE-048 trial for both the comparisons of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (see Section 4.5.2 of this ERG report). The ERG agrees with the company's assessment of PH and agrees with the company's decision that performing NMAs using methods that allow for time-varying HRs is more appropriate than performing NMAs based on constant HRs.

The company used a method developed by Jansen[36] to model hazard functions of the interventions in each trial using known parametric survival functions, such as the Weibull and Gompertz survival functions, or fractional polynomials. A multidimensional treatment effect can be estimated for each trial and incorporated into an NMA. To implement Jansen's method, the company required K-M OS and PFS data for each intervention from each trial. These data were available from the KEYNOTE-048 trial and the company obtained data from the other trials by digitising the K-M data presented in the published papers.

The company considered using the following survival functions to model hazard functions: Weibull, Gompertz, and second order fractional polynomials including p1=0 or 1 and p2=-1, 0.5, 0, 0.5, or 1. The company inspected the deviance information criteria (DIC) to compare the goodness-of-fit of competing survival models and considered a difference in DIC of 5 points to be meaningful. The company states that they also considered the plausibility of the HRs estimated by the models as part of the model selection process (Appendix D to the CS, p61), although details of this assessment process were not provided in the CS.

In Appendix D to the CS (p60) it is stated that when using second order fractional polynomials to model hazard functions, the company assessed models that assume 1) treatment only has an impact on two of the three hazard function parameters (i.e., one scale and one shape parameter), and 2) treatment has an impact on all three hazard function parameters (i.e., one scale and two shape parameters). It is not clear to the ERG how the company assessed both types of model; in the model selection results provided in Appendix D to the CS (pp74-88), no differentiation between these types of model is provided.

All analyses were performed in a Bayesian framework, using non-informative priors for both mean hazards and treatment effects. As most treatment comparisons were informed by only one trial, it would have been difficult for a model to estimate between study heterogeneity and, therefore, the company used fixed-effects models rather than random-effects models. The ERG considers the company's use of fixed-effects models rather than random-effects models was appropriate.

4.9.2 Studies identified for inclusion in the network meta-analyses

The search carried out as part of the company's literature review (SLR) described in Appendix D of the CS was used to identify studies that could be included in the indirect comparisons. The company's SLR identified studies conducted in both first-line treatment (1L) and in platinum/chemotherapy progressed (PCP) populations; however, only studies conducted in the 1L population are of relevance to this STA. Furthermore, the company noted that across the trials conducted in the 1L population, eligibility criteria and patient characteristics differed

substantially. The company, therefore, constructed a tier system to classify 1L studies, with Tier 1 indicating the most strictly defined 1L population, and Tier 3 indicating the least strictly defined 1L population (Table 26)

Table 26 Tier system for classification of trials (1L patient population)

Tier	Definition
1	No prior systemic therapy in the R/M setting; systemic therapy for LA disease allowed if received >6 months before study entry
2	No prior systemic therapy in the R/M setting; systemic therapy for LA disease allowed if received >3 months before study entry
3	All patients in the R/M setting; no timeframe or setting provided for previous exposure to systemic therapy; ≤20% with prior systemic therapy in the trial

1L=first-line setting; LA=locally advanced; R/M=recurrent and/or metastatic
Source: Appendix D to the CS, Table 10

In total, 80 RCTs were identified by the company's SLR. However, only 29 RCTs were conducted in 1L populations: 21 RCTs were Tier 1, five RCTs were Tier 2, and three RCTs were Tier 3. Of these 29 RCTs, nine trials formed a connected network (seven Tier 1 trials: KEYNOTE-048, Jacobs 1992,[28] Hong 1983,[37] Forastiere 1992,[25] E1395,[27] EXTREME124[20] and B490; EXTREME124[20] and B490;[23] two Tier 2 trials: Burtness 2005[24] and CETMET[26]).

However, the company subsequently decided to exclude studies that were published before 1990 from the NMAs, with the justification that *"investigation procedures, data collection methods, and the general accuracy of the reported data are likely to have been different in those older studies than the ones from the more recent trials"* (Appendix D to the CS, p43). As a result, Hong 1983[37] was excluded from the NMAs. Consequently, the "final full network", which was used in the company's base case NMAs, included eight RCTs. Clinical advice to the ERG is that it is not appropriate to exclude studies based on date assuming poor quality and inaccuracies of reporting.

For the KEYNOTE-048 trial, the company used data (Supplementary Document [July 2019]) from the PD-L1 CPS≥1 subgroup of patients; for all other trials, the company used data from the overall trial populations. Clinical effectiveness evidence for patients with PD-L1 CPS≥1 disease treated with pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU, and cetuximab+PLAT+5-FU were available from the KEYNOTE-048 trial. The company assumed that, for all other treatments in the networks, effectiveness results for patients with unknown PD-L1 disease status reflected effectiveness in a population with PD-L1 CPS≥1 disease.

The final full network is provided in Figure 2.

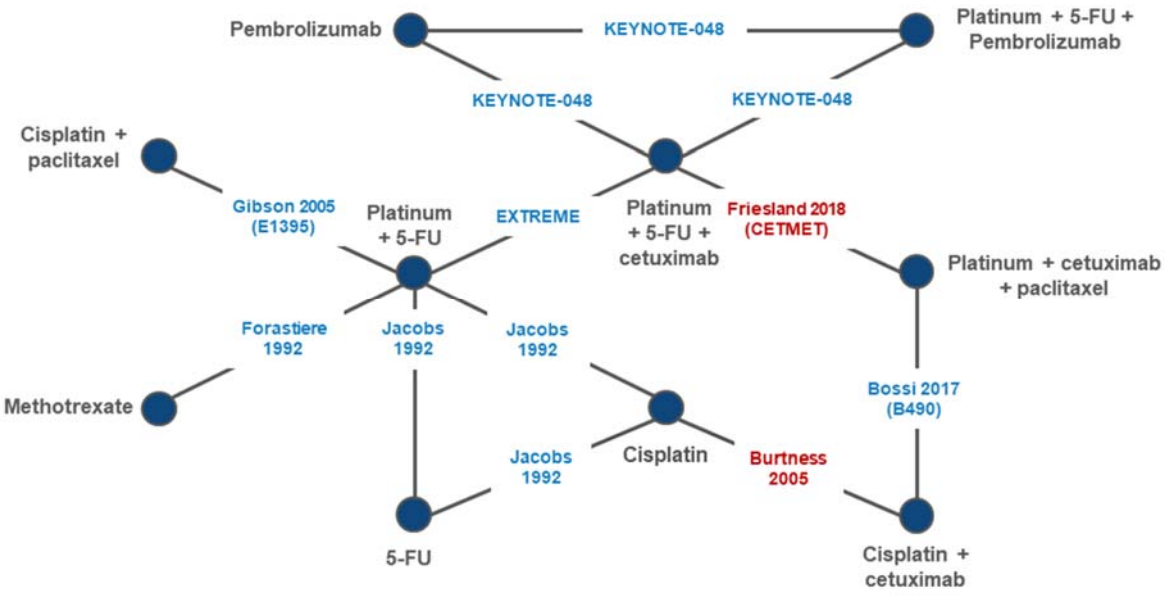

Figure 2 Final full network of RCTs used in the company's base-case NMAs

Trials in blue are Tier 1 trials, trials in red are Tier 2 trials
5-FU=fluorouracil; NMA=network meta-analysis; RCT=randomised controlled trial
Source: appendix D to the CS, Figure 5

4.9.3 Characteristics of studies included in the network meta-analyses

Key study characteristics and eligibility criteria

Key characteristics and eligibility criteria for the eight trials included in the company's final full network are summarised in Table 27.

Table 27 Summary of key trial characteristics and eligibility criteria for the eight trials included in the company's NMAs

Study	Phase	Masking	Eligible patients	PS	NPC	Prior chemotherapy
Tier 1 trials						
KEYNOTE-048	III	Open-label	R/M HNSCC patients ≥18 years old	ECOG 0-1	Excluded	Not allowed in the R/M setting. Allowed if received in the LA setting ≥6 months BSE
B490[23]	II	Open-label	R/M HNSCC patients >18 years old	ECOG 0-1	Excluded	No prior systemic chemotherapy or biologic therapy during the last 6 months; no previous therapy for R/M disease
E1395[27]	III	Not stated	HNSCC patients ≥18 years old who are not curable with surgery or RT	ECOG 0-1	Excluded	Not allowed for recurrent disease. Allowed if delivered as part of initial curative therapy (treatment with paclitaxel or FU had to be completed ≥12 months BSE and treatment with cisplatin had to be completed ≥6 months BSE)
EXTREME[20]	III	Open-label	HNSCC patients ≥18 years old who are not eligible for local therapy	KPS ≥70	Excluded	Not allowed unless part of multimodal treatment for LA disease completed ≥6 months BSE
Forastiere 1992[25]	III	Not stated	HNSCC patients who are either recurrent after attempted cure with surgery and RT or newly diagnosed disease with distant metastases	ECOG 0-2	Not excluded	Not allowed for recurrent disease. Allowed if received in the LA setting ≥6 months BSE
Jacobs 1992[28]	III	Not stated	HNSCC patients ≥18 years old with recurrence after primary therapy or metastatic at diagnosis	ECOG 0-3	Not excluded	Not allowed in any setting
Tier 2 trials						
Burtness 2005[24]	III	Double-blind	HNSCC patients ≥18 years old who are recurrent after locoregional therapy or metastatic	ECOG 0-1	Not excluded	Not allowed in the R/M setting. Induction or adjuvant chemotherapy allowed if completed ≥3 months BSE
CETMET[26]	II	Open-label	R/M HNSCC patients >18 years old	ECOG 0-1	Excluded	Not allowed in the R/M setting or if completed in the LA setting <3 months BSE

BSE=before study entry; ECOG=Eastern Cooperative Oncology Group; FU=fluorouracil; HNSCC=head and neck squamous cell carcinoma; KPS=Karnofsky performance status; LA=locally advanced; NMA=network meta-analysis; NPC=nasopharyngeal carcinoma; PS=performance status; RT=radiotherapy; R/M=recurrent and/or metastatic
Source: adapted from Table 16, Appendix D to the CS

All included studies were multi-centre RCTs and the majority were phase III trials. All trials enrolled patients with R/M HNSCC who had not received prior chemotherapy in the R/M disease setting. One trial (Jacobs 1992[28]) recruited patients who had never received prior chemotherapy. Five trials (KEYNOTE-048, Forastiere 1992,[25] E1395,[27] EXTREME,[20] and B490[23]) allowed patients to have received prior chemotherapy in the locally advanced disease setting if it had been completed more than 6 months prior to study entry. The Burtness 2005[24] and CETMET[26] trials allowed patients to have received prior chemotherapy in the locally advanced setting if it was completed more than 3 months prior to study entry.

In terms of performance status (PS), eligibility criteria were consistent across most of the included trials: KEYNOTE-048, E1395,[27] Burtness 2005,[24] B490,[23] and CETMET[26] all recruited patients with ECOG PS 0-1, while EXTREME[20] recruited patients with KPS≥70. The company states that ECOG PS 0-1 and KPS≥70 are equivalent; the ERG notes that this statement is in accordance with a conversion system provided by NICE in TA23.[38] The ERG also notes that in the European Society for Medical Oncology (ESMO) guidelines (Performance-Scales),[39] a KPS of 70 is considered equivalent to ECOG 2; however, this is of little concern as very few patients with KPS=70 were included in the EXTREME trial.[20] Patients with poorer PS were eligible for inclusion in Forastiere 1992[25] (ECOG PS 0-2) and Jacobs 1992[28] (ECOG PS 0-3).

The company provides a summary of the interventions investigated in the eight trials included in the company's NMAs in Table 17 of Appendix D to the CS. Overall, dosing and treatment schedules of the included interventions were comparable across trials.

Patient characteristics

Baseline characteristics for the patient populations of the included trials are presented in Table 28.

Table 28 Summary of patient baseline characteristics for trials included in the company's NMAs

Study	Treatment (N)	Age median (range)	Male n (%)	White n (%)	ECOG score n (%)				HPV n (%)	Recurrent n (%)	Metastatic n (%)
					0	1	2	3			
KEYNOTE-048 (PD-L1 CPS≥1)	Pembrolizumab+PLAT+5-FU (n=242)	61 (20-85)	188 (77.7)	178 (73.6)	92 (38)	150 (62)	0 (0)	0 (0)	+: 53 (21.9) -: 189 (78.1)	65 (26.9)	173 (71.5)
	Cetuximab+PLAT+5-FU (comparison with pembrolizumab+PLAT+5-FU) (n=235)	61 (24-84)	203 (86.4)	173 (73.6)	94 (40)	141 (60)	0 (0)	0 (0)	+: 50 (21.3) -: 185 (78.7)	78 (33.2)	154 (65.5)
	Pembrolizumab monotherapy (n=257)	62 (22-94)	209 (81.3)	188 (73.2)	104 (40.5)	153 (59.5)	0 (0)	0 (0)	+: 54 (21) -: 203 (79)	75 (29.2)	179 (69.6)
	Cetuximab+PLAT+5-FU (comparison with pembrolizumab monotherapy) (n=255)	61 (24-84)	220 (86.3)	189 (74.1)	101 (39.6)	154 (60.4)	0 (0)	0 (0)	+: 55 (21.6) -:200 (78.4)	84 (32.9)	168 (65.9)
EXTREME[20]	Cetuximab+PLAT+5-FU (n=222)	56	197 (89)	--	KPS (median, IQR): 80, 80-90				--	--	104 (47)
	PLAT+5-FU (n=220)	57	202 (92)		KPS (median, IQR): 80, 80-90				--	--	102 (46)
B490[23]	Cisplatin+cetuximab (n=100)	63 (41-83)	74 (74)	--	51 (51)	49 (49)	0 (0)	0 (0)	+: 6 (16.2) -: 6 (16.2) Miss: 25 (25)[a]	63 (63)	62 (62)
	Cisplatin+cetuximab+paclitaxel (n=91)	62 (33-77)	75 (82.4)		46 (50.6)	45 (49.5)	0 (0)	0 (0)	+: 7 (21.2) -: 10 (30.3) Miss: 16 (27.5)[a]	66 (72.6)	46 (50.6)
Burtness 2005[24]	Cisplatin (n=60)	58.3 (32-84)	50 (83.3)	--	24 (40)	36 (60)	0 (0)	0 (0)	--	56 (98.2)	35 (61.4)
	Cisplatin+cetuximab (n=57)	60.6 (40-86)	41 (71.9)		24 (42.1)	33 (57.9)	0 (0)	0 (0)	--	57 (95)	41 (68.3)
Forastiere 1992[25]	Cisplatin+5-FU (n=87)	61 (39-82)	76 (87)	67 (77)	63 (72)		24 (28)	0 (0)	--	81 (93)	6 (7)
	Carboplatin+5-FU (n=86)	61 (43-77)	71 (83)	71 (83)	61 (71)		25 (29)	0 (0)	--	82 (95)	4 (5)

Study	Treatment (N)	Age median (range)	Male n (%)	White n (%)	ECOG score n (%)				HPV n (%)	Recurrent n (%)	Metastatic n (%)
					0	1	2	3			
	Methotrexate (n=88)	60 (28-80)	73 (83)	68 (77)		63 (72)	25 (28)	0 (0)	--	80 (91)	8 (9)
CETMET[26]	Cetuximab+PLAT+5-FU (n=42)	59.1 (10)[b, c]	33 (78.6)	--	14 (34.1)	27 (65.9)	0 (0)	0 (0)	+: 11 (26.2) -: 24 (57.1) Miss: 7 (16.7)	41 (97.6)[d]	1 (2.4)
	Carboplatin+cetuximab+paclitaxel (n=43)	59.1 (7)[b, c]	26 (60.5)		15 (34.9)	27 (62.8)	1 (2.3)	0 (0)	+: 15 (34.9) -: 27 (62.8) Miss: 1 (2.3)	43 (100)[e]	0 (0)
E1395[27]	PLAT+5-FU (n=104)	61 (35-84)	87 (83.6)	83 (79.8)	29 (27.9)	74 (71.1)	1 (1)	--	--	90 (86.5)	63 (60.6)
	Cisplatin+paclitaxel (n=100)	61 (37-81)	78 (78)	77 (77)	25 (25)	75 (75)	0 (0)	--	--	89 (89)	52 (52)
Jacobs 1992[28]	Cisplatin (n=83)	59[b]	78 (94)	--		53 (63.9)		30 (36.1)	--	73 (88)	10 (12)
	5-FU (n=83)	58[b]	73 (88)			48 (57.8)		35 (42.2)	--	76 (91.6)	7 (8.4)
	Cisplatin+5-FU (n=79)	57[b]	75 (95)			50 (63.3)		29 (36.7)	--	70 (88.6)	9 (11.4)

Double-dashes indicate that the value was not reported.
a) HPV status was evaluated only in those with cancer of the oropharynx
b) Mean is reported
c) Standard deviation is reported
d) At least 41 patients are assumed to be recurrent (only one metastatic case was reported)
e) Since none of the patients had metastatic disease, all are assumed to be recurrent.
5-FU=fluorouracil; CPS=combined positive score; ECOG=Eastern Cooperative Oncology Group; HPV=human papillomavirus; IQR=interquartile range; KPS=Karnofsky performance status; miss=missing; NMA=network meta-analysis; PD-L1; programmed death-ligand 1
Source: adapted from Table 21, Appendix D to the CS

Overall, patients were similar in terms of age and sex across the trials included in the final full network of evidence. Race/ethnicity was only reported in three of the included trials; the percentage of Caucasians was comparable between these trials (73.6% in KEYNOTE-048; 78.9% in Forastiere 1992;[25] 78.4% in E1395[27]).

Trials were heterogenous in terms of the proportions of patients with metastatic disease, which ranged from 1.2% in the CETMET trial[26] to 69.0% in the KEYNOTE-048 trial (CPS. The proportion of patients with recurrent disease was also lower in the KEYNOTE-048 trial (29.7%) than in the other trials (range: 67.5% in the B490 trial[23] to 98.8% in the CETMET trial[26]).

There was also variability in terms of PS across the included studies. Based on the company's assumption that ECOG PS 0-1 is equivalent to KPS≥70, the proportion of patients with ECOG PS 0-1 ranged from 61.6% in Jacobs 1992[28] to 100% in the KEYNOTE-048, EXTREME,[20] Burtness 2005[24] and B490[23] trials. Clinical advice to the ERG is that a population of patients with ECOG PS 0-1 is not reflective of the real-life R/M HNSCC population.

HPV status was poorly reported across the included studies and clinical advice to the ERG is that HPV is now considered to be an important prognostic factor. No studies (except for the KEYNOTE-048 trial) reported smoking status. It is, therefore, not possible to assess the comparability of trials in terms of these patient characteristics.

The company also provided a summary of primary tumour location (CS, Appendix D, Table 22). With regards to tumour location, in four trials (KEYNOTE-048, Burtness 2005,[24] Jacobs 1992,[28] EXTREME[20]) the majority of patients had lesions in either the oral cavity or the oropharynx. In the CETMET trial,[26] the majority of patients had non-hypopharynx cancers. In the E1395 trial,[27] patients had various primary tumour locations including the hypopharynx, larynx, oropharynx and oral cavity. Little or no information on tumour location was reported in the B490[23] and Forastiere 1992[25] trials.

Reported outcomes

The company provides a summary of efficacy and safety results reported in the included studies in the CS (Appendix D, Table 19 and Table 20). These tables include results from the IA2 analysis of the KEYNOTE-048 trial. Notably, all trials reported on ORR, and all trials except for Jacobs 1992[28] reported results for adverse events. However, the company only presented NMA results for OS and PFS. The OS and PFS results from each trial included in the NMAs (including data from the final analysis of the KEYNOTE-048 trial) are summarised in Table 29.

Table 29 OS and PFS results from studies included in the NMAs

Regimen	Treatment	Study	N	OS,[a] median (95% CI)	PFS,[a] median (95% CI)
PD-1 inhibitor in combination	Pembrolizumab+PLAT+5-FU	KEYNOTE-048 (PD-L1 CPS≥1 subgroup)	242	13.6 (10.7 to15.5)	5.1 (4.7 to 6.2)
Single-agent PD-1 inhibitor	Pembrolizumab	KEYNOTE-048 (PD-L1 CPS≥1 subgroup)	257	12.3 (10.8 to 14.3)	3.2 (2.2 to 3.4)
Platinum-based combination chemotherapy	Cetuximab+PLAT+5-FU	KEYNOTE-048 (PD-L1 CPS≥1 subgroup, comparison with pembrolizumab+PLAT+5-FU)	235	10.3 (9.0 to 11.5)[b]	5.0 (4.8 to 6.0)
		KEYNOTE-048 (PD-L1 CPS≥1 subgroup, comparison with pembrolizumab monotherapy)	255	10.1 (9.0 to 11.5)[b]	5.0 (4.8 to 6.0)
		CETMET [26]	42	8.4 (5.3 to 11.5)	4.4 (2.9 to 5.9)
		EXTREME - Vermoken 2008 paper[19]	222	10.1 (8.6 to 11.2)	5.6 (5 to 6)
		EXTREME - 5 year survival results[20]	221	10.1 (8.6 to 11.2)	-
	Cisplatin+cetuximab	B490[23]	100	13 (10 to 16)	6 (5 to 7)
		Burtness 2005[24]	57	9.2 (7.1 to 12.1)	4.2 (3.7 to 5.6)
	Cisplatin+5-FU	Forastiere 1992[25]	87	6.6	-
		E1395[27]	104	8.7 (6.7 to 12.2)	-
		Jacobs 1992[28]	79	5.5 (4 to 8.8)	
		EXTREME - Vermoken 2008 paper[19]	220	7.4 (6.4 to 8.3)	3.3 (2.9 to 4.3)
		EXTREME - 5 year survival results[20]	220	7.4 (6.4 to 8.3)	-
	Carboplatin+5-FU	Forastiere 1992[25]	86	5	-
	Cisplatin+paclitaxel	E1395[27]	100	8.1 (6.1 to 10)	-
	Cisplatin+cetuximab+paclitaxel	B490[23]	91	11 (9 to 14)	7 (6 to 8)
	Carboplatin+cetuximab+paclitaxel	CETMET[26]	43	10.2 (5.4 to 15)	6.5 (4.8 to 8.2)
Platinum-based single-agent chemotherapy	Cisplatin	Burtness 2005[24]	60	8 (6.1 to 10.6)	2.7 (1.9 to 3.8)
		Jacobs 1992[28]	83	5 (4.1 to 7.2)	-
Non-platinum based single agent chemotherapy	5-FU	Jacobs 1992[28]	83	6.1 (4.6 to 7.2)	-
	Methotrexate	Forastiere 1992[25]	88	5.6	-

Double-dashes indicate that the value was not reported
[a] Survival rates, response durations, and their 95% CIs that were not reported in months were converted to months assuming (1 month = 365/12 days)
[b] Results from the 2-stage adjusted analysis of OS
5-FU=fluorouracil; CI=confidence interval; CPS=combined positive score; NMA=network meta-analysis; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival
Source: Appendix D to the CS, Table 19; Supplementary Document (July 2019), Table 6, Table 9, Table 27 and Table 30

All included studies presented K-M data for OS; there was some heterogeneity between trials in terms of median OS times. For example, median OS for patients receiving cisplatin+cetuximab was reported to be 13 months in the B490 trial[23] and 9.2 months in the Burtness 2005 trial.[24] Median OS for patients receiving cisplatin+5-FU ranged from 5.5 months in the Jacobs 1992 trial[28] to 8.7 months in the E1395 trial.[27] Median OS for patients receiving cisplatin monotherapy ranged from 5 months in the Jacobs 1992 trial[28] to 8 months in the Burtness 2005 trial.[24]

Only five trials reported K-M PFS data (KEYNOTE-048, EXTREME,[20] CETMET,[26] B490,[23] and Burtness 2005[24]). Median PFS results were reasonably comparable across trials for regimens for which PFS data were available from more than one trial.

Overall, the ERG considers that despite some heterogeneity in terms of patient characteristics and reported outcomes, it is reasonable to synthesise data from the studies in the NMAs.

4.9.4 Assessment of risk of bias of the trials included in the network meta-analyses

The company carried out risk of bias assessments for the eight trials included in the NMAs using the risk of bias assessment tool for RCTs recommended by the Cochrane Collaboration.[22] The results of the company's risk of bias assessments are provided in Table 30.

The ERG generally agrees with the company's assessment of the risk of bias assessment for the trials included in the company's NMAs. However, the ERG considers that the EXTREME trial[20] has an unclear risk of bias for the domain of 'any other risk of bias', as the EXTREME trial[20] was funded by a pharmaceutical company.

Table 30 Company's risk of bias assessment and ERG comment

Risk of bias criterion	KEYNOTE-048[13]	B490[23]	E1395[27]	EXTREME[20]	Forastiere 1992[25]	Jacobs 1992[28]	Burtness 2005[24]	CETMET[26]	ERG comment
Random sequence generation	Low	Low	Low	Low	Unclear	Low	Low	Unclear	Agree
Allocation concealment	Low	Unclear	Low	Low	Unclear	Low	Unclear	Unclear	Agree
Blinding of participants	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Agree
Blinding of outcome assessment	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Agree
Incomplete outcome data	Low	Low	Unclear	Low	Low	Unclear	Low	Unclear	Agree
Selective reporting	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low	Agree
Any other sources of bias	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	The EXTREME trial[20] was funded by a pharmaceutical company and is therefore considered to be at an unclear risk of bias.

Source: adapted from Table 23 (CS, Appendix)

4.9.5 Results from the network meta-analyses: pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and PLAT+5-FU

Overall survival

All eight trials included in the company's final full network reported K-M curves for OS, and so could be included in the company's NMA for OS. The company's model selection process identified the best fitting model for OS for the comparison of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and versus PLAT+5-FU to be the second-order fractional polynomial with p1=0 and p2=0.5. The company's model selection process identified the best fitting model for OS for the comparison of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and versus PLAT+5-FU to be the second-order fractional polynomial with p1=1 and p2=0.

Time-varying HRs for pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and PLAT+5-FU are provided in Table 31. The company also generated OS proportions over time for each treatment included in the final full network; these are summarised in Figure 22 and Figure 26 of Appendix S to the CS.

Table 31 Results of the NMA for OS; time-varying HRs for pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and PLAT+5-FU; PD-L1 CPS≥1 subgroup

Time point (month)	Pembrolizumab monotherapy		Pembrolizumab+PLAT+5-FU	
	Cetuximab+PLAT+5-FU	PLAT+5-FU	Cetuximab+PLAT+5-FU	PLAT+5-FU
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals
Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab monotherapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1.
CPS=combined positive score; HR=hazard ratio; NMA=network meta-analysis; OS=overall survival; PD-L1=programmed death ligand 1
Source: Supplementary Document (July 2019), Table 42 and Table 44

The results suggest that from month 6 onwards, pembrolizumab monotherapy statistically significantly improves OS in comparison to both cetuximab+PLAT+5-FU and PLAT+5-FU. The results also suggest that in the early stages of treatment (month 1 to month 6), pembrolizumab+PLAT+5-FU has little effect on OS in comparison to cetuximab+PLAT+5-FU. However, from 9 months onwards, the HRs demonstrate a statistically significant improvement in OS for pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. Similarly, for the comparison of pembrolizumab+PLAT+5-FU versus PLAT+5-FU, pembrolizumab is shown to statistically significantly improve OS from month 6 onwards.

Progression-free survival

Five trials included in the company's final full network (KEYNOTE-048, EXTREME,[20] CETMET,[26] B490,[23] and Burtness 2005[24]) reported K-M curves for PFS, and so could be included in the company's NMA for PFS. These five trials form networks for the comparisons of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and PLAT+5-FU; as shown in Figure 3 and Figure 4.

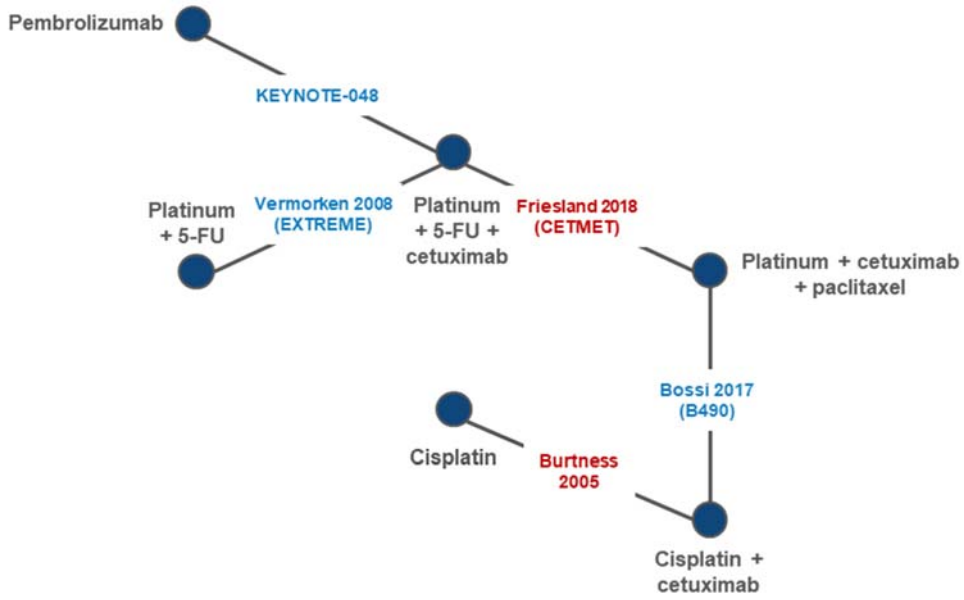

Figure 3 Network of trials used in the company's base-case NMA for PFS (pembrolizumab monotherapy versus comparators)

Trials in blue are Tier 1 trials, trials in red are Tier 2 trials
5-FU=fluorouracil; NMA=network-meta-analysis; PFS=progression-free survival

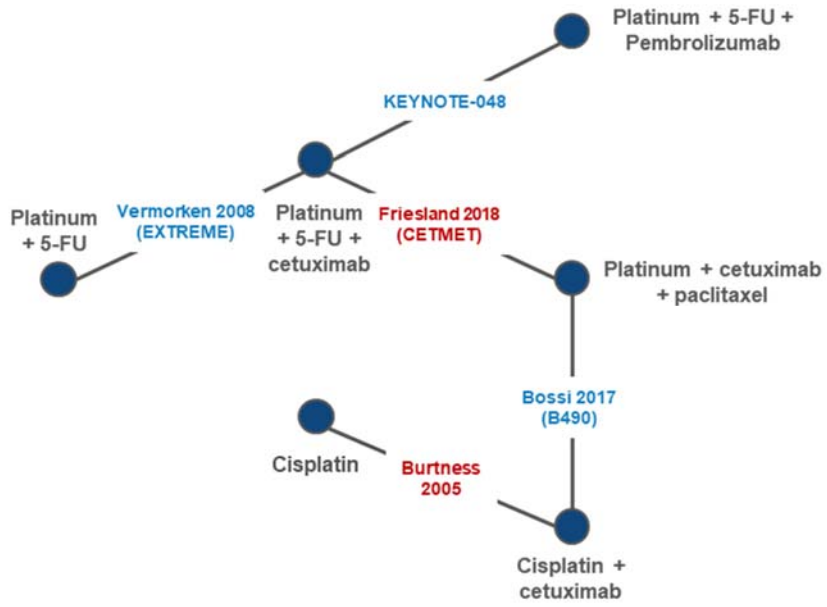

Figure 4 Network of trials used in the company's base-case NMA for PFS (pembrolizumab+PLAT+5-FU versus comparators)

Trials in blue are Tier 1 trials, trials in red are Tier 2 trials
5-FU=fluorouracil; NMA=network-meta-analysis; PFS=progression-free survival

The company's model selection process identified the best fitting model for PFS for the comparisons of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and versus PLAT+5-FU to be the second-order fractional polynomial with p1=0 and p2=-1, and for the comparisons of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and versus PLAT+5-FU to be the second-order fractional polynomial with p1=0 and p2=0.5.

Time-varying HRs for pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and PLAT+5-FU are provided in Table 32. The company also generated PFS proportions over time for each treatment included in the PFS network; these are summarised in Figure 24 and Figure 28 of Appendix S to the CS.

Table 32 Results of the NMA for PFS; time-varying HRs for pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and PLAT+5-FU; PD-L1 CPS≥1 subgroup

Time point (month)	Pembrolizumab monotherapy		Pembrolizumab+PLAT+5-FU	
	Cetuximab+PLAT+5-FU	PLAT+5-FU	Cetuximab+PLAT+5-FU	PLAT+5-FU
1	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
21	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
27	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
33	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]

Values in parentheses are credible intervals
Cells shaded in green indicate a statistically meaningful improvement with pembrolizumab monotherapy versus the comparator at the given timepoint, evidenced by a hazard ratio <1 and 95% credible intervals not crossing 1. Cells shaded in red indicate that pembrolizumab was less efficacious at the given time point
CPS=combined positive score; HR=hazard ratio; NMA=network meta-analysis; PD-L1=programmed death ligand 1; PFS=progression-free survival
Source: Supplementary Document (July 2019), Table 43

The results suggest that in the early stages of treatment (month 1 to month 3), pembrolizumab monotherapy is statistically significantly less efficacious than cetuximab+PLAT+5-FU in terms of PFS. However, the trend changes over time, with HRs favouring pembrolizumab monotherapy from 6 months (and statistically significant results from 9 months onwards). For the comparison of pembrolizumab monotherapy versus PLAT+5-FU, no differences are observed between the two treatments until month 6, when pembrolizumab monotherapy is shown to statistically significantly improve PFS from this time-point onwards.

The results also suggest that in the early stages of treatment (month 1 to month 3), pembrolizumab+PLAT+5-FU has little effect on PFS in comparison to cetuximab+PLAT+5-FU. However, from month 6 onwards, the HRs demonstrate a statistically significant improvement in PFS for pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. Similarly, for the comparison of pembrolixumab+PLAT+5-FU versus PLAT+5-FU, pembrolizumab+PLAT+5-FU is shown to statistically significantly improve OS from month 3 onwards.

4.9.6 ERG critique of the company's network meta-analyses

Generally, the ERG considers that the company's methodological approach to performing NMAs is appropriate and the ERG agrees that it is not suitable to summarise effectiveness for pembrolizumab (monotherapy or with PLAT+5-FU) in comparison with cetuximab+PLAT+5-FU or PLAT+5-FU using HRs that remain constant over time. Overall, the NMA results suggest that benefit from treatment with pembrolizumab (monotherapy or with PLAT+5-FU) in comparison to cetuximab+PLAT+5-FU or PLAT+5-FU is often not seen in the early stages of treatment. In fact, cetuximab+PLAT+5-FU was shown to statistically significantly improve PFS in comparison to pembrolizumab monotherapy in the early stages of treatment (month 1 to month 3).

The ERG has concerns about the usefulness and validity of the results of the company's NMAs. Firstly, the company states that they considered the plausibility of the HRs estimated by the FP models as part of the model selection process (Appendix D to the CS, p61), however no assessments of plausibility were provided in the CS and therefore the ERG is uncertain regarding the clinical plausibility of the results of the NMAs. Furthermore, the company states that they assessed two categories of second order FP models that assume 1) treatment only has an impact on two of the three hazard function parameters over time, and 2) treatment has an impact on all three hazard function parameters over time (Appendix D to the CS, p60). However, no information is provided in the CS on how these two categories of FP models were assessed. According to the methods described by Jansen,[36] treatment has an impact on all three hazard function parameters for all second order fractional polynomial models. Therefore, the ERG is unsure whether the second order FP models presented in the CS have been estimated correctly

Furthermore, for the KEYNOTE-048 trial, the company used data from the PD-L1 CPS≥1 subgroup of patients; for all other trials, the company used data from the overall trial populations. The ERG considers that this approach is likely to have introduced heterogeneity into the NMAs.

Finally, the company's NMAs do not provide results that are stratified by primary tumour location: oral cavity versus non-oral cavity. The majority of trials included in the NMAs include both patients with oral cavity cancer and non-oral cavity cancer (see Section 4.9.3 of this ERG report). Treatment with cetuximab+PLAT+5-FU is recommended by NICE for patients with R/M HNSCC whose cancer originated in the oral cavity. Clinical advice to the ERG suggests that the SoC for all other patients (non-oral cavity patients) with R/M HNSCC is treatment with PLAT+5-FU only.

In summary, the ERG considers that the company's NMAs do not provide any reliable evidence for pembrolizumab (monotherapy or with PLAT+5-FU) versus either of the relevant comparators in the relevant patient populations.

Network including only the KEYNOTE-048 and EXTREME trials

The ERG notes that a simple network could be formed including only data from the KEYNOTE-048 and EXTREME[20] trials which would allow comparisons between pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU, PLAT+5-FU, and cetuximab+PLAT+5-FU. However, it would be necessary to use methods which allow for time-varying HRs when estimating treatment effects within this network since the PH assumption is violated for survival data from the KEYNOTE-048 trial. Methods that allow for time-varying HRs involve the estimation of multiple parameters and a small network of only two trials may provide insufficient data to provide robust estimates of these parameters.

4.9.7 Survival evidence for patients treated with cetuximab+PLAT+5-FU and PLAT+5-FU

In this section of this ERG report, the ERG demonstrates how it is possible to obtain evidence for the comparisons of interest in this appraisal without using an NMA.

Patients whose cancer originated in the oral cavity

Treatment with cetuximab+PLAT+5-FU is recommended by NICE for patients with R/M HNSCC whose cancer originated in the oral cavity. Direct evidence of the effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU is available from the KEYNOTE-048 trial.

Clinical advice to the ERG is that many oral cavity patients will not be fit enough to receive cetuximab+PLAT+5-FU and that these patients will be prescribed PLAT+5-FU or will only receive best supportive care. However, as the company has only submitted trial evidence that relates only to those who **are** fit enough to receive cetuximab+PLAT+5-FU, all statistical (and economic) evidence presented in the CS and in this ERG report only relates to this group of patients.

Patients whose cancer did not originate in the oral cavity

As well as oral cavity patients, the KEYNOTE-048 trial also included patients whose cancer did not originate in the oral cavity (non-oral cavity patients); however, cetuximab+PLAT+5-FU is not recommended by NICE for treating this subgroup of patients. Clinical advice to the ERG is that the SoC for non-oral cavity patients is treatment with PLAT+5-FU only.

The company indirectly assessed the effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus PLAT+5-FU via NMAs (without any stratification for oral and non-oral cavity patients). However, the ERG considers that, based on evidence from the EXTREME trial (a multi-centre, phase III trial of cetuximab+PLAT+5-FU versus PLAT+5-FU in patients with R/M HNSCC), the clinical trial data used in an NMA should be stratified by oral and non-oral cavity patients or, ideally, separate NMAs should be carried out for oral and non-oral cavity patients. This is because survival results from the EXTREME trial (Table 33) show that median OS for oral cavity patients receiving PLAT+5-FU is approximately half that of non-oral cavity patients receiving PLAT+5-FU. To include oral and non-oral cavity patients without stratification in an NMA designed to estimate the effectiveness of PLAT+5-FU, a treatment which is only SoC for non-oral cavity patients, will, therefore, underestimate the true OS for non-oral cavity patients receiving PLAT+5-FU and overestimate the OS for oral cavity patients. As there is no published OS K-M data from the EXTREME trial for non-oral cavity patients, it is not possible to include results for this population in an NMA. As the EXTREME trial was the landmark trial of cetuximab+PLAT+5-FU compared to PLAT+5-FU in patients with R/M HNSCC, the ERG considers that any NMA that excluded this trial would be critically flawed.

Table 33 Survival results from the EXTREME trial

Subgroup	OS cetuximab+PLAT+5-FU vs PLAT+5-FU		PFS cetuximab+PLAT+5-FU vs PLAT+5-FU	
	Median (months)	Hazard ratio 95% CI	Median (months)	Hazard ratio 95% CI
Oral cavity patients (n=88)	11.0 vs 4.4	0.42 (0.26 to 0.67)	6.1 vs 2.8	0.34 (0.21 to 0.55)
Non-oral cavity patients				
Oropharynx (n=149)	10.9 vs 7.9	0.85 (0.58 to 1.23)	5.9 vs 4.3	0.50 (0.34 to 0.74)
Larynx (n=111)	8.6 vs 8.4	0.99 (0.65 to 1.52)	5.4 vs 4.1	0.67 (0.48 to 1.03)
Hypopharynx (n=62)	8.4 vs 8.9	1.14 (0.64 to 2.04)	5.7 vs 4.1	0.80 (0.44 to 1.47)

PFS=progression-free survival; OS=overall survival; CI=confidence interval
NB: 32 patients in the EXTREME trial had 'other' primary tumour sites

Given that results from the company NMAs cannot provide robust estimates of effectiveness of treatment with PLAT+5-FU for patients whose cancer did not originate in the oral cavity (and also for those patients whose cancer did originate in the oral cavity), an alternative approach to estimating the effectiveness of PLAT+5-FU in this group of patients is required.

Overall survival: non-oral cavity patients

Results from the EXTREME trial show that, for each of the three non-oral patient subgroups, there was no statistically significant evidence that treatment with cetuximab+PLAT+5-FU increased OS versus treatment with PLAT+5-FU. The ERG, therefore, considers that OS data from the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial can be used as a proxy for the experience of non-oral cavity patients receiving PLAT+5-FU only. This approach has the advantage over an NMA as there is no need to account for heterogeneity between trials as the evidence for both the intervention and comparator are drawn from the same high quality trial.

Progression-free survival: non-oral cavity patients

Following an examination of the PFS results for all three non-oral subgroups in the EXTREME trial (Table 33), results from the EXTREME trial suggest that, for the non-oral subgroup overall, the gain in median PFS from treatment with cetuximab+PLAT+5-FU versus PLAT+5-FU is unlikely to be more than 1.6 months. If treatment with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU deliver better PFS than treatment with cetuximab+PLAT+5-FU then, if treatment with pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU were compared with PLAT+5-FU then the expected benefit would be greater than when compared with cetuximab+PLAT+5-FU. This difference should be considered when estimating the cost effectiveness of pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU compared with PLAT+5-FU.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company (Supplementary Document [July 2019]) in support of the use of pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU as a first-line treatment for adults with R/M HNSCC. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.2 Company's systematic review of cost effectiveness evidence

5.2.1 Objective of the company's systematic review

The company performed a systematic review of the literature to identify published studies that evaluated the cost effectiveness of treatments for R/M HNSCC. The search was not restricted to treatments in the first-line setting.

5.2.2 Company searches

The company searched databases listed in Table 34 for published articles from inception to 15 April 2019 (Embase), 17 April 2019 (PubMed and the Cochrane Library) and 22 April 2019 (HTA documents). Details of the search strategies used by the company are provided in Appendix G of the CS.

Table 34 Databases searched for economic evidence

Database	Interface
Excerpta Medical Database (Embase)	Ovid
Medical Literature Analysis and Retrieval System Online (MEDLINE)	PubMed
Health Technology Assessment databases (HTA)	Ovid
The Cochrane Library	Cochrane

Source: CS, adapted from Appendix G

The company also carried out searches to identify relevant proceedings from the following conferences:

- American Head and Neck Society (AHNC)
- American Society of Clinical Oncology (ASCO)
- European Head and Neck Society (EHNS)
- European Society for Medical Oncology (ESMO)
- International Society of Pharmacoeconomic and Outcomes Research (ISPOR).

The conference proceedings were searched on April 15, 2019 except for proceedings from the AHNC (May 02, 2019) and EHNS (April 22, 2019) conferences. The time periods of the search for the conference proceeding varied; ASCO and ESMO proceedings were searched from inception, AHNS from 2018, ISPOR from 2017 and the search period for EHNS was not reported.

5.2.3 Eligibility criteria used in study selection

The main inclusion criteria used by the company to select studies are shown in Table 35. Full details of the eligibility criteria used by the company are available in Appendix G of the CS.

Table 35 Key criteria for identification of cost effectiveness studies

Characteristic	Inclusion criteria
Population	• Adults population with HNSCC, including oropharyngeal, laryngeal, hypolaryngeal, pharyngeal, oral/oral cavity cancers • Adult population with R/M HNSCC
Intervention(s) / comparator	• Systemic therapy assessed in the economic evaluation
Outcomes	• Incremental costs, LYs gained, QALYs, and any other measure of effectiveness reported together with costs • Model type, structure, source of input parameters and assumptions • Cost drivers as reported in sensitivity analyses
Study design	• Cost effectiveness analyses • Cost utility analyses • Cost minimisation analyses • Cost benefit analyses
Country*	• Not stated in the Appendix G of the CS
Language	• Studies published in English

*=relevant information not provided
HNSCC=head and neck squamous cell carcinoma; LY=life year; QALY=quality adjusted life year; R/M=recurrent or metastatic
Source: CS Appendix G, Table 119

The company search identified 14 publications[17,18,40-51] linked to 13 studies (an abstract [Carroll 2017][44] and a full-text [Tringale 2017][45] were from the same study) that met the inclusion criteria. However, none of the identified studies evaluated the cost effectiveness of pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU versus any systemic therapy in the first-line setting. Details of the company's screening process and the reasons for the exclusion of studies are presented in the CS (Section B.3.1 and Appendix G).

5.2.4 Findings from the company's literature review

The company did not identify any cost effectiveness studies that were relevant to this technology appraisal as none of the identified studies included treatment with pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU as an intervention or a comparator.

5.2.5 ERG critique of the company's literature review

A summary of the ERG appraisal of the company search and selection processes is provided in Table 36. The ERG considers that the databases searched and the search terms used appear to be reasonable. However, the ERG notes that more information could have been provided explaining how some databases were searched. For instance, it is unclear whether the company searched the website of the Scottish Medicine Consortium (SMC), All Wales Medicine Strategy Group (AWMSG) or Canadian Agency for Drugs and Technologies in Health (CADTH) for publicly available technology appraisal documents. Overall, the ERG is satisfied that the company has not missed any relevant economic studies.

Table 36 ERG appraisal of systematic review methods

Review process	ERG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix G, Systematic literature review objective
Were appropriate sources searched?	Yes	Sources included PubMed, Embase and the Cochrane Library. The company also searched conference abstracts and HTA websites
Was the timespan of the searches appropriate?	Yes	Databases were searched from inception
Were appropriate search terms used?	Yes	-
Were the eligibility criteria appropriate to the decision problem?	Yes	-
Was study selection applied by two or more reviewers independently?	Yes	-
Was data extracted by two or more reviewers independently?	Yes	-
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	NA	Risk of bias was not assessed as none of the studies evaluated the cost effectiveness of treatment with pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU
Was the quality assessment conducted by two or more reviewers independently?	Yes	-
Were attempts to synthesise evidence appropriate?	N/A	No relevant study was found

Source: in-house LRiG checklist

5.3 ERG summary of the company's submitted economic evaluation

The company developed a de novo economic model to compare the cost effectiveness of treatment with two interventions (pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU) versus two comparators (cetuximab+PLAT+5-FU and PLAT+5-FU) as first-line treatments for adults with R/M HNSCC whose tumours tested positive for PD-L1 expression defined as CPS≥1.

5.3.1 Model structure

The company model structure (a partitioned survival model) is shown in Figure 5. It comprises three mutually exclusive health states that are designed to reflect the natural course of the disease. The modelled population enters the model in the pre-progression (progression-free [PF]) health state. At the end of each weekly cycle, patients in the PF health state can remain in that health state or experience disease progression and enter the post-progression (PP) health state. Patients in the PP health state can, at the end of each cycle, remain in that health state but they cannot return to the PF health state. Transitions to the death health state can occur from either the PF health state or the PP health state. Death is an absorbing health state from which transitions to other health states are not permitted. The company model structure is consistent with that used in previous NICE technology appraisals of head and neck cancer (TA473[18] and TA490[17]).

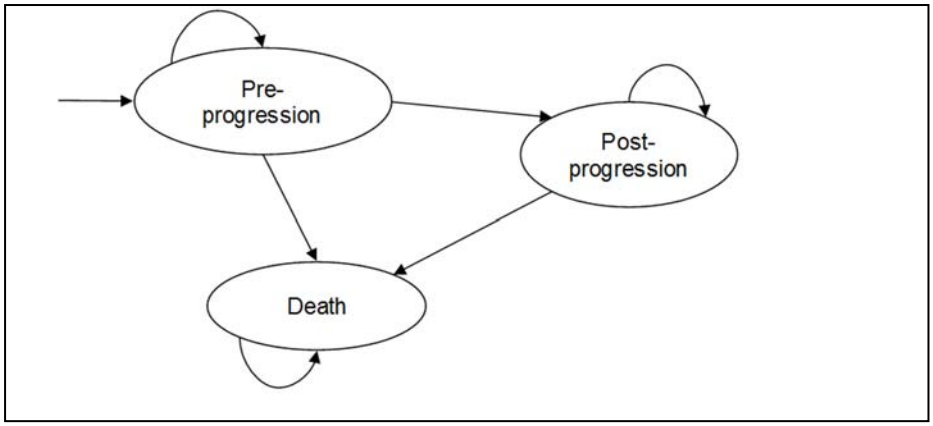

Figure 5 Structure of the company model

Source: CS, Section B.3.2 Figure 33

5.3.2 Population

The population reflected in the company model comprises adults with R/M HNSCC previously untreated in the recurrent or metastatic setting and whose tumours tested positive for PD-L1 expression (CPS≥1). This population is a subset of the KEYNOTE-048 trial population and is a subset of the population described in the final scope[1] issued by NICE (in the trial/scope the population was not restricted by level of PD-L1 expression). However, it is stated in the final

scope[1] issued by NICE that, if the evidence allows, subgroups based on tumour expression of PD-L1 status will be considered.

5.3.3 Interventions and comparators

Intervention

Treatment with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU are implemented in the model in line with the licensed dosing regimen that the company expects to receive from the European Medicine Agency (EMA).[52] Treatment with pembrolizumab monotherapy is implemented as IV infusion of 200mg of pembrolizumab on day 1 of every 3-week cycle up to a maximum of 2 years. For treatment with pembrolizumab+PLAT+5-FU, pembrolizumab is implemented as 200mg IV infusion on day 1 of every 3-week cycle up to a maximum of 2 years whilst PLAT+5-FU is implemented as an IV infusion of (a) 500mg of carboplatin or 100mg/m^2 of cisplatin on day 1 of every 3-week cycle up to a maximum of six cycles, and (b) 1000mg/m^2/day of 5-FU on days 1 to 4 of every 3-week cycle up to a maximum of 6 weeks.

Comparators

The company notes that treatment with cetuximab+PLAT+5-FU is only recommended by NICE[18] for use in the first-line setting to treat patients with R/M HNSCC originating in the oral cavity. Treatment with cetuximab+PLAT+5-FU is implemented in the model as an IV infusion of 400mg/m^2 of cetuximab on day 1 of week 1 then 250mg/m^2 on day 1 of subsequent weeks (no maximum treatment duration). The PLAT+5-FU regimen, in combination with cetuximab or alone, is as described when delivered in combination with pembrolizumab.

5.3.4 Perspective, time horizon and discounting

The company states that costs are considered from the perspective of the NHS and Personal Social Services (PSS). The model cycle length is 1 week, and the time horizon is set at 20 years, which the company considers to be similar to a lifetime time horizon for the defined population. Relevant costs and outcomes have been discounted at 3.5% per annum.

5.3.5 Treatment effectiveness and extrapolation in the base case

Parameter values used in the company model have, primarily, been estimated using individual patient-level data (IPD) from patients in the KEYNOTE-048 trial with CPS≥1 and the results from the company's updated NMA. The follow-up period in the KEYNOTE-048 trial was shorter than the required length of the economic evaluation and, therefore, extrapolations of the trial OS, PFS and time on treatment (ToT) data were necessary.

Methods used by the company to determine the best approach to modelling survival

The company carried out tests to determine whether pairs of KEYNOTE-048 K-M data were proportional (i.e., comparisons of proportionality between data for each intervention with each comparator). In all case, the company concluded that the pairs of data were not proportional. The company, therefore, chose cut-off points (80 weeks for OS and 52 weeks for PFS) that allowed the greatest utilisation of the trial data whilst still allowing sufficient data to conduct extrapolations. Selection of the best fitting function was determined using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values, visual inspection and external validation using data from the EXTREME trial.[20] This approach is in line with NICE Decision Support Unit guidelines (Technical Document 14).[53]

Approach used in the company model to model overall survival

The approach used to model OS in the company model is summarised in Table 37.

Table 37 Approach used by the company to model overall survival

Treatment	Company approach to modelling overall survival
Comparisons with pembrolizumab monotherapy	
Pembrolizumab monotherapy	KEYNOTE-048 trial data to 80 weeks, then log-logistic function
Cetuximab+PLAT+5-FU	KEYNOTE-048 trial data to 80 weeks, then log-logistic function
PLAT+5-FU	HR from company NMA applied to pembrolizumab monotherapy model of OS
Comparisons with pembrolizumab+PLAT+5-FU	
Pembrolizumab+PLAT+5-FU	KEYNOTE-048 trial data to 80 weeks then log-normal function
Cetuximab+PLAT+5-FU	KEYNOTE-048 trial K-M data to 80 weeks, then log-normal function
PLAT+5-FU	HR from company NMA applied to pembrolizumab+PLAT+5-FU model of OS

HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival
Source: Supplementary Document (July 2019)

Approach used in the company model to represent progression-free survival

The definition of PFS used for the economic modelling was based on the central assessment by independent review committee. The approach used to model PFS in the company model is summarised in Table 38.

Table 38 Approach used by the company to model progression-free survival

Treatment	Company approach to modelling overall survival
Comparisons with pembrolizumab monotherapy	
Pembrolizumab monotherapy	KEYNOTE-048 trial data to 52 weeks, then exponential function
Cetuximab+PLAT+5-FU	KEYNOTE-048 trial data to 52 weeks, then exponential function
PLAT+5-FU	HR from company NMA applied to pembrolizumab monotherapy representation of PFS
Comparisons with pembrolizumab+PLAT+5-FU	
Pembrolizumab+PLAT+5-FU	KEYNOTE-048 trial data to 52 weeks then exponential function
Cetuximab+PLAT+5-FU	KEYNOTE-048 trial K-M data to 52 weeks, then exponential function
PLAT+5-FU	HR from company NMA applied to pembrolizumab+PLAT+5-FU representation of PFS

HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival
Source: Supplementary Document (July 2019)

Time on treatment

The company considered that the ToT K-M data available from the KEYNOTE-048 trial were sufficiently mature to allow them to be used directly in the model, i.e., without any need for extrapolation.

In line with the KEYNOTE-048 protocol, a stopping rule was implemented in the model whereby patients did not receive pembrolizumab therapy beyond 24 months. There was no stopping rule for patients receiving cetuximab. For the PLAT+5-FU (alone or in combination with either pembrolizumab or cetuximab) a maximum treatment duration of 18 weeks (6 cycles) was permitted.

5.3.6 Health-related quality of life

Patients in the KEYNOTE-048 trial completed the EQ-5D-3L[33] questionnaire during treatment cycles 1 to 4, and then every 2 cycles (cycle 6, cycle 8 etc.) up to a year or the end of treatment, depending on which occurred first. Patients also completed the questionnaire during the treatment discontinuation visit and during the 30-day post-treatment discontinuation visit. Patient responses to the EQ-5D-3L[33] questionnaire were then converted to utility values using the UK preference-based value set.[54] This approach is consistent with the NICE position statement[55] on the use of EQ-5D-3L[33] data within its technology appraisal process.

Two mixed model linear regressions were subsequently carried out to estimate the mean health state utility values used in the model (Table 39).

Table 39 Utility values used in the company model for all treatments

Health state	Utility value (SE)
Progression-free	[redacted]
Post-progression	[redacted]

SE=standard error
Source: Company model

5.3.7 Adverse events

Grade 3+ AEs occurring in ≥5% of patients in any treatment arm of the KEYNOTE-048 trial were used to represent the experience of patients treated with pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU in the company model. Rates for those treated with PLAT+5-FU were obtained from the SPECTRUM trial.[56] The unit costs associated with the occurrence of the different modelled AEs are available in Table 70 and Table 84 of the CS and Section B.3.4.of the Supplementary Document (July 2019).

5.3.8 Resources and costs

Drug costs

A confidential Commercial Access Agreement (CAA) discount is available for pembrolizumab and a Patient Access Scheme (PAS) discount is available for cetuximab. However, the PAS discount for cetuximab is not known to the company. The dosing schedules used in the company model for pembrolizumab, cetuximab and carboplatin, cisplatin and 5-FU are provided in Section 3.2 of this report and are reproduced in Table 40. Vial sharing was not assumed in the base case analysis.

All first-line drugs (pembrolizumab, cetuximab, carboplatin, cisplatin and 5-FU) are administered via IV infusion and therefore incur treatment administration costs. The estimated cost of administering pembrolizumab and cetuximab as single agents was £174. The cost of administering treatment with PLAT+5-FU was £1,311; this includes the cost of hospital treatment over four consecutive days. Select details of first-line intervention and comparator drug costs are presented in Table 40 of this ERG report, whilst full details of first-line and subsequent treatments are available in Section B.3.5 of the CS.

Table 40 First-line drug acquisition costs used in the company model

Treatment	Formulation per vial/cap	Unit cost	Dosage	Total average dose	Average profile method		
					Vials used	Total cost per dose	Cost per week
Pembrolizumab	100mg	[redacted]	200mg	200mg	2	[redacted]	[redacted]
Cetuximab	100mg/20ml	£178.1	Loading=400mg/m^2 Subsequent =250 mg/m^2	437.20mg	Loading=3; subsequent=0	loading=£1,424.80 subsequent=£890.50	£1,781.00
	500mg/100ml	£890.5			Loading=1; subsequent=1		
Cisplatin	10mg	£1.84	100mg/m^2	174.88mg/m^2	0	£8.96	£2.99
	50mg	£4.48			4		
	50mg	£4.48			4		
	450mg	£18.73			1		
Carboplatin	50mg	£3.18	100mg/m^2	174.88mg/m^2	1	£4.77	£1.59
	150mg	£6.35			1		
5-FU	1,000mg	£1.29	1000mg/m^2	1748.80mg/m^2	2	£2.59	£3.44

Loading=loading dose; mg=milligram; ml=millilitre; subsequent=subsequent dose. All unit cost have been sourced from the British National Formulary
Source: adapted from CS, Section B.3.5 (Table 79)

Subsequent treatment costs

The company initially considered modelling subsequent therapy based on the frequencies with which the five most commonly prescribed second-line therapies were prescribed to patients participating in the KEYNOTE-048 trial. However, nivolumab is only currently available, via the CDF, as a treatment for R/M HNSCC after first-line platinum-based chemotherapy.[17] The NICE position on treatments/products that are available via the CDF (such as nivolumab) is that such treatments should not be considered as comparators, or be included in treatment sequences, in appraisals of new cancer products.[32] In addition, although cetuximab and cetuximab combination therapies were commonly used as subsequent treatments in the KEYNOTE-048 trial, these therapies are not recommended as second-line treatments by NICE for use in the UK. Therefore, the proportions of use for cetuximab, cetuximab combination therapies and nivolumab were redistributed between the remaining subsequent therapies (carboplatin+paclitaxel, docetaxel, methotrexate and paclitaxel). Table 41 shows the distribution and weekly cost of subsequent therapies that were used in the economic model.

Table 41 Distribution of subsequent therapies and associated costs in the economic model

Primary treatment	Subsequent treatment			
	Docetaxel	Paclitaxel	Carboplatin + paclitaxel	Methotrexate
Pembrolizumab monotherapy				
Pembrolizumab	13.39%	11.61%	18.04%	8.39%
Cetuximab+PLAT+5-FU	25.83 %	26.82%	14.90%	5.96%
PLAT+5-FU	25.83 %	26.82%	14.90%	5.96%
Mean duration (months)	2.89	4.06	2.80	3.45
Weekly cost	£80.35	£90.68	£94.33	£59.78
AE costs	£9.85	£31.02	£31.02	£0.30
Pembrolizumab+PLAT+5-FU				
Pembrolizumab + PLAT+5-FU	20.32%	25.08%	0.00%	18.41%
Cetuximab+PLAT+5-FU	31.52%	28.26%	0.00%	19.20%
PLAT+5-FU	31.52%	28.26%	0.00%	19.20%
Mean duration (months)	2.66	2.69	0.00	1.77
Weekly cost	£80.35	£90.68	£0.00	£59.78
AE costs	£9.85	£31.02	£0.00	£0.30

AE=adverse event
Source: adapted from CS, Section B.3.3 (Table 71 and Table 72)

Resource use by health state

In addition to drug costs, patients in the PF and PP health states are modelled to incur costs of £123.26 and £64.31 per week, respectively, for routine care (Table 42). Full details of the health resource use estimates in the economic model are provided in the CS, Section B.3.5.

Table 42 Weekly resource use costs used in the company model

Resource use	Unit cost	HRG code/Source	Usage per week	
			PF health state	PP health state
Dental therapy for radiotherapy effects	£121.94	RF (2017/18): SC 450	0.06	0.03
Depression assessment & management	£81.31	RF (2017/18): A06A1	0.03	0.03
Nutritional support	£110.23	RF (2017/18): N16AF	0.2	0.16
Pain and symptom management / any supportive care	£104.17	RF (2017/18): N21AF	0.17	0.19
Speech and swallowing therapy	£95.52	RF (2017/18): A13A1	0.06	0.02
Management of oral and gastrointestinal mucositis	£5.65	BNF (2017): benzamine	0.08	0.04
Antiemetics	£6.41	eMit (2018): ondansetron	0.2	0.12
Xerostomia Management	£41.89	BNF (2017): pilocarpine	0.07	0.04
Hematologic Growth Factor/Transfusion	£174.65	NG24 (2015)	0.07	0.03
Oncologist Visit	£132.10	RF (2017/18): SC 370	0.25	0.08
CT Scan	£132.66	RF (2017/18): RD22Z	0.13	0
Cell blood count	£2.51	RF (2017/18): DAPS05	0.25	0.08
Total cost per week			£123.26	£64.31

BNF=British national formulary; CT=computed tomography; eMiT=electronic marketing information tool; HRG=health care resource group; NG24=National Institute for Health and Care Excellence Guideline 24; PF=progression-free; PP=post-progression; RF=NHS reference cost
Source: adapted from CS, Section B.3.5 (Table 81 and Table 82)

Other costs

The company applied a one-off end of life/terminal care cost of £7,797.92[57] as patients entered the model death health state to account for palliative/terminal care costs.

5.3.9 Cost effectiveness results

Base case results

The base case pairwise incremental cost effectiveness ratios (ICERs) per QALY gained for the comparison of treatment with pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and versus PLAT+5-FU are shown in Table 43 and, for the comparison of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and versus PLAT+5-FU are shown in Table 44. These results have been calculated using CAA discount for pembrolizumab and list prices for all other treatments.

Table 43 Base case pairwise cost effectiveness results: pembrolizumab monotherapy (CAA discount)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY
				Cost	LYG	QALYs	
Pembrolizumab monotherapy	£48,945	2.40	1.69	-	-	-	-
Cetuximab+PLAT+5-FU	£51,832	1.27	0.91	-£2,886	1.13	0.78	Dominant
PLAT+5-FU	£20,616	1.10	0.78	£28,329	1.30	0.91	£31,212

CAA=commercial access agreement; LYG=life year gained; QALY=quality adjusted life year
Source: Supplementary Document (July 2019), Table 70

Table 44 Base case pairwise cost effectiveness results: pembrolizumab+PLAT+5-FU (CAA discount)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			Incremental cost per QALY
				Cost	LYG	QALYs	
Pembrolizumab+PLAT+5-FU	£64,414	3.05	2.12	-	-	-	-
Cetuximab+PLAT+5-FU	£52,597	1.18	0.85	£11,817	1.88	1.28	£9,255
PLAT+5-FU	£19,652	0.96	0.68	£44,762	2.10	1.44	£31,070

CAA=commercial access agreement; LYG=life year gained; QALY=quality adjusted life year
Source: Supplementary Document (July 2019), Table 71

5.3.10 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out an extensive range of one-way sensitivity analyses (OWSA).

For the comparison of treatment with pembrolizumab monotherapy versus treatment with cetuximab+PLAT+5-FU, results from the OWSAs showed that the body surface area of modelled patients (which is directly related to cost of treatments) was the only comparator that affected the company's cost effectiveness result (leading to an ICER of nearly £4,500 per QALY gained).

Results from the OWSAs for the comparison of treatment with pembrolizumab monotherapy versus PLAT+5-FU show that the discount rate for health outcomes (LYs and QALYs) and the function used to extrapolate OS K-M data from the KEYNOTE-048 trial have the greatest impact on the size of the ICER per QALY gained (see Figure 6).

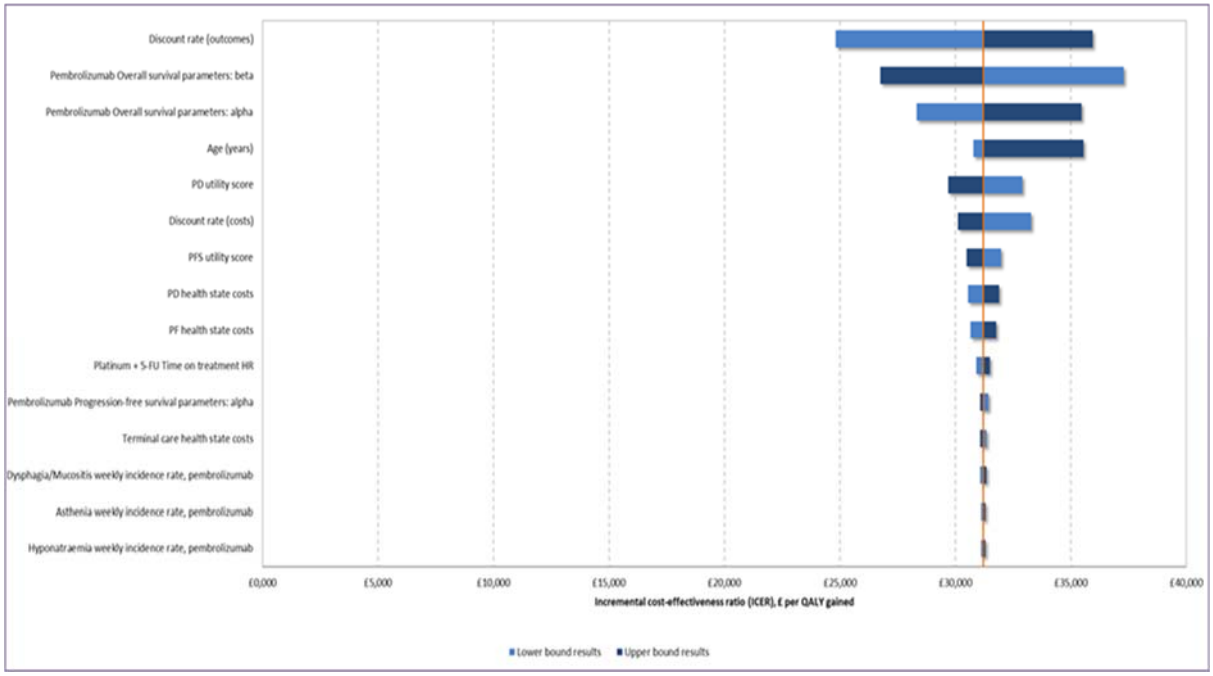

Figure 6 OWSA results: pembrolizumab monotherapy versus PLAT+5-FU

ICER=incremental cost-effectiveness ratio; PD=progressed-disease; PF=progression-free; PFS=progression-free survival;
Source: Supplementary Document (July 2019), Figure 62

For the comparison of treatment with pembrolizumab+PLAT+5-FU versus treatment with cetuximab+PLAT+5-FU, results from the OWSAs show that body surface area and the discount rate for health outcomes have the greatest impact on the size of the ICER per QALY gained (see Figure 7).

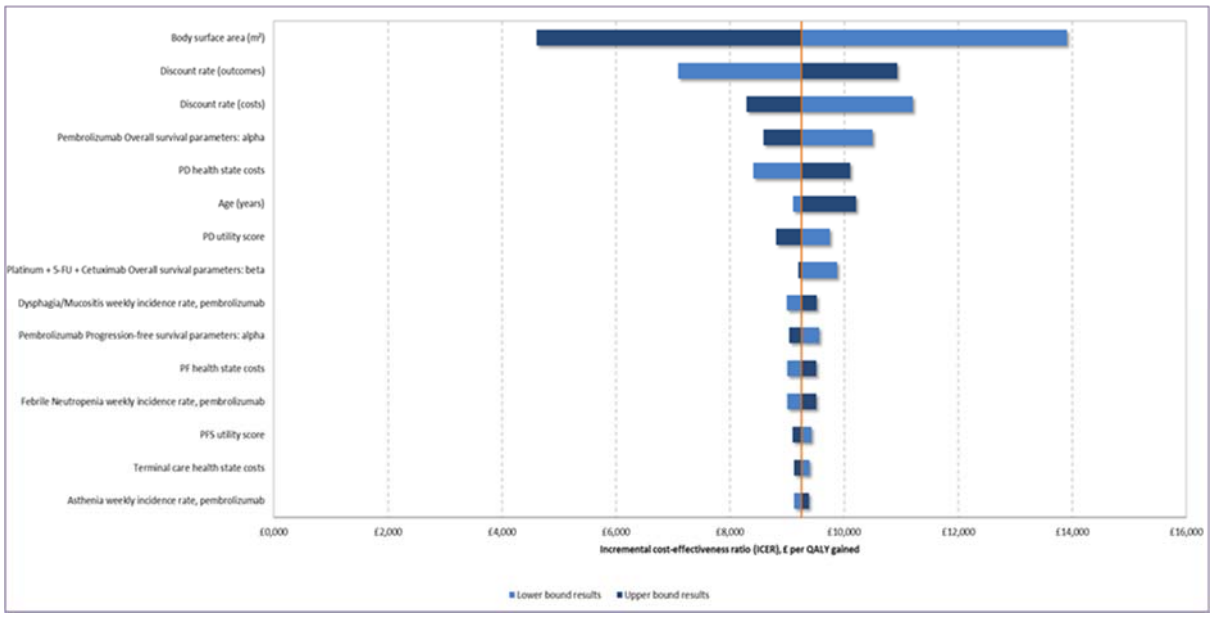

Figure 7 OWSA results: pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU

OWSA=one way sensitivity analysis; PD=progressed-disease; PF=progression-free; PFS=progression-free survival;
Source: Supplementary Document (July 2019), Figure 63

For the comparison of treatment with pembrolizumab+PLAT+5-FU versus PLAT+5-FU, results from the OWSAs show that discount rate for health outcomes and the OS function parameters for pembrolizumab+PLAT+5-FU have the greatest impact on the size of the ICER per QALY gained (see Figure 8).

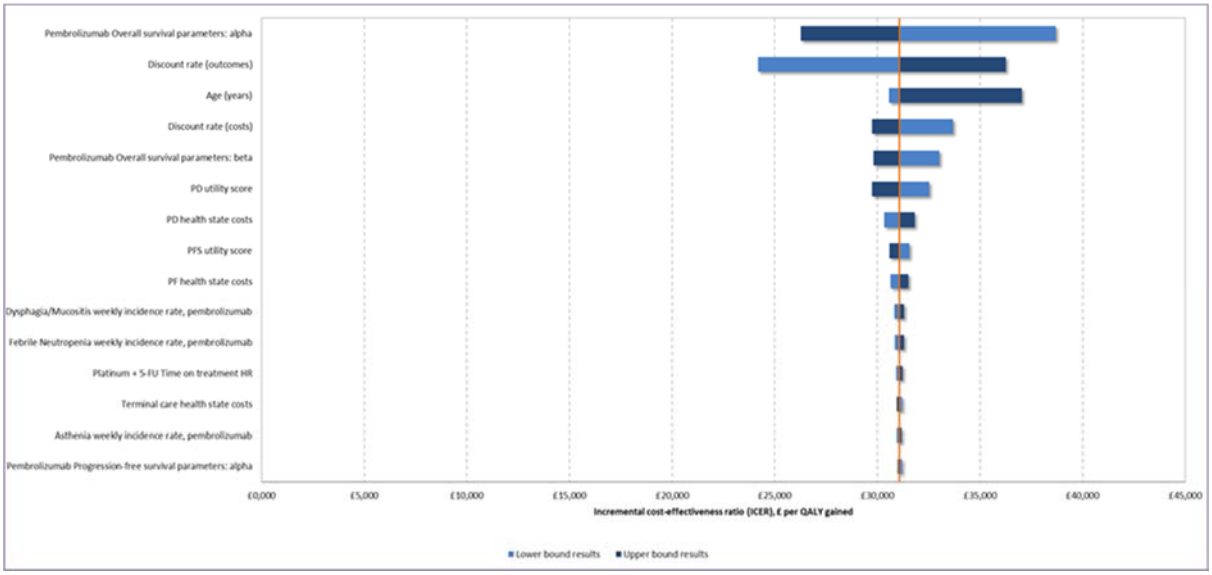

Figure 8 OWSA results: pembrolizumab+PLAT+5-FU versus PLAT+5-FU

OWSA=one-way sensitivity analysis; PD=progressed-disease; PF=progression-free; PFS=progression-free survival
Source: Supplementary Document (July 2019), Figure 64

Probabilistic sensitivity analysis

The company varied a large number of input parameters in its probabilistic sensitivity analysis (PSA). The cost effectiveness results from the company's PSA are very similar to the company's deterministic results (Table 45).

Table 45 Company deterministic and probabilistic cost effectiveness results

	ICER per QALY gained	
	Deterministic	**Probabilistic**
Pembrolizumab monotherapy		
Cetuximab+PLAT+5-FU	Dominant	Dominant
PLAT+5-FU	£31,212	£31,832
Pembrolizumab+PLAT+5-FU		
Cetuximab+PLAT+5-FU	£9,255	£9,552
PLAT+5-FU	£31,070	£32,043

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: Supplementary Document (July 2019)

5.3.11 Scenario analyses

The results of the scenario analyses are robust to all the parameter changes for the comparison of treatment with pembrolizumab monotherapy (Table 46) or pembrolizumab+PLAT+5-FU (Table 47) versus treatment with cetuximab+PLAT+5-FU.

For the comparison of treatment with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus treatment with PLAT+5-FU, the results of the scenario analyses are largely robust to changes in most parameters except for changes to the time horizon, pembrolizumab monotherapy OS function (Weibull).

Table 46 Scenario analyses results: pembrolizumab monotherapy

Description	Base case	Scenario analysis	Versus cetuximab +PLAT+5-FU	Versus PLAT+ 5-FU
Base case			**Dominant**	**£32,212**
Time horizon	20 years	10 years	Dominant	£39,141
OS function: pembrolizumab monotherapy	K-M+loglogistic-80	K-M+lognormal-80 (alternative good fit)	Dominant	£28,391
OS function: pembrolizumab monotherapy	K-M+loglogistic-80	K-M+Weibull-80 (conservative extrapolation)	Dominant	£40,546
OS function: pembrolizumab monotherapy	K-M+loglogistic-80	K-M+lognormal-45 (align with IA analysis)	Dominant	£31,721
OS function: pembrolizumab monotherapy	K-M+loglogistic-80	Loglogistic-80 (best statistical fit)	Dominant	£35,225
PFS function: pembrolizumab monotherapy	K-M+exponential-52	K-M+gompertz-52 (second best fit)	Dominant	£31,984
PFS function: pembrolizumab monotherapy	K-M+exponential-52	K-M+Gompertz-52 (best statistical fit)	Dominant	£31,397
Treatment waning 3 years	20 years	3 years	Dominant	£31,303
Treatment waning 5 years	20 years	5 years	Dominant	£31,265
Include cost and efficacy of nivolumab (subsequent therapy)	No	Yes	Dominant	£29,277
Health state utility values	Mixed regression model	Mean utility value	Dominant	£31,707
Pembrolizumab monotherapy dosage	200mg fixed dose every 3 weeks	400mg fixed dose every 6 weeks	Dominant	£32,089
Allow vial sharing	No	Yes	Dominant	£31,229
Modelling of time-on-treatment	Trial K-M data throughout	Parametric function with best statistical fit	Dominant	£29,178

Exponential-52=exponential function appended at week 52; Gompertz-52=Gompertz function appended at week 52; IA=interim analysis; K-M=Kaplan-Meier data; loglogistic-80=log-logistic function appended at week 80; lognormal-80=log-normal function appended at week 80; mg=milligram; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; Weibull-80=Weibull function appended at week 80
Source: Supplementary Document (July 2019), adapted from Table 76 and Table 77

Table 47 Scenario analyses results: pembrolizumab+PLAT+5-FU

Description	Base case	Scenario analysis	Versus cetuximab +PLAT+5-FU	Versus PLAT+ 5-FU
Base case			**£9,255**	**£31,070**
Time horizon	20 years	10 years	£10,578	£39,895
OS function: pembrolizumab monotherapy	K-M+lognormal-80	K-M+gamma-80 (better fit to observed data)	£8,575	£26,084
OS function: pembrolizumab monotherapy	K-M+lognormal-80	K-M+Weibull-80 (conservative extrapolation)	£11,437	£38,639
OS function: pembrolizumab monotherapy	K-M+lognormal-80	K-M+log-normal-45 (align with IA analysis)	£9,755	£35,951
OS function: pembrolizumab monotherapy	K-M+lognormal-80	Gompertz (best statistical fit)	£10,854	£33,085
PFS function: pembrolizumab monotherapy	K-M+exponential-52	K-M+Gompertz-52 (second best fit)	£10,235	£31,517
PFS function: pembrolizumab monotherapy	K-M+exponential-52	Log-logistic (best statistical fit)	£9,238	£31,088
Treatment waning 3 years	20 years	3 years	£9,270	£35,056
Treatment waning 5 years	20 years	5 years	£9,261	£34,959
Include cost and efficacy of nivolumab (subsequent therapy)	No	Yes	£6,641	£29,117
Health state utility values	Mixed regression model	Mean utility value	£9,645	£32,253
Allow vial sharing	No	Yes	£11,236	£31,071
Modelling of time-on-treatment	Trial K-M data throughout	Parametric function with best statistical fit	£7,890	£28,572

Exponential-52=exponential function appended at week 52; ggamma-80=generalised gamma function appended at week 80; Gompertz=fully parametric Gompertz function; Gompertz-52=Gompertz function appended at week 52; K-M=Kaplan-Meier data; loglogistic=fully parametric log-logistic function; lognormal-45=log-normal function appended at week 45; lognormal-80=log-normal function appended at week 80; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year; Weibull-80=Weibull function appended at week 80
Source: Supplementary Document (July 2019), adapted from Table 78 and Table 79

5.3.12 Model validation and face validity check

The company compared outcomes from the model against clinical trial evidence to validate results. Additionally, internal quality control was undertaken by the model developers on behalf of the company. No report of any further validation of the model is included in the Supplementary Document (July 2019).

5.4 ERG critique of the company cost effectiveness model

5.4.1 NICE Reference Case checklist

Table 48 NICE Reference case checklist completed by the ERG

Attribute	Reference Case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective costs	NHS and PSS	Yes
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Yes
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Yes
Outcome measure	Health effects should be expressed in QALYs	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=Personal Social Services

5.4.2 Drummond checklist

Table 49 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partly	Effectiveness was only established over the period for which data from the KEYNOTE-048 trial were available for all patients and had not been established for oral cavity patients or analysed for non-oral cavity patients. Lifetime treatment effect - notably OS - was not established
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Partly	A full incremental analysis should have been performed of all alternatives together. Only pairwise analyses were presented in the CS
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	There was no detailed discussion of the difference in standard of care between oral and non-oral cavity patients and the impact this could have on cost-effectiveness results

OS=overall survival

5.5 ERG critique of the company model

The ERG received an updated model and CS during the post-clarification period. The ERG commends the company for producing a model, using MS Excel, to address what is a complex decision problem. The complexity arises as the company base case includes two different interventions with two different comparators. It is simple for the model user to navigate between input and result sheets, however, it is difficult to perform algorithm checks as the model includes multiple hidden sheets and employs lengthy visual basic code to make changes to the model each time the interventions and comparators are changed. The ERG was able to stress test the model but has checked the key algorithms driving the model and, other than an error in how treatment waning was calculated (discussed in Section 5.4.3, is satisfied that the cost effectiveness results produced by the model are likely to be an accurate reflection of the model structure and inputs described in the CS and Supplementary Document (July 2019), which was received during the post-clarification period.

The ERG has made revisions to the company model that will generate more credible cost effective results than those generated using the company base case model. Revisions were made in the following areas:

- using a single cetuximab+PLAT+5-FU arm
- using a Weibull distribution to extrapolate KEYNOTE-048 K-M OS data
- lifetime duration of treatment effect on OS (treatment waning)
- modelling time to treatment discontinuation.

In addition, the ERG considers that oral cavity and non-oral cavity patients should be considered separately in the economic model as the standard of care for each group is different (cetuximab+PLAT+5-FU for oral cavity patients and PLAT+5-FU for non-oral cavity patients). The company has only presented cost effectiveness results for all patients with R/M HNSCC; the ERG's rationale for considering oral and non-oral cavity patients separately are discussed in Section 4.9.7.

5.5.1 A single cetuximab+PLAT+5-FU arm

From a statistical perspective, the ERG understands why the company has used separate cetuximab+PLAT+5-FU comparator arms when analysing the KEYNOTE-048 trial data; slightly different numbers of patients are in each of the comparator groups depending on whether the intervention is pembrolizumab monotherapy (n=255) or pembrolizumab+PLAT+5-FU (n=235) due to a patient enrolment decision (Section 4.5.4). However, for the economic model, the ERG considers that modelling cetuximab+PLAT+5-FU using two separate arms depending on the intervention is unnecessary and creates an implausible situation where the costs and outcomes associated with treatment with cetuximab+PLAT+5-FU change

depending on the intervention (i.e., pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU). The ERG highlights that results from statistical analyses show (Section 4.9.7 of this ERG report) that outcomes for both the whole cetuximab+PLAT+5-FU arm and the reduced size arm are very similar. The ERG has, therefore chosen to use data from the whole cetuximab+PLAT+5-FU arm (i.e., no patients excluded) in the economic analysis to represent patient experience both when the intervention is pembrolizumab monotherapy and when it is pembrolizumab+PLAT+5-FU.

5.5.2 Modelling overall survival

Choice of distribution for extrapolating OS

The company's approach to modelling OS for pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU is to use KEYNOTE-048 trial K-M OS data up to 80 weeks and then, for the remainder of the model time horizon, represent patient experience using a parametric distribution (Table 50).

Table 50 Company approach to modelling OS

Arm	First 80 weeks	From 80 weeks to 20 years (lifetime of model)
Pembrolizumab monotherapy	KEYNOTE-048 trial K-M data	Log-logistic extrapolation
Pembrolizumab+PLAT+5-FU	KEYNOTE-048 trial K-M data	Log-normal extrapolation
Cetuximab+PLAT+5-FU (compared to pembrolizumab monotherapy)	KEYNOTE-048 trial K-M data	Log-logistic extrapolation
Cetuximab+PLAT+5-FU (compared to pembrolizumab+PLAT+5-FU)	KEYNOTE-048 K-M data for subset of patients receiving cetuximab+PLAT+5-FU randomised whilst patients were being actively recruited to the pembrolizumab+PLAT+5-FU arm	Log-normal extrapolation

K-M=Kaplan-Meier; OS=overall survival

The ERG supports the use of K-M data for as long as there are sufficient patients alive to make the K-M data informative and is satisfied that the company's choice of cut-off point is reasonable and justified. However, the ERG is not convinced by the company's choices of distributions to extrapolate K-M OS data beyond 80 weeks up to 20 years. The company selected each distribution by employing two techniques: (i) comparing AIC and BIC values and (ii) for cetuximab+PLAT+5-FU, assessing model 3- and 5-year survival rates with 3- and 5-year survival rates for the cetuximab+PLAT+5-FU arm of the EXTREME trial.[20]

Analysis of AIC and BIC values (CS, Table 49 and Table 53) for each parametric distribution considered by the company shows that the values, for each intervention, for each of the different alternative distributions considered, are very similar in magnitude. This means that it is not possible to choose the most appropriate distribution based on the AIC or BIC values.

Thus, clinical plausibility is the only approach that can be used to select the most appropriate of these distributions.

The ERG considers that the log-normal and log-logistic distributions are frequently shown to poorly represent OS for patients with cancer. This is because both distributions have long tails with hazard rates that decline over time. The long tail means that notable proportions of patients remain alive after many years and the declining hazard rate means that there is danger of the projected hazard rate falling below that of background mortality. In the company base case the mortality hazard rate falls below that of the general population after approximately 18 years for patients treated with pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU; this also happens at a later time-point for patients treated with cetuximab+PLAT+5-FU. Whilst the company has used an algorithm to ensure that mortality can never be lower than background mortality, the ERG considers that the need to employ such an approach strongly suggests that the company's log-logistic and log-normal extrapolations are clinically implausible.

The ERG considers that, of the selection of distributions considered by the company, the Weibull distribution is the most clinically plausible distribution to use to extrapolate the OS K-M data from the KEYNOTE-048 trial beyond 80 weeks for pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU. The ERG notes that, when the Weibull distribution is used to extrapolate cetuximab+PLAT+5-FU KEYNOTE-048 trial OS K-M data, it potentially underestimates OS by a percentage point compared to data from the EXTREME trial for the cetuximab+PLAT+5-FU arm at 5 years, but still provides clinically plausible OS projections over 5 years, and does not produce a clinically implausible survival tail.

Cost effectiveness results generated using the company's Weibull distributions to extrapolate OS K-M data from the KEYNOTE-048 trial beyond 80 weeks are shown in Table 51.

Table 51 Results from using the company's Weibull distributions to extrapolate OS K-M data from the KEYNOTE-048 trial beyond 80 weeks

Intervention	Comparator	Company ICER per QALY gained
Pembrolizumab monotherapy	Cetuximab+PLAT+5-FU	Pembrolizumab dominant
	PLAT+5-FU	£40,546
Pembrolizumab+PLAT+5-FU	Cetuximab+PLAT+5-FU	£11,437
	PLAT+5-FU	£38,639

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

Oral and non-oral cavity patients

The company has not provided separate cost effectiveness results for oral and non-oral cavity patients despite the NHS standard of care being different for these two subgroups. Importantly, cetuximab+PLAT+5-FU is only recommended by NICE for treating patients whose cancer originated in the oral cavity. Evidence from the KEYNOTE-048 trial is only for patients (oral and non-oral cavity) who were fit enough to receive cetuximab+PLAT+F-5U. No data have been provided that demonstrate the effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU for those patients (oral and non-oral cavity) who are not fit enough to be receive cetuximab+PLAT+5-FU. Thus, the cost effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU for less fit (oral and non-oral cavity) patients versus any comparator cannot be determined.

The ERG requested OS K-M data from each arm of the KEYNOTE-048 trial for three groups of patients: all patients, oral cavity patients and non-oral cavity patients; however, the company only provided OS K-M data for all patients and for the oral cavity subgroup.

Oral cavity patients

The OS K-M data for all patients, and the subgroup of oral cavity patients, treated with cetuximab+PLAT+5-FU are shown in Figure 9.

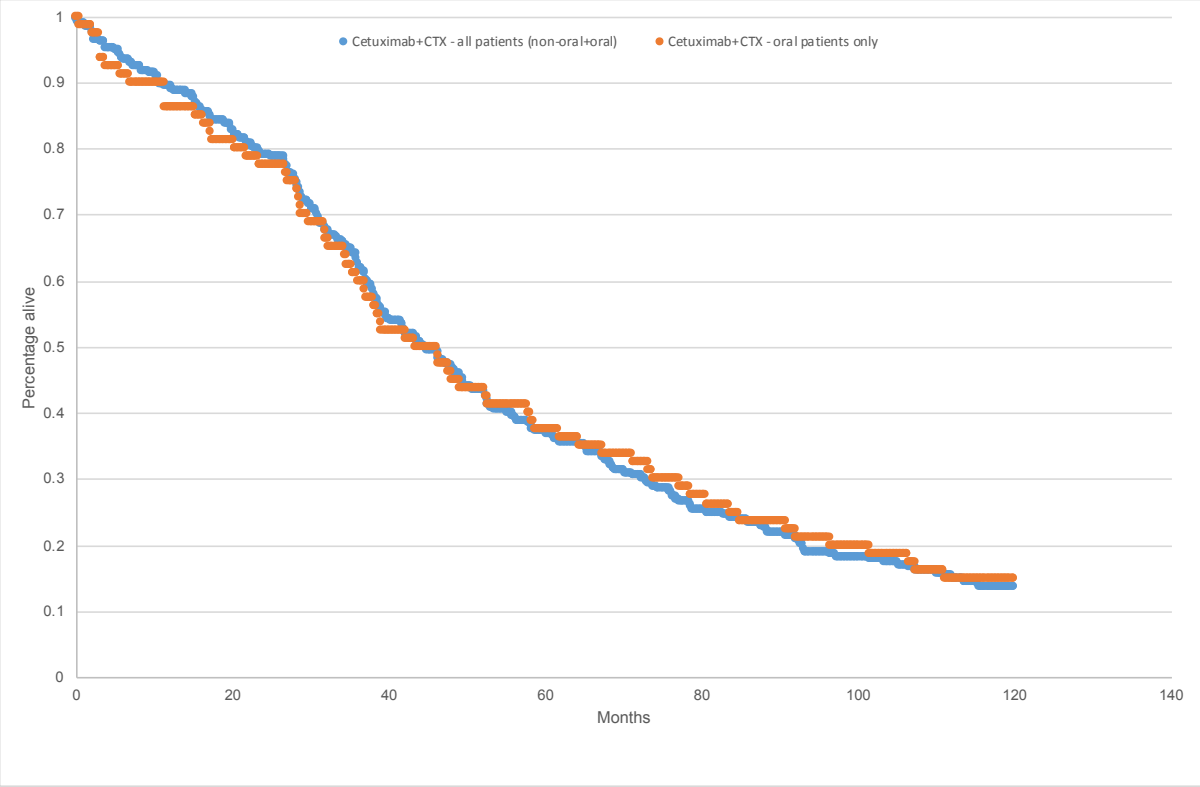

Figure 9 KEYNOTE-048 OS K-M curves for all patients with CPS≥1 and oral cavity patients with CPS≥1

The ERG considers that, based on visual inspection, the OS K-M data for all patients and for the oral cavity subgroup in the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial appear identical as they cross multiple times. Furthermore, results from the log-rank test showed no statistically significant difference between the curves. The ERG is, therefore, satisfied that using data from all patients in the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial to represent OS for oral cavity patients treated with cetuximab+PLAT+5-FU would produce the same curves as if data from the whole trial arm were used. The ERG considers that there is no benefit from using the separate OS K-M data for oral cavity patients (which has a smaller sample size and, therefore, more "steps" in the K-M data) and that using the data for all patients, as the company has done, will produce accurate estimates of OS for oral cavity patients only.

The results from the KEYNOTE-048 trial for oral cavity patients, showed a non-statistically significant difference in OS for the comparison of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and for the comparison of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (Section 5.6). As the KEYNOTE-048 trial was not powered to show a difference in OS for oral cavity patients, the ERG considers that separately modelling the effect on OS for patients receiving pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU may result in potentially misleading results. Therefore, when modelling the effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU, the ERG has used all the data from these arms rather than developing different models depending on the origin of the cancer.

Non-oral cavity patients

The OS data for non-oral cavity patients receiving PLAT+5-FU can be drawn directly from results from the KEYNOTE-048 trial for all patients receiving cetuximab+PLAT+5-FU.

Results from the EXTREME trial show that the oral cavity patients who had received cetuximab+PLAT+5-FU had very similar/the same OS as the non-oral cavity patients who had received PLAT+5-FU. This means that data from the cetuximab+PLAT+5-FU arm can be used to represent the experience of patients with non-oral cancer treated with PLAT+5-FU.

The cetuximab+PLAT+5-FU OS K-M data for all patients in the KEYNOTE-048 trial (i.e., data from both oral cavity and non-oral cavity patients) is similar/the same as the cetuximab+PLAT+5-FU data from the oral cavity patients in the KEYNOTE trial (as shown in Figure 1). This suggests that the KEYNOTE-048 trial cetuximab+PLAT+5-FU OS K-M data for non-oral, oral and all patients must be similar/the same.

Given the above, and because the company did not provide separate K-M data for non-oral cavity patients from the KEYNOTE-048 trial, the KEYNOTE-048 trial OS K-M data for all patients with CPS≥1 has been used by the ERG to represent the experience of non-oral cavity patients receiving PLAT+5-FU.

5.5.3 Lifetime duration of treatment effect on OS (treatment waning)

In the company model, from 6 months until the end of the model time horizon (20 years), the mortality rates for patients treated with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU are lower than the mortality rates for patients treated with cetuximab+PLAT+5-FU and PLAT+5-FU. The ERG considers that such an effect requires substantial support from clinical evidence; this evidence has not been presented by the company. Furthermore, in previous appraisals of immunotherapies, such as TA520 (Atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy),[58] scenarios where mortality rates for immunotherapies become the same as those for comparator therapies (also known as 'treatment waning') over 3 and 5 years have been explored.

In the Supplementary Document (July 2019), the company has reported the effects of treatment waning at 3 and 5 years (Tables 76 to Table 79, pp80-83). However, the methods used to generate these results are not described. The ERG identified an algorithmic error in the model that affects the results generated when the effect of treatment waning is incorporated into any analysis. The correct results, shown in Table 52, demonstrate that, when the impact of a life-time effect of treatment with pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU is removed from the model, this makes the intervention (pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU) less cost effective in all cases, although pembrolizumab monotherapy remains dominant versus cetuximab+PLAT+5-FU.

Table 52 Model results associated with implementing treatment waning

Intervention	Comparator	Company base case	Corrected company ICER per QALY gained	
			3-year waning	5-year waning
Pembrolizumab monotherapy	Cetuximab+PLAT+5-FU	Pembrolizumab dominant	Pembrolizumab dominant	Pembrolizumab dominant
	PLAT+5-FU	£31,212	£92,888	£59,846
Pembrolizumab+PLAT+5-FU	Cetuximab+PLAT+5-FU	£9,255	£12,358	£10,417
	PLAT+5-FU	£31,070	£76,057	£57,011

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year

5.5.4 Modelling of PFS and ToT

Progression-free survival

As explained in Section 4.9.7, for non-oral cavity patients treated with PLAT+5-FU, the ERG considers that evidence from the cetuximab+PLAT+5-FU arm of KEYNOTE-048 trial may be used to estimate PFS. However, in Section 4.9.7, it was also noted that use of KEYNOTE-048 trial data in this way may underestimate the true PFS gain of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU compared to PLAT+5-FU. It is, therefore, important to understand the potential economic impact of this underestimation of PFS benefit for pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU.

In the company model, the utility associated with being in the PFS state is 0.06 higher than being in the progressed disease (PD) health state (PFS utility: 0.76, PD utility: 0.70). The non-treatment costs associated with being in the PFS health state are also higher than the non-treatment costs associated with being in the PD health state (PFS: £123.26, PD: £64.31).

If the median PFS gain for patients treated with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU compared to PLAT+5-FU in non-oral cavity patients has been underestimated by a maximum of 1.6 months (6.4 weeks assuming 4 week months), then use of the cetuximab+PLAT+5-FU arm of the KEYNOTE-048 trial for PFS in the company economic model would translate into an underestimation of the (undiscounted) QALY gain and additional (undiscounted) costs with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU compared to PLAT+5-FU of approximately 0.007 QALYs and £377.28.

For non-oral cavity patients, for the comparison of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU compared to PLAT+5-FU, this underestimation of additional QALYs would result in an overestimation of the ICERs per QALY gained and this underestimation of the additional costs would result in an underestimation of the ICERs per QALY gained. On balance, the ERG considers the potential impact on cost effectiveness results, from using PFS data from the cetuximab+PLAT+5-FU arm (all patients) in the KEY-NOTE-048 trial as a proxy for PFS for non-oral cavity patients, would be negligible and not influence any conclusions that could be drawn on the cost effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus PLAT+5-FU.

5.5.5 Modelling time to treatment discontinuation

In the company model, the costs of treatment with pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU are estimated using ToT data from

the KEYNOTE-048 trial. The ERG considers that it was appropriate to use KEYNOTE-048 trial ToT data to estimate the cost of pembrolizumab monotherapy. However, the approach used by the company to model ToT for patients receiving pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU was inaccurate; patients were costed as having received the full treatment if they had received at least one component of the treatment regimen. This method could result in an overestimate of the costs of treatment with pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU.

Additionally, the costs of PLAT+5-FU in the company model are based on PFS from the company NMAs; clinical advice to the ERG is that, for treatment with PLAT+5-FU, PFS is a poor proxy for actual time on treatment as PLAT+5-FU is rarely given to patients for more than four cycles. In the company model, 34.8% of patients receive six cycles of PLAT+5-FU, thus potentially overestimating the cost of treatment with PLAT+5-FU considerably.

During the clarification process, the ERG requested ToT K-M data from the KEYNOTE-048 trial for the pembrolizumab+PLAT+5-FU arm and the cetuximab+PLAT+5-FU arm separated by each constituent component (pembrolizumab/cetuximab, platinum chemotherapy and 5-FU) (Question B.1). The company responded that these data could not be provided as they were not available. Without the separate treatment data, the ERG was unable to provide more accurate costs for the pembrolizumab+PLAT+5-FU, cetuximab+PLAT+5-FU and PLAT+5-FU treatments.

To explore the impact of the potential overestimation of cost of PLAT+5-FU in particular, the ERG limited the number of cycles received by patients to four (from six). This increased the size of the ICER by between £35 and £943 per QALY gained depending on the intervention and comparator combination. Therefore, if the cost of PLAT+5-FU used in the company base case is an overestimate, the effect on cost effectiveness results is not of a magnitude that is likely to have a major impact on decisions about the cost effectiveness of the interventions versus the comparators.

In addition, the ERG highlights that, in the company model, the cost of administering PLAT+5-FU includes the cost of hospital treatment over four consecutive days. However, clinical advice to the ERG is that a number of units would use a Baxter infusion bottle which allows a continuous delivery of chemotherapy through an IV line as an outpatient. When the infusion is complete, the patient can be disconnected from the line by a district nurse in the community. Patients therefore do not have to attend hospital for four consecutive days.

5.6 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The ERG has made the following revisions to the company base case:

1. Used data from all patients in the cetuximab+PLAT+5-FU arm to model OS, PFS and ToT for patients receiving cetuximab+PLAT+5-FU (for oral cavity patients only) or PLAT+5-FU (for non-oral cavity patients only) (R1)
2. Used a Weibull distribution for OS extrapolation beyond 80 weeks for pembrolizumab monotherapy, pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU (R2)
3. Introduced a limit to the duration of treatment effect of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU (3- and 5-year durations) (R3 and R4)
4. Limited the number of cycles of PLAT+5-FU received by patients to four (R5).

The ERG's revised ICERs per QALY gained are shown in Table 53 to Table 56.

The ERG presents a preferred scenario, applying the first two revisions only with 3- and 5-year waning applied to this preferred scenario.

Details of all Microsoft Excel revisions carried out by the ERG to the updated company model are provided in Appendix 4.

Table 53 ERG adjustments to company base case: oral cavity patients – pembrolizumab monotherapy versus cetuximab+PLAT+5-FU

Scenario/ERG amendment	Pembrolizumab monotherapy			Cetuximab+PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£48,945***	***1.688***	***2.401***	***£51,832***	***0.912***	***1.271***	***-£2,886***	***0.777***	***1.130***	***Dominant***	
R1) Using all patients from the cetuximab+ PLAT+5-FU arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab+PLAT+5-FU	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
R2) Using Weibull distribution for OS projections beyond 80 weeks	£47,644	1.422	1.996	£50,025	0.839	1.162	-£2,381	0.583	0.834	Dominant	-
R3) 3-year duration of treatment effect	£47,555	1.406	1.976	£51,832	0.912	1.271	-£4,276	0.494	0.705	Dominant	-
R4) 5-year duration of treatment effect	£48,283	1.554	2.195	£51,832	0.912	1.271	-£3,548	0.642	0.924	Dominant	-
R5) Limiting maximum number of cycles of PLAT+5-FU to 4	£48,945	1.688	2.401	£51,123	0.912	1.271	-£2,178	0.777	1.130	Dominant	-
B. ERG preferred scenario (R1, R2)	**£47,644**	**1.422**	**1.996**	**£50,025**	**0.839**	**1.162**	**-£2,381**	**0.583**	**0.834**	**Dominant**	-
C. ERG preferred scenario with 3-year duration of treatment effect (R1-R3)	**£46,390**	**1.174**	**1.628**	**£50,025**	**0.839**	**1.162**	**-£3,635**	**0.335**	**0.466**	**Dominant**	-
D. ERG preferred scenario with 5-year duration of treatment effect (R1, R2, R4)	**£46,907**	**1.282**	**1.786**	**£50,025**	**0.839**	**1.162**	**-£3,118**	**0.443**	**0.624**	**Dominant**	-

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year:

Table 54 ERG adjustments to company base case: oral cavity patients – pembrolizumab+ PLAT+5-FU versus cetuximab+ PLAT+5-FU

Scenario/ERG amendment	Pembrolizumab+PLAT+5-FU			Cetuximab+ PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£64,414***	***2.122***	***3.054***	***£52,597***	***0.845***	***1.178***	***£11,817***	***1.277***	***1.876***	***£9,255***	**-**
R1) Using all patients from the cetuximab+PLAT+5-FU arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab+PLAT+5-FU	£64,414	2.122	3.054	£51,832	0.912	1.271	£12,582	1.210	1.783	£10,398	+£1,143
R2) Using Weibull distribution for OS projections beyond 80 weeks	£61,956	1.771	2.517	£50,771	0.793	1.100	£11,185	0.978	1.417	£11,437	+£2,182
R3) 3-year duration of treatment effect	£59,489	1.403	1.966	£52,597	0.845	1.178	£6,892	0.558	0.788	£12,358	+£3,103
R4) 5-year duration of treatment effect	£61,097	1.661	2.349	£52,597	0.845	1.178	£8,500	0.816	1.171	£10,417	+£1,162
R5) Limiting maximum number of cycles of PLAT+5-FU to 4	£63,750	2.122	3.054	£51,888	0.845	1.178	£11,862	1.277	1.876	£9,290	+£35
B. ERG preferred scenario (R1, R2)	**£61,956**	**1.771**	**2.517**	**£50,025**	**0.839**	**1.162**	**£11,931**	**0.932**	**1.355**	**£12,802**	**+£3,547**
C. ERG preferred scenario with 3-year duration of treatment effect (R1-R3)	**£58,106**	**1.195**	**1.657**	**£50,025**	**0.839**	**1.162**	**£8,081**	**0.356**	**0.495**	**£22,699**	**+£13,444**
D. ERG preferred scenario with 5-year duration of treatment effect (R1, R2, R4)	**£59,129**	**1.389**	**1.940**	**£50,025**	**0.839**	**1.162**	**£9,104**	**0.550**	**0.778**	**£16,553**	**+£7,298**

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year

Table 55 ERG adjustments to company base case: non-oral cavity patients – pembrolizumab monotherapy versus PLAT+5-FU

Scenario/ERG amendment	Pembrolizumab monotherapy			PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£48,945***	***1.688***	***2.401***	***£20,616***	***0.781***	***1.097***	***£28,329***	***0.908***	***1.304***	***£31,212***	**-**
R1) Using all patients from the cetuximab+ PLAT+5-FU arm of KEYNOTE-048 trial to model OS, PFS and TTD for non-oral cavity patients receiving PLAT+5-FU	£48,945	1.688	2.401	£22,445	0.912	1.271	£26,501	0.777	1.130	£34,124	+£2,912
R2) Using Weibull distribution for OS projections beyond 80 weeks	£47,644	1.422	1.996	£20,472	0.752	1.054	£27,172	0.670	0.942	£40,546	+£9,334
R3) 3-year duration of treatment effect	£46,073	1.055	1.458	£20,616	0.781	1.097	£25,456	0.274	0.361	£92,888	+£61,676
R4) 5-year duration of treatment effect	£46,797	1.218	1.692	£20,616	0.781	1.097	£26,181	0.437	0.596	£59,846	+£28,634
R5) Limiting maximum number of cycles of PLAT+5-FU to 4	£48,945	1.688	2.401	£19,760	0.781	1.097	£29,185	0.908	1.304	£32,155	+£943
B. ERG preferred scenario (R1, R2)	**£47,644**	**1.422**	**1.996**	**£22,076**	**0.839**	**1.162**	**£25,568**	**0.583**	**0.834**	**£43,856**	**+£12,644**
C. ERG preferred scenario with 3-year duration of treatment effect (R1-R3)	**£46,390**	**1.174**	**1.628**	**£22,076**	**0.839**	**1.162**	**£24,315**	**0.335**	**0.466**	**£72,579**	**+£41,367**
D. ERG preferred scenario with 5-year duration of treatment effect (R1, R2, R4)	**£46,907**	**1.282**	**1.786**	**£22,076**	**0.839**	**1.162**	**£24,832**	**0.443**	**0.624**	**£56,085**	**+£24,873**

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year

Table 56 ERG adjustments to company base case: non-oral cavity patients – pembrolizumab+ PLAT+5-FU versus PLAT+5-FU

Scenario/ERG amendment	Pembrolizumab+PLAT+5-FU			PLAT+5-FU			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	***£64,414***	***2.122***	***3.054***	***£19,652***	***0.681***	***0.958***	***£44,762***	***1.441***	***2.096***	***£31,070***	**-**
R1) Using all patients from the cetuximab+ PLAT+5-FU arm of KEYNOTE-048 trial to model OS, PFS and TTD for non-oral cavity patients receiving PLAT+5-FU	£64,414	2.122	3.054	£22,445	0.912	1.271	£41,969	1.21	1.783	£34,685	+£3,615
R2) Using Weibull distribution for OS projections beyond 80 weeks	£61,956	1.771	2.517	£19,615	0.675	0.949	£42,341	1.096	1.568	£38,639	+£7,569
R3) 3-year duration of treatment effect	£58,013	1.186	1.645	£19,652	0.681	0.958	£38,361	0.504	0.687	£76,057	+£44,987
R4) 5-year duration of treatment effect	£58,933	1.370	1.913	£19,652	0.681	0.958	£39,281	0.689	0.955	£57,011	+£25,941
R5) Limiting maximum number of cycles of PLAT+5-FU to 4	£63,750	2.122	3.054	£18,796	0.681	0.958	£44,953	1.441	2.096	£31,202	+£132
B. ERG preferred scenario (R1, R2)	**£61,956**	**1.771**	**2.517**	**£22,076**	**0.839**	**1.162**	**£39,880**	**0.932**	**1.355**	**£42,790**	**+£11,720**
C. ERG preferred scenario with 3-year duration of treatment effect (R1-R3)	**£58,106**	**1.195**	**1.657**	**£22,076**	**0.839**	**1.162**	**£36,030**	**0.355**	**0.495**	**£101,375**	**+£70,305**
D. ERG preferred scenario with 5-year duration of treatment effect (R1, R2, R4)	**£59,129**	**1.389**	**1.940**	**£22,076**	**0.839**	**1.162**	**£37,053**	**0.550**	**0.778**	**£67,386**	**+£36,316**

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALY=quality adjusted life year

5.6.1 Conclusions of the cost effectiveness section

Oral cavity patients

In this ERG report, the ERG is unable to comment on the cost effectiveness of pembrolizumab monotherapy or pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU. Please see Confidential Appendix 1 where the ERG's conclusions are presented using the CAA price for pembrolizumab and the PAS price for cetuximab.

Non-oral cavity patients

The company's cost effectiveness results show that, at a willingness to pay threshold of £50,000 per QALY gained, treatment with pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus PLAT+5-FU are likely to be cost effective. However, the ERG considers that, as there are two interventions a full incremental cost effectiveness analysis is required. Table 57 shows the results of a full incremental cost effectiveness analysis using the ERG's preferred scenario (R1-R2).

Table 57 Incremental analysis for non-oral cavity patients

Treatment	Total costs	Total QALYS	Incremental costs	Incremental QALYs	ICER per QALY gained
PLAT+5-FU	£22,076	0.839	-	-	-
Pembrolizumab monotherapy	£47,644	1.422	£25,568	0.583	£43,856
Pembrolizumab+PLAT+5-FU	£61,956	1.771	£14,312	0.349	£41,009

Whilst noting that the results of any incremental analysis may change when treatment waning is taken into account, the incremental analysis suggests that a willingness to pay threshold of £50,000 per QALY gained that pembrolizumab+PLAT+5-FU is the most cost effective option for non-oral cavity patients.

6 END OF LIFE CRITERIA

A technology meets NICE End of Life criteria[59] if (i) life expectancy with standard of care treatments for the target population is under 24 months and (ii) the increase in life expectancy with the technology being appraised is at least 3 months.

In the CS (pp156-157), the company makes the case that pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU meet NICE End-of-Life criteria.

After applying the ERG revisions to the company model, mean OS for oral and non-oral cavity patients was around 12 months and mean life expectancy gain, even in the most pessimistic scenarios considered by the ERG, was over 3 months.

The ERG is, therefore, satisfied that pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU meet both components of the NICE End of Life criteria[59] for the populations under consideration when compared with treatment with either cetuximab+PLAT+5-FU or PLAT+5-FU.

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8 APPENDICES

8.1 Appendix 1 Statistical treatment switching adjustment methods

The company employed three statistical treatment switching adjustment methods: the simplified 2-stage method, the rank preserving structural failure time model (RPSFTM), and the inverse probability of censoring weights (IPCW) method. The company details how each of these methods were applied in Appendix L to the CS. In the company's base-case network meta-analyses (NMAs), the company uses OS data from the KEYNOTE-048 trial that have been adjusted for treatment switching using the simplified 2-stage method.

In the ERG clarification letter, the ERG asked the company to provide their rationale for using results from the simplified 2-stage method in the base-case NMAs, instead of using results from the RPSFTM or the IPCW method. In their response to the ERG clarification letter, the company highlighted that the IPCW method relies on the "no unmeasured confounders" assumption, i.e., data are available on all baseline and time-dependent prognostic factors for mortality that independently predict treatment switching. The company concluded that the IPCW method was unlikely to be the most appropriate method to adjust OS data from the KEYNOTE-048 trial for treatment switching, as data on important predictors of both mortality and treatment switching may be missing. The ERG agrees with the company's conclusion.

The company also provided details of the limitations of the RPSFTM approach. However, the ERG does not consider it necessary to discuss the strengths and limitations of the RPSFTM approach in detail here; this method cannot be used to adjust for treatment switching to a non-study therapy. The RPSFTM was developed to adjust for patients in the control arm switching to receive treatment that was given to patients in the experimental arm (and/or vice versa). The RPSFTM incorporates data on how long each individual spent "on treatment", i.e., received the experimental treatment, and "off treatment" i.e., received the control treatment; patients who were initially randomised to the experimental arm and patients who were initially randomised to the control arm are included in the analysis. However, the company has attempted to adjust for patients in the control arm switching to non-study therapy. In this case it is not possible to define "on treatment" and "off treatment" consistently across the intervention (pembrolizumab [monotherapy or combination therapy]) and control (cetuximab+PLAT+5-FU) arms. The company's exact methodology is not clear to the ERG, although the ERG considers it is likely that the company has misinterpreted the RPSFTM and concludes that the results of the RPSFTM are not reliable.

In addition, the company explained that the simplified 2-stage model is particularly suitable for adjusting for treatment switching that occurs soon after disease progression, as in the KEYNOTE-048 trial. Disease progression can be used as a secondary “baseline”, under the assumption that all patients are at a similar stage of disease at this time (a reasonable assumption in the context of the KEYNOTE-048 trial). An accelerated failure time model (including covariates measured at the time of progression and a covariate indicating treatment switch) can be fitted to the post-progression control group data to estimate the treatment effect received by patients who switched compared to control group patients who did not switch. The resulting acceleration factor can then be used to “shrink” the survival times of switching patients in order to derive a counterfactual dataset unaffected by switching. The company concludes, and the ERG agrees, that the simplified 2-stage method is the most appropriate method to adjust for treatment switching in the KEYNOTE-048 trial.

8.2 Appendix 2 Adverse events: pembrolizumab monotherapy and cetuximab+PLAT+5-FU (overall trial population).

Table 58 Drug-related adverse events by decreasing incidence (incidence ≥5% in either treatment group), pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (overall population)

Adverse event	Pembrolizumab monotherapy N=300	Cetuximab+PLAT+5-FU N=287
	n(%)	n(%)
One or more drug-relate AE	175 (58.3)	278 (96.9%)
Fatigue	43 (14.3)	83 (28.9)
Hypothyroidism	39 (13.0)	1 (0.3)
Rash	25 (8.3)	101 (35.2)
Pruritus	22 (7.3)	24 (8.4)
Decreased appetite	16 (5.3)	62 (21.6)
Diarrhoea	17 (5.7)	76 (26.5)
Anaemia	12 (4.0)	118 (41.1)
Nausea	12 (4.0)	131 (45.6)
Hyponatraemia	10 (3.3)	19 (6.6)
Constipation	9 (3.0)	31 (10.8)
Weight decreased	9 (3.0)	30 (10.5)
Mucosal inflammation	8 (2.7)	76 (26.5)
Alanine aminotransferase increased	7 (2.3)	15 (5.2)
Aesthenia	7 (2.3)	30 (10.5)
Vomiting	7 (2.3)	64 (22.3)
Dermatitis acneiform	6 (2.0)	82 (28.6)
Dry skin	6 (2.0)	27 (9.4)
Dysgeusia	6 (2.0)	15 (5.2)
Hypokalaemia	4 (1.3)	36 (12.5)
Thrombocytopenia	4 (1.3)	62 (21.6)
Hypomagnesaemia	3 (1.0)	95 (33.1)
Neutropenia	3 (1.0)	89 (31.0)
Blood creatinine increased	2 (0.7)	16 (5.6)
Leukopenia	2 (0.7)	38 (13.2)
Stomatitis	2 (0.7)	70 (24.4)
White blood cell count decreased	2 (0.7)	43 (15.0)
Hypophosphataemia	1 (0.3)	19 (6.6)
Infusion related reaction	1 (0.3)	16 (5.6)
Neutrophil count decreased	1 (0.3)	54 (18.8)
Palmar-plantar erythrodysaesthesia syndrome	1 (0.3)	20 (7.0)
Platelet count decreased	1(0.3)	46 (16.0)
Paronychia	0 (0.0)	34 (11.8)
Skin fissures	0 (0.0)	36 (12.5)
Tinnitus	0 (0.0)	16 (5.6)

AE=adverse event Source: Supplementary Document Appendices July 2019, Appendix F, Table 72

Table 59 Drug-related Grade 3 to 5 adverse events by decreasing incidence (incidence ≥5% in either treatment group), pembrolizumab monotherapy versus cetuximab+PLAT+5-FU l(overall population)

Adverse event	Pembrolizumab monotherapy N=300	Cetuximab+PLAT+5-FU N=287
	n(%)	n(%)
One or more drug-relate AE	51 (17.0)	199 (69.3)
Hyponatraemia	6 (2.0)	8 (2.8)
Pneumonitis	4 (1.3)	1 (0.3)
Fatigue	3 (1.0)	11 (3.8)
Anaemia	2 (0.7)	43 (15.0)
Mucosal inflammation	2 (0.7)	14 (4.9)
Rash	2 (0.7)	17 (5.9)
Aspartate aminotransferase increased	1 (0.3)	3 (1.0)
Asthenia	1 (0.3)	6 (2.1)
Decreased appetite	1 (0.3)	8 (2.8)
Dehydration	1 (0.3)	3 (1.0)
Diarrhoea	1 (0.3)	5 (1.7)
Hypokalaemia	1 (0.3)	11 (3.8)
Lymphocyte count decreased	1 (0.3)	6 (2.1)
Lymphopenia	1 (0.3)	4 (1.4)
Pneumonia	1 (0.3)	7 (2.4)
Thrombocytopenia	1 (0.3)	24 (8.4)
Abdominal pain	0 (0.0)	4 (1.4)
Dermatitis acneiform	0 (0.0)	6 (2.1)
Febrile neutropenia	0 (0.0)	13 (4.5)
Hyperkalaemia	0 (0.0)	3 (1.0)
Hypomagnesaemia	0 (0.0)	11 (3.8)
Hypophosphataemia	0 (0.0)	5 (1.7)
Infusion related reaction	0 (0.0)	3 (1.0)
Leukopenia	0 (0.0)	16 (5.6)
Nausea	0 (0.0)	16 (5.6)
Neutropenia	0 (0.0)	58 (20.2)
Neutrophil count decreased	0 (0.0)	35 (12.2)
Pancytopenia	0 (0.0)	3 (1.0)
Platelet count decreased	0 (0.0)	9 (3.1)
Stomatitis	0 (0.0)	10 (3.5)
Vomiting	0 (0.0)	5 (1.7)
White blood cell count decreased	0 (0.0)	22 (7.7)

AE=adverse event
Source: Supplementary Document Appendices July 2019, Appendix F, Table 74

Table 60 Drug-related serious adverse events by decreasing incidence (incidence ≥1% in either treatment group) pembrolizumab monotherapy versus cetuximab+PLAT+5-FU (overall population)

Adverse event	Pembrolizumab monotherapy N=300	Cetuximab+PLAT+5-FU N=287
	n(%)	n(%)
One or more drug-relate AE	28 (9.3)	72 (25.1)
Pneumonitis	3 (1.0)	1 (0.3)
Anaemia	1 (0.3)	8 (2.8)
Diarrhoea	1 (0.3)	4 (1.4)
Fatigue	1 (0.3)	3 (1.0)
Pneumonia	1 (0.3)	7 (2.4)
Febrile neutropenia	0 (0.0)	10 (3.5)
Infusion related reaction	0 (0.0)	3 (1.0)
Nausea	0 (0.0)	7 (2.4)
Neutropenia	0 (0.0)	4 (1.4)
Neutrophil count decreased	0 (0.0)	3 (1.0)
Stomatitis	0 (0.0)	4 (1.4)
Vomiting	0 (0.0)	3 (1.0)

AE=adverse event
Source: : Supplementary Document Appendices July 2019, Appendix F, Table 76

8.3 Appendix 3 Adverse events: pembrolizumab+PLAT+5-FU and cetuximab+PLAT+5-FU (overall trial population).

Table 61 Drug-related AEs by decreasing incidence (incidence ≥5% in one either treatment group), pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (overall population)

Adverse event	Pembrolizumab+PLAT+5-FU N=276	Cetuximab+PLAT+5-FU N=287
	n(%)	n(%)
One or more drug-related AE	264 (95.7)	278 (96.9)
Anaemia	134 (48.6)	118 (41.1)
Nausea	125 (45.3)	131 (45.6)
Neutropenia	91 (33.0)	89 (31.0)
Fatigue	84 (30.4)	83 (28.9)
Mucosal inflammation	77 (27.9)	76 (26.5)
Thrombocytopenia	75 (27.2)	62 (21.6)
Vomiting	75 (27.2)	64 (22.3)
Stomatitis	69 (25.0)	70 (24.4)
Decreased appetite	62 (22.5)	62 (21.6)
Platelet count decreased	51 (18.5)	46 (16.0)
Diarrhoea	50 (18.1)	76 (26.5)
Neutrophil count decreased	45 (16.3)	54 (18.8)
White blood cell count decreased	36 (13.0)	43 (15.0)
Hypothyroidism	36 (13.0)	1 (0.3)
Leukopenia	34 (12.3)	38 (13.2)
Aesthenia	32 (11.6)	30 (10.5)
Blood creatinine increased	31 (11.2)	16 (5.6)
Hypomagnesaemia	29 (10.5)	95 (33.1)
Constipation	28 (10.1)	31 (10.8)
Hyponatraemia	23 (8.3)	19 (6.6)
Rash	23 (8.3)	101 (35.2)
Febrile neutropenia	22 (8.0)	13 (4.5)
Weight decreased	21 (7.6)	30 (10.5)
Malaise	18 (6.5)	9 (3.1)
Dysgeusia	16 (5.8)	15 (5.2)
Hypokalaemia	16 (5.8)	36 (12.5)
Pyrexia	16 (5.8)	12 (4.2)
Acute kidney injury	15 (5.4)	6 (2.1)
Peripheral sensory neuropathy	15 (5.4)	6 (2.1)
Tinnitus	15 (5.4)	16 (5.6)
Pruritus	14 (5.1)	24 (8.4)
Alanine aminotransferase increased	9 (3.3)	15 (5.2)
Lymphopenia	7 (2.5)	15 (5.2)
Hypophosphataemia	6 (2.2)	19 (6.6)
Dry skin	5 (1.8)	27 (9.4)
Palmar-plantar erythrodysaesthesia syndrome	4 (1.4)	20 (7.0)
Infusion related reaction	2 (0.7)	16 (5.6)
Skin fissures	2 (0.7)	36 (12.5)

Dermatitis acneiform	1 (0.4)	82 (28.6)
Paronychia	0 (0.0)	34 (11.8)

AE=adverse event
Source: Supplementary Document Appendices July 2019, Appendix F, Table 82

Table 62 Drug-related Grade 3 to 5 adverse events by decreasing incidence (incidence ≥1% in either treatment group), pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (overall population)

Adverse event	Pembrolizumab monotherapy N=276	Cetuximab+PLAT+5-FU N=287
	n(%)	n(%)
One or more drug-related AE	198 (71.7)	199 (69.3)
Anaemia	54 (19.6)	43 (15.0)
Neutropenia	49 (17.8)	58 (20.2)
Neutrophil count decreased	27 (9.8)	35 (12.2)
Mucosal inflammation	26 (9.4)	14 (4.9)
Thrombocytopenia	24 (8.7)	24 (8.4)
Stomatitis	22 (8.0)	10 (3.5)
Febrile neutropenia	22 (8.0)	13 (4.5)
Fatigue	19 (6.9)	11 (3.8)
Nausea	15 (5.4)	16 (5.6)
White blood cell count decreased	15 (5.4)	22 (7.7)
Platelet count decreased	14 (5.1)	9 (3.1)
Decreased appetite	12 (4.3)	8 (2.8)
Hyponatraemia	10 (3.6)	8 (2.8)
Hypokalaemia	9 (3.3)	11 (3.8)
Lymphocyte count decreased	9 (3.3)	6 (2.1)
Leukopenia	8 (2.9)	16 (5.6)
Aesthenia	7 (2.5)	6 (2.1)
Vomiting	7 (2.5)	5 (1.7)
Septic shock	6 (2.2)	0 (0.0)
Pneumonia	5 (1.8)	7 (2.4)
Acute kidney injury	4 (1.4)	1 (0.3)
Syncope	4 (1.4)	2 (0.7)
Diarrhoea	3 (1.1)	5 (1.7)
Hyperglycaemia	3 (1.1)	0 (0.0)
Hypotension	3 (1.1)	0 (0.0)
Hypomagnesaemia	3 (1.1)	11 (3.8)
Peripheral sensory neuropathy	3 (1.1)	2 (0.7)
Pneumonitis	3 (1.1)	1 (0.3)
Aspartate aminotransferase increased	1 (0.4)	3 (1.0)
Hypophosphataemia	2 (0.7)	5 (1.7)
Pancytopenia	2 (0.7)	3 (1.0)
Abdominal pain	1 (0.4)	4 (1.4)
Dehydration	1 (0.4)	3 (1.0)
Lymphopenia	1 (0.4)	4 (1.4)
Rash	1 (0.4)	17 (5.9)
Dermatitis acneiform	0 (0.0)	6 (2.1)
Hyperkalaemia	0 (0.0)	3 (1.0)
Infusion-related reaction	0 (0.0)	3 (1.0)

AE=adverse event
Source: Supplementary Document Appendices July 2019, Appendix F, Table 84

Table 63 Drug-related serious adverse events by decreasing incidence (incidence ≥1% in either treatment group) pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU (overall population)

Adverse event	Pembrolizumab monotherapy N=276	Cetuximab+PLAT+5-FU N=287
	n(%)	n(%)
One or more drug-related AE	103 (37.0)	72 (25.1)
Febrile neutropenia	15 (5.4)	10 (3.5)
Anaemia	11 (4.0)	8 (2.8)
Stomatitis	8 (2.9)	4 (1.4)
Neutropenia	6 (2.2)	4 (1.4)
Mucosal inflammation	6 (2.2)	1 (0.3)
Nausea	6 (2.2)	7 (2.4)
Septic shock	6 (2.2)	0 (0.0)
Thrombocytopenia	6 (2.2)	0 (0.0)
Acute kidney injury	5 (1.8)	1 (0.3)
Decreased appetite	5 (1.8)	2 (0.7)
Pneumonia	5 (1.8)	7 (2.4)
Hyponatraemia	4 (1.4)	0 (0.0)
Interstitial lung disease	3 (1.1)	1 (0.3)
Platelet count decreased	3 (1.1)	1 (0.3)
Vomiting	3 (1.1)	3 (1.0)
Fatigue	1 (0.4)	3 (1.0)
Diarrhoea	0 (0.0)	4 (1.4)
Infusion related reaction	0 (0.0)	3 (1.0)
Neutrophil count decreased	0 (0.0)	3 (1.0)

AE=adverse event
Source: Supplementary Document Appendices July 2019, Appendix F, Table 86

8.4 Appendix 4 ERG revisions to the company model

Instructions detailing the ERG's revisions to the company model are described in Table 64.

Table 64 ERG instructions re company model

ERG Section 5 results table revision	Implementation instructions
R1. Using all patients from the cetuximab+PLAT+5-FU arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab+PLAT+5-FU	**For ORAL cavity patients only** No change in model. Use costs and QALYs generated for cetuximab+PLAT+5-FU when pembrolizumab monotherapy is the intervention for when pembrolizumab+PLAT+5-FU is the intervention **For NON-ORAL cavity patients only** In Sheet 'costs' Set value in cell E88=0 Set value in cell E89=0 Set value in cell E90=0 Set value in cell E140=0 Set value in cell E141=0 Use costs and QALYs generated for cetuximab+PLAT+5-FU when pembrolizumab monotherapy is the intervention for when pembrolizumab+PLAT+5-FU is the intervention
R2) Using Weibull distribution for OS projections beyond 80 weeks	In Sheet 'Survival' Set value in cell H15="Weibull"
R3) 3-year duration of treatment effect	In Sheet 'PSM' Set value in cell CF18=CHOOSE(F18,CE18,(CF17*(IFERROR(CJ18/CJ17,0)))) Copy cell formula from CF18 to range CF2097 In Sheet 'Settings' Set value in cell H47="3 years"
R4) 5-year duration of treatment effect	In Sheet 'PSM' Set value in cell CF18=CHOOSE(F18,CE18,(CF17*(IFERROR(CJ18/CJ17,0)))) Copy cell formula from CF18 to range CF2097 In Sheet 'Settings' Set value in cell H47="5 years"

ERG Section 5 results table revision	Implementation instructions
R5) Limiting maximum number of cycles of PLAT+5-FU to 4	**When intervention = pembrolizumab+PLAT+5-FU** In Sheet 'costs' Set value in cell I25=3 Set value in cell L25=3 Set value in cell O25=3 **When comparator = PLAT+5-FU** In Sheet 'costs' Set value in cell F64=3 Set value in cell I64=3 Set value in cell L64=3 **When comparator = cetuximab+PLAT+5-FU** In Sheet 'costs' Set value in cell I64=3 Set value in cell L64=3 Set value in cell O64=3

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 2 September 2019** 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.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 PD-L1 expression definition

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
At the end of paragraph of section 1.2 on page 10 it states that "At baseline, a pre-defined subgroup of 754 patients in the KEYNOTE-048 trial had tumours that tested positive for PD-L1 expression."	The sentence should be changed to: "At baseline, a pre-defined subgroup of 754 patients in the KEYNOTE-048 trial had tumours that tested positive for PD-L1 expression defined as a combined positive score (CPS) ≥1."	To remove the potential for ambiguity.	Thank you. The text has been updated to include 'defined as a combined positive score (CPS) ≥1'.

Issue 2 Incremental QALYs incorrect

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 1 on page 23, Incremental QALYs for Pembrolizumab monotherapy is 0.834, which is incorrect.	This should be changed to 0.583.	Minor number incorrect. Wider impact negligible.	Thank you. The table has been amended as advised.

Issue 3 Teleconference clarification

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 3.1 under the "Population in the licensed indications" subheading, on page 32 it states that "During the clarification telephone conference, the company explained that treatment with pembrolizumab+PLAT+5-FU would	This was not the description we provided and so this sentence should be changed to: "During the clarification telephone conference, the company explained that treatment with pembrolizumab+PLAT+5-FU would be most suitable for patients for whom a rapid response was desirable, as is MSD's	To clarify an explanation we gave.	Thank you for the clarification. The text has been amended to: During the clarification telephone conference, the company explained that treatment with pembrolizumab+PLAT+5-FU

be most suitable for patients who were so unwell that it would be unethical to prescribe pembrolizumab monotherapy due to the delayed response (circa 3 to 6 months) that is characteristic of immunotherapy treatments", which is incorrect.	understanding from treating clinicians".		would be most suitable for patients for whom a rapid response is desirable.

Issue 4 Patient demographics typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 7 on page 41, row 9 column 2, number (%) with Race information Missing in the Pembrolizumab + PLAT+5-FU arm, the number shown is "2 (0.8)", which is incorrect.	This should be changed to: "0 (0.0)", to match Table 9 of the CS.	Minor number incorrect. Wider impact negligible.	Thank you. The value has been amended as advised.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 20 on page 50, Number of patients for Pembrolizumab monotherapy, the number shown in 237, which is incorrect.	This should be changed to 256, to match Table 46 of the Supplementary Document (July 2019).	Minor number incorrect. Wider impact negligible.	Thank you. The value has been amended as advised.

Issue 6 Adverse event typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57 under the "Grade 3-5 drug-related adverse events" subheading, it is stated that the proportion of patients who experienced anaemia in the cetuximab+PLAT+5-FU arm is 14.6%, which is incorrect.	This should be changed to 15.0%, to match Table 74 of the Supplementary Document – Appendices (July 2019).	Minor number incorrect. Wider impact negligible.	Thank you. The value has been amended as advised.

Issue 7 Adverse events typo 2

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 57 under the "Drug-related serious adverse events" subheading, it is stated that "The data in Table 60 (Appendix 2) show that fewer patients in the pembrolizumab monotherapy arm experienced a SAE (incidence of ≥1%) compared with the cetuximab+PLAT+5-FU arm (9.0% vs 25.4%)", which is incorrect.	This should be changed to "The data in Table 60 (Appendix 2) show that fewer patients in the pembrolizumab monotherapy arm experienced a drug-related SAE (incidence of ≥1%) compared with the cetuximab+PLAT+5-FU arm (9.3% vs 25.1%)", to match Table 76 of the Supplementary Document – Appendices (July 2019).	Minor numbers incorrect. Wider impact negligible.	Thank you. The values have been amended as advised.

Issue 8 Patients numbers typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Table 21 on page 59, Number of patients for Pembrolizumab+PLAT+5-FU and Cetuximab+PLAT+5-FU are shown as 276 and 287, respectively, which are incorrect.	These should be changed to 237 and 245 for embrolizumab+PLAT+5-FU and Cetuximab+PLAT+5-FU, respectively, to match Table 47 of the Supplementary Document (July 2019).	Minor numbers incorrect. Wider impact negligible.	Thank you. The values have been amended as advised.

Issue 9 Mis-labelling of treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 60 under the "Grade 3-4 drug-related adverse events" "ERG agrees with the company that, compared with the pembrolizumab monotherapy arm, rates of all Grade 3 to Grade 5 drug-related AEs were greater in the cetuximab+PLAT+5-FU arm."	"ERG agrees with the company that, compared with the pembrolizumab+PLAT+5-FU arm, rates of all Grade 3 to Grade 5 drug-related AEs were similar to the cetuximab+PLAT+5-FU arm."	This is under the pembrolizumab+PLAT+5-FU section not the pembrolizumab monotherapy	Thank you. The text has been amended as advised.

Issue 10 Adverse event typo 3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 60 under the "Adverse events of special interest" subheading, it is that: • Patients in the pembrolizumab+PLAT+5-FU arm had higher rates of hypothyroidism (15.2% versus 6.3%), pneumonitis (5.4% vs 1.0%), hyperthyroidism (4.7% versus 1.0%) and colitis compared with patients in the cetuximab+PLAT+5-FU arm The values underlined above are incorrect.	The sentence should be changed to: • Patients in the pembrolizumab+PLAT+5-FU arm had higher rates of hypothyroidism (15.9% versus 6.3%), pneumonitis (5.4% vs 1.0%), hyperthyroidism (4.3% versus 1.0%) and colitis compared with patients in the cetuximab+PLAT+5-FU arm In order to match Table 90 of the Supplementary Document – Appendices (July 2019).	Minor numbers incorrect. Wider impact negligible.	Thank you. The values have been amended as advised.

Issue 11 Adverse event typo 4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 60 under the "Adverse events of special interest" subheading, it is that: • Fewer patients in the pembrolizumab arm discontinued treatment due to a drug-related AEOSI (2.3% versus 6.6%) than patients in the cetuximab+PLAT+5-FU arm. This statement is incorrect.	The sentence should be changed to: • Fewer patients in the pembrolizumab+PLAT+5-FU arm discontinued treatment due to a drug-related AEOSI (3.3% versus 6.6%) than patients in the cetuximab+PLAT+5-FU arm. In order to match Table 89 of the Supplementary Document – Appendices (July 2019).	Minor wording and number incorrect. Wider impact negligible.	Thank you. The values and text have been amended as advised.

Issue 12 Fractional polynomials typo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 78 it states that: "The company's model selection process identified the best fitting model for PFS for both of the comparisons of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and versus PLAT+5-FU to be the second-order fractional polynomial with p1=0 and p2=-1." This statement is incorrect.	The sentence should be amended to note that the best fitting model for PFS for the comparison of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and versus PLAT+5-FU, the second-order fractional polynomial with p1=0 and p2=0.5, in order to match Section B.2.9.2 of the Supplementary Document (July 2019) and Table 9 of the Supplementary Document – Appendices (July 2019)	Minor numbers incorrect. Wider impact negligible.	Thank you for the clarification. The text has been amended to read: The company's model selection process identified the best fitting model for PFS for the comparisons of pembrolizumab monotherapy versus cetuximab+PLAT+5-FU and versus PLAT+5-FU to be the second-order fractional polynomial with p1=0 and p2=-1, and for the comparisons of pembrolizumab+PLAT+5-FU versus cetuximab+PLAT+5-FU and versus PLAT+5-FU to be the second-order fractional polynomial with p1=0 and p2=0.5

Issue 13 Incorrect description of progression-free survival modelling

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 90

The data contained in this table is incorrect.

Table 1 Approach used by the company to model progression-free survival</td>
<td>Table 2 Approach used by the company to model progression-free survival
<table>
<tr><th>Treatment</th><th>Company approach to modelling overall survival</th></tr>
<tr><td colspan="2">Comparisons with pembrolizumab monotherapy</td></tr>
<tr><td>Pembrolizumab monotherapy</td><td>KEYNOTE-048 trial data to 52 weeks, then exponential function</td></tr>
<tr><td>Cetuximab+PLAT+5-FU</td><td>KEYNOTE-048 trial data to 52 weeks, then exponential function</td></tr>
<tr><td>PLAT+5-FU</td><td>HR from company NMA applied to pembrolizumab monotherapy representation of PFS</td></tr>
<tr><td colspan="2">Comparisons with pembrolizumab+PLAT+5-FU</td></tr>
<tr><td>Pembrolizumab+PLAT+5-FU</td><td>KEYNOTE-048 trial data to 52 weeks then exponential function</td></tr>
<tr><td>Cetuximab+PLAT+5-FU</td><td>KEYNOTE-048 trial K-M data to 52 weeks, then exponential function</td></tr>
<tr><td>PLAT+5-FU</td><td>HR from company NMA applied to pembrolizumab+PLAT+5-FU representation of PFS</td></tr>
</table>
HR=hazard ratio; K-M=Kaplan-Meier; NMA=network meta-analysis; OS=overall survival
Source: Supplementary Document (July 2019)</td>
<td>Stated cut points are incorrect.</td>
<td>The cut points have been amended as advised.</td>
</tr>
</table>

Issue 14 Incorrect description of methodology in TSD 14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 104 it says "Thus, clinical plausibility is the only approach that can be used to select the most appropriate of these distributions."	"Thus, clinical plausibility and validation against external data are the only approaches that can be used to select the most appropriate of these distributions."	External data is another key source of model validation outlined in TSD 14.	The ERG did not quote from the TSD publication. The ERG considered that clinical plausibility was the only option remaining when choosing the most appropriate distribution. The ERG considers that this approach should include review of external data to assess clinical plausibility. No change is required.

Issue 15 Unsubstantiated statement regarding plausible survival extrapolations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 104 it says "The ERG considers that the log-normal and log-logistic distributions are frequently shown to poorly represent OS for patients with cancer."	Remove statement entirely.	Whilst this is the ERGs opinion, it is not supported by any presented evidence and is contradictory to the long-term evidence for pembrolizumab.	This is not a factual inaccuracy but an opinion. In the report, the ERG provides details and explains why the log-normal and log-logistic distributions are clinically implausible in the long-term for pembrolizumab. No change is required.

Issue 16 ERG survival assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 104 it says "The ERG notes that, when the Weibull distribution is used to extrapolate cetuximab+PLAT+5-FU KEYNOTE-048 trial OS K-M data, it potentially underestimates OS by a percentage point compared to data from the EXTREME trial for the cetuximab+PLAT+5-FU arm at 5 years, but still provides clinically plausible OS projections over 5 years, and does not produce a clinically implausible survival tail."	"The ERG notes that, when the Weibull distribution is used to extrapolate cetuximab+PLAT+5-FU KEYNOTE-048 trial OS K-M data, it potentially underestimates OS by a percentage point compared to data from the EXTREME trial for the cetuximab+PLAT+5-FU arm at 5 years.	Given the loglogistic (for monotherapy) and lognormal (for combination therapy) provide overall survival estimates that better match the data, MSD do not believe the final part of that statement can be factually accurate.	Please see ERG response to issues 14 and 15. This is not a factual inaccuracy and no change is required.

Issue 17 Description of trial entry criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 105 it says "Evidence from the KEYNOTE-048 trial is only for patients (oral and non-oral cavity) who were fit enough to receive cetuximab+PLAT+F-5U. No data have been provided that demonstrate the effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU for those patients (oral and non-oral cavity) who are not fit enough to be receive cetuximab+PLAT+5-FU."	"Evidence from the KEYNOTE-048 trial is only for patients (oral and non-oral cavity) who were PS 0-1 and met the other inclusion criteria for the trial. No data have been provided that demonstrate the effectiveness of pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU for those patients (oral and non-oral cavity) who did not meet these inclusion criteria."	This more accurately described the enrolled criteria for KEYNOTE-048	This is not a factual inaccuracy and this specific inclusion criterion is one that the ERG considered was pertinent to the submission and so needed to be highlighted. No change is required.

Issue 18 Description of ERG assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 106 it says "This means that data from the cetuximab+PLAT+5-FU arm can be used to represent the experience of patients with oral cancer treated with PLAT+5-FU"	As the ERG state they do not consider PLAT+5-FU to be a comparator for oral cavity patients, we presume this is an error and should instead read "This means that data from the cetuximab+PLAT+5-FU arm can be used to represent the experience of patients with non-oral cancer treated with PLAT+5-FU"	MSD assume this is a typo.	This is a typo and has been corrected to: "This means that data from the cetuximab+PLAT+5-FU arm can be used to represent the experience of patients with non-oral cancer treated with PLAT+5-FU."

Issue 19 Presentation of ERG results typo 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 113, table 55 **Scenario B. ERG preferred scenario (R1,R2)** **Incremental QALYs** | **Incremental LYs** **0.834** | **1.162**	Amend to **Incremental QALYs** | **Incremental LYs** **0.583** | **0.834**	Incorrect incremental QALYs and life years	This is a typo and has been corrected with the proposed amendment.

Issue 20 Presentation of ERG results typo 2

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 114, table 56

Scenario C. ERG preferred scenario with 3-year duration of treatment effect (R1-R3)
<table>
<tr><th>Inc. Cost</th><th>Inc. QALYs</th><th>Inc. LYs</th><th>£/QALY</th><th>Change from base case</th></tr>
<tr><td>36,550</td><td>0.402</td><td>0.557</td><td>91,028</td><td>+59,958</td></tr>
</table>
</td>
<td>Amend to

<table>
<tr><th>Inc. Cost</th><th>Inc. QALYs</th><th>Inc. LYs</th><th>£/QALY</th><th>Change from base case</th></tr>
<tr><td>36,030</td><td>0.355</td><td>0.495</td><td>101,375</td><td>+70,305</td></tr>
</table>
</td>
<td>Incorrect calculations of incremental QALYs and life years for ERG scenario</td>
<td>This is a typo and has been corrected with the proposed amendment.</td>
</tr>
</table>

Issue 21 Presentation of ERG results typo 3

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 114, table 56

Scenario D. ERG preferred scenario with 3-year duration of treatment effect (R1, R2, R4)
<table>
<tr><th>Inc. Cost</th><th>Inc. QALYs</th><th>Inc. LYs</th><th>£/QALY</th><th>Change from base case</th></tr>
<tr><td>37,537</td><td>0.596</td><td>0.840</td><td>63,044</td><td>+31,974</td></tr>
</table>
</td>
<td>Amend to

<table>
<tr><th>Inc. Cost</th><th>Inc. QALYs</th><th>Inc. LYs</th><th>£/QALY</th><th>Change from base case</th></tr>
<tr><td>37,053</td><td>0.550</td><td>0.778</td><td>67,386</td><td>+36,316</td></tr>
</table>
</td>
<td>Incorrect calculations of incremental QALYs and life years for ERG scenario</td>
<td>This is a typo and has been corrected with the proposed amendment.</td>
</tr>
</table>

NICE National Institute for Health and Care Excellence

Technical engagement response form

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical 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 questions below. You do not have to answer every question. 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 summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **18 October 2019**

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 technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- 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. 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)	Merck Sharp & Dohme
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Neither [redacted] nor Merck Sharp & Dohme have any past or current, direct or indirect links to, or funding from, the tobacco industry.

Questions for engagement

Issue 1: 2-year stopping rule for pembrolizumab	
Is a 2-year stopping rule for pembrolizumab appropriate?	Though Keynote 048 protocol states that treatment should continue until disease progression or unacceptable toxicity, the maximum possible treatment duration with pembrolizumab monotherapy and combination was 35 cycles. Implementing a 2-year stopping rule is consistent with other NICE technology appraisal guidance such as untreated NSCLC (TA531 and TA557). This was confirmed by the clinical experts during the technical engagement call.
Issue 2: Treatment choice	
What factors affect the decision on whether pembrolizumab monotherapy is preferred over pembrolizumab combination therapy? In particular: • Which patients would likely receive pembrolizumab monotherapy? • Which patients would likely receive pembrolizumab combination therapy?	After conducting interviews with clinicians, the consensus was the decision to use either monotherapy or combination therapy will be done on a case-by-case basis where clinicians practising patient-centred care will, in discussion with patients, determine the benefit versus the risk of either monotherapy or combination therapy regimen and administer based on a mutual discussion. As further discussed below, factors that will be assessed on an individual basis will include rate of tumour growth, patient fitness, and risk versus benefit in each situation. Fast-growing tumours will require a more immediate response to reduce proliferation of the cancer cells; as such the combination therapy will enable a quick response. According to clinician feedback, there will be a percentage of patients who will have these rapid growing tumours and will be fit enough to tolerate combination therapy. There will also be recurrent patients who have relapsed after having chemotherapy as part of multi-modality treatment with radiation and/or surgery; for these cohort of patients the combination therapy would prove beneficial. When clinicians were asked to give in their view what proportion of patients would have the required fitness to be administered the combination therapy, the response was within the intended requirement

	for use CPS ≥1 with a PS 0 – 1, any patient who requires combination therapy should be able to tolerate the combination therapy. In summary, the decision between monotherapy and combination therapy will be done on a case-by-case basis where clinicians practising patient-centred care will, in discussion with patients, determine the benefit versus the risk of either monotherapy or combination therapy regimen and administer based on a mutual discussion, based on the following: • Monotherapy patients will be those patients with a low burden of disease with the tumour rate not faster than usual and who may not be fit to tolerate combination therapy. • Combination therapy will be used in patients with a very heavy burden of disease, with the disease progressing rapidly. Even with the burden of disease, clinician feedback is there will be a proportion of these patients who will be fit enough to be administered the combination therapy. They will also be patients who have relapsed after having chemotherapy treatment. The questionnaire used to illicit responses from clinical experts by MSD has been included as an appendix.
Issue 3: Generalisability of KEYNOTE-048 results: Cetuximab as a comparator	
Are the results from the KEYNOTE trial generalisable to all patients with recurrent or metastatic head and neck squamous cell carcinoma whose tumours expressed PD-L1 with a CPS≥1 irrespective of where the cancer started?	The results of the KEYNOTE-048 study presented as part of the company's submission for patients whose tumours expressed PD-L1 with a combined positive score ≥1 are generalisable to all patients with recurrent or metastatic head and neck squamous cell carcinoma whose tumours expressed PD-L1 with a combined positive score ≥1 irrespective of where the cancer started. This is because the baseline characteristics of these patients in the KEYNOTE-048 study are similar to these patients who will be encountered in United Kingdom clinical practice. With regard to the specific concern raised that "if cetuximab in combination with platinum chemotherapy 5-fluorouracil is less effective in patients whose cancer starts outside the oral cavity than in those whose cancer starts in the oral cavity, the effectiveness of pembrolizumab monotherapy or pembrolizumab combination therapy may be overestimated for patients with cancer starting outside the oral cavity seen in NHS clinical practice", it should be noted that the appropriate comparator to

pembrolizumab monotherapy or pembrolizumab combination therapy for patients with cancer starting outside the oral cavity seen in National Health Service clinical practice is platinum-based chemotherapy plus 5-fluorouracil (not cetuximab in combination with platinum chemotherapy 5-fluorouracil), and the company have made this comparison in the manufacturer's submission via the network meta-analyses that would yield results that would be generalisable to patient with cancer starting outside the oral cavity (described in more detail in the response to the next issue).

Furthermore, the results of the KEYNOTE-048 study show that the overall survival of patients with PD-L1 combined positive score ≥1 treated with cetuximab in combination with platinum chemotherapy 5-fluorouracil are very similar between those patients whose cancer originated in the oral cavity and those patients irrespective of where the cancer started:

Patient population	**Treatment with cetuximab in combination with platinum and 5-fluorouracil chemotherapy**
	Median overall survival, intention-to-treat analysis, KEYNOTE-048 study, Months (95% confidence interval)
Patients with PD-L1 combined positive score ≥1 irrespective of where the cancer started (n=255)	10.3 (9.0, 11.5)
Patients with PD-L1 combined positive score ≥1 and whose cancer originated in the oral cavity* (academic/commercial in confidence information removed)	academic/commercial in confidence information removed
Database Cut-off Date: 25 February 2019.	

	These KEYNOTE-048 trial data therefore do not show that cetuximab in combination with platinum chemotherapy plus 5-fluorouracil is less effective in patients whose cancer starts outside the oral cavity. Additionally, the data from the EXTREME study also do not show a difference in the effectiveness of treatment with cetuximab in combination with platinum chemotherapy plus 5-flurouracil between patients whose cancer originated in different sites (oral cavity versus non-oral cavity), this is explained in greater detail in the response to Issue 4.
Is it appropriate to consider subgroups by cancer location?	For the purpose of this appraisal, it is not feasible to rigorously consider subgroups by cancer location as the KEYNOTE-048 study was not pre-specified to conduct subgroup analyses based on cancer location. Consequently, the study was not sufficiently powered to detect statistically significant differences between the interventions in these specific subgroups due to the small number of patients in these subgroups, and due to the imbalance in important baseline characteristics of patients in the different treatment groups (i.e. randomisation would be broken for comparisons made in these subgroups). Therefore, it is not possible to consider subgroups by cancer location using the available information on pembrolizumab. There is also no underlying biological rationale for why the clinical effectiveness of pembrolizumab would differ depending on cancer location in the head and neck. It is important to note that the restriction of cetuximab in combination with platinum chemotherapy and 5-fluorouracil to only patients with oral cavity cancer in United Kingdom clinical practice is due primarily to cost/cost-effectiveness considerations in the original TA172 appraisal as opposed to any rationale based on the underlying biology of the disease, as it is stated in section 4.3 (and noted again in section 4.15) of the Final Appraisal Determination document of TA172 that “the specialists were not aware of any biological reason for cetuximab to be more clinically effective in oral cavity tumours”, which is in line with clinical expert advice that Merck Sharp and Dohme have also received. Indeed, the regulatory approval given to cetuximab for treatment of patients with squamous cell cancer of the head neck by the European Medicines Agency, whose decisions are based only on clinical considerations, is not restricted to patients with cancer originating in the oral cavity. The results of the EXTREME study did not actually show that the efficacy of cetuximab in combination with platinum chemotherapy and 5-fluorouracil, either in absolute terms or in comparison to platinum-based chemotherapy plus 5-fluorouracil, differs by cancer location (this is described in greater detail in

	the response to Issue 4). The results of the KEYNOTE-048 study also do not suggest the efficacy of cetuximab in combination with platinum chemotherapy and 5-fluorouracil differs depending on tumour location (as described in the response above).
Issue 4: Network meta-analyses: comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil	
Mindful that there are challenges with all approaches for comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil (5-FU), which is the best comparison to use in this appraisal? • the company's network meta-analyses? **or** • the ERG's approach to using data from the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048 as a proxy for the effect of treatment with platinum chemotherapy and 5-FU?	Merck Sharp & Dohme believe that the company's network meta-analysis is the best comparison to use in this appraisal, as it is based on a comparison of the actual interventions of interest, via an established analytical method, that takes into account the study-observed differences between the treatment effects of the different interventions, and produces results that are generalisable to/more likely to reflect the true relative effectiveness of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil including from the perspective of patients whose cancer originated outside the oral cavity. While there may be uncertainties associated with the company's network meta-analysis (sources of uncertainty that are commonly associated with network meta-analyses, a well-established methodology for making indirect treatment comparisons), the Evidence Review Group's approach is reliant upon underlying assumptions that are associated with no less uncertainty than the company's approach and also introduce additional bias/overestimation of comparator treatment effect that the Evidence Review Group themselves note exist, as well as additional bias/overestimation of comparator treatment effect and cost-effectiveness arising from the implementation of the approach: The Evidence Review Group's approach assumes that the relative efficacy, in terms of overall survival, of cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil differs significantly between patients who had cancer that started in the oral cavity and patients whose cancer originated elsewhere in the head and neck. However, the data from the EXTREME study presented in Table 33 of the ID1140 Evidence Review Group Report to support this assertion show that the 95% confidence intervals for the overall survival hazard ratios for cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil in the oral cavity patients subgroup and in each of the non-oral cavity patients subgroups (oropharynx, larynx, and hypopharynx) overlap, which does not show that the efficacy in terms of overall survival of

	cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil differs significantly between patients whose cancer started in the oral cavity and those whose cancer did not. It is actually noted in section 4.3 (and again in section 4.15) of the Final Appraisal Determination document of the TA172 assessment of cetuximab in this indication where this data was first presented to NICE that "the specialists were not aware of any biological reason for cetuximab to be more clinically effective in oral cavity tumours". The Evidence Review Group also raised in their report (in section 4.9.7) the possibility that the company's network meta-analysis, by not stratifying by oral cavity versus non-oral cavity patients, may underestimate the true overall survival for non-oral cavity patients who receive platinum-based chemotherapy plus 5-fluorouracil, based on results from the EXTREME study which suggest that median overall survival for oral cavity patients receiving platinum-based chemotherapy plus 5-fluorouracil is approximately half that of non-oral cavity patients receiving platinum-based chemotherapy plus 5-fluorouracil (presented in Table 33 of the ID1140 Evidence Review Group Report). However, those median overall survival values are for the point estimates only, without confidence intervals, and not from an adequately powered statistical analysis to compare the relative effectiveness of platinum-based chemotherapy plus 5-fluorouracil in between patient subgroups with different primary tumour locations. Therefore, these point-estimates of median overall survival do not demonstrate with confidence that the true overall survival (or clinical effectiveness) associated with treatment with platinum-based chemotherapy plus 5-fluorouracil differs between patients whose cancer originated in the oral cavity and patients whose cancer originated outside the oral cavity. The Evidence Review Group's approach also assumes that in patients whose cancer did not start in the oral cavity, the effectiveness of cetuximab in combination with platinum chemotherapy plus 5-fluorouracil is the same as that of platinum chemotherapy plus 5-fluorouracil. This assumption is based on the results of the subgroup analyses of the EXTREME study which found a statistically significant difference in overall survival (hazard ratios) between patients treated with cetuximab in combination with platinum chemotherapy plus 5-fluorouracil versus platinum chemotherapy plus 5-fluorouracil in the oral cavity site of tumour origin subgroup but did not find statistically significant differences between these treatment regimens in patients in the oropharynx, hypopharynx, larynx, and "other" sites of tumour origin subgroups (each subgroup analysed separately). However, the

	EXTREME study was only adequately powered to detect a statistically significant difference between treatment regimens in terms of overall survival in the full population (as described in section 6.3.5 of the manufacturer's submission for TA172 for cetuximab in this indication, which stated that 420 patients needed to be randomised for the analysis to be adequately powered) and so the subgroup analyses by site of tumour origin (where the numbers of patients in the subgroups ranged from only 32 to 149) were not sufficiently powered to detect statistically significant differences between the treatment regimens. Furthermore, randomisation in the EXTREME study was stratified only by patients' previous chemotherapy (yes/no) and Karnofsky score (<80/≥80) therefore randomisation was very likely to have been broken for the site of tumour origin subgroup analyses, further compromising the validity of the results of these analyses. Therefore, the statistically non-significant results in the non-oral cavity subgroups do not mean that there is no difference between the effects of the two different treatment regimens in these subgroups as these could be "false negatives" from the underpowered statistical tests. Furthermore, the Evidence Review Group also noted that results from the EXTREME trial showed that, for patients whose cancer did not start in the oral cavity, treatment with cetuximab in combination with platinum chemotherapy and 5-fluorouracil may give a small benefit compared with treatment with platinum chemotherapy and 5-fluorouracil (i.e. the observed data contradict the assumption of equivalence between the two regimens) and so have noted that their approach may overestimate the effectiveness of platinum plus 5-fluorouracil chemotherapy, and consequently will underestimate the relative treatment effect of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil in the cost-effectiveness analyses. The Evidence Review Group's approach also effectively assumes that the shape of the overall survival Kaplan-Meier curves in non-oral cavity patients in the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm and in the platinum and 5-fluorouracil arm in the EXTREME study are the same. However, there is no published overall survival Kaplan-Meier data from the EXTREME trial for non-oral cavity patients and so this assumption cannot be verified from the study data. Furthermore, it can be seen when comparing the overall survival Kaplan-Meier curves for cetuximab plus chemotherapy versus chemotherapy alone from the EXTREME study (in all patients irrespective of primary tumour site) that the shapes of the curves differ noticeably between the two

	treatment regimens (the two curves cross, indicating they are not even similar enough for proportional hazards to be true). This would suggest it is unlikely that the shape of a platinum chemotherapy and 5-flurouracil overall survival curve would not differ significantly to that of a cetuximab in combination with platinum chemotherapy and 5-fluorouracil overall survival in non-oral cavity patients, and so it would not be appropriate to use the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm of the KEYNOTE-048 study as a proxy for the effect of treatment with platinum chemotherapy and 5-fluorouracil in cost-effectiveness analyses. Additionally, the Evidence Review Group's approach to assessing the efficacy of pembrolizumab (monotherapy and combination therapy) in patients whose cancer did not originate in the oral cavity has been to use the data from the KEYNOTE-048 study's cetuximab in combination with platinum chemotherapy plus 5-fluorouracil arm from patients with any/all primary tumour location (i.e. including patients whose cancer originated in the oral cavity) as the proxy for platinum chemotherapy plus 5-fluorouracil in patients whose cancer did not start in the oral cavity. This means that if, as the Evidence Review Group asserts, treatment with cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil is more effective in patients whose cancer originated in the oral cavity than in patients whose cancer originated elsewhere then this will further overestimate the effectiveness of platinum chemotherapy plus 5-fluorouracil and consequently further underestimate the relative effectiveness of pembrolizumab (monotherapy and combination therapy). Furthermore, it is unlikely that the adverse event profiles associated with treatment with cetuximab in combination with platinum chemotherapy and 5-fluorouracil and with treatment with platinum and 5-fluorouracil, in non-oral cavity patients, would be the same. The adverse event data from the EXTREME study (in the full population regardless of primary tumour site) show differences between the groups treated with these two regimens. As adverse events affect both costs and utilities, this further indicates that using these different interventions as proxies for each other would not be appropriate. When the Evidence Review Group amended the model only the cost of cetuximab was changed to zero, no changes were made to the adverse events in terms of costs and utilities, further raising uncertainty within the methodology employed.

	With regard to the company's network meta-analysis, while it was conducted for, and used data from, all patients regardless of their primary tumour location, the results of the analysis are generalisable to the subgroup of patients whose cancer started outside of the oral cavity. This is because the comparisons between pembrolizumab (as monotherapy or in combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil in the network meta-analysis are driven primarily by the KEYNOTE-048 study's comparison of pembrolizumab (monotherapy and combination therapy) versus cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil in patients irrespective of where the cancer started, and the EXTREME study's comparison of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil versus platinum-based chemotherapy plus 5-fluorouracil also in patients irrespective of where the cancer started. If cetuximab in combination with platinum chemotherapy plus 5-fluorouracil is less effective in patients whose cancer starts outside the oral cavity than in those whose cancer starts in the oral cavity, then in both studies the relative effectiveness of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil would be an overestimate from the perspective of patients whose cancer originated outside the oral cavity as both studies included a proportion of patients whose cancer originated in the oral cavity. Consequently, across the indirect comparison of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil used in the company's approach, the effects of any hypothetical overestimations of the effectiveness of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil from the perspective of patients whose cancer originated outside the oral cavity from the two studies would balance/cancel each other out in the analysis, giving results for the relative effectiveness of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil that are unlikely to overestimate the effectiveness of pembrolizumab (monotherapy and combination therapy) from the perspective of patients whose cancer started outside the oral cavity. In effect, the company's network meta-analysis would be able to provide the appropriate estimate of the relative effectiveness pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil in either case of whether or not it is true that the effectiveness of cetuximab in combination with platinum

	chemotherapy plus 5-fluorouracil differs in patients with oral cavity versus non-oral cavity primary tumour disease. Furthermore, as the KEYNOTE-048 study included a higher proportion of patients with cancer that originated in the oral cavity (≈30%) than in the EXTREME study (≈20%), if the effectiveness of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil were to be more effective in patients with cancer that originated in the oral cavity (a hypothesis which is not supported in neither the KEYNOTE-048 nor the EXTREME study), then it would be more likely that the company's approach to this comparison would produce results that are an underestimate of the relative effectiveness of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil from the perspective of patients whose cancer originated outside the oral cavity. With regard to the other specific concerns raised by the Evidence Review Group about the validity of the results of the company's network meta-analyses: 1. The plausibility of the hazard ratios results was assessed first by reviewing the estimated survival curves for all treatments relative to the survival curve of the reference treatment (pembrolizumab monotherapy or pembrolizumab in combination with platinum chemotherapy and 5-fluorouracil). The fit of the modelled curves to trial specific Kaplan-Meier data were then examined to ensure they were plausible. With regard to how the two categories of fractional polynomial models were assessed, during the initial analyses it was determined that including treatment effects on the second shape parameter led to implausible results, which is a function of the significant flexibility that is inherent in such models. As a result, only those models with treatment effects on the scale and first shape parameter were presented and used in the submission. 2. The company used data from the PD-L1 combined positive score ≥1 subgroup of patients from only the KEYNOTE-048 study because PD-L1 combined positive score ≥1 subgroup data were not available from the other studies included in the network meta-analysis. As PD-L1 status is unlikely to be a treatment effect modifier for any of the other interventions in the network (as none of the other interventions have a method of action involving interaction

between PD-1 and PD-L1), while this may have introduced some heterogeneity into the analysis, it does not bias the results of the analysis.

3. The company did not provide network meta-analysis results that are stratified by primary tumour location (oral cavity versus non-oral cavity) because the KEYNOTE-048 study (the sole study providing data on pembrolizumab) was not designed to be powered to analyse subgroup data based on the site of cancer origin, and so it would not be possible for network meta-analyses using such data from the KEYNOTE-048 study to provide meaningful and statistically significant information on relative clinical effectiveness versus pembrolizumab in such subgroups. It should be noted that the results of the analysis for the comparison between pembrolizumab (in monotherapy and in combination therapy) versus platinum plus 5-fluorouracil chemotherapy in all patients (not stratified by primary tumour location) would not be an overestimate of the effectiveness of pembrolizumab (in monotherapy and in combination therapy) in non-oral cavity patients, as explained earlier.

Issue 5: Extrapolation of overall survival (OS)

What proportion of patients in the pembrolizumab monotherapy and combination therapy arms would be expected to be alive at 1, 2, 3, 5 and 10 years?

Company base case assumes as the table below:

	Pembrolizumab monotherapy	**Pembrolizumab combination therapy**
Years after starting treatment	**People still alive**	**People still alive**
1	50.4%	54.1%
2	29.6%	31.8%
3	21.2%	25.3%
5	14.0%	19.3%
10	7.8%	13.1%

Clinical input to the company suggests the overall survival assumptions are broadly in line with reality. However, a common thread amongst clinical experts was that it is difficult to estimate actual survival beyond the end of the trial, as there is no experience with the use of pembrolizumab in Head and

<table>
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<td>Neck Cancer. However, in view of previous experience with other cancer sites such as lung, they felt the estimations seemed reasonable. Most clinicians felt there was greater uncertainty in predicting a 10-year overall survival due to lack of clinical data.

However, using 5-year follow-up data from other pembrolizumab clinical studies, as referenced in the long-term follow-up study from KN001, titled ‘Five-Year Overall Survival for Patients with Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results from the Phase I KN001 Study’, we see that the 5-year overall survival rate with pembrolizumab was 23.2% in treatment-naïve patients, providing confidence in the choice of survival extrapolation at year 5 (1) (see Figure 5).</td>
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<td>What proportion of patients receiving the cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU would be expected to be alive at 1, 2, 3, 5 and 10 years?</td>
<td>Company base case assumes as the table below:

<table>
<tr><td></td><td colspan="2">Pembrolizumab monotherapy</td><td colspan="2">Pembrolizumab combination therapy</td></tr>
<tr><td>Years after starting treatment</td><td>Cetuximab plus platinum chemotherapy and 5-FU</td><td>Platinum plus 5-FU</td><td>Cetuximab plus platinum chemotherapy and 5-FU</td><td>Platinum plus 5-FU</td></tr>
<tr><td></td><td>MSD</td><td>MSD</td><td>MSD</td><td>MSD</td></tr>
<tr><td>1</td><td>42.2</td><td>36.5</td><td>42.0</td><td>36.7</td></tr>
<tr><td>2</td><td>14.4</td><td>13.1</td><td>13.5</td><td>10.7</td></tr>
<tr><td>3</td><td>7.2</td><td>6.3</td><td>6.1</td><td>4.7</td></tr>
<tr><td>5</td><td>3.3</td><td>2.3</td><td>2.4</td><td>0.7</td></tr>
<tr><td>10</td><td>1.3</td><td>0.5</td><td>0.6</td><td>0</td></tr>
</table>
The estimates by the company are in line with long term follow-up of the EXTREME study in Table 1 below.</td>
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<table>
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<td>Table 1: 5-year Follow-up Data of the EXTREME Study (2)

<table>
<tr><th>Years after starting treatment</th><th>Cetuximab plus platinum chemotherapy and 5-FU</th><th>Platinum plus 5-FU</th></tr>
<tr><td>3</td><td>7.1</td><td>4.4</td></tr>
<tr><td>5</td><td>2.9</td><td>1.7</td></tr>
</table>
As can be seen from table 1, the extrapolation curves selected by the company closely match the follow-up data from the EXTREME study and were validated by clinical expert opinion.</td>
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<td>Which extrapolation of overall survival is most clinically plausible?</td>
<td>According to clinical input, it was felt the loglogistic and lognormal curves were good predictors for the overall survival, certainly for 5-years. Clinicians were hesitant to put a prediction for the OS at year 10 but agreed that from cancers such as Non–Small-Cell Lung Cancer there was a plateau seen. As such, it would be plausible to assume this effect will also be seen in Head and Neck cancer, supporting the choice of curves by the company.

However, as the NICE DSU technical support document 14 states, several other factors including clinical plausibility/validity should also be used to determine the most ideal curve. The factors are listed below and a summary of the company choice versus the ERG choice is summarised below:

1. AIC/BIC tests
2. Visual inspection
3. Clinical validity
4. External data</td>
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1. **The AIC/BIC test**; MSD has included the goodness-of-fit summary for both monotherapy and combination therapy below.

Table 2: Monotherapy Goodness-of-fit

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	455.20	457.78	1	353.23	355.27	5
Weibull	454.27	459.44	4	354.40	358.48	6
Gompertz	454.20	459.37	3	351.13	355.22	3
Log-logistic	453.95	459.12	2	350.75	354.84	2
Log-normal	455.86	461.03	5	349.61	353.69	1
Generalised Gamma	-39870	-39863.	6	351.01	357.14	4

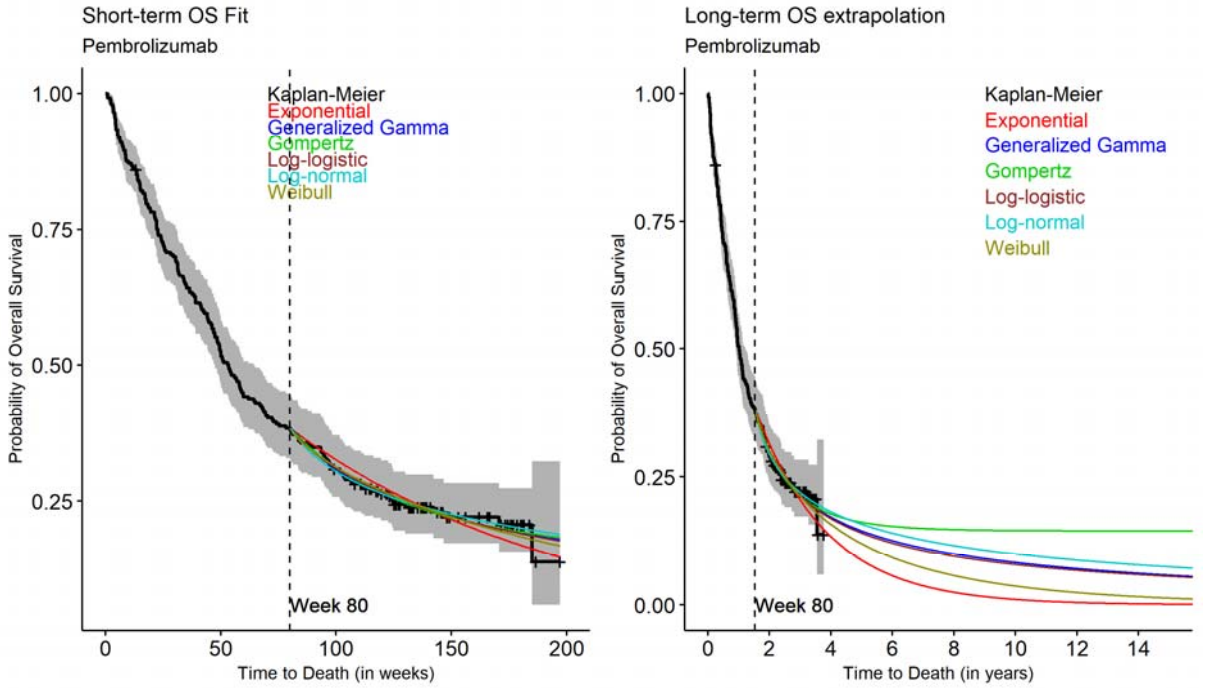
Table 3: Combination therapy goodness-of-fit

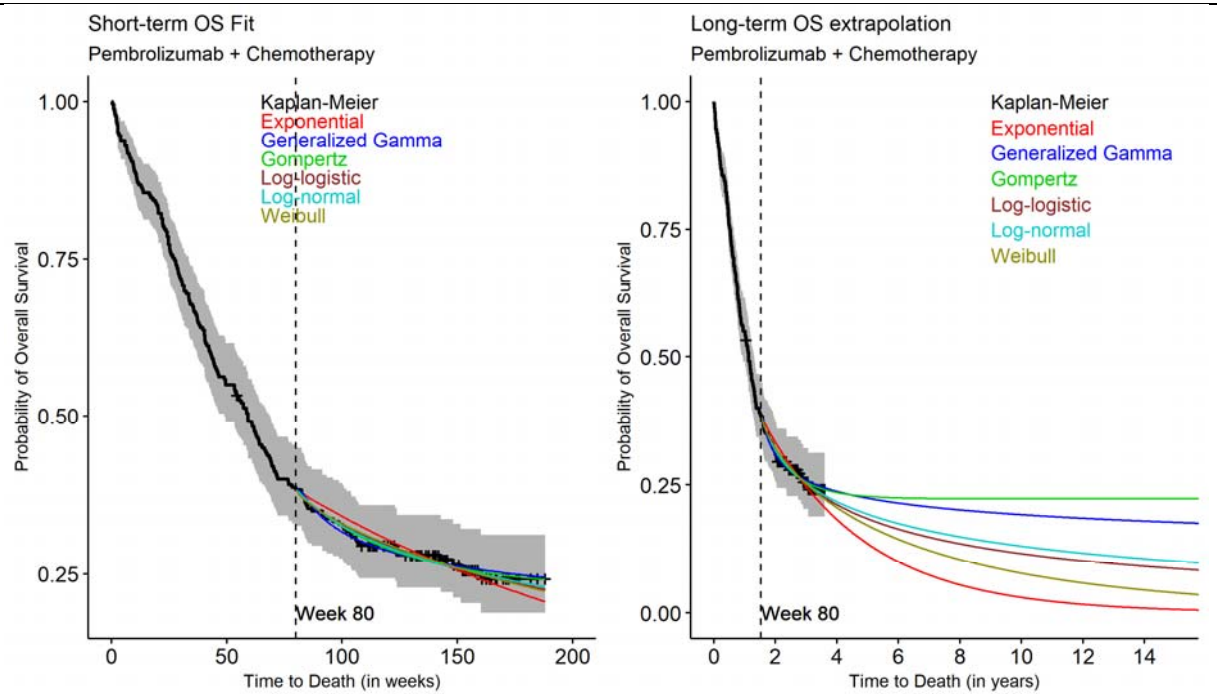
Fitted Function	Pembrolizumab Combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	346.95	349.48	5	331.15	333.10	3
Weibull	346.38	351.42	6	333.08	336.98	6
Gompertz	344.80	349.84	2	331.82	335.72	4
Log-logistic	345.59	350.63	4	330.17	334.07	2
Log-normal	343.75	348.79	1	329.49	333.40	1

Generalised Gamma	343.82	351.39	3	331.41	337.27	5

As tables 2 and 3 above show, the Weibull curve gives the worst goodness-of-fit and as the use of 5-year trial data shows underestimates the OS of the EXTREME arm **(*see explanation in External Validity subsection*)**. MSD have gone for the best fit for both treatment arm pairings, as is the methodology preferred by NICE.

2. **Visual inspection** was used to determine how well each parametric survival model fit the clinical trial data through close alignment with the Kaplan Meier curve. The representation of the visual inspection can be seen in the figures below.


Short-term OS Fit
Pembrolizumab
Kaplan-Meier
Exponential
Generalized Gamma
Gompertz
Log-logistic
Log-normal
Weibull
Probability of Overall Survival
1.00
0.75
0.50
0.25
Week 80
0
50
100
150
200
Time to Death (in weeks)
Long-term OS extrapolation
Pembrolizumab
Kaplan-Meier
Exponential
Generalized Gamma
Gompertz
Log-logistic
Log-normal
Weibull
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
Week 80
0
2
4
6
8
10
12
14
Time to Death (in years)



From the figures above, besides the exponential curve, the visual inspection shows no discernible difference between the remaining parametric curves with all fitting the clinical trial data reasonably. Whilst five of the six parametric models follow the Kaplan Meier , the difference is in the tails and to determine the plausibility of such tails, clinical and external data validation were employed.

3. **Clinical validity** was employed to further determine the choice of curve especially in assessing the plausibility of the extrapolated portions of the parametric survival. Elicitation from clinicians substantiated the survival extrapolation of the company at 3 and 5 years for

both pembrolizumab arms. This was also corroborated by the clinicians interviewed by NICE who stated “pembrolizumab monotherapy 5 and 10 year estimates plausible”. There was however, concern by clinicians as to the robustness of giving estimates for year 10, as there is little experience with the use of pembrolizumab for 10 years and certainly none within the Head and Neck cancer space. They agree there is a plateau phase seen with pembrolizumab in other cancer sites between 3 and 5 years and responses suggested the same could be assumed in Head and Neck cancer, with the appropriate caveats. The questionnaire used to elicit responses can be seen in the appendix.

4. **External data validation**, as the intervention pembrolizumab is new, especially in Head and Neck cancer, external data validation using the control treatment proved a viable option to assess parametric curve choice. Since the original submission: Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck, 5-year follow-up data of the EXTREME study has become available. MSD believes this data would be useful and the most robust method to validate longer-term survival estimates for cetuximab plus platinum-based chemotherapy and platinum-based chemotherapy. The table of which can be found below:

Table 4: 5-year Follow-up Data of the EXTREME Study at Random Time Points (2)

Treatment arm	% of patients alive at 28 months (1376 days)	% of patients alive at 36 months (1769 days)	% of patients alive at 42 months (2064 days)	% of patients alive at 59.5 months (2924 days)
	Trial	Trial	Trial	Trial
Cetuximab	11.7	7.1	6.5	2.9

Standard of Care *(platinum +5-FU)*	8.3	4.4	4.4	1.7
Increment	**3.4**	**2.7**	**2.1**	**1.2**

MSD has included a summary of the survival estimates using the preferred extrapolation curves of the company and the ERG below:

Table 5: Summary of Survival Estimates Based on Curve Selection by the Company and the ERG

	Pembrolizumab monotherapy				**Pembrolizumab combination therapy**			
Years after starting treatment	**Cetuximab plus platinum chemotherapy and 5-FU**		**Platinum plus 5-FU**		**Cetuximab plus platinum chemotherapy and 5-FU**		**Platinum plus 5-FU**	
	MSD	**ERG**	**MSD**	**ERG**	**MSD**	**ERG**	**MSD**	**ERG**
1	42.2	42.7	36.5	36.5	42.0	42.0	36.7	36.7
2	14.4	14.7	13.1	13.4	13.5	13.8	10.7	11.1
3	7.2	7.4	6.3	6.2	6.1	5.6	4.7	4.6
5	3.3	2.1	2.3	1.6	2.4	0.9	0.7	0.3
10	1.3	0.1	0.5	0.1	0.6	0	0	0

As can be seen from the table, and confirmed by the ERG, the choice of Weibull curve underestimates the overall survival of the both comparator arms. For instance, at year 5, for monotherapy regimens the ERG extrapolation predicts 2.1% for cetuximab plus platinum chemotherapy and 5-FU whilst the company extrapolation estimates 3.3% and for the comparison to combination therapy the predictions are 0.9% and 2.4% respectively. This shows the extrapolation of

	the company is more able to predict the overall survival at percentages closer to 2.9% as opposed to the ERG extrapolation. For the platinum + 5-FU treatment arm, the EXTREME study has a 5-year overall survival of 1.7%. The ERG extrapolation is close to this figure for the monotherapy regimen but again underestimates it at 0.3% for the combination regimen whereas the company extrapolation shows a closer prediction at 0.7%. Furthermore, clinician feedback has agreed the estimates produced by the company choice of overall survival curves closely reflected what is expected to be seen with these treatments in clinical practice. As above, most clinicians felt estimating for 10-year overall survival introduced uncertainty due to limited experience. Based on the approaches listed above, the curves chosen by the company fit most of the criteria set out for extrapolation versus the curve chosen by the ERG, who provide limited evidence to support their choice of curve.
Issue 6: Duration of treatment effect	
What is the most plausible assumption of duration of treatment effect?	MSD understand it is uncertain what the long-term treatment effect of pembrolizumab monotherapy, or in combination, is for the unobserved time period (i.e. after current follow-up for KEYNOTE-048). However, there is substantial data to suggest that the treatment waning effects proposed by the ERG are inappropriate – which will be outlined below.

KN048 reports 3-year overall survival data which provides visible evidence of a treatment effect with pembrolizumab, therefore the use of 3-year treatment waning will be inappropriate as the intervention effect is already known. Tables showing the follow-up time in KN048 can be found in Table 6 and Table 7.

Table 6: Summary of Theoretical Follow-up Time Pembrolizumab Monotherapy versus Cetuximab + Chemotherapy (Intention-to-Treat Population with CPS≥1)

	Study: KEYNOTE 048[a]		
	Pembrolizumab N[c] = 257	**Cetuximab + Chemotherapy[b]** N[c] = 255	**Total** N[c] = 512
Theoretical Follow-up Time (Months)[d]			
Mean (SD)	33.74 (5.44)	33.79 (5.47)	33.76 (5.45)
Median (Q1; Q3)	33.09 (29.24; 37.75)	33.15 (29.18; 37.88)	33.15 (29.21; 37.82)
Min; Max	25.33; 45.70	25.30; 45.44	25.30; 45.70

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Calculated from date of randomization until database cut-off date
5-FU: 5-Fluorouracil; CPS: Combined Positive Score; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation.

Table 7: Summary of Theoretical Follow-up Time Pembrolizumab Combination Therapy versus Cetuximab + Chemotherapy (Intention-to-Treat Population with CPS≥1)

	Study: KEYNOTE 048[a]		
	Pembrolizumab + Chemotherapy[b] N[c] = 242	**Cetuximab + Chemotherapy[b]** N[c] = 235	**Total** N[c] = 477
Theoretical Follow-up Time (Months)[d]			
Mean (SD)	33.35 (5.23)	33.13 (5.18)	33.24 (5.20)
Median (Q1; Q3)	32.84 (29.18; 37.29)	32.43 (28.88; 36.83)	32.63 (28.95; 36.96)

Min; Max	25.33; 46.26	25.30; 45.44	25.30; 46.26

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Calculated from date of randomization until database cut-off date
5-FU: 5-Fluorouracil; CPS: Combined Positive Score; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation.

The 3-year data summarising the overall survival of patients (Intention-to-treat population with CPS ≥ 1) can be seen in Table 8 and Table 9.

Table 8: Summary of Overall Survival Rate Over Time (Pembrolizumab Monotherapy versus Cetuximab + Chemotherapy)

Overall Survival	Study: KEYNOTE 048[a]					
	Pembrolizumab (N[c] = 257)			Cetuximab + Chemotherapy[b] (N[c] = 255)		
	N at Risk[d]	N Events[e]	Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]	N at Risk[d]	N Events[e]	Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]
Month 6	182	74	71.1 [65.2; 76.3]	200	54	78.7 [73.2; 83.3]
Month 12	129	127	50.4 [44.1; 56.4]	110	143	43.6 [37.4; 49.6]
Month 18	99	157	38.7 [32.7; 44.6]	67	186	26.6 [21.3; 32.1]
Month 24	73	182	28.9 [23.5; 34.5]	44	209	17.4 [13.0; 22.4]
Month 30	43	193	23.9 [18.7; 29.3]	21	223	11.3 [7.7; 15.7]
Month 36	19	195	22.1 [16.9; 27.8]	9	228	8.0 [4.8; 12.3]
Month 42	4	196	20.7 [15.3; 26.7]	0	229	-

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Number of patients at risk at specified time point
e: Number of events observed from randomization to specified time point
f: From the product-limit (Kaplan-Meier) method for censored data
5-FU: 5-Fluorouracil; CI: confidence interval; CPS: Combined Positive Score.

Table 9: Summary of Overall Survival Rate Over Time (Pembrolizumab Combination Therapy versus Cetuximab + Chemotherapy)

Overall Survival	Study: KEYNOTE 048[a]					
	Pembrolizumab + Chemotherapy[b] (N[c] = 242)			Cetuximab + Chemotherapy[b] (N[c] = 235)		
	N at Risk[d]	N Events[e]	Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]	N at Risk[d]	N Events[e]	Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]
Month 6	183	59	75.6 [69.7; 80.5]	184	50	78.6 [72.8; 83.4]
Month 12	133	109	55.0 [48.5; 61.0]	101	132	43.5 [37.0; 49.7]
Month 18	94	147	39.1 [33.0; 45.2]	62	171	26.7 [21.2; 32.5]
Month 24	74	167	30.8 [25.1; 36.7]	39	194	16.8 [12.3; 21.9]
Month 30	52	173	28.0 [22.4; 33.8]	17	207	10.6 [6.9; 15.0]
Month 36	23	176	25.6 [19.9; 31.6]	5	212	6.5 [3.3; 11.1]
Month 42	2	177	24.2 [18.4; 30.5]	0	213	-

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Number of patients at risk at specified time point
e: Number of events observed from randomization to specified time point
f: From the product-limit (Kaplan-Meier) method for censored data
5-FU: 5-Fluorouracil; CI: confidence interval; CPS: Combined Positive Score.

An illustration of the extrapolation curves with and without the 3-year treatment waning effect on pembrolizumab can be found in Figure 1 and Figure 2.

Figure 1:Pembrolizumab Combination Therapy without 3-year Treatment Waning Effect

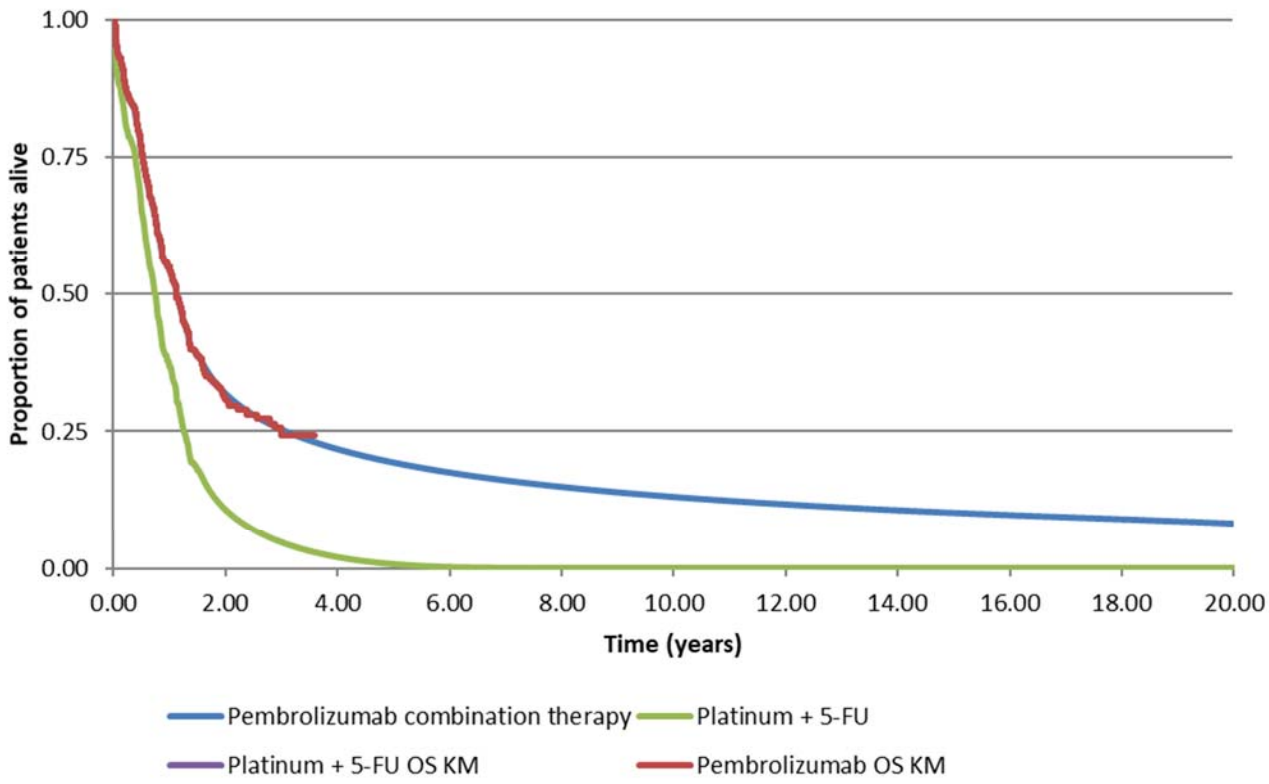
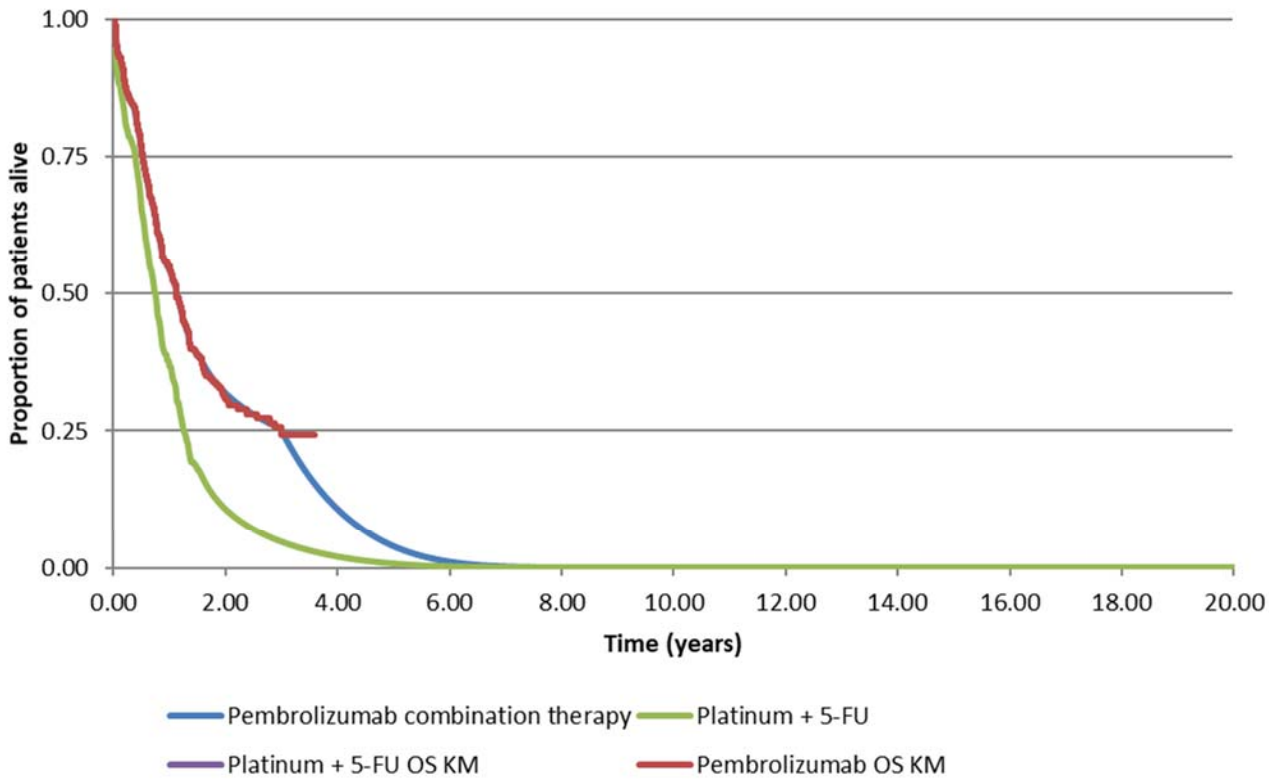


Figure 2: Pembrolizumab Combination Therapy with 3-year Treatment Waning Effect



Given the evidence presented below on the long-term treatment effect of pembrolizumab in other tumours, MSD do not believe that it is clinically plausible that the I-O plateau would simply drop off after 5 years, an arbitrarily chosen time point. For illustrative purposes, MSD has provided the curves of a pembrolizumab regimen with and without a treatment waning effect of 5 years:

Figure 3: Pembrolizumab Combination Therapy without Treatment Waning Effect

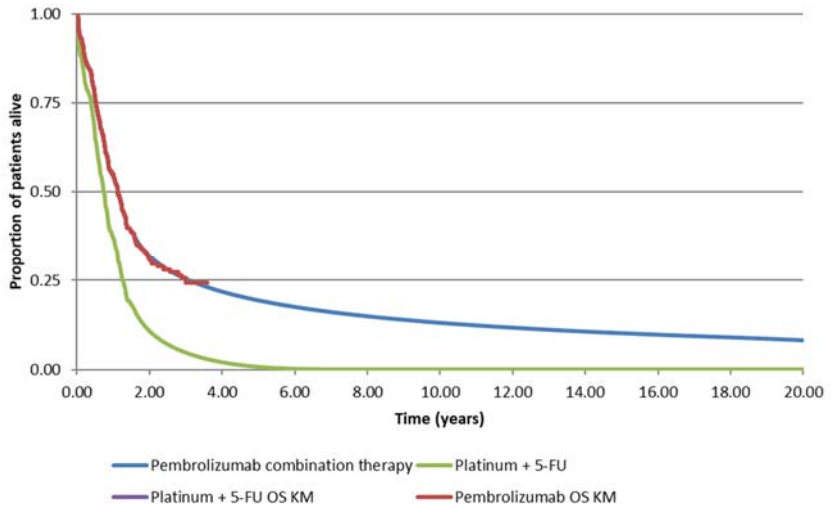
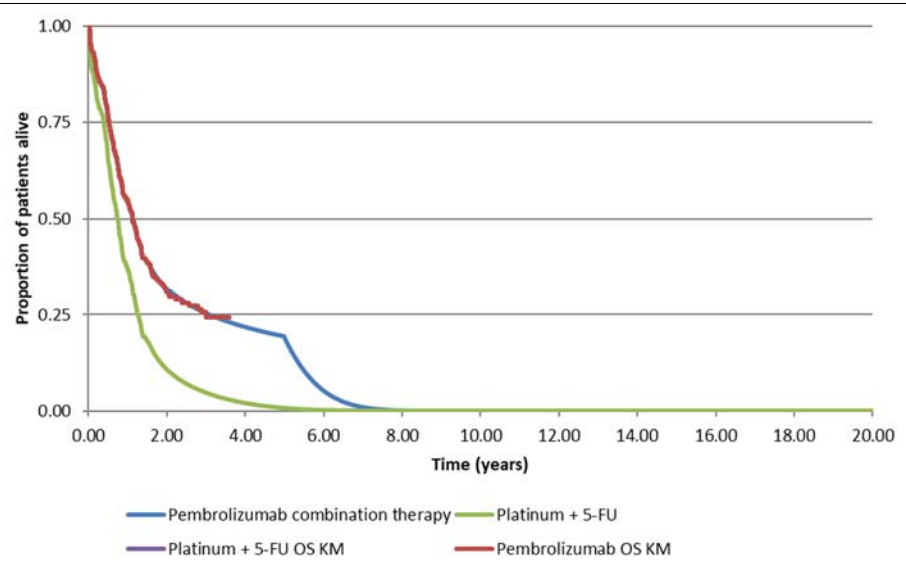
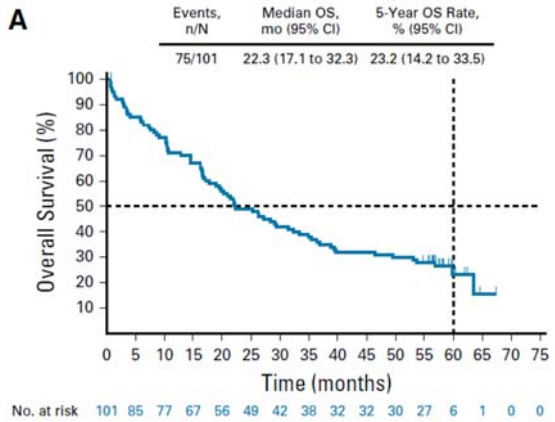


Figure 4: Pembrolizumab Combination Therapy with 5-year Treatment Waning Effect



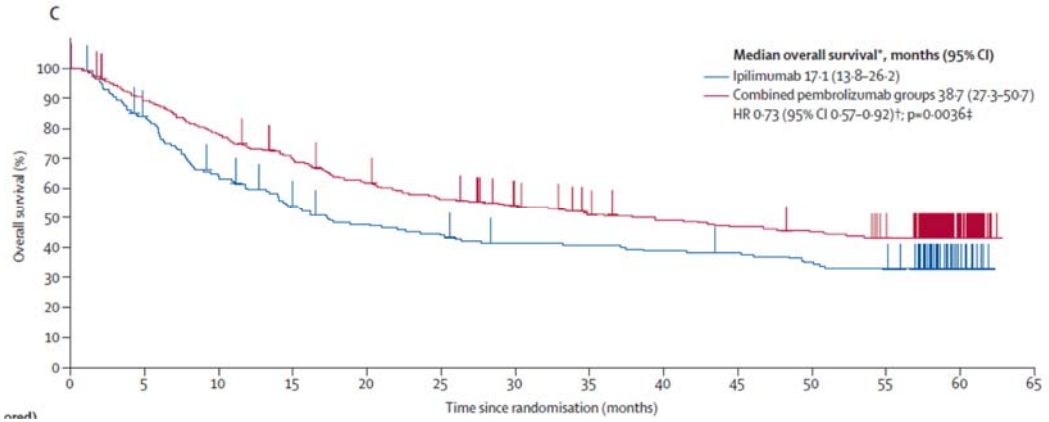
Using KN001 melanoma and Non-Small-Cell Lung Cancer (NSCLC) cohorts; evidence provided by the recently published KN001 study provided 5-year follow up data in patients with advanced NSCLC. Patients treated with pembrolizumab continued to respond with a 5-year survival. As can be seen in Figure 5 below, the plateau phase of the curve starts at month 40 and extends through to year 5.

Figure 5: Kaplan-Meier Estimates of 5-year Overall Survival for Patients with Advanced NSCLC Treated with Pembrolizumab (1)



In KN006, Pembrolizumab versus ipilimumab in advanced melanoma the overall survival estimates can be seen in the figure below. Figure 6 shows the beginnings of a plateau phase from 35 months.

Figure 6: Overall Survival in Patients Receiving 1st-line Pembrolizumab versus Ipilimumab in Advanced Melanoma (3)



In relation to KN048, Figure 7 and Figure 8 show the overall survival for CPS ≥ 1 in pembrolizumab monotherapy and combination therapy respectively. As can be seen from the figures, at roughly 35 months in both intervention arms a plateau phase has begun. Based on this, one can surmise, that similar to KN001 and KN006 we can expect this plateau phase to extend beyond this point through to 5 years. The evidence for KN001 and KN006 proves patients were not only alive at 5 years but also achieved durable responses, which based on the trajectory of responses from KN048 can be assumed to be applicable.

Figure 7: Kaplan-Meier Estimates of Overall Survival (Pembrolizumab Monotherapy versus Control) (4)

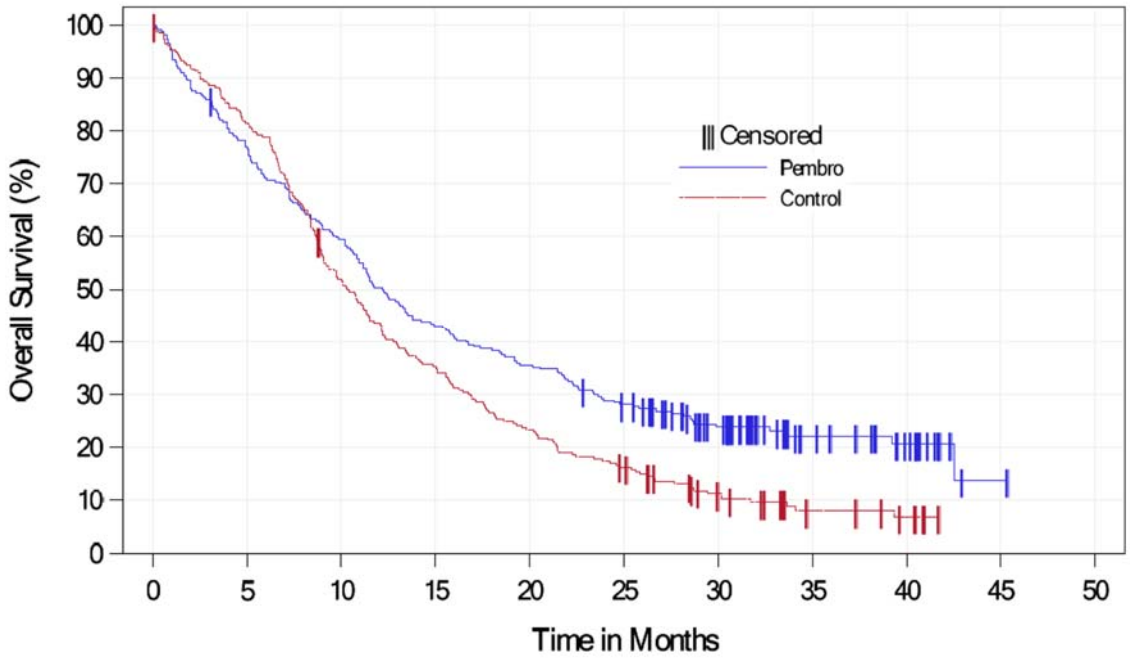
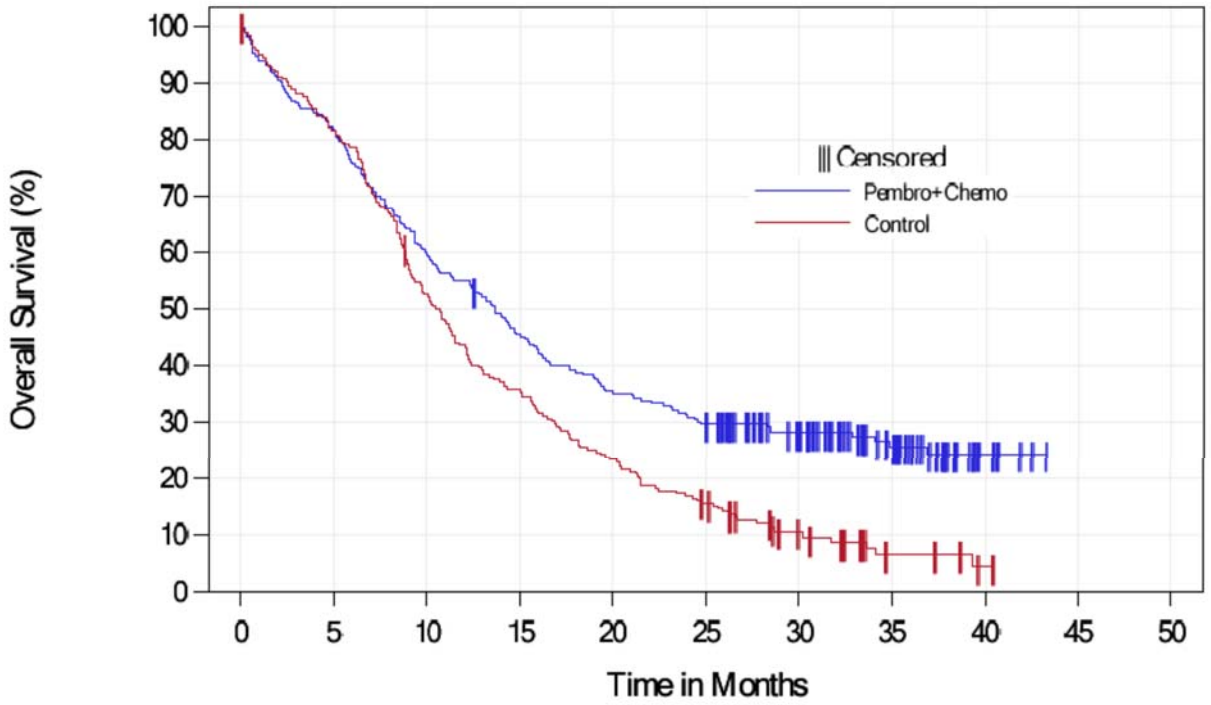


Figure 8: Kaplan-Meier Estimates of Overall Survival (Pembrolizumab Combination Therapy versus Control) (4)



MSD would also like to refer to the clinical expert input provided as part of TA490, Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy, which states that “I believe that the majority of patients who enter the plateau phase will continue to enjoy the health benefits (including out to 5 – 10 years)”. This is also supported by clinical expert interviews conducted by the NICE team for this submission. The responses stated, “duration of treatment effect with pembrolizumab or other IO agents are likely to be 5 years or more, but unlikely to be 10 years; at least with current experience and we need actual long-term clinical follow-up data”. The second clinician interviewed by the NICE team also stated, “all treatment effect beyond 5 years is by definition due to the pembrolizumab as there are almost zero survivors without pembrolizumab beyond 5 years”.

Based on the data provided, and clinician responses, the effect of pembrolizumab is highly likely to last out to 5 years and beyond, although acknowledging there is more uncertainty at 10 years.,. Based on this MSD have explored a duration of treatment effect range from between 5 and 10 years.

MSD does acknowledge treatment waning has been used in previous immunotherapy appraisals and as such have explored a range of potential timepoints to allow the committee to characterise the current long-term uncertainty which was acknowledged above. A summary of the ICERs using different annual treatment waning effects with both the company and the ERG preferred extrapolation curves.

Table 10: Treatment Waning ICERs for Company and ERG Preferred Extrapolation Curves (Non-oral Cavity Patients)

Treatment Waning	Pembrolizumab Monotherapy	Pembrolizumab Combination Therapy

	MSD	ERG	MSD	ERG
5 years	£43,158	£51,063	£57,011	£60,242
6 years	£40,209	£48,071	£51,742	£54,828
7 years	£38,122	£46,047	£47,836	£51,050
8 years	£36,570	£44,617	£44,775	£48,257
9 years	£35,378	£43,580	£42,320	£46,146
10 years	£34,442	£42,812	£40,317	£44,523

Table 11: Treatment Waning ICERs for Company and ERG Preferred Extrapolation Curves (Oral Cavity Patients)

Treatment Waning	Pembrolizumab Monotherapy		Pembrolizumab Combination Therapy	
	MSD	ERG	MSD	ERG
5 years	Dominant	Dominant	£10,417	£14,023
6 years	Dominant	Dominant	£10,110	£13,270
7 years	Dominant	Dominant	£9,921	£12,819
8 years	Dominant	Dominant	£9,785	£12,501

	<table><tr><td>9 years</td><td>Dominant</td><td>Dominant</td><td>£9,682</td><td>£12,267</td></tr><tr><td>10 years</td><td>Dominant</td><td>Dominant</td><td>£9,602</td><td>£12,092</td></tr></table> As can be seen from the Table 10 and Table 11 above, monotherapy in non-oral cavity patients is a cost-effective option from 6 year waning effect with ERG (highly conservative overall survival extrapolation) and always cost effective with company overall survival extrapolation, whilst it is dominant in the oral-cavity patients with all treatment waning effects in both the company and ERG preferred extrapolation curves. For the combination therapy, in non-oral cavity patients in the company preferred extrapolation it is cost-effective from 7 years and with the ERG preference 8 years. In oral cavity patients it is cost effective at all treatment waning points from 5 years.
Issue 7: End of life criteria	
What is the life expectancy of the patient group receiving standard of care, (that is, either cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU?	The EXTREME study found that, in this indication: • Patients treated with cetuximab in combination with platinum-based chemotherapy with 5-fluorouracil had a median overall survival of 10.1 months with a 95% confidence interval of 8.6 months to 11.2 months (this agrees well with what was observed in the KEYNOTE-048 study where patients in the cetuximab in combination with platinum-based chemotherapy with 5-

	fluorouracil arm had a median overall survival of 10.7 months with a 95% confidence interval of 9.3 months to 11.7 months). • Patients treated with platinum-based chemotherapy with 5-fluorouracil had a median overall survival of 7.4 months with a 95% confidence interval of 6.4 months to 8.3 months.
Does the life expectancy of the patient group receiving standard of care differ between those whose cancer started in the oral cavity and those whose started outside the oral cavity?	Differences in life expectancy between patients whose cancer started in the oral cavity and those whose started outside the oral cavity exist and are attributable to differences in standard of care received and not to any underlying biological differences in life expectancy between these patient groups. In the United Kingdom, patients whose cancer started in the oral cavity would receive treatment with cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil while patients whose cancer started outside the oral cavity would receive only platinum-based chemotherapy plus 5-fluorouracil. As demonstrated in the EXTREME trial, the addition of cetuximab to platinum-based chemotherapy with 5-fluorouracil significantly prolongs overall survival in comparison with platinum-based chemotherapy plus 5-fluorouracil (as described in the response above, with a hazard ratio for death of 0.80 with 95% confidence intervals of 0.64 to 0.99, P=0.04). In contrast, the data from the EXTREME study (also described in the response above) show that the 95% confidence intervals for the overall survival hazard ratios for cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil in the oral cavity patients subgroup and in each of the non-oral cavity patients subgroups (oropharynx, larynx, and hypopharynx) overlap, which does not show that the efficacy in terms of overall survival of cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil differs significantly between patients whose cancer started in the oral cavity and those whose cancer did not.

What is the extension to life of the patient group receiving pembrolizumab monotherapy or pembrolizumab combination therapy?	As described in section B.3.7 of ID1140 Pembrolizumab Evidence Review Group clarification letter – Supplementary Document Final: • The incremental life years gained in patients with PD-L1 combined positive score ≥1 treated with pembrolizumab monotherapy is 1.13 years versus patients treated with cetuximab + chemotherapy, and 1.30 years versus patients treated with platinum + 5-fluorouracil. • The incremental life years gained in patients with PD-L1 combined positive score ≥1 treated with pembrolizumab combination therapy is 1.88 years versus patients treated with cetuximab + chemotherapy, and 2.10 years versus patients treated with platinum + 5- fluorouracil.

References

1. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced NonSmall-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019;37(28):2518-27.
2. NICE. Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck (review of TA172) [ID1016]. CDF Rapid Reconsideration [Internet]. 2016 17-OCT-2019. Available from: https://www.nice.org.uk/guidance/ta473/documents/committee-papers.
3. 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. 2019;20(9):1239-51.
4. Merck Sharp & Dohme. KEYNOTE-048 Clinical Study Report - MSD data on file. 2019.

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Technical engagement response form

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

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- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
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- 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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About you

Your name	**Dr Shanmugasundaram Ramkumar**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**NA**

Questions for engagement

Issue 1: 2-year stopping rule for pembrolizumab	
Is a 2-year stopping rule for pembrolizumab appropriate?	Yes
Issue 2: Treatment choice	
What factors affect the decision on whether pembrolizumab monotherapy is preferred over pembrolizumab combination therapy? In particular: • Which patients would likely receive pembrolizumab monotherapy? • Which patients would likely receive pembrolizumab combination therapy?	Pembrolizumab monotherapy- Good Performance status, previously treated with chemotherapy (neoadjuvant chemotherapy and/or high dose concurrent chemoradiotherapy patient) with residual chemotherapy induced toxicities Pembrolizumab combination therapy -Good performance, not heavily pre-treated with chemotherapy or patients with no residual chemotherapy induced toxicities where a rapid response is needed, not for borderline/poor performance status due to advanced disease with airway compromise, etc
Issue 3: Generalisability of KEYNOTE-048 results: Cetuximab as a comparator	
Are the results from the KEYNOTE trial generalisable to all patients with recurrent or metastatic head and neck squamous cell carcinoma whose tumours expressed PD-L1 with a CPS≥1 irrespective of where the cancer started?	Yes
Is it appropriate to consider subgroups by cancer location?	Yes Head and Neck cancer in different sub-sites have variable prognosis Good prognosis - p16 overexpressed oropharyngeal cancer, glottic cancers, nasopharyngeal cancer Poor Prognosis- oral cavity, hypopharynx, supraglottic and subglottic laryngeal cancers

Issue 4: Network meta-analyses: comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil	
Mindful that there are challenges with all approaches for comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil (5-FU), which is the best comparison to use in this appraisal? • the company's network meta-analyses? **or** • the ERG's approach to using data from the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048 as a proxy for the effect of treatment with platinum chemotherapy and 5-FU?	ERG's approach
Issue 5: Extrapolation of overall survival (OS)	
What proportion of patients in the pembrolizumab monotherapy and combination therapy arms would be expected to be alive at 1, 2, 3, 5 and 10 years?	Company's data possibly valid up to 5 years, no clinical data currently support 10 year survival
What proportion of patients receiving the cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU would be expected to be alive at 1, 2, 3, 5 and 10 years?	EXTREME trial and Company's data plausible for up to 5 years, No patients alive at 10 years in routine clinical practise
Which extrapolation of overall survival is most clinically plausible?	
Issue 6: Duration of treatment effect	
What is the most plausible assumption of duration of treatment effect?	

Issue 7: End of life criteria	
What is the life expectancy of the patient group receiving standard of care, (that is, either cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU?	12 - 15 months
Does the life expectancy of the patient group receiving standard of care differ between those whose cancer started in the oral cavity and those whose started outside the oral cavity?	Oral cavity cancer patients respond better to cetuximab in combination with platinum and 5FU as evidenced by EXTREME trial data
What is the extension to life of the patient group receiving pembrolizumab monotherapy or pembrolizumab combination therapy?	Around additional 3-months median OS based on Keynote 048 trial data

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Technical engagement response form

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer [ID1140]

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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.	**NA**

Questions for engagement

Issue 1: 2-year stopping rule for pembrolizumab	
Is a 2-year stopping rule for pembrolizumab appropriate?	Yes-based on the trial data. This has no foundation in the biology however.
Issue 2: Treatment choice	
What factors affect the decision on whether pembrolizumab monotherapy is preferred over pembrolizumab combination therapy? In particular: • Which patients would likely receive pembrolizumab monotherapy? • Which patients would likely receive pembrolizumab combination therapy?	It is a balance between toxicity and desired response rate. In the case of rapid progressing/symptomatic disease our experts would prefer higher response at the expense of increased expected toxicity from combination therapy. Other patients may be more inclined to consider monotherapy.
Issue 3: Generalisability of KEYNOTE-048 results: Cetuximab as a comparator	
Are the results from the KEYNOTE trial generalisable to all patients with recurrent or metastatic head and neck squamous cell carcinoma whose tumours expressed PD-L1 with a CPS≥1 irrespective of where the cancer started?	Yes broadly generalizable irrespective of site
Is it appropriate to consider subgroups by cancer location?	This could be considered as they may be biologically and clinically divergent by location
Issue 4: Network meta-analyses: comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil	

Mindful that there are challenges with all approaches for comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil (5-FU), which is the best comparison to use in this appraisal? • the company's network meta-analyses? **or** • the ERG's approach to using data from the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048 as a proxy for the effect of treatment with platinum chemotherapy and 5-FU?	The ERGs approach seems reasonable.
Issue 5: Extrapolation of overall survival (OS)	
What proportion of patients in the pembrolizumab monotherapy and combination therapy arms would be expected to be alive at 1, 2, 3, 5 and 10 years?	This is difficult to predict. The company modelled survival percentages in the draft technical report (Sep 2019) seem plausible, however the ERG modelled data in seems more realistic.
What proportion of patients receiving the cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU would be expected to be alive at 1, 2, 3, 5 and 10 years?	Both company and ERG models seem plausible although my impression is the actual figure lies somewhere between the two.
Which extrapolation of overall survival is most clinically plausible?	The ERG modelled data seems most plausible for the pembro and pembro//chemo survival. Both seem clinically plausible for the chemotherapy outcomes.
Issue 6: Duration of treatment effect	
What is the most plausible assumption of duration of treatment effect?	The duration of treatment effect for the sub-group that get significant benefit would be expected to be beyond the 2 years of therapy extending to 5 years and 10 years in some patients. This is in

	the absence of this technology under review, the 5 year survival would be less than 10% and ten year survival would be negligible. Given both models show a five year survival on c.20% and 10 year survival of 5-10% it is only possible that this is due to the new treatment.
Issue 7: End of life criteria	
What is the life expectancy of the patient group receiving standard of care, (that is, either cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU?	Median survival less than 12 months, 3 year survival less than 10% and negligible 10 year survival.
Does the life expectancy of the patient group receiving standard of care differ between those whose cancer started in the oral cavity and those whose started outside the oral cavity?	Not significantly all other prognostic variables being equal.
What is the extension to life of the patient group receiving pembrolizumab monotherapy or pembrolizumab combination therapy?	As above, 3 year survival being doubled and 10 year survival of 4-8% (monotherapy) or 8-13% (combination) is a meaningful extension of life never previously seen in this patient group, albeit for only a sub-group of patients.

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- 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. 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)	Merck Sharp & Dohme
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Neither [redacted] nor Merck Sharp & Dohme have any past or current, direct or indirect links to, or funding from, the tobacco industry.

Questions for engagement

Issue 1: 2-year stopping rule for pembrolizumab	
Is a 2-year stopping rule for pembrolizumab appropriate?	Though Keynote 048 protocol states that treatment should continue until disease progression or unacceptable toxicity, the maximum possible treatment duration with pembrolizumab monotherapy and combination was 35 cycles. Implementing a 2-year stopping rule is consistent with other NICE technology appraisal guidance such as untreated NSCLC (TA531 and TA557). This was confirmed by the clinical experts during the technical engagement call.
ERG comment	No comment.
Issue 2: Treatment choice	
What factors affect the decision on whether pembrolizumab monotherapy is preferred over pembrolizumab combination therapy? In particular: • Which patients would likely receive pembrolizumab monotherapy? • Which patients would likely receive pembrolizumab combination therapy?	After conducting interviews with clinicians, the consensus was the decision to use either monotherapy or combination therapy will be done on a case-by-case basis where clinicians practising patient-centred care will, in discussion with patients, determine the benefit versus the risk of either monotherapy or combination therapy regimen and administer based on a mutual discussion. As further discussed below, factors that will be assessed on an individual basis will include rate of tumour growth, patient fitness, and risk versus benefit in each situation. Fast-growing tumours will require a more immediate response to reduce proliferation of the cancer cells; as such the combination therapy will enable a quick response. According to clinician feedback, there will be a percentage of patients who will have these rapid growing tumours and will be fit enough to tolerate combination therapy. There will also be recurrent patients who have relapsed after having

	chemotherapy as part of multi-modality treatment with radiation and/or surgery; for these cohort of patients the combination therapy would prove beneficial. When clinicians were asked to give in their view what proportion of patients would have the required fitness to be administered the combination therapy, the response was within the intended requirement for use CPS ≥1 with a PS 0 – 1, any patient who requires combination therapy should be able to tolerate the combination therapy. In summary, the decision between monotherapy and combination therapy will be done on a case-by-case basis where clinicians practising patient-centred care will, in discussion with patients, determine the benefit versus the risk of either monotherapy or combination therapy regimen and administer based on a mutual discussion, based on the following: • Monotherapy patients will be those patients with a low burden of disease with the tumour rate not faster than usual and who may not be fit to tolerate combination therapy. • Combination therapy will be used in patients with a very heavy burden of disease, with the disease progressing rapidly. Even with the burden of disease, clinician feedback is there will be a proportion of these patients who will be fit enough to be administered the combination therapy. They will also be patients who have relapsed after having chemotherapy treatment. The questionnaire used to illicit responses from clinical experts by MSD has been included as an appendix.
ERG comment	No comment.
Issue 3: Generalisability of KEYNOTE-048 results: Cetuximab as a comparator	
Are the results from the KEYNOTE trial generalisable to all patients with recurrent or metastatic head and neck squamous cell carcinoma whose tumours expressed PD-L1 with a CPS≥1 irrespective of where the cancer started?	The results of the KEYNOTE-048 study presented as part of the company's submission for patients whose tumours expressed PD-L1 with a combined positive score ≥1 are generalisable to all patients with recurrent or metastatic head and neck squamous cell carcinoma whose tumours expressed PD-L1 with a combined positive score ≥1 irrespective of where the cancer started. This is because the

baseline characteristics of these patients in the KEYNOTE-048 study are similar to these patients who will be encountered in United Kingdom clinical practice.

With regard to the specific concern raised that "if cetuximab in combination with platinum chemotherapy 5-fluorouracil is less effective in patients whose cancer starts outside the oral cavity than in those whose cancer starts in the oral cavity, the effectiveness of pembrolizumab monotherapy or pembrolizumab combination therapy may be overestimated for patients with cancer starting outside the oral cavity seen in NHS clinical practice", it should be noted that the appropriate comparator to pembrolizumab monotherapy or pembrolizumab combination therapy for patients with cancer starting outside the oral cavity seen in National Health Service clinical practice is platinum-based chemotherapy plus 5-fluorouracil (not cetuximab in combination with platinum chemotherapy 5-fluorouracil), and the company have made this comparison in the manufacturer's submission via the network meta-analyses that would yield results that would be generalisable to patient with cancer starting outside the oral cavity (described in more detail in the response to the next issue).

Furthermore, the results of the KEYNOTE-048 study show that the overall survival of patients with PD-L1 combined positive score ≥1 treated with cetuximab in combination with platinum chemotherapy 5-fluorouracil are very similar between those patients whose cancer originated in the oral cavity and those patients irrespective of where the cancer started:

Patient population	**Treatment with cetuximab in combination with platinum and 5-fluorouracil chemotherapy**
	Median overall survival, intention-to-treat analysis, KEYNOTE-048 study, Months (95% confidence interval)
Patients with PD-L1 combined positive score ≥1 irrespective of where the cancer started (n=255)	10.3 (9.0, 11.5)

	Patients with PD-L1 combined positive score ≥1 and whose cancer originated in the oral cavity* [redacted] | [redacted] Database Cut-off Date: 25 February 2019. These KEYNOTE-048 trial data therefore do not show that cetuximab in combination with platinum chemotherapy plus 5-fluorouracil is less effective in patients whose cancer starts outside the oral cavity. Additionally, the data from the EXTREME study also do not show a difference in the effectiveness of treatment with cetuximab in combination with platinum chemotherapy plus 5-flurouracil between patients whose cancer originated in different sites (oral cavity versus non-oral cavity), this is explained in greater detail in the response to Issue 4.
ERG comment	The population recruited to the KEYNOTE-048 trial is only representative of the fittest patients in the NHS with R/M HNSCC, i.e., those patients who are fit enough to receive cetuximab+PLAT+5-FU. Clinical advice to the ERG is that in NHS practice cetuximab+PLAT+5-FU is rarely used to treat cancer that originated in the oral cavity as only a minority of patients with this type of cancer are fit enough to tolerate the treatment. The company highlights a concern relating to the effectiveness of cetuximab+PLAT+5-FU differing by origin of cancer (oral/non-oral cavity). The ERG is unclear of the origin of this concern.
Is it appropriate to consider subgroups by cancer location?	For the purpose of this appraisal, it is not feasible to rigorously consider subgroups by cancer location as the KEYNOTE-048 study was not pre-specified to conduct subgroup analyses based on cancer location. Consequently, the study was not sufficiently powered to detect statistically significant differences between the interventions in these specific subgroups due to the small number of patients in these subgroups, and due to the imbalance in important baseline characteristics of patients in the different treatment groups (i.e. randomisation would be broken for comparisons made in these subgroups). Therefore, it is not possible to consider subgroups by cancer location using the available

	information on pembrolizumab. There is also no underlying biological rationale for why the clinical effectiveness of pembrolizumab would differ depending on cancer location in the head and neck. It is important to note that the restriction of cetuximab in combination with platinum chemotherapy and 5-fluorouracil to only patients with oral cavity cancer in United Kingdom clinical practice is due primarily to cost/cost-effectiveness considerations in the original TA172 appraisal as opposed to any rationale based on the underlying biology of the disease, as it is stated in section 4.3 (and noted again in section 4.15) of the Final Appraisal Determination document of TA172 that "the specialists were not aware of any biological reason for cetuximab to be more clinically effective in oral cavity tumours", which is in line with clinical expert advice that Merck Sharp and Dohme have also received. Indeed, the regulatory approval given to cetuximab for treatment of patients with squamous cell cancer of the head neck by the European Medicines Agency, whose decisions are based only on clinical considerations, is not restricted to patients with cancer originating in the oral cavity. The results of the EXTREME study did not actually show that the efficacy of cetuximab in combination with platinum chemotherapy and 5-fluorouracil, either in absolute terms or in comparison to platinum-based chemotherapy plus 5-fluorouracil, differs by cancer location (this is described in greater detail in the response to Issue 4). The results of the KEYNOTE-048 study also do not suggest the efficacy of cetuximab in combination with platinum chemotherapy and 5-fluorouracil differs depending on tumour location (as described in the response above).
ERG comment	Cetuximab+PLAT+5-FU is only recommended for the treatment of cancer that originates in the oral cavity. This means that the treatment options available to patients with cancer that originated in the oral cavity and those for patients whose cancer originated elsewhere are different and thus these two populations need to be considered separately.
Issue 4: Network meta-analyses: comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil	
Mindful that there are challenges with all approaches for comparing pembrolizumab (monotherapy or in combination) with platinum	Merck Sharp & Dohme believe that the company's network meta-analysis is the best comparison to use in this appraisal, as it is based on a comparison of the actual interventions of interest, via an established analytical method, that takes into account the study-observed differences between the

chemotherapy and 5-fluorouracil (5-FU), which is the best comparison to use in this appraisal? • the company's network meta-analyses? **or** • the ERG's approach to using data from the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048 as a proxy for the effect of treatment with platinum chemotherapy and 5-FU?	treatment effects of the different interventions, and produces results that are generalisable to/more likely to reflect the true relative effectiveness of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil including from the perspective of patients whose cancer originated outside the oral cavity. While there may be uncertainties associated with the company's network meta-analysis (sources of uncertainty that are commonly associated with network meta-analyses, a well-established methodology for making indirect treatment comparisons), the Evidence Review Group's approach is reliant upon underlying assumptions that are associated with no less uncertainty than the company's approach and also introduce additional bias/overestimation of comparator treatment effect that the Evidence Review Group themselves note exist, as well as additional bias/overestimation of comparator treatment effect and cost-effectiveness arising from the implementation of the approach: The Evidence Review Group's approach assumes that the relative efficacy, in terms of overall survival, of cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil differs significantly between patients who had cancer that started in the oral cavity and patients whose cancer originated elsewhere in the head and neck. However, the data from the EXTREME study presented in Table 33 of the ID1140 Evidence Review Group Report to support this assertion show that the 95% confidence intervals for the overall survival hazard ratios for cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil in the oral cavity patients subgroup and in each of the non-oral cavity patients subgroups (oropharynx, larynx, and hypopharynx) overlap, which does not show that the efficacy in terms of overall survival of cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil differs significantly between patients whose cancer started in the oral cavity and those whose cancer did not. It is actually noted in section 4.3 (and again in section 4.15) of the Final Appraisal Determination document of the TA172 assessment of cetuximab in this indication where this data was first presented to NICE that "the specialists were not aware of any biological reason for cetuximab to be more clinically effective in oral cavity tumours". The Evidence Review Group also raised in their report (in section 4.9.7) the possibility that the company's network meta-analysis, by not stratifying by oral cavity versus non-oral cavity patients,

	may underestimate the true overall survival for non-oral cavity patients who receive platinum-based chemotherapy plus 5-fluorouracil, based on results from the EXTREME study which suggest that median overall survival for oral cavity patients receiving platinum-based chemotherapy plus 5-fluorouracil is approximately half that of non-oral cavity patients receiving platinum-based chemotherapy plus 5-fluorouracil (presented in Table 33 of the ID1140 Evidence Review Group Report). However, those median overall survival values are for the point estimates only, without confidence intervals, and not from an adequately powered statistical analysis to compare the relative effectiveness of platinum-based chemotherapy plus 5-fluorouracil in between patient subgroups with different primary tumour locations. Therefore, these point-estimates of median overall survival do not demonstrate with confidence that the true overall survival (or clinical effectiveness) associated with treatment with platinum-based chemotherapy plus 5-fluorouracil differs between patients whose cancer originated in the oral cavity and patients whose cancer originated outside the oral cavity. The Evidence Review Group's approach also assumes that in patients whose cancer did not start in the oral cavity, the effectiveness of cetuximab in combination with platinum chemotherapy plus 5-fluorouracil is the same as that of platinum chemotherapy plus 5-fluorouracil. This assumption is based on the results of the subgroup analyses of the EXTREME study which found a statistically significant difference in overall survival (hazard ratios) between patients treated with cetuximab in combination with platinum chemotherapy plus 5-fluorouracil versus platinum chemotherapy plus 5-fluorouracil in the oral cavity site of tumour origin subgroup but did not find statistically significant differences between these treatment regimens in patients in the oropharynx, hypopharynx, larynx, and "other" sites of tumour origin subgroups (each subgroup analysed separately). However, the EXTREME study was only adequately powered to detect a statistically significant difference between treatment regimens in terms of overall survival in the full population (as described in section 6.3.5 of the manufacturer's submission for TA172 for cetuximab in this indication, which stated that 420 patients needed to be randomised for the analysis to be adequately powered) and so the subgroup analyses by site of tumour origin (where the numbers of patients in the subgroups ranged from only 32 to 149) were not sufficiently powered to detect statistically significant differences between the treatment regimens. Furthermore, randomisation in the EXTREME study was stratified only by patients' previous chemotherapy (yes/no) and Karnofsky score (<80/≥80) therefore randomisation was

	very likely to have been broken for the site of tumour origin subgroup analyses, further compromising the validity of the results of these analyses. Therefore, the statistically non-significant results in the non-oral cavity subgroups do not mean that there is no difference between the effects of the two different treatment regimens in these subgroups as these could be "false negatives" from the underpowered statistical tests. Furthermore, the Evidence Review Group also noted that results from the EXTREME trial showed that, for patients whose cancer did not start in the oral cavity, treatment with cetuximab in combination with platinum chemotherapy and 5-fluorouracil may give a small benefit compared with treatment with platinum chemotherapy and 5-fluorouracil (i.e. the observed data contradict the assumption of equivalence between the two regimens) and so have noted that their approach may overestimate the effectiveness of platinum plus 5-fluorouracil chemotherapy, and consequently will underestimate the relative treatment effect of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil in the cost-effectiveness analyses. The Evidence Review Group's approach also effectively assumes that the shape of the overall survival Kaplan-Meier curves in non-oral cavity patients in the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm and in the platinum and 5-fluorouracil arm in the EXTREME study are the same. However, there is no published overall survival Kaplan-Meier data from the EXTREME trial for non-oral cavity patients and so this assumption cannot be verified from the study data. Furthermore, it can be seen when comparing the overall survival Kaplan-Meier curves for cetuximab plus chemotherapy versus chemotherapy alone from the EXTREME study (in all patients irrespective of primary tumour site) that the shapes of the curves differ noticeably between the two treatment regimens (the two curves cross, indicating they are not even similar enough for proportional hazards to be true). This would suggest it is unlikely that the shape of a platinum chemotherapy and 5-flurouracil overall survival curve would not differ significantly to that of a cetuximab in combination with platinum chemotherapy and 5-fluorouracil overall survival in non-oral cavity patients, and so it would not be appropriate to use the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm of the KEYNOTE-048 study as a proxy for the effect of treatment with platinum chemotherapy and 5-fluorouracil in cost-effectiveness analyses.

	Additionally, the Evidence Review Group's approach to assessing the efficacy of pembrolizumab (monotherapy and combination therapy) in patients whose cancer did not originate in the oral cavity has been to use the data from the KEYNOTE-048 study's cetuximab in combination with platinum chemotherapy plus 5-fluorouracil arm from patients with any/all primary tumour location (i.e. including patients whose cancer originated in the oral cavity) as the proxy for platinum chemotherapy plus 5-fluorouracil in patients whose cancer did not start in the oral cavity. This means that if, as the Evidence Review Group asserts, treatment with cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil is more effective in patients whose cancer originated in the oral cavity than in patients whose cancer originated elsewhere then this will further overestimate the effectiveness of platinum chemotherapy plus 5-fluorouracil and consequently further underestimate the relative effectiveness of pembrolizumab (monotherapy and combination therapy). Furthermore, it is unlikely that the adverse event profiles associated with treatment with cetuximab in combination with platinum chemotherapy and 5-fluorouracil and with treatment with platinum and 5-fluorouracil, in non-oral cavity patients, would be the same. The adverse event data from the EXTREME study (in the full population regardless of primary tumour site) show differences between the groups treated with these two regimens. As adverse events affect both costs and utilities, this further indicates that using these different interventions as proxies for each other would not be appropriate. When the Evidence Review Group amended the model only the cost of cetuximab was changed to zero, no changes were made to the adverse events in terms of costs and utilities, further raising uncertainty within the methodology employed. With regard to the company's network meta-analysis, while it was conducted for, and used data from, all patients regardless of their primary tumour location, the results of the analysis are generalisable to the subgroup of patients whose cancer started outside of the oral cavity. This is because the comparisons between pembrolizumab (as monotherapy or in combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil in the network meta-analysis are driven primarily by the KEYNOTE-048 study's comparison of pembrolizumab (monotherapy and combination therapy) versus cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil in patients irrespective of where the cancer started, and the EXTREME study's comparison of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil versus platinum-based

	chemotherapy plus 5-fluorouracil also in patients irrespective of where the cancer started. If cetuximab in combination with platinum chemotherapy plus 5-fluorouracil is less effective in patients whose cancer starts outside the oral cavity than in those whose cancer starts in the oral cavity, then in both studies the relative effectiveness of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil would be an overestimate from the perspective of patients whose cancer originated outside the oral cavity as both studies included a proportion of patients whose cancer originated in the oral cavity. Consequently, across the indirect comparison of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil used in the company's approach, the effects of any hypothetical overestimations of the effectiveness of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil from the perspective of patients whose cancer originated outside the oral cavity from the two studies would balance/cancel each other out in the analysis, giving results for the relative effectiveness of pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil that are unlikely to overestimate the effectiveness of pembrolizumab (monotherapy and combination therapy) from the perspective of patients whose cancer started outside the oral cavity. In effect, the company's network meta-analysis would be able to provide the appropriate estimate of the relative effectiveness pembrolizumab (monotherapy and combination therapy) versus platinum-based chemotherapy plus 5-fluorouracil in either case of whether or not it is true that the effectiveness of cetuximab in combination with platinum chemotherapy plus 5-fluorouracil differs in patients with oral cavity versus non-oral cavity primary tumour disease. Furthermore, as the KEYNOTE-048 study included a higher proportion of patients with cancer that originated in the oral cavity (≈30%) than in the EXTREME study (≈20%), if the effectiveness of cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil were to be more effective in patients with cancer that originated in the oral cavity (a hypothesis which is not supported in neither the KEYNOTE-048 nor the EXTREME study), then it would be more likely that the company's approach to this comparison would produce results that are an underestimate of the relative effectiveness of pembrolizumab (monotherapy and combination therapy) versus platinum-

	based chemotherapy plus 5-fluorouracil from the perspective of patients whose cancer originated outside the oral cavity. With regard to the other specific concerns raised by the Evidence Review Group about the validity of the results of the company's network meta-analyses: 1. The plausibility of the hazard ratios results was assessed first by reviewing the estimated survival curves for all treatments relative to the survival curve of the reference treatment (pembrolizumab monotherapy or pembrolizumab in combination with platinum chemotherapy and 5-fluorouracil). The fit of the modelled curves to trial specific Kaplan-Meier data were then examined to ensure they were plausible. With regard to how the two categories of fractional polynomial models were assessed, during the initial analyses it was determined that including treatment effects on the second shape parameter led to implausible results, which is a function of the significant flexibility that is inherent in such models. As a result, only those models with treatment effects on the scale and first shape parameter were presented and used in the submission. 2. The company used data from the PD-L1 combined positive score ≥1 subgroup of patients from only the KEYNOTE-048 study because PD-L1 combined positive score ≥1 subgroup data were not available from the other studies included in the network meta-analysis. As PD-L1 status is unlikely to be a treatment effect modifier for any of the other interventions in the network (as none of the other interventions have a method of action involving interaction between PD-1 and PD-L1), while this may have introduced some heterogeneity into the analysis, it does not bias the results of the analysis. 3. The company did not provide network meta-analysis results that are stratified by primary tumour location (oral cavity versus non-oral cavity) because the KEYNOTE-048 study (the sole study providing data on pembrolizumab) was not designed to be powered to analyse subgroup data based on the site of cancer origin, and so it would not be possible for network meta-analyses using such data from the KEYNOTE-048 study to provide meaningful and statistically significant information on relative clinical effectiveness versus pembrolizumab in such subgroups. It should be noted that the results of the analysis for the comparison between

<table>
<tr><td></td><td>pembrolizumab (in monotherapy and in combination therapy) versus platinum plus 5-fluorouracil chemotherapy in all patients (not stratified by primary tumour location) would not be an overestimate of the effectiveness of pembrolizumab (in monotherapy and in combination therapy) in non-oral cavity patients, as explained earlier.</td></tr>
<tr><td>ERG comment</td><td>Both methods are subject to uncertainty. The ERG's method has the advantages of being simple, transparent and based on data from a high-quality trial. The company's method has the advantages of including data from many studies and allowing adjustments to be made to ameliorate the effect of heterogeneity between trials. However, if effectiveness differs by origin of cancer (as suggested by OS differences for the subgroups of patients with cancer that did/ did not originate in the oral cavity who received PLAT+5-FU in the EXTREME trial) then the company's NMA results will be compromised.</td></tr>
<tr><td colspan="2">Issue 5: Extrapolation of overall survival (OS)</td></tr>
<tr><td>What proportion of patients in the pembrolizumab monotherapy and combination therapy arms would be expected to be alive at 1, 2, 3, 5 and 10 years?</td><td>Company base case assumes as the table below:

<table>
<tr><th></th><th>Pembrolizumab monotherapy</th><th>Pembrolizumab combination therapy</th></tr>
<tr><th>Years after starting treatment</th><th>People still alive</th><th>People still alive</th></tr>
<tr><td>1</td><td>50.4%</td><td>54.1%</td></tr>
<tr><td>2</td><td>29.6%</td><td>31.8%</td></tr>
<tr><td>3</td><td>21.2%</td><td>25.3%</td></tr>
<tr><td>5</td><td>14.0%</td><td>19.3%</td></tr>
<tr><td>10</td><td>7.8%</td><td>13.1%</td></tr>
</table>
Clinical input to the company suggests the overall survival assumptions are broadly in line with reality. However, a common thread amongst clinical experts was that it is difficult to estimate actual survival beyond the end of the trial, as there is no experience with the use of pembrolizumab in Head and Neck Cancer. However, in view of previous experience with other cancer sites such as lung, they felt</td></tr>
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<table>
<tr><td></td><td>the estimations seemed reasonable. Most clinicians felt there was greater uncertainty in predicting a 10-year overall survival due to lack of clinical data.

However, using 5-year follow-up data from other pembrolizumab clinical studies, as referenced in the long-term follow-up study from KN001, titled ‘Five-Year Overall Survival for Patients with Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results from the Phase I KN001 Study’, we see that the 5-year overall survival rate with pembrolizumab was 23.2% in treatment-naïve patients, providing confidence in the choice of survival extrapolation at year 5 (1) (see Figure 5).</td></tr>
<tr><td>ERG comment</td><td>In the absence of evidence this is a matter of conjecture.</td></tr>
<tr><td>What proportion of patients receiving the cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU would be expected to be alive at 1, 2, 3, 5 and 10 years?</td><td>Company base case assumes as the table below:

<table>
<tr><td></td><td colspan="2">Pembrolizumab monotherapy</td><td colspan="2">Pembrolizumab combination therapy</td></tr>
<tr><td>Years after starting treatment</td><td>Cetuximab plus platinum chemotherapy and 5-FU</td><td>Platinum plus 5-FU</td><td>Cetuximab plus platinum chemotherapy and 5-FU</td><td>Platinum plus 5-FU</td></tr>
<tr><td></td><td>MSD</td><td>MSD</td><td>MSD</td><td>MSD</td></tr>
<tr><td>1</td><td>42.2</td><td>36.5</td><td>42.0</td><td>36.7</td></tr>
<tr><td>2</td><td>14.4</td><td>13.1</td><td>13.5</td><td>10.7</td></tr>
<tr><td>3</td><td>7.2</td><td>6.3</td><td>6.1</td><td>4.7</td></tr>
<tr><td>5</td><td>3.3</td><td>2.3</td><td>2.4</td><td>0.7</td></tr>
<tr><td>10</td><td>1.3</td><td>0.5</td><td>0.6</td><td>0</td></tr>
</table>
The estimates by the company are in line with long term follow-up of the EXTREME study in Table 1 below.</td></tr>
</table>

<table>
<tr><td></td><td>Table 1: 5-year Follow-up Data of the EXTREME Study (2)
<table><tr><th>Years after starting treatment</th><th>Cetuximab plus platinum chemotherapy and 5-FU</th><th>Platinum plus 5-FU</th></tr><tr><td>3</td><td>7.1</td><td>4.4</td></tr><tr><td>5</td><td>2.9</td><td>1.7</td></tr></table>As can be seen from table 1, the extrapolation curves selected by the company closely match the follow-up data from the EXTREME study and were validated by clinical expert opinion.</td></tr>
<tr><td>ERG comment</td><td>In the absence of evidence this is a matter of conjecture.</td></tr>
<tr><td>Which extrapolation of overall survival is most clinically plausible?</td><td>According to clinical input, it was felt the loglogistic and lognormal curves were good predictors for the overall survival, certainly for 5-years. Clinicians were hesitant to put a prediction for the OS at year 10 but agreed that from cancers such as Non–Small-Cell Lung Cancer there was a plateau seen. As such, it would be plausible to assume this effect will also be seen in Head and Neck cancer, supporting the choice of curves by the company.

However, as the NICE DSU technical support document 14 states, several other factors including clinical plausibility/validity should also be used to determine the most ideal curve. The factors are listed below and a summary of the company choice versus the ERG choice is summarised below:

1. AIC/BIC tests
2. Visual inspection
3. Clinical validity</td></tr>
</table>

4. External data

1. **The AIC/BIC test**; MSD has included the goodness-of-fit summary for both monotherapy and combination therapy below.

Table 2: Monotherapy Goodness-of-fit

Fitted Function	Pembrolizumab Monotherapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	455.20	457.78	1	353.23	355.27	5
Weibull	454.27	459.44	4	354.40	358.48	6
Gompertz	454.20	459.37	3	351.13	355.22	3
Log-logistic	453.95	459.12	2	350.75	354.84	2
Log-normal	455.86	461.03	5	349.61	353.69	1
Generalised Gamma	-39870	-39863.	6	351.01	357.14	4

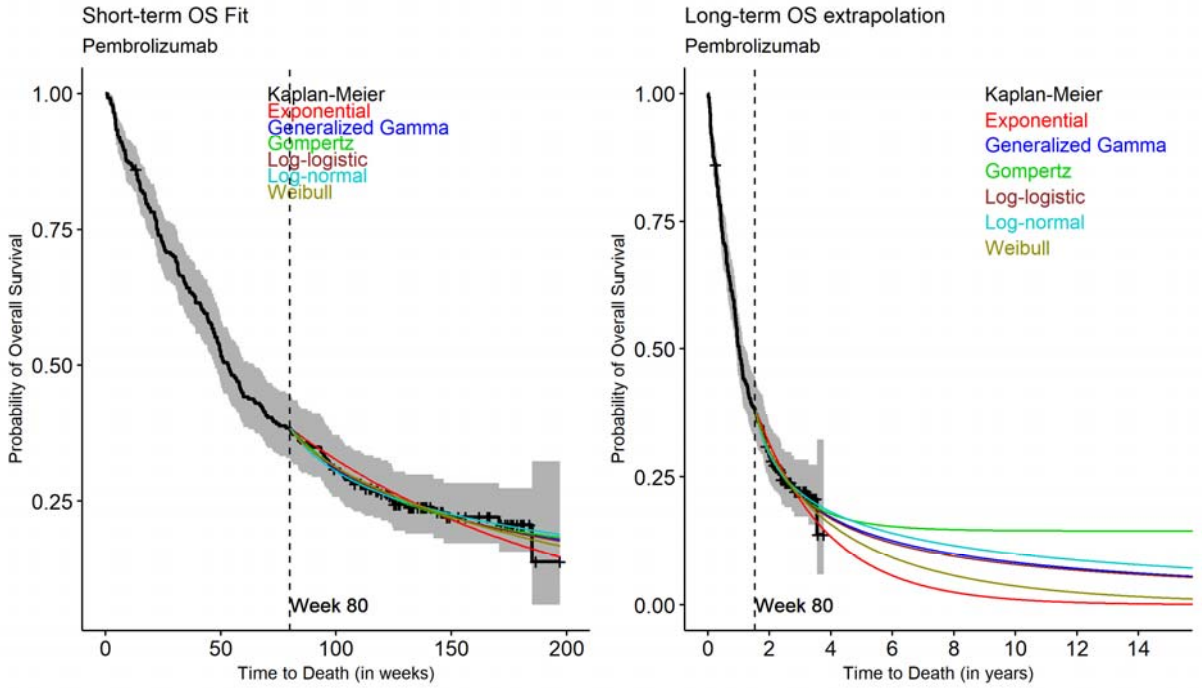
Table 3: Combination therapy goodness-of-fit

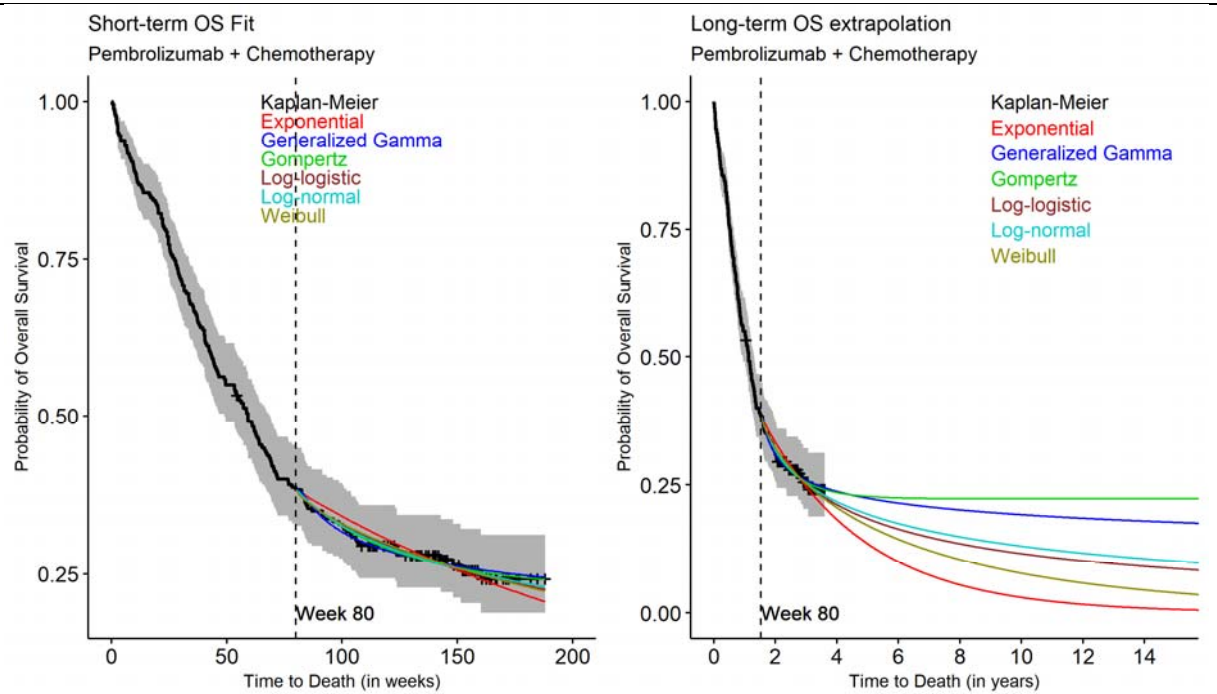
Fitted Function	Pembrolizumab Combination therapy		Statistical Rank	Platinum + 5-FU + Cetuximab		Statistical Rank
	AIC	BIC		AIC	BIC	
Exponential	346.95	349.48	5	331.15	333.10	3
Weibull	346.38	351.42	6	333.08	336.98	6
Gompertz	344.80	349.84	2	331.82	335.72	4

Log-logistic	345.59	350.63	4	330.17	334.07	2
Log-normal	343.75	348.79	1	329.49	333.40	1
Generalised Gamma	343.82	351.39	3	331.41	337.27	5

As tables 2 and 3 above show, the Weibull curve gives the worst goodness-of-fit and as the use of 5-year trial data shows underestimates the OS of the EXTREME arm (***see explanation in External Validity subsection***). MSD have gone for the best fit for both treatment arm pairings, as is the methodology preferred by NICE.

2. **Visual inspection** was used to determine how well each parametric survival model fit the clinical trial data through close alignment with the Kaplan Meier curve. The representation of the visual inspection can be seen in the figures below.


Short-term OS Fit
Pembrolizumab
Kaplan-Meier
Exponential
Generalized Gamma
Gompertz
Log-logistic
Log-normal
Weibull
Probability of Overall Survival
1.00
0.75
0.50
0.25
Week 80
0
50
100
150
200
Time to Death (in weeks)
Long-term OS extrapolation
Pembrolizumab
Kaplan-Meier
Exponential
Generalized Gamma
Gompertz
Log-logistic
Log-normal
Weibull
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
Week 80
0
2
4
6
8
10
12
14
Time to Death (in years)



From the figures above, besides the exponential curve, the visual inspection shows no discernible difference between the remaining parametric curves with all fitting the clinical trial data reasonably. Whilst five of the six parametric models follow the Kaplan Meier , the difference is in the tails and to determine the plausibility of such tails, clinical and external data validation were employed.

3. **Clinical validity** was employed to further determine the choice of curve especially in assessing the plausibility of the extrapolated portions of the parametric survival. Elicitation from clinicians substantiated the survival extrapolation of the company at 3 and 5 years for

both pembrolizumab arms. This was also corroborated by the clinicians interviewed by NICE who stated “pembrolizumab monotherapy 5 and 10 year estimates plausible”. There was however, concern by clinicians as to the robustness of giving estimates for year 10, as there is little experience with the use of pembrolizumab for 10 years and certainly none within the Head and Neck cancer space. They agree there is a plateau phase seen with pembrolizumab in other cancer sites between 3 and 5 years and responses suggested the same could be assumed in Head and Neck cancer, with the appropriate caveats. The questionnaire used to elicit responses can be seen in the appendix.

4. **External data validation**, as the intervention pembrolizumab is new, especially in Head and Neck cancer, external data validation using the control treatment proved a viable option to assess parametric curve choice. Since the original submission: Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck, 5-year follow-up data of the EXTREME study has become available. MSD believes this data would be useful and the most robust method to validate longer-term survival estimates for cetuximab plus platinum-based chemotherapy and platinum-based chemotherapy. The table of which can be found below:

Table 4: 5-year Follow-up Data of the EXTREME Study at Random Time Points (2)

Treatment arm	% of patients alive at 28 months (1376 days)	% of patients alive at 36 months (1769 days)	% of patients alive at 42 months (2064 days)	% of patients alive at 59.5 months (2924 days)
	Trial	Trial	Trial	Trial
Cetuximab	11.7	7.1	6.5	2.9

Standard of Care *(platinum +5-FU)*	8.3	4.4	4.4	1.7
Increment	**3.4**	**2.7**	**2.1**	**1.2**

MSD has included a summary of the survival estimates using the preferred extrapolation curves of the company and the ERG below:

Table 5: Summary of Survival Estimates Based on Curve Selection by the Company and the ERG

	Pembrolizumab monotherapy				**Pembrolizumab combination therapy**			
Years after starting treatment	**Cetuximab plus platinum chemotherapy and 5-FU**		**Platinum plus 5-FU**		**Cetuximab plus platinum chemotherapy and 5-FU**		**Platinum plus 5-FU**	
	MSD	**ERG**	**MSD**	**ERG**	**MSD**	**ERG**	**MSD**	**ERG**
1	42.2	42.7	36.5	36.5	42.0	42.0	36.7	36.7
2	14.4	14.7	13.1	13.4	13.5	13.8	10.7	11.1
3	7.2	7.4	6.3	6.2	6.1	5.6	4.7	4.6
5	3.3	2.1	2.3	1.6	2.4	0.9	0.7	0.3
10	1.3	0.1	0.5	0.1	0.6	0	0	0

As can be seen from the table, and confirmed by the ERG, the choice of Weibull curve underestimates the overall survival of the both comparator arms. For instance, at year 5, for monotherapy regimens the ERG extrapolation predicts 2.1% for cetuximab plus platinum chemotherapy and 5-FU whilst the company extrapolation estimates 3.3% and for the comparison to combination therapy the predictions are 0.9% and 2.4% respectively. This shows the extrapolation of

	the company is more able to predict the overall survival at percentages closer to 2.9% as opposed to the ERG extrapolation. For the platinum + 5-FU treatment arm, the EXTREME study has a 5-year overall survival of 1.7%. The ERG extrapolation is close to this figure for the monotherapy regimen but again underestimates it at 0.3% for the combination regimen whereas the company extrapolation shows a closer prediction at 0.7%. Furthermore, clinician feedback has agreed the estimates produced by the company choice of overall survival curves closely reflected what is expected to be seen with these treatments in clinical practice. As above, most clinicians felt estimating for 10-year overall survival introduced uncertainty due to limited experience. Based on the approaches listed above, the curves chosen by the company fit most of the criteria set out for extrapolation versus the curve chosen by the ERG, who provide limited evidence to support their choice of curve.
ERG comment	In the absence of evidence this is largely a matter of conjecture. However, the following points should be borne in mind: • As stated in the ERG report, the log-logistic and log-normal distributions used in the company base case lead to patients who have had a diagnosis of R/M HNSCC having a lower probability of dying than the general population • AIC/BIC statistics can only be used to assess the extent to which a parametric distribution describes existing data; they are not measures of predictive validity

	• Visual comparison of a parametric distribution to Kaplan-Meier data is only a descriptive assessment, not a predictive assessment.
Issue 6: Duration of treatment effect	
What is the most plausible assumption of duration of treatment effect?	MSD understand it is uncertain what the long-term treatment effect of pembrolizumab monotherapy, or in combination, is for the unobserved time period (i.e. after current follow-up for KEYNOTE-048). However, there is substantial data to suggest that the treatment waning effects proposed by the ERG are inappropriate – which will be outlined below. KN048 reports 3-year overall survival data which provides visible evidence of a treatment effect with pembrolizumab, therefore the use of 3-year treatment waning will be inappropriate as the intervention effect is already known. Tables showing the follow-up time in KN048 can be found in Table 6 and Table 7.

Table 6: Summary of Theoretical Follow-up Time Pembrolizumab Monotherapy versus Cetuximab + Chemotherapy (Intention-to-Treat Population with CPS≥1)

	Study: KEYNOTE 048[a]		
	Pembrolizumab N[c] = 257	**Cetuximab + Chemotherapy[b]** N[c] = 255	**Total** N[c] = 512
Theoretical Follow-up Time (Months)[d]			
Mean (SD)	33.74 (5.44)	33.79 (5.47)	33.76 (5.45)
Median (Q1; Q3)	33.09 (29.24; 37.75)	33.15 (29.18; 37.88)	33.15 (29.21; 37.82)
Min; Max	25.33; 45.70	25.30; 45.44	25.30; 45.70

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Calculated from date of randomization until database cut-off date
5-FU: 5-Fluorouracil; CPS: Combined Positive Score; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation.

Table 7: Summary of Theoretical Follow-up Time Pembrolizumab Combination Therapy versus Cetuximab + Chemotherapy (Intention-to-Treat Population with CPS≥1)

	Study: KEYNOTE 048[a]		
	Pembrolizumab + Chemotherapy[b] N[c] = 242	**Cetuximab + Chemotherapy[b]** N[c] = 235	**Total** N[c] = 477
Theoretical Follow-up Time (Months)[d]			
Mean (SD)	33.35 (5.23)	33.13 (5.18)	33.24 (5.20)
Median (Q1; Q3)	32.84 (29.18; 37.29)	32.43 (28.88; 36.83)	32.63 (28.95; 36.96)
Min; Max	25.33; 46.26	25.30; 45.44	25.30; 46.26

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Calculated from date of randomization until database cut-off date
5-FU: 5-Fluorouracil; CPS: Combined Positive Score; Max: Maximum; Min: Minimum; Q1: First Quartile; Q3: Third Quartile; SD: Standard Deviation.

The 3-year data summarising the overall survival of patients (Intention-to-treat population with CPS ≥ 1) can be seen in Table 8 and Table 9.

Table 8: Summary of Overall Survival Rate Over Time (Pembrolizumab Monotherapy versus Cetuximab + Chemotherapy)

Overall Survival	**Study: KEYNOTE 048[a]**					
	Pembrolizumab (N[c] = 257)			**Cetuximab + Chemotherapy[b] (N[c] = 255)**		
	N at Risk[d]	**N Events[e]**	**Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]**	**N at Risk[d]**	**N Events[e]**	**Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]**
Month 6	182	74	71.1 [65.2; 76.3]	200	54	78.7 [73.2; 83.3]
Month 12	129	127	50.4 [44.1; 56.4]	110	143	43.6 [37.4; 49.6]

Month 18	99	157	38.7 [32.7; 44.6]	67	186	26.6 [21.3; 32.1]
Month 24	73	182	28.9 [23.5; 34.5]	44	209	17.4 [13.0; 22.4]
Month 30	43	193	23.9 [18.7; 29.3]	21	223	11.3 [7.7; 15.7]
Month 36	19	195	22.1 [16.9; 27.8]	9	228	8.0 [4.8; 12.3]
Month 42	4	196	20.7 [15.3; 26.7]	0	229	-

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Number of patients at risk at specified time point
e: Number of events observed from randomization to specified time point
f: From the product-limit (Kaplan-Meier) method for censored data
5-FU: 5-Fluorouracil; CI: confidence interval; CPS: Combined Positive Score.

Table 9: Summary of Overall Survival Rate Over Time (Pembrolizumab Combination Therapy versus Cetuximab + Chemotherapy)

Overall Survival	**Study: KEYNOTE 048[a]**					
	Pembrolizumab + Chemotherapy[b] (N[c] = 242)			**Cetuximab + Chemotherapy[b] (N[c] = 235)**		
	N at Risk[d]	**N Events[e]**	**Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]**	**N at Risk[d]**	**N Events[e]**	**Kaplan-Meier Rate at Specified Timepoint, % [95%-CI][f]**
Month 6	183	59	75.6 [69.7; 80.5]	184	50	78.6 [72.8; 83.4]
Month 12	133	109	55.0 [48.5; 61.0]	101	132	43.5 [37.0; 49.7]
Month 18	94	147	39.1 [33.0; 45.2]	62	171	26.7 [21.2; 32.5]
Month 24	74	167	30.8 [25.1; 36.7]	39	194	16.8 [12.3; 21.9]
Month 30	52	173	28.0 [22.4; 33.8]	17	207	10.6 [6.9; 15.0]
Month 36	23	176	25.6 [19.9; 31.6]	5	212	6.5 [3.3; 11.1]
Month 42	2	177	24.2 [18.4; 30.5]	0	213	-

a: Database Cutoff Date: 25FEB2019
b: Chemotherapy: Carboplatin or Cisplatin + 5-FU
c: Number of patients: intention-to-treat population with CPS≥1
d: Number of patients at risk at specified time point
e: Number of events observed from randomization to specified time point
f: From the product-limit (Kaplan-Meier) method for censored data
5-FU: 5-Fluorouracil; CI: confidence interval; CPS: Combined Positive Score.

An illustration of the extrapolation curves with and without the 3-year treatment waning effect on pembrolizumab can be found in Figure 1 and Figure 2.

Figure 1:Pembrolizumab Combination Therapy without 3-year Treatment Waning Effect

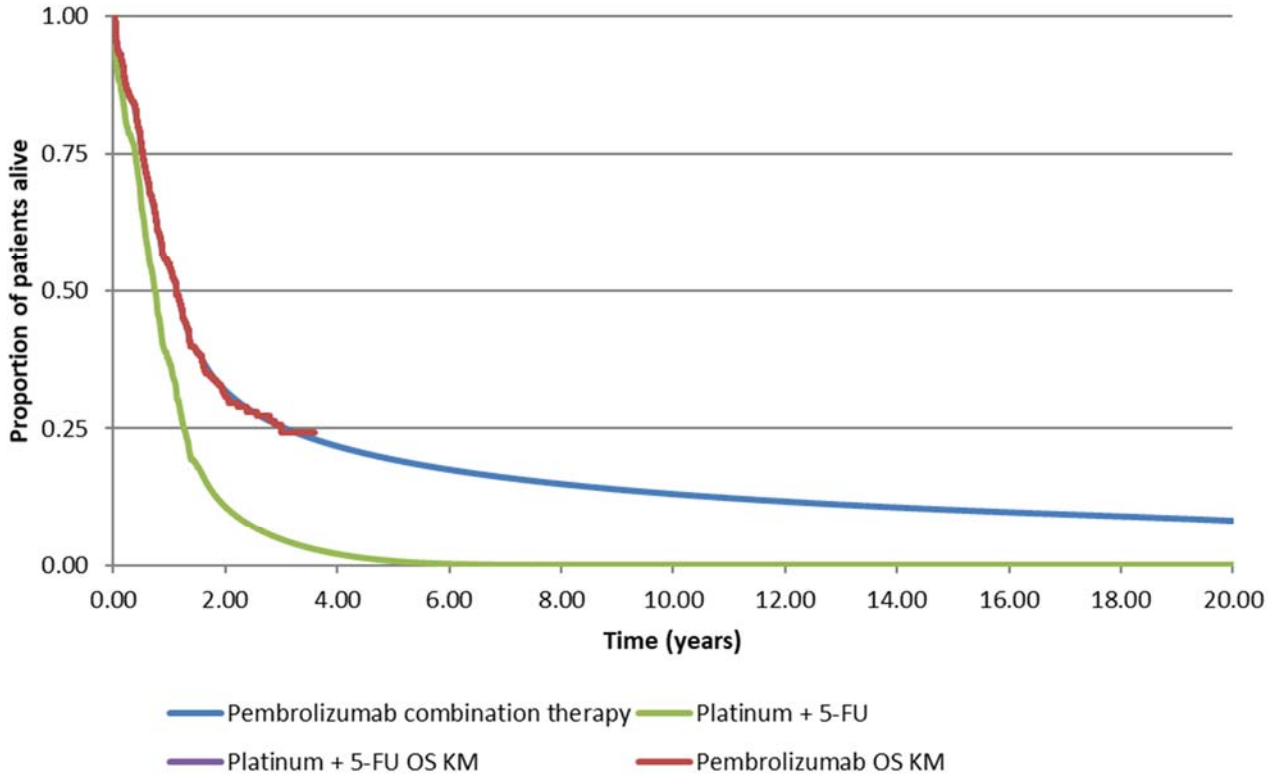
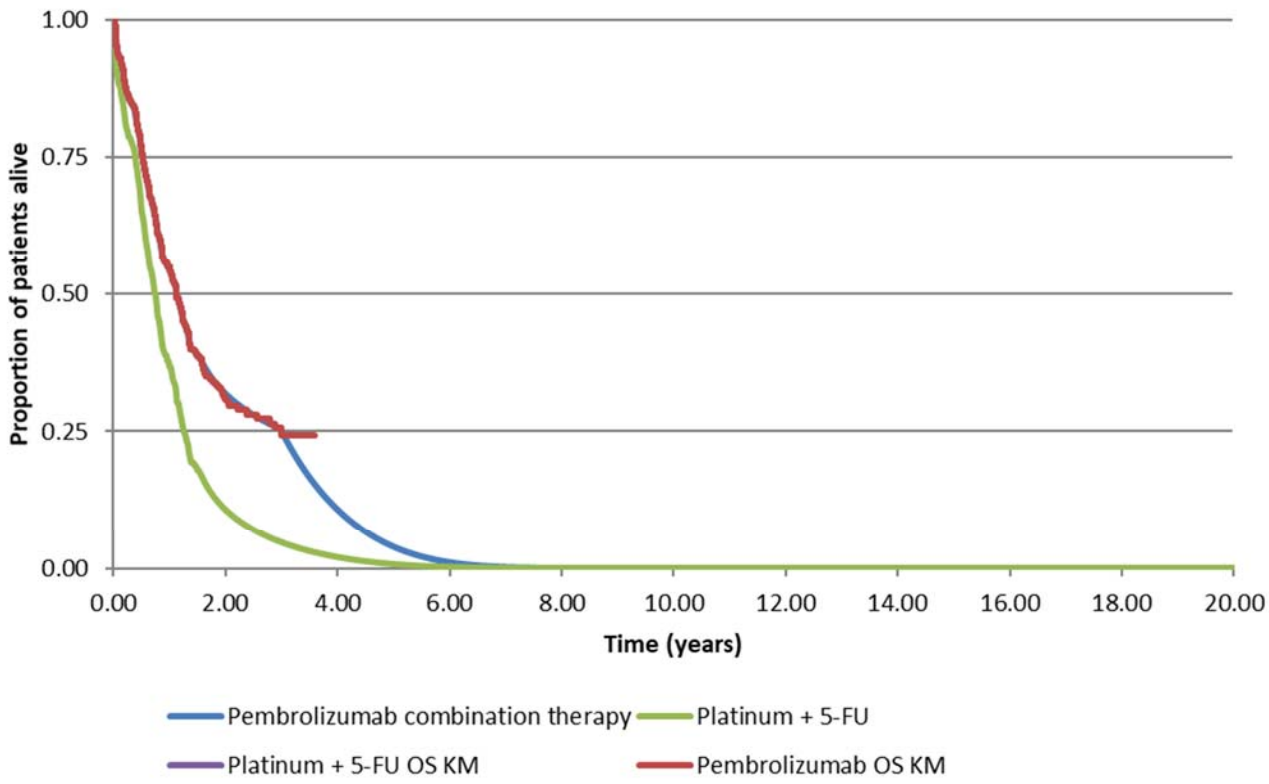


Figure 2: Pembrolizumab Combination Therapy with 3-year Treatment Waning Effect



Given the evidence presented below on the long-term treatment effect of pembrolizumab in other tumours, MSD do not believe that it is clinically plausible that the I-O plateau would simply drop off after 5 years, an arbitrarily chosen time point. For illustrative purposes, MSD has provided the curves of a pembrolizumab regimen with and without a treatment waning effect of 5 years:

Figure 3: Pembrolizumab Combination Therapy without Treatment Waning Effect

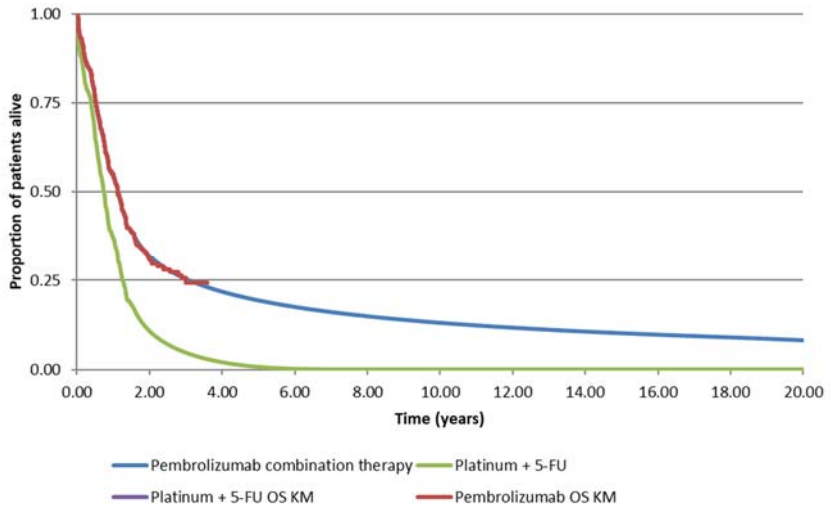
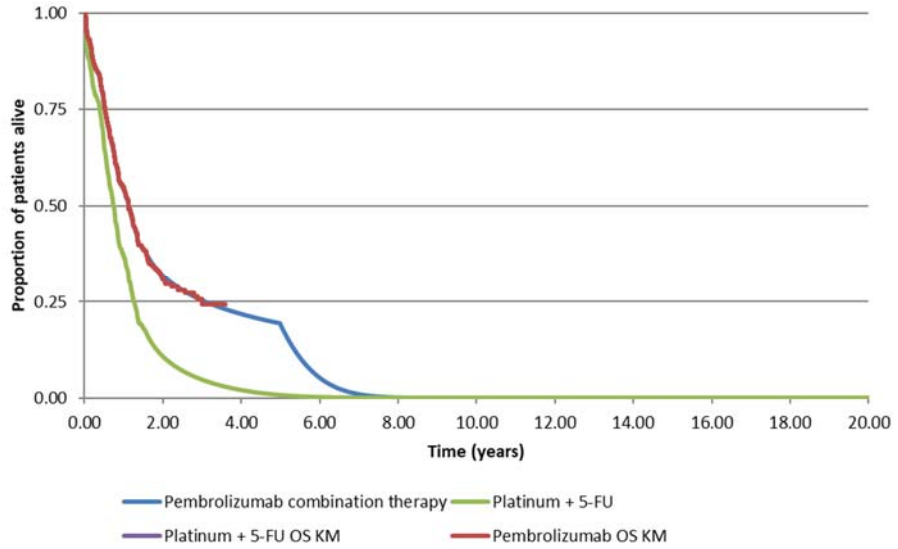
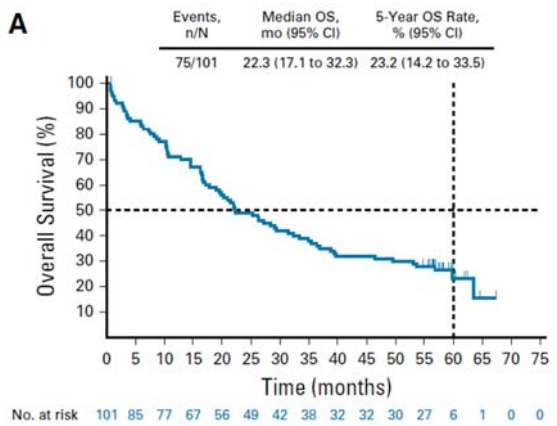


Figure 4: Pembrolizumab Combination Therapy with 5-year Treatment Waning Effect



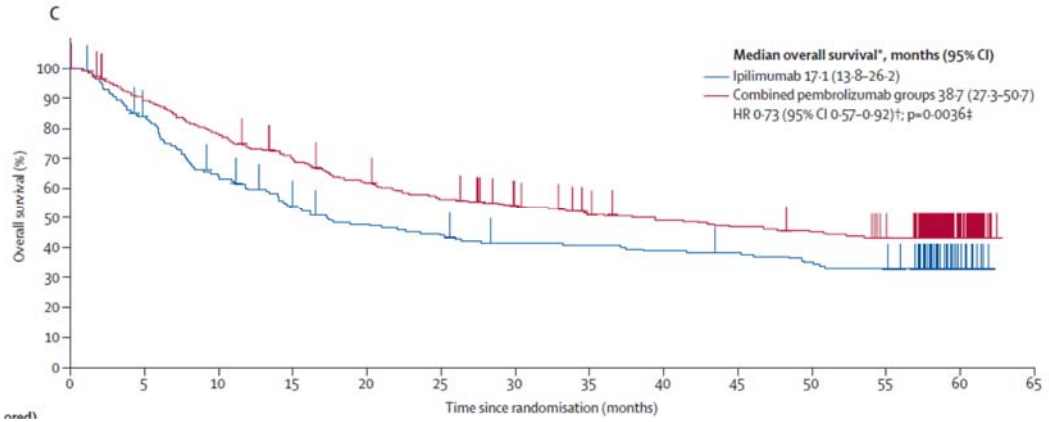
Using KN001 melanoma and Non-Small-Cell Lung Cancer (NSCLC) cohorts; evidence provided by the recently published KN001 study provided 5-year follow up data in patients with advanced NSCLC. Patients treated with pembrolizumab continued to respond with a 5-year survival. As can be seen in Figure 5 below, the plateau phase of the curve starts at month 40 and extends through to year 5.

Figure 5: Kaplan-Meier Estimates of 5-year Overall Survival for Patients with Advanced NSCLC Treated with Pembrolizumab (1)



In KN006, Pembrolizumab versus ipilimumab in advanced melanoma the overall survival estimates can be seen in the figure below. Figure 6 shows the beginnings of a plateau phase from 35 months.

Figure 6: Overall Survival in Patients Receiving 1st-line Pembrolizumab versus Ipilimumab in Advanced Melanoma (3)



In relation to KN048, Figure 7 and Figure 8 show the overall survival for CPS ≥ 1 in pembrolizumab monotherapy and combination therapy respectively. As can be seen from the figures, at roughly 35 months in both intervention arms a plateau phase has begun. Based on this, one can surmise, that similar to KN001 and KN006 we can expect this plateau phase to extend beyond this point through to 5 years. The evidence for KN001 and KN006 proves patients were not only alive at 5 years but also achieved durable responses, which based on the trajectory of responses from KN048 can be assumed to be applicable.

Figure 7: Kaplan-Meier Estimates of Overall Survival (Pembrolizumab Monotherapy versus Control) (4)

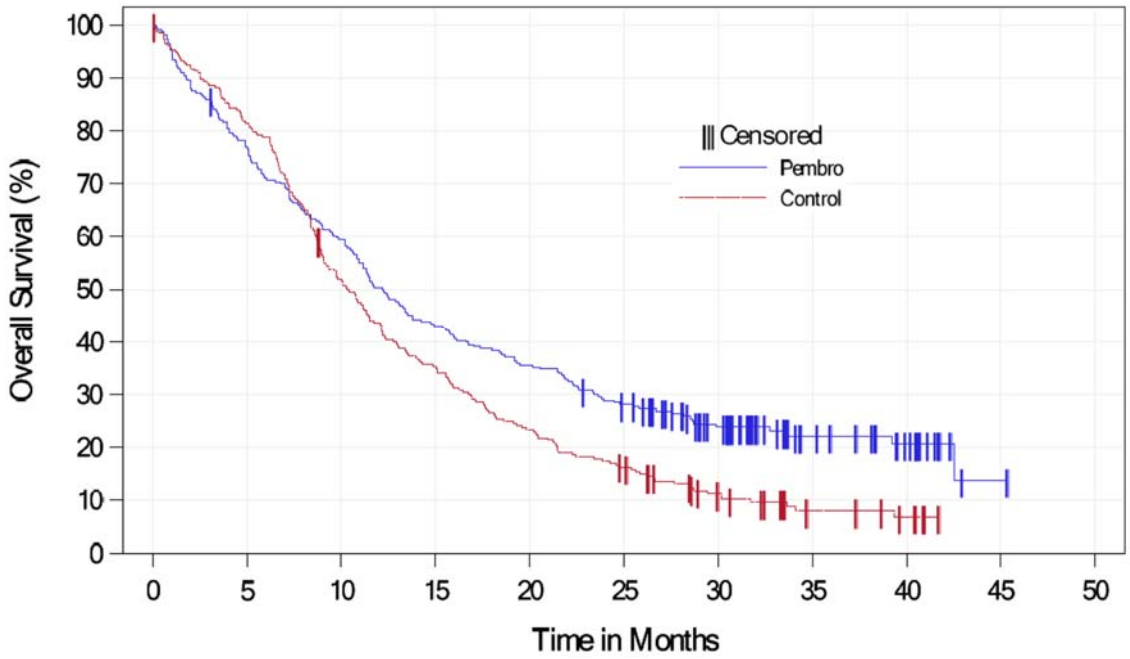
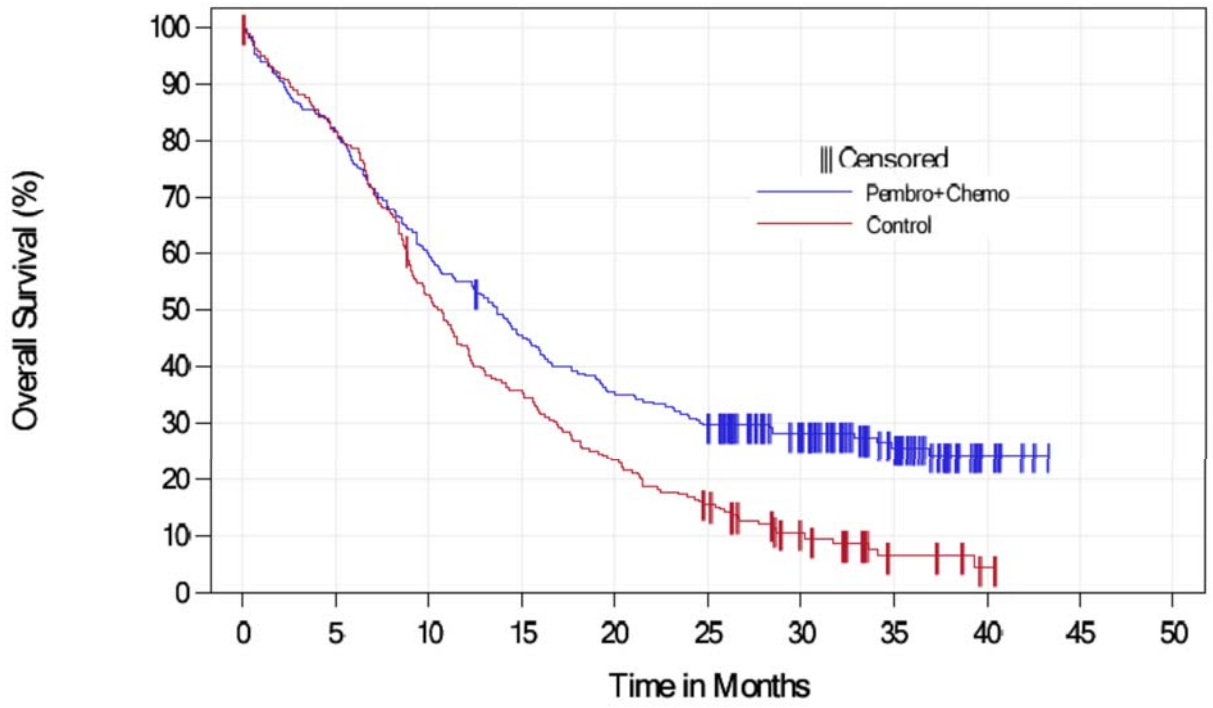


Figure 8: Kaplan-Meier Estimates of Overall Survival (Pembrolizumab Combination Therapy versus Control) (4)



MSD would also like to refer to the clinical expert input provided as part of TA490, Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy, which states that “I believe that the majority of patients who enter the plateau phase will continue to enjoy the health benefits (including out to 5 – 10 years)”. This is also supported by clinical expert interviews conducted by the NICE team for this submission. The responses stated, “duration of treatment effect with pembrolizumab or other IO agents are likely to be 5 years or more, but unlikely to be 10 years; at least with current experience and we need actual long-term clinical follow-up data”. The second clinician interviewed by the NICE team also stated, “all treatment effect beyond 5 years is by definition due to the pembrolizumab as there are almost zero survivors without pembrolizumab beyond 5 years”.

Based on the data provided, and clinician responses, the effect of pembrolizumab is highly likely to last out to 5 years and beyond, although acknowledging there is more uncertainty at 10 years.,. Based on this MSD have explored a duration of treatment effect range from between 5 and 10 years.

MSD does acknowledge treatment waning has been used in previous immunotherapy appraisals and as such have explored a range of potential timepoints to allow the committee to characterise the current long-term uncertainty which was acknowledged above. A summary of the ICERs using different annual treatment waning effects with both the company and the ERG preferred extrapolation curves.

Table 10: Treatment Waning ICERs for Company and ERG Preferred Extrapolation Curves (Non-oral Cavity Patients)

Treatment Waning	Pembrolizumab Monotherapy	Pembrolizumab Combination Therapy

	MSD	ERG	MSD	ERG
5 years	£43,158	£51,063	£57,011	£60,242
6 years	£40,209	£48,071	£51,742	£54,828
7 years	£38,122	£46,047	£47,836	£51,050
8 years	£36,570	£44,617	£44,775	£48,257
9 years	£35,378	£43,580	£42,320	£46,146
10 years	£34,442	£42,812	£40,317	£44,523

Table 11: Treatment Waning ICERs for Company and ERG Preferred Extrapolation Curves (Oral Cavity Patients)

Treatment Waning	Pembrolizumab Monotherapy		Pembrolizumab Combination Therapy	
	MSD	ERG	MSD	ERG
5 years	Dominant	Dominant	£10,417	£14,023
6 years	Dominant	Dominant	£10,110	£13,270
7 years	Dominant	Dominant	£9,921	£12,819
8 years	Dominant	Dominant	£9,785	£12,501

	<table><tr><td>9 years</td><td>Dominant</td><td>Dominant</td><td>£9,682</td><td>£12,267</td></tr><tr><td>10 years</td><td>Dominant</td><td>Dominant</td><td>£9,602</td><td>£12,092</td></tr></table> As can be seen from the Table 10 and Table 11 above, monotherapy in non-oral cavity patients is a cost-effective option from 6 year waning effect with ERG (highly conservative overall survival extrapolation) and always cost effective with company overall survival extrapolation, whilst it is dominant in the oral-cavity patients with all treatment waning effects in both the company and ERG preferred extrapolation curves. For the combination therapy, in non-oral cavity patients in the company preferred extrapolation it is cost-effective from 7 years and with the ERG preference 8 years. In oral cavity patients it is cost effective at all treatment waning points from 5 years.
ERG comment	In the absence of evidence this is a matter of conjecture.
Issue 7: End of life criteria	
What is the life expectancy of the patient group receiving standard of care, (that is, either cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU?	The EXTREME study found that, in this indication: • Patients treated with cetuximab in combination with platinum-based chemotherapy with 5-fluorouracil had a median overall survival of 10.1 months with a 95% confidence interval of 8.6 months to 11.2 months (this agrees well with what was observed in the KEYNOTE-048 study where patients in the cetuximab in combination with platinum-based chemotherapy with 5-

	fluorouracil arm had a median overall survival of 10.7 months with a 95% confidence interval of 9.3 months to 11.7 months). • Patients treated with platinum-based chemotherapy with 5-fluorouracil had a median overall survival of 7.4 months with a 95% confidence interval of 6.4 months to 8.3 months.
ERG comment	No comment.
Does the life expectancy of the patient group receiving standard of care differ between those whose cancer started in the oral cavity and those whose started outside the oral cavity?	Differences in life expectancy between patients whose cancer started in the oral cavity and those whose started outside the oral cavity exist and are attributable to differences in standard of care received and not to any underlying biological differences in life expectancy between these patient groups. In the United Kingdom, patients whose cancer started in the oral cavity would receive treatment with cetuximab in combination with platinum-based chemotherapy plus 5-fluorouracil while patients whose cancer started outside the oral cavity would receive only platinum-based chemotherapy plus 5-fluorouracil. As demonstrated in the EXTREME trial, the addition of cetuximab to platinum-based chemotherapy with 5-fluorouracil significantly prolongs overall survival in comparison with platinum-based chemotherapy plus 5-fluorouracil (as described in the response above, with a hazard ratio for death of 0.80 with 95% confidence intervals of 0.64 to 0.99, P=0.04). In contrast, the data from the EXTREME study (also described in the response above) show that the 95% confidence intervals for the overall survival hazard ratios for cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil in the oral cavity patients subgroup and in each of the non-oral cavity patients subgroups (oropharynx, larynx, and hypopharynx) overlap, which does not show that the efficacy in terms of overall survival of cetuximab in combination with platinum chemotherapy and 5-fluorouracil versus platinum and 5-fluorouracil differs significantly between patients whose cancer started in the oral cavity and those whose cancer did not.
ERG comment	No comment.

What is the extension to life of the patient group receiving pembrolizumab monotherapy or pembrolizumab combination therapy?	As described in section B.3.7 of ID1140 Pembrolizumab Evidence Review Group clarification letter – Supplementary Document Final: • The incremental life years gained in patients with PD-L1 combined positive score ≥1 treated with pembrolizumab monotherapy is 1.13 years versus patients treated with cetuximab + chemotherapy, and 1.30 years versus patients treated with platinum + 5-fluorouracil. • The incremental life years gained in patients with PD-L1 combined positive score ≥1 treated with pembrolizumab combination therapy is 1.88 years versus patients treated with cetuximab + chemotherapy, and 2.10 years versus patients treated with platinum + 5- fluorouracil.
ERG comment	Results from the ERG's most pessimistic scenarios show that pembrolizumab monotherapy and pembrolizumab+PLAT+5-FU extend life by more than 3 months when compared with cetuximab+PLAT+5-FU (oral cavity patients) or PLAT+5-FU (non-oral cavity patients).

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1. Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-Year Overall Survival for Patients With Advanced NonSmall-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019;37(28):2518-27.
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3. 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. 2019;20(9):1239-51.
4. Merck Sharp & Dohme. KEYNOTE-048 Clinical Study Report - MSD data on file. 2019.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Pembrolizumab for treating recurrent or metastatic squamous cell head and neck cancer

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it 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 appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: November 2019

1. Topic background

1.1 Disease background

Head and neck cancers describe a group of cancers that arise most often from the oral cavity, oropharynx, hypopharynx, and larynx. More than 90% of head and neck cancers are squamous cell carcinomas (HNSCC), originating from the epithelium of the mucosal lining of the upper aerodigestive tract. They are commonly aggressive, resulting in significant destructive disease above the clavicle, with the development of local (cervical) lymph node metastases and distant metastases even after effective local therapy. Head and neck cancer accounts for approximately 3% of all new cancer cases and HNSCC occurs at approximately a 2:1 male: female ratio.

1.2 Incidence

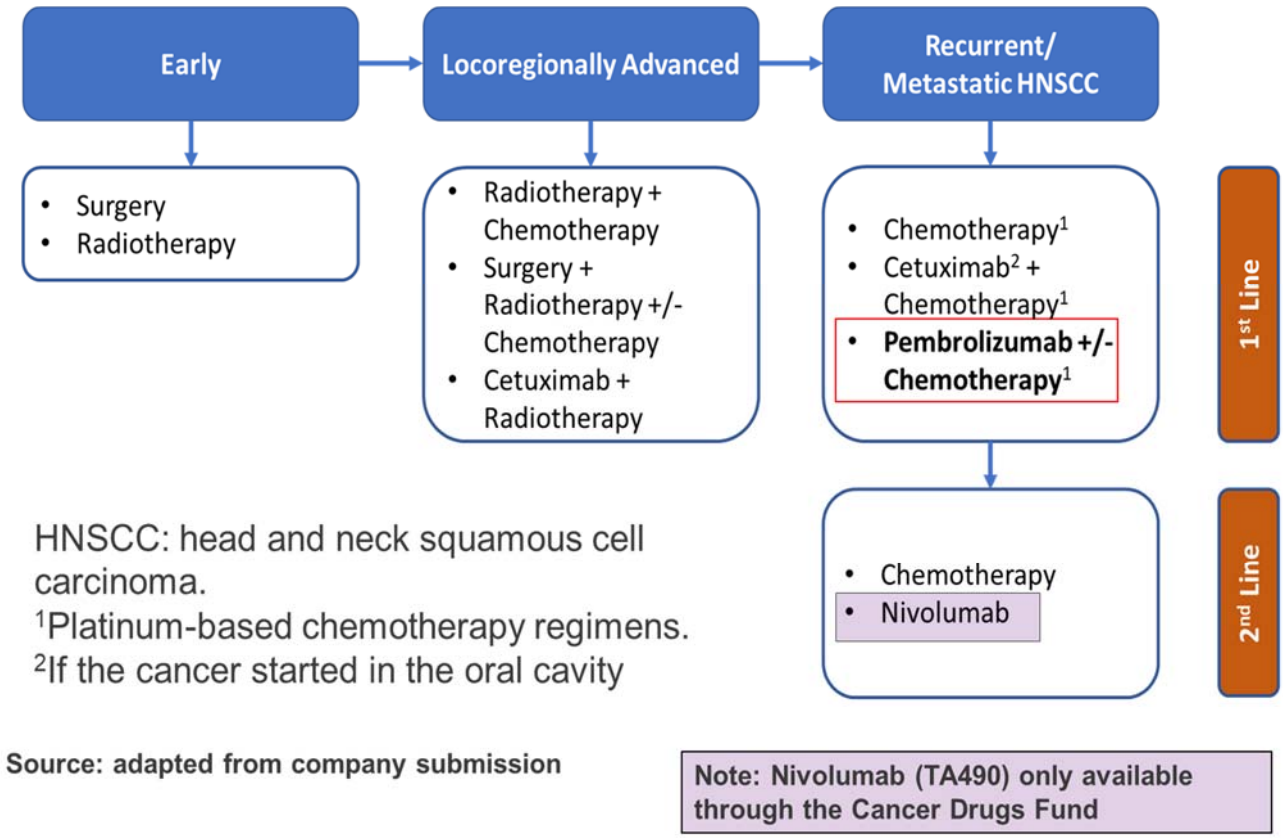
Head and neck cancer is the 8th most common cancer in the UK, accounting for 3% of all new cancer with approximately 9,000 diagnoses in England each year. Approximately 60% of head and neck cancers are where the tumour started inside the oral cavity (that is, the lips, gums, palate, tongue, tonsils, and under the tongue). Where the tumour started outside of the oral cavity (that is, the sinus', nasal cavity, middle ear, larynx, parotid gland and the naso, oro and hypo pharynx's) this makes up approximately 40% of head and neck cancers.

1.3 Pembrolizumab (Keytruda, Merck Sharp & Dohme)

Mechanism	Monoclonal antibody that binds to the PD-1 receptor blocking the interaction with the receptor ligands, PD-L1 and PD-L2. 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 inactivity.
Marketing authorisation	The technology does not currently have a UK marketing authorisation for this indication. Positive CHMP opinion received October 2019.

Administration and dose	• Pembrolizumab monotherapy: 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) intravenously • Pembrolizumab in combination with platinum-based chemotherapy 200 mg every 3 weeks (Q3W) intravenously
Indicative list price	£2,630 per 100 mg vial.
Other indications	• Melanoma, NSCLC, Relapsed or refractory classical Hodgkin lymphoma (cHL), Urothelial carcinoma, Recurrent or metastatic head and neck squamous cell carcinoma PD-L1 with a ≥50% TPS and progressing on or after platinum-containing chemotherapy.

1.4 Treatment pathway



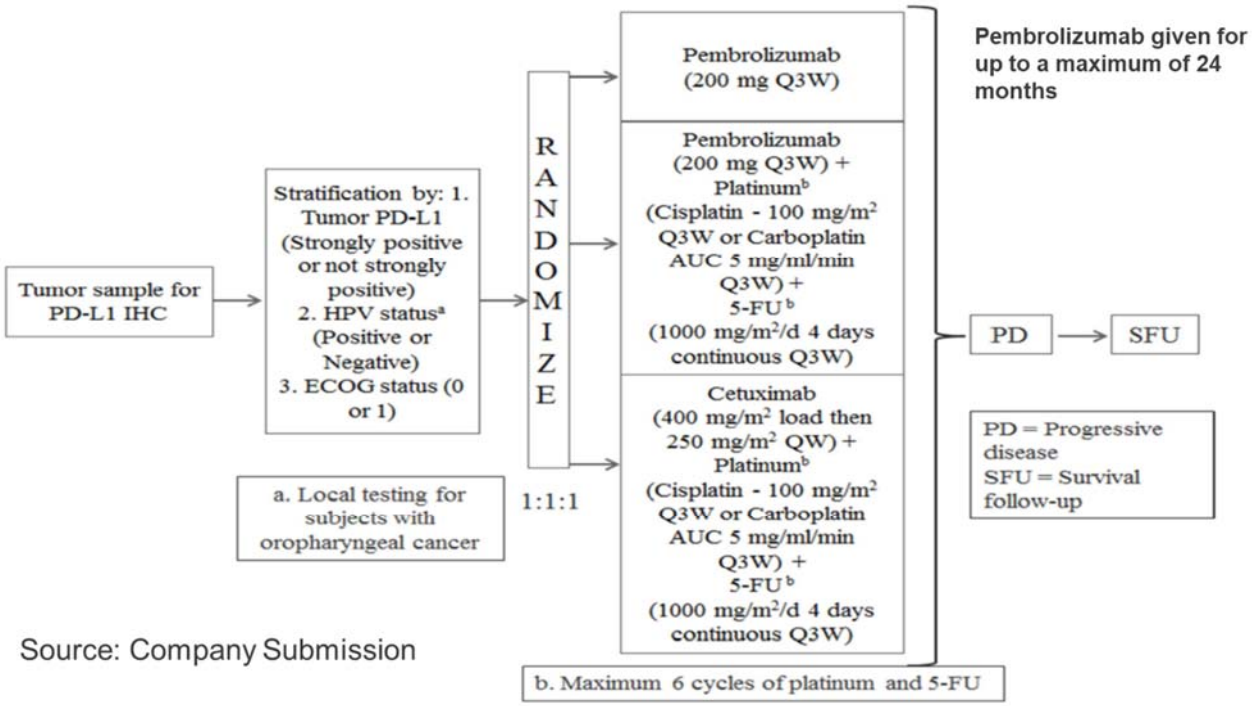
Source: adapted from company submission

Note: Nivolumab (TA490) only available through the Cancer Drugs Fund

1.5 Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission
Population	Adults with recurrent or metastatic squamous cell carcinoma of the head and neck previously untreated in the recurrent or metastatic setting	As per scope but with programmed cell death ligand 1 expression defined as ≥1 combined positive score (CPS)
Intervention	Pembrolizumab alone or in combination with platinum-based chemotherapy	As per scope
Comparator	• Platinum-based chemotherapy regimens • Cetuximab in combination with platinum-based chemotherapy (only if the cancer started in the oral cavity)	• Platinum-based chemotherapy regimens • Cetuximab in combination with platinum-based chemotherapy
Outcomes	Overall survival Progression-free survival Response rates Adverse effects of treatment Health-related quality of life	Overall survival Progression-free survival Response rates Duration of response Adverse effects of treatment Health-related quality of life

1.6 Study design – KEYNOTE 048



Source: Company Submission

*HPV status for patients without oropharynx cancer (e.g. cancers of the oral cavity, hypopharynx and larynx) were considered HPV negative.

Following disease progression, patients in the cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) arm could receive subsequent treatments, including the anti-PD-1 treatment, nivolumab. Nivolumab is currently available, through the Cancer Drugs Fund (CDF), as a treatment for HNSCC after platinum-based chemotherapy (TA490). However, as treatments that are available through the CDF cannot be considered as comparators, the company adjusted for the effect of subsequent treatment with immune checkpoint inhibitors using statistical methods which adjust overall survival for treatment switching.

1.7 KEYNOTE-048 analyses

- Results are from a pre-specified subgroup of people with programmed cell death ligand 1 PD-L1) expression defined as ≥1 combined positive score (CPS).

- Results for **all patients** (that is, all people in KEYNOTE-048 irrespective of primary tumour location) and for **oral cavity patients** (that is, people in KEYNOTE-048 whose primary tumour location was in the oral cavity) were provided by the company at the clarification stage of the appraisal.

- No clinical data was presented for people whose primary tumour location was **not** in the oral cavity.

1.8 Key trial results – Overall survival: All patients

Pembrolizumab monotherapy vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil for the combined positive score ≥1 subgroup.

Treatment	n	Number of events (%)	Median OS (months) (95% CI)	OS rate at month 12 in % (95% CI)	Pembrolizumab vs cetuximab + PLAT +5-FU	
					HR (95% CI)	p-value
Unadjusted for subsequent anti-PD-1 treatment, all patients						
Pembrolizumab	257	197 (76.7)	12.3 (10.8 to 14.3)	50.4 (44.1 to 56.4)	0.74 (0.61 to 0.90)	0.0013§
Cetuximab+ PLAT + 5-FU	255	229 (89.8)	10.3 (9.0 to 11.5)	43.6 (37.4 to 49.6)		
Adjusted for subsequent anti-PD-1 treatment via simplified 2-stage method, all patients						
Pembrolizumab	257	197 (76.7)	12.3 (10.8 to 14.3)	50.4 (44.1 to 56.4)	0.71 (0.57 to 0.89)	Log-rank: 0.0027¶ Cox model: 0.0027‖
Cetuximab+ PLAT + 5-FU 2-stage adjusted	255	229 (89.8)	10.1 (9.0 to 11.5)	43.1 (37.0 to 49.1)		

§ One-sided p-value based on log-rank test
¶ Two-sided p-value based on Cox model, analysis not adjusted for treatment switch
‖ Two-sided p-value based on log-rank test, analysis not adjusted for treatment switch

Pembrolizumab combination vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil for the combined positive score ≥1 subgroup

Treatment	n	Number of events (%)	Median OS (months) (95% CI)	OS rate at month 12 in % (95% CI)	Pembrolizumab combination vs cetuximab + PLAT + 5-FU	
					HR (95% CI)	p-value
Unadjusted for subsequent anti-PD-1 treatment, all patients						
Pembrolizumab + PLAT + 5-FU	242	177 (73.1)	13.6 (10.7 to 15.5)	55.0 (48.5 to 61.0)	0.65 (0.53 to 0.80)	0.00002§
Cetuximab + PLAT + 5-FU	235	213 (90.6)	10.4 (9.1 to 11.7)	43.5 (37.0 to 49.7)		
Adjusted for subsequent anti-PD-1 treatment via simplified 2-stage method, all patients						
Pembrolizumab + PLAT + 5-FU	242	177 (73.1)	13.6 (10.7 to 15.5)	55.0 (48.5 to 61.0)	0.62 (0.50 to 0.78)	Cox model: <0.0001¶ Log-rank: <0.0001‖
Cetuximab + PLAT + 5-FU 2-stage adjusted	235	213 (90.6)	10.3 (9.0 to 11.5)	43.0 (36.6 to 49.2)		

§ One-sided p-value based on log-rank test
¶ Two-sided p-value based on Cox model, analysis not adjusted for treatment switch
‖ Two-sided p-value based on log-rank test, analysis not adjusted for treatment switch

1.9 Key trial results – Overall survival: oral cavity patients

Pembrolizumab monotherapy vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil for the combined positive score ≥1 subgroup

Pembrolizumab combination vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil for the combined positive score ≥1 subgroup

[redacted]

1.10 Key trial results – Progression-free survival

Pembrolizumab monotherapy vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil for the combined positive score (CPS) ≥1 subgroup

Treatment	n	Number of events (%)	Median PFS (months) (95% CI)	PFS rate at months 6 in % (95% CI)	Pembrolizumab vs cetuximab + PLAT + 5-FU	
					HR (95% CI)	p-value
All patients						
Pembrolizumab	257	228 (88.7)	3.2 (2.2 to 3.4)	28.7 (23.3 to 34.4)	1.13 (0.94 to 1.36)	0.8958§
Cetuximab + PLAT + 5-FU	255	237 (92.9)	5.0 (4.8 to 6.0)	43.9 (37.6 to 49.9)		
Patients whose cancer originated in the oral cavity						

[redacted]

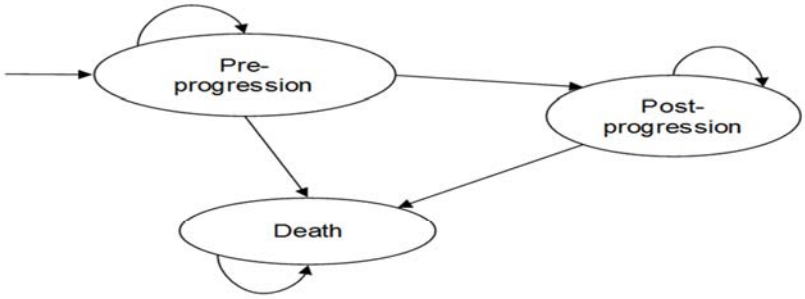
Pembrolizumab combination vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil for the combined positive score (CPS) ≥1 subgroup

Treatment	n	Number of events (%)	Median PFS (months) (95% CI)	PFS rate at months 6 in % (95% CI)	Pembrolizumab combination vs cetuximab + PLAT + 5-FU	
					HR (95% CI)	p-value
All patients						
Pembrolizumab + PLAT + 5-FU	242	212 (87.6)	5.1 (4.7 to 6.2)	44.9 (38.5 to 51.1)	0.84 (0.69 to 1.02)	0.0370[§]
Cetuximab + PLAT + 5-FU	235	221 (94.0)	5.0 (4.8 to 6.0)	43.3 (36.9 to 49.6)		
Patients whose cancer originated in the oral cavity						

[redacted]

1.11 Model structure

Partitioned survival model



Factor	Chosen values
Time horizon	20 years
Cycle length	1 week
Half cycle correction	No
Source of utilities	EQ-5D-3L
Treatment waning effect	No
Discount rate	3.5%
Perspective	NHS and Personal and Social Services (PSS)
Stopping rule	2-years
Treatment effect	Lifetime

1.12 Key model assumptions

Comparators	No use of nivolumab as a subsequent therapy despite its use in KEYNOTE-048 (NICE position statement: exclusion as comparators or subsequent treatments, any drugs currently available in the Cancer Drugs Fund) Cross-over adjustment conducted to remove its effect on overall survival curve - cost not included in economic model
Adverse events	Incidence of AEs from KEYNOTE-048 and published trials assumed to reflect that observed in practice Based on results of KEYNOTE-048 trial and published trials for platinum chemotherapy and 5-FU
Utility values	Adjusted by UK general population utility where utility decreases with age - *Ara and Brazier* (2010)
Costs and resource use	Assumed to be equal between pembrolizumab and cetuximab in combination with platinum chemotherapy and 5-fluorouracil / platinum chemotherapy and 5-FU arms Resource use assumed to be equal by treatment arm in the pre- and post- progression health states

2. Summary of the draft technical report

After technical engagement the technical team has collated the comments received and, if relevant, updated the preliminary judgement by the technical team and rationale. Judgements that have been updated after engagement are highlighted in **bold** below.

2.1 In summary, the technical team considered the following:

Issue 1 Following input from the clinical experts a 2-year stopping rule for pembrolizumab is appropriate for decision making (see issue 1)

Issue 2 **Following input from the clinical experts, the patient populations who receive pembrolizumab monotherapy or combination therapy should be considered separately and so a pairwise comparison for cost-effectiveness analysis would be appropriate** (see issue 2)

Issue 3 **The results from KEYNOTE-048 are broadly generalisable to clinical practice in England and it is appropriate to consider subgroups by cancer location** (see issue 3)

Issue 4 Network meta-analyses for HNSCC (see issue 4)

Issue 5 Extrapolation of overall survival (see issue 5)

Issue 6 Duration of treatment effect (see issue 6)

Issue 7 **Pembrolizumab monotherapy and pembrolizumab combination therapy meet the end of life criteria** specified in NICE's guide to the methods of technology appraisal (see issue 7)

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- There are no head-to-head trials comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluouracil in recurrent or metastatic squamous cell head and neck cancer.
- Standard care (that is cetuximab in combination with platinum chemotherapy and 5-fluorouracil) in KEYNOTE-048 only included people with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

2.3 The cost-effectiveness results include a commercial access agreement for pembrolizumab and the list prices for the comparators. The company base case, which assumed a 20-year benefit of treatment, included people whose cancer started in the oral cavity or outside of the oral cavity.

The results gave the following pairwise incremental cost-effectiveness ratios (ICERs):

	Deterministic ICER (£ per QALY gained)	Probabilistic ICER (£ per QALY gained)
Pembrolizumab monotherapy vs Cetuximab + platinum chemotherapy + 5-fluorouracil	Dominated	Dominated
Pembrolizumab monotherapy vs platinum chemotherapy + 5-fluorouracil	£31,212	£31,832
Pembrolizumab + platinum chemotherapy + 5-fluorouracil vs Cetuximab + platinum chemotherapy + 5-fluorouracil	£9,255	£9,552

Pembrolizumab platinum chemotherapy + 5-fluorouracil vs platinum chemotherapy + 5-fluorouracil	£31,070	£32,043

2.4 The technical team's preferred assumptions (see tables 1a, 1b,1c,1d, 1e and 1f) where people with cancers starting in the oral cavity or outside of the oral cavity are considered separately in the economic model. This is because the standard of care in the NHS for each group is different (cetuximab in combination with platinum chemotherapy and 5-fluorouracil for people whose cancer started in the oral cavity and platinum chemotherapy and 5-fluorouracil for people whose cancer started outside of the oral cavity). The preferred assumptions result in the following pairwise ICERs:

- For people whose cancer started in the oral cavity:
  - Pembrolizumab combination therapy vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil, the ICER is £16,533 per QALY gained. After incorporating the commercial arrangements for cetuximab, the ICER is below £50,000 per QALY gained. The exact ICER cannot be given because the commercial arrangements for cetuximab are confidential and cannot be reported here.
  - Pembrolizumab monotherapy vs cetuximab in combination with platinum chemotherapy and 5-fluorouracil: pembrolizumab monotherapy dominates. After incorporating the commercial arrangements for cetuximab, the ICER is below £30,000 per QALY gained. The exact ICER cannot be given because the commercial

arrangements for cetuximab are confidential and cannot be reported here.

- For people whose cancer started outside the oral cavity:
  - Pembrolizumab combination therapy vs platinum chemotherapy and 5-fluorouracil, the ICER is £67,386 per QALY gained;
  - Pembrolizumab monotherapy vs platinum chemotherapy and 5-fluorouracil, the ICER is £56,085 per QALY gained.

2.5 Based on the modelling assumptions, the intervention is likely to meet the end-of-life criteria (see issue 7).

2.6 The technology is unlikely to be considered innovative (see table 3).

2.7 No equality issues were identified by the company, consultees and their nominated clinical experts and patient experts (see table 3).

3. Key issues for consideration

Issue 1 – 2-year stopping rule for pembrolizumab

This issue was resolved at technical engagement and is addressed in Table 3.

Issue 2 – Treatment choice

Questions for engagement	2. What factors affect the decision on whether pembrolizumab monotherapy is preferred over pembrolizumab combination therapy? In particular: • Which patients would likely receive pembrolizumab monotherapy? • Which patients would likely receive pembrolizumab combination therapy?
Background/description of issue	**The company** stated that, in clinical practice, the choice of pembrolizumab monotherapy or pembrolizumab combination therapy would be made by the treating clinician in consultation with the patient. It noted that treatment with pembrolizumab combination therapy would be better for people who were so unwell that it would be unethical to give pembrolizumab monotherapy because there is a delayed response of approximately 3 to 6 months that is characteristic of immunotherapy treatments. **The ERG** noted that if people were so unwell that an immediate response to treatment was necessary, then they may also be too ill to tolerate the level of adverse events associated with pembrolizumab combination therapy.
Why this issue is important	It is unclear which patient populations would choose to take pembrolizumab monotherapy or pembrolizumab combination therapy in clinical practice. It is important to identify the factors that affect patient and clinician treatment choice so that the most appropriate treatment comparisons can be used in the cost effectiveness analysis. If the patient populations receiving pembrolizumab monotherapy or pembrolizumab combination therapy are clinically distinct populations then a pairwise comparison (pembrolizumab monotherapy compared and pembrolizumab combination

	therapy compared with cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy 5-FU chemotherapy regimens) would be appropriate. If the 2 populations are not clinically distinct then a fully incremental analysis (platinum chemotherapy with/ or without cetuximab in combination with platinum chemotherapy and 5-FU [depending on whether the cancer starts in or outside the oral cavity] compared with pembrolizumab monotherapy which in turn is then compared with pembrolizumab combination therapy) would be appropriate. For example, for people with cancer which started outside the oral cavity, the ERG's preferred scenario results in ICERs of £43,856 per QALY gained and £42,790 per QALY gained for pembrolizumab monotherapy and pembrolizumab combination therapy compared with platinum and 5-FU respectively. Both ICERs have the potential to be considered cost effective if the committee accepts the ERG's scenario along with accepting that pembrolizumab monotherapy and pembrolizumab combination therapy meet NICE's End of Life criteria (see Issue 7). However, if a fully incremental analysis is used for the same scenario (see table 1e), only pembrolizumab combination therapy has the potential to be considered cost effective with an ICER of £42,790 per QALY gained compared with platinum chemotherapy and 5-FU. This is because pembrolizumab monotherapy is 'extendedly dominated', that is it is less effective and has a higher ICER than pembrolizumab combination therapy.
Technical team preliminary judgement and rationale	It is possible that people with recurrent and metastatic squamous head and neck cancer will have different preferences for treatment. As a result, any variability in reasoning behind treatment choice is uncertain. The choice of cost effectiveness analysis will be determined by whether pembrolizumab monotherapy and pembrolizumab combination therapy will be given to different distinct patient populations.
Summary of comments	Comments received from company Decision to use either monotherapy or combination therapy will be done on a case-by-case basis (benefit versus risk) based on: • Monotherapy - patients with low burden of disease, tumour rate not faster than usual and who may not be fit to tolerate combination therapy. • Combination therapy - patients with very heavy burden of disease, disease progressing rapidly. Patients whose disease has relapsed after having chemotherapy treatment.

	Comments received from clinical experts Pembrolizumab monotherapy - patient would need a good Performance Status (PS), previous treatment with chemotherapy (neoadjuvant chemotherapy and/or high dose concurrent chemoradiotherapy) with residual chemotherapy induced toxicities. Pembrolizumab combination therapy - patient would need a good PS, disease have not been heavily pre-treated with chemotherapy or have no residual chemotherapy induced toxicities where a rapid response is needed. Not suitable for borderline/poor PS because of advanced disease with airway compromise, etc. NCRI-ACP-RCP-RCR Balance between toxicity and desired response rate. For rapid progressing/symptomatic disease would prefer higher response at expense of increased expected toxicity from combination therapy. Other patients may be more inclined to consider monotherapy.
Technical team judgement after engagement	The consensus of clinical experts was that the decision on whether a patient would receive monotherapy or combination would be on a case-by-case basis considering several clinical factors. Although some of these factors are similar in both groups, such as the requirement of a good performance status, there are differences, such as disease burden and speed of disease progression. The technical team consider that the populations should be considered separately and so a pairwise comparison would be appropriate. However, committee may wish to explore this further with the clinical experts at the appraisal committee meeting.

Issue 3 – Generalisability of KEYNOTE-048 results: Cetuximab as a comparator

Questions for engagement	3. Are the results from the KEYNOTE trial generalisable to all patients with recurrent or metastatic head and neck squamous cell carcinoma whose tumours expressed PD-L1 with a CPS≥1 irrespective of where the cancer started? 4. Is it appropriate to consider subgroups by cancer location?

Background/description of issue	The comparator in the KEYNOTE-048 trial was cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) and was given to all patients randomised to the comparator arm of the trial irrespective of where their cancer started. **The company** stated that this was to maintain randomisation and powering of the study (that is, it would not have enough people in each arm of the trial, so the results would be below the statistical power needed to provide valid answers), as KEYNOTE-048 was not designed to analyse subgroup data based on site of cancer origin, such as the oral cavity. **The ERG** highlighted that cetuximab in combination with platinum chemotherapy and 5-FU is recommended by NICE (TA473) as an option only for treating adults with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that started in the oral cavity. This recommendation was based on an evaluation of clinical effectiveness data (which informed the cost effectiveness analyses) from a pre-planned subgroup of patients in the EXTREME trial. It noted that in the comparator arm of KEYNOTE-048, only 31% of patients had cancer that started in the oral cavity with 69% of patients receiving treatment that is not standard of care in the NHS (that is, they received cetuximab in combination with platinum chemotherapy and 5-FU even when the cancer did not start in the oral cavity). In response to clarification, the company provided data from KEYNOTE-048 from the subgroup of patients whose cancer started in the oral cavity. No evidence has been provided for the subgroup whose cancer started outside the oral cavity. The company highlighted that the subgroup analysis was not powered to detect statistically significant differences between treatments in the oral cavity subgroup. The ERG agreed that this is an important limitation of the available data.
Why this issue is important	Issues with generalisability increases the uncertainty in the clinical and cost effectiveness estimates from KEYNOTE. This is because it is unclear what the potential effect of cetuximab in combination with platinum chemotherapy and 5-FU in patients whose cancer has started outside the oral cavity has on the relative effectiveness of pembrolizumab monotherapy or pembrolizumab combination therapy and cetuximab in combination with platinum chemotherapy and 5-FU in the whole trial population. If cetuximab in combination with platinum chemotherapy and 5-FU is less effective in patients whose cancer starts outside the oral cavity than in those whose cancer starts in the oral cavity, the effectiveness of pembrolizumab monotherapy or pembrolizumab combination therapy may be overestimated for patients with cancer starting outside the oral cavity seen in NHS clinical practice.

	As the subgroup of patients with cancer outside of the oral cavity was taken from an already pre-planned subgroup (that is tumours expressing PD-L1 with a CPS≥1), the subgroup is not powered to detect statistically significant differences between treatments in this subgroup. It is therefore difficult to draw firm conclusions about the relative effectiveness of pembrolizumab monotherapy versus cetuximab in combination with platinum chemotherapy and 5-FU or for pembrolizumab in combination versus cetuximab in combination with platinum chemotherapy and 5-FU for this subgroup.
Technical team preliminary judgement and rationale	Problems with the generalisability of the trial to clinical practice and the potential need to use subgroup analyses increases the uncertainty in both the clinical and cost-effectiveness estimates. However, KEYNOTE-048 remains the best available source of evidence for this appraisal. The technical team is concerned that the results suggested in KEYNOTE-048 (in the whole population and the subgroup of patients whose cancer started in the oral cavity) from pembrolizumab monotherapy or pembrolizumab combination therapy may not be extended to patients seen in clinical practice in the NHS in England. The technical team would like clinical expert input regarding the generalisability of the results from the whole population in KEYNOTE-048 and the subgroup analysis for patients whose cancer started in the oral cavity to patients seen in clinical practice. Uncertainty in the clinical effectiveness estimates for patients whose cancer started outside of the oral cavity could be explored through an additional subgroup analysis.
Summary of comments	Comments received from company KEYNOTE-048 results are generalisable to all patients with HNSCC because the baseline characteristics of those in KEYNOTE-048 are similar to patients in UK clinical practice. Appropriate comparator for patients with cancer starting outside the oral cavity seen in NHS clinical practice is platinum-based chemotherapy and 5-FU (not cetuximab in combination with platinum chemotherapy 5-FU) – comparison made via NMAs that would yield results generalisable to patients with cancer starting outside the oral cavity. • KEYNOTE-048 results show overall survival of patients with PD-L1 combined positive score ≥1 receiving cetuximab in combination with platinum chemotherapy 5-FU very similar between subgroups:

	Patient population	Treatment with cetuximab in combination with platinum and 5-fluorouracil chemotherapy
		Median overall survival, intention-to-treat analysis, KEYNOTE-048 study, Months (95% confidence interval)
	Patients with PD-L1 combined positive score ≥1 irrespective of where the cancer started (n=255)	10.3 (9.0, 11.5)
	Patients with PD-L1 combined positive score ≥1 and whose cancer started in the oral cavity* [redacted]	[redacted]
	Database Cut-off Date: 25 February 2019 *Please note that this was not a pre-specified analysis of the KEYNOTE-048 study and was not powered for this analysis.	

- KEYNOTE-048 data do not show cetuximab in combination with platinum chemotherapy and 5-FU is less effective in patients whose cancer started outside the oral cavity. Additionally, data from EXTREME study: no difference in effectiveness of cetuximab in combination with platinum chemotherapy and 5-FU between patients whose cancer started in different sites

Not feasible to consider subgroups by cancer location:

- KEYNOTE-048 not pre-specified to conduct subgroup analyses based on cancer location

	• Not powered to detect statistically significant differences - small number of patients, imbalance in baseline patient characteristics (i.e. randomisation would be broken for comparisons made in these subgroups). No underlying biological rationale why clinical effectiveness of pembrolizumab would differ depending on cancer location: o Final Appraisal Determination document of TA172 (sections 4.3 and 4.15) stated "the specialists were not aware of any biological reason for cetuximab to be more clinically effective in oral cavity tumours" o European Medicines Agency decision for cetuximab is not restricted to patients with cancer originating in the oral cavity Comments received from clinical experts • Agree that results from KEYNOTE-048 generalisable to all patients with HNSCC. • Appropriate to consider primary tumour location as subgroups because they have different prognosis: Good prognosis - p16 (tumour suppressor protein) overexpressed,

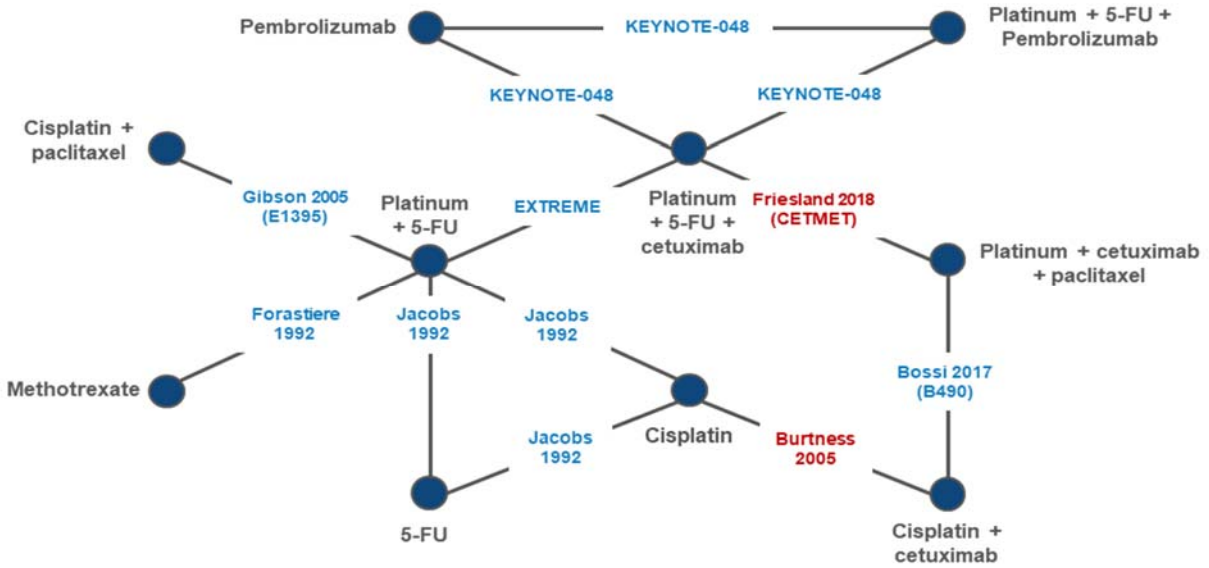
	oropharyngeal, glottic and nasopharyngeal cancers. Poor Prognosis - hypopharynx, supraglottic and subglottic laryngeal cancers (oral cavity). NCRI-ACP-RCP-RCR • Agree that results from KEYNOTE broadly generalisable irrespective of site • Primary tumour location as subgroups could be considered as they may be biologically and clinically divergent ERG considerations on company comments received during technical engagement: • Population recruited to KEYNOTE-048 trial only representative of the fittest patients in the NHS with R/M HNSCC, i.e. fit enough to receive cetuximab in combination with platinum chemotherapy and 5-FU. • Clinical advice to ERG is that in NHS practice cetuximab in combination with platinum chemotherapy and 5-FU is rarely used to treat cancer that started in the oral cavity as only a minority of patients with this type of cancer are fit enough to tolerate the treatment. • Cetuximab in combination with platinum chemotherapy and 5-FU only recommended for the treatment of cancer that starts in the oral cavity. Treatment options for those with cancer that started in the oral cavity and those whose cancer started elsewhere are different and therefore these 2 populations need to be considered separately.
Technical team judgement after engagement	Technical team consider that the results from KEYNOTE-048 are broadly generalisable to clinical practice in England and it is appropriate to consider subgroups by cancer location.

Issue 4 – Network meta-analyses: comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil

Questions for engagement	5. Mindful that there are challenges with all approaches for comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil (5-FU), which is the best comparison to use in this appraisal?

	• the company's network meta-analyses? **or** • the ERG's approach to using data from the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048 as a proxy for the effect of treatment with platinum chemotherapy and 5-FU?
Background/description of issue	**The company** did individual network meta-analyses (NMAs) of randomised controlled trials (RCTs) for pembrolizumab monotherapy and pembrolizumab combination therapy to compare their clinical effectiveness with platinum-based chemotherapy regimens because there was no head-to-head trial evidence. The base case NMA (see diagram below) for overall survival included the data from both pembrolizumab regimens in KEYNOTE-048 that was adjusted for subsequent therapy using the 2-stage method. It was a fixed-effect model (that is, it is assumed that all the included studies share a common effect size) using methods that allowed for time-varying hazard ratios (that is, a statistical method of calculating the chance of an event occurring in the treatment arm against the chance of an event occurring in the control arm) when the proportional hazards assumption (that is, the

chance of an event happening associated with the intervention and comparator data is proportional over time) is violated.



- Trials in blue are Tier 1 (No prior systemic therapy in the recurrent / metastatic setting; systemic therapy for locally advanced disease allowed if received >6 months before study entry)
- Trials in red are Tier 2 trials (No prior systemic therapy in the recurrent / metastatic setting; systemic therapy for locally advanced disease allowed if received >3 months before study entry)
- 5-FU = 5-fluorouracil

Source: appendix D to the company submission, Figure 5 and Table 10

	The company stated that for patients in the combined positive score (CPS) ≥1 subgroup, the NMA results show an improvement in overall survival (OS) for pembrolizumab monotherapy in comparison with cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU), with OS benefit increasing steadily from month 6 ([redacted]) to month 36 ([redacted]). In addition, it stated that pembrolizumab monotherapy also showed an improvement in OS in comparison with platinum plus 5-FU chemotherapy, with OS benefit increasing over time from month 6 ([redacted]) to month 36 ([redacted]). **The ERG** agreed with the company's decision to use fixed-effects model NMAs and methods that allow for time-varying hazard ratios but highlighted that the results did not show a benefit, in the early stages of treatment, for pembrolizumab (monotherapy or in combination) in comparison with cetuximab in combination with platinum chemotherapy and 5-FU or platinum chemotherapy and 5-FU chemotherapy regimens. In addition, the cetuximab in combination with platinum chemotherapy and 5-FU regimen statistically significantly improved PFS in comparison with pembrolizumab monotherapy in the early stages of treatment (month 1 to month 3). The ERG was concerned about the validity of the results of the company's NMAs: 1. The company stated that it considered the plausibility of the HRs estimated by the fractional polynomial (FP) models as part of the model selection process (Appendix D to the company submission, page 61), but no assessments of plausibility were provided. In addition, The ERG stated that the company assessed 2 categories of 2nd order FP models that assumed: o treatment only has an impact on 2 of the 3 hazard function parameters over time, and o treatment has an impact on all 3 hazard function parameters over time (Appendix D to the company submission, page 60). However, no information was provided on how these two categories of FP models were assessed. According to the methods described by Jansen et al. (2011) treatment has an impact on all three hazard function parameters for all 2nd order fractional polynomial models. So, the ERG is unsure if the 2nd order FP models have been estimated correctly.

	2. For KEYNOTE-048, the company used data from the PD-L1 CPS≥1 subgroup of patients. For all other trials, the company used data from the overall trial populations. The ERG considered that this approach was likely to have introduced heterogeneity into the NMAs. 3. The NMAs do not provide results that are stratified by primary tumour location: oral cavity versus non-oral cavity. Most trials included in the NMAs included both patients with oral and non-oral cavity cancer. Treatment with cetuximab in combination with platinum chemotherapy and 5-FU is recommended by NICE for patients with recurrent or metastatic HNSCC whose cancer originated in the oral cavity (oral patients). Standard care for all other patients (non-oral patients) with recurrent or metastatic HNSCC is treatment with platinum chemotherapy and 5-FU. The ERG considered that the company's NMAs do not provide reliable evidence for pembrolizumab (monotherapy or in combination) compared with cetuximab in combination with platinum chemotherapy and 5-FU or platinum chemotherapy and 5-FU in the relevant populations. It considered that an alternative to using NMA evidence was to use evidence directly from KEYNOTE- 048. The ERG stated that the company provided evidence of effectiveness (overall survival [OS] and progression free survival [PFS]), for pembrolizumab (monotherapy and in combination) compared with cetuximab in combination with platinum chemotherapy and 5-FU from KEYNOTE-048 for the subgroup of people whose cancer originated in the oral cavity. The results from the EXTREME trial (the main source of evidence for cetuximab in combination with platinum chemotherapy and 5-fluorouracil [5-FU]) showed that, for patients whose cancer did not start in the oral cavity, the OS of patients having cetuximab in combination with platinum chemotherapy and 5-FU was not statistically significantly different from that of patients having platinum chemotherapy and 5-FU. The ERG considered that because of this finding, the OS Kaplan-Meier (K-M) data from patients in the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048 can be used to represent patients whose cancer did not start in the oral cavity and who had platinum chemotherapy and 5-FU. For patients whose cancer did not start in the oral cavity, results from the EXTREME trial showed that treatment with cetuximab in combination with platinum chemotherapy and 5-FU may give a small benefit compared with treatment with platinum chemotherapy and 5-FU. It stated that although using data from the cetuximab in combination with platinum chemotherapy and 5-FU arm in KEYNOTE-048 to represent the effect of

	treatment with platinum chemotherapy and 5-FU may over-estimate effectiveness, this approach still represented a reasonable proxy.
Why this issue is important	A lack of direct comparative evidence means the comparison of effectiveness between pembrolizumab (monotherapy and in combination) and platinum chemotherapy and 5-fluouracil has to be estimated. However, the effect of the limitations with the company's NMAs increase the uncertainty in the estimates of treatment effect. Because the results from the NMA are included in the economic model, this also leads to uncertainty in the cost effectiveness estimates. Using the ERG's approach increases the ICER for the pembrolizumab combination by £1,143 per QALY gained for patients whose cancer started in the oral cavity and by £3,615 per QALY gained for patients whose cancer started outside the oral cavity. There was no change in the pembrolizumab monotherapy ICER for patients whose cancer started in the oral cavity but increased the ICER by £2,912 per QALY gained for patients whose cancer started outside of the cavity.
Technical team preliminary judgement and rationale	The technical team consider that the challenges of performing a network meta-analysis greatly increase the uncertainty in the estimates of treatment effect. On this basis, the technical team prefer a treatment comparison using the ERG's approach (albeit overestimating the effectiveness). The technical team would like clinical expert input to confirm that the ERG's approach is clinically plausible.
Summary of comments	Comments received from company NMA best comparison to use because: • the method takes into account study-observed differences between treatment effects. • produces results that are generalisable to/more likely to reflect true relative effectiveness of pembrolizumab (monotherapy and combination therapy) vs platinum-based chemotherapy and 5-FU including where the cancer started outside the oral cavity. • only fractional polynomial models with treatment effects on the scale and first shape parameter were used. • PD-L1 status is unlikely to be a treatment effect modifier for any of the other interventions in the network (as none have a method of action involving interaction between PD-1 and PD-

	L1), while this may have introduced some heterogeneity into the analysis, it does not bias the results. Inappropriate to use cetuximab in combination with platinum chemotherapy and 5-FU arm of the KEYNOTE-048 study as a proxy for the effectiveness of platinum chemotherapy and 5-FU in cost-effectiveness analyses because: • ERG's approach reliant on underlying assumptions which are associated with no less uncertainty than the company's approach (possibly introduce additional bias/overestimation of comparator treatment effect that ERG note exists): o assumes relative efficacy of overall survival (OS) of cetuximab in combination with platinum chemotherapy and 5-FU vs platinum and 5-FU differs significantly between subgroups (oral and non-oral). However, data from EXTREME study (table 33 of ERG report) shows 95% confidence intervals for OS hazard ratios in oral cavity subgroup and non-oral cavity subgroups (oropharynx, larynx, and hypopharynx) overlap - does not show efficacy differs significantly. • ERG report (section 4.9.7) notes possibility that NMA, by not stratifying patients by where the cancer started (inside the oral cavity or outside the oral cavity), may underestimate true OS for patients whose cancer started outside the oral cavity who receive platinum-based chemotherapy and 5-FU (based on EXTREME study results - median OS for patients whose cancer started in the oral cavity is approximately half that for patients whose cancer started outside the oral cavity). However, these are for point estimates only, without confidence intervals, and not from adequately powered statistical analysis to compare the relative effectiveness between subgroups - do not demonstrate with confidence that the true OS (or clinical effectiveness) differs. • ERG's approach assumes (for non-oral subgroup) that effectiveness of cetuximab in combination with platinum chemotherapy and 5-FU is the same as platinum chemotherapy and 5-FU. Based on subgroup analyses of EXTREME study: o statistically significant difference in OS (hazard ratios) in oral cavity subgroup o no statistically significant differences in the oropharynx, hypopharynx, larynx, and "other" sites of tumour origin subgroups (each subgroup analysed separately).

	However, EXTREME study only adequately powered to detect a statistically significant difference in the full population (section 6.3.5 of the company's submission for Technology appraisal 172 for cetuximab) which stated that 420 patients needed to be randomised for analysis to be adequately powered (numbers ranged from 32 to 149). Furthermore, randomisation in the EXTREME study stratified only by patients' previous chemotherapy and Karnofsky score - randomisation likely to have been broken for the site of tumour origin subgroup analyses. Therefore, statistically non-significant results in non-oral cavity subgroups do not mean no difference between the effects of treatment regimens as these could be "false negatives" from the underpowered statistical tests. • ERG noted its approach may overestimate the effectiveness of platinum chemotherapy and 5-FU, and so underestimate the relative treatment effect of pembrolizumab (monotherapy and combination therapy) compared with platinum-based chemotherapy and 5-FU in the cost-effectiveness analyses. • ERG's approach assumes that the shape of the OS Kaplan-Meier curves for patients whose cancer started outside the oral cavity in the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm and in the platinum and 5-fluorouracil arm in the EXTREME study are the same. However, there is no published OS K-M data from EXTREME for patients whose cancer started outside the oral cavity and so the assumption cannot be verified. In addition, for all patients irrespective of primary tumour site, the curves cross, indicating that the proportional hazards assumption may not hold. This suggests it is unlikely that the shape of a platinum chemotherapy and 5-FU OS curve would not differ significantly to that of a cetuximab in combination with platinum chemotherapy and 5-FU in patients whose cancer did not start in the oral cavity, and so it would not be appropriate to use the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048 as a proxy for the effect of treatment with platinum chemotherapy and 5-FU in cost-effectiveness analyses. The ERG's approach assumes cetuximab in combination with platinum-based chemotherapy and 5-FU is more effective in patients whose cancer started in the oral cavity. This will further overestimate the effectiveness of platinum chemotherapy and 5-FU and underestimate the relative effectiveness of pembrolizumab (monotherapy and combination therapy).

	• Unlikely adverse event profiles of cetuximab in combination with platinum chemotherapy and 5-FU same as platinum and 5-FU for patients whose cancer started outside the oral cavity. EXTREME study adverse event data (in the full population regardless of primary tumour site) show differences between the groups. When ERG amended model only the cost of cetuximab was changed to zero (no changes made to adverse events in terms of costs and utility values). As adverse events affect both costs and utilities, this further indicates that using these different interventions as proxies for each other would not be appropriate. • KEYNOTE-048 included higher proportion of patients with cancer that started in the oral cavity (≈30%) than in the EXTREME study (≈20%). If cetuximab in combination with platinum-based chemotherapy and 5-FU more effective in oral cavity, then company's approach would produce results that are an underestimate of the relative effectiveness of pembrolizumab (monotherapy and combination therapy) compared with platinum-based chemotherapy and 5-FU for cancer that started outside the oral cavity. Comments received from clinical experts Agree with the ERG's approach for comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil. NCRI-ACP-RCP-RCR ERG's approach seems reasonable. ERG considerations on company comments received during technical engagement: • Both methods are subject to uncertainty. • ERG's method has advantages of being simple, transparent and based on data from a high-quality trial. Company's method has advantages of including data from many studies and allowing adjustments to be made to ameliorate the effect of heterogeneity between trials. • If effectiveness differs by origin of cancer (as suggested by OS differences for the subgroups of patients with cancer that did/ did not originate in the oral cavity who received platinum

	chemotherapy and 5-FU in the EXTREME trial) then the company's NMA results will be compromised.
Technical team judgement after engagement	Uncertainty in the estimates of treatment effect remain because of a lack of direct head to head data. There are contradictory views regarding the choice of methodology for comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluorouracil although clinical experts agree with ERG's approach. The technical team preference is for a treatment comparison using the ERG's approach.

Issue 5 – Extrapolation of overall survival (OS)

Questions for engagement	6. What proportion of patients in the pembrolizumab monotherapy and combination therapy arms would be expected to be alive at 1, 2, 3, 5 and 10 years? 7. What proportion of patients receiving the cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU would be expected to be alive at 1, 2, 3, 5 and 10 years? 8. Which extrapolation of overall survival is most clinically plausible?
Background/description of issue	Some people were still alive at the end of the trial, so overall survival (OS) needs to be extrapolated over the model time horizon. **The company** used a piecewise model using observed Kaplan-Meier (K-M) data up to 80 weeks followed by a parametric distribution to model overall survival beyond the observed data period. A log-logistic (for pembrolizumab monotherapy compared with cetuximab in combination with platinum chemotherapy and [5-FU]) or a log-normal distribution (for pembrolizumab combination therapy compared with cetuximab in combination with platinum chemotherapy and 5-FU) were used to extrapolate OS up to 20 years (the lifetime horizon of the model). **The ERG** highlighted that these types of distributions have very long tails and hazard rates that decrease over time. The long tail means that a number of patients remain alive after many years and the declining hazard rate means that the projected hazard rate may fall below that of the background mortality. In the company base case the mortality hazard rate fell below that of the general population after approximately 18 years for people having pembrolizumab monotherapy or pembrolizumab combination therapy. For people having cetuximab in combination with platinum chemotherapy and 5-

FU this is likely to happen after this point. Although the company used an algorithm in the economic model to ensure that mortality could never be lower than background mortality, the ERG considered that the need to use such an approach suggested that the log-normal and log-logistic extrapolations were clinically implausible.

The ERG noted that a piecewise model using the observed overall survival K-M data from KEYNOTE-048 up to 80 weeks followed by a Weibull distribution gave the most clinically plausible survival distribution and should be used to extrapolate all 3 treatment arms of the trial. It stated that when the Weibull distribution was used to extrapolate the cetuximab in combination with platinum chemotherapy and 5-FU arm of KEYNOTE-048, it potentially underestimated OS. This is because, OS at 5 years was underestimated by a percentage point when compared with the cetuximab in combination with platinum chemotherapy and 5-FU arm in the EXTREME trial. However, the ERG believe it still provided clinically plausible OS projections over 5 years, and that it did not produce a clinically implausible survival tail.

Clinical experts stated that people receiving either cetuximab in combination with platinum chemotherapy and 5-FU or platinum and 5-FU were unlikely to survive for more than 5 years after starting treatment and approximately 2% would be alive at 5 years. They agreed that people receiving immunotherapies were likely to survive longer with the 5- and 10-year survival estimates for pembrolizumab monotherapy being plausible but noted that the company 10-year survival estimate for pembrolizumab combination therapy was less plausible.

Pembrolizumab monotherapy

	Pembrolizumab monotherapy		**Cetuximab in combination with platinum chemotherapy and 5-FU**		**Platinum plus 5-FU**	
Years after starting treatment	Company modelled people still alive (%)	ERG modelled	Company modelled people still alive (%)	ERG modelled	Company modelled people still alive (%)	ERG modelled
1	50.4	50.4	42.2	42.7	36.5	36.5

2	29.6	28.9	14.4	14.7	13.1	13.4
3	21.2	21.1	7.2	7.4	6.3	6.2
5	14.0	11.9	3.3	2.1	2.3	1.6
10	7.8	3.7	1.3	0.1	0.5	0.1

Pembrolizumab combination therapy

	Pembrolizumab combination therapy		**Cetuximab in combination with platinum chemotherapy and 5-FU**		**Platinum plus 5-FU**	
Years after starting treatment	Company modelled people still alive (%)	ERG modelled	Company modelled people still alive (%)	ERG modelled	Company modelled people still alive (%)	ERG modelled
1	54.1	54.1	42.0	42.0	36.7	36.7
2	31.8	32.2	13.5	13.8	10.7	11.1
3	25.3	24.2	6.1	5.6	4.7	4.6
5	19.3	17.2	2.4	0.9	0.7	0.3
10	13.1	7.8	0.6	0.0	0.0	0.0

Why this issue is important	The choice of distribution has an impact on the ICER. It is important that the methods used result in clinically plausible survival probabilities and a valid rationale is given for the choice of any statistical method used. Using the piecewise Weibull distribution increases the ICER from the company base case by approximately £2,000 per QALY gained for people whose cancer started in the oral cavity and between £7,000 per QALY gained (monotherapy) to £9,000 per QALY gained (combination therapy) for people whose cancer started outside the oral cavity.

Technical team preliminary judgement and rationale	There is some uncertainty with the extrapolation of survival estimates generated for pembrolizumab monotherapy, pembrolizumab combination therapy, cetuximab in combination with platinum chemotherapy and 5-FU and platinum chemotherapy and 5-FU. Those generated using the company's preferred piecewise model (K-M data from KEYNOTE- 048 up to 80 weeks followed by a log-logistic for pembrolizumab monotherapy or a log-normal distribution for pembrolizumab combination therapy) and those using the ERG's preferred piecewise model (K-M data from KEYNOTE- 048 up to 80 weeks followed by a Weibull distribution) both provided clinically plausible results 5 years after starting treatment. However, the technical team accepts the ERG's argument that the distributions preferred by the company have very long tails and clinical expert feedback that indicated that the 10-year survival estimates are clinically less plausible. For this reason, the technical team prefer a piecewise model (K-M data from KEYNOTE-048 up to 80 weeks) followed by a Weibull distribution.
Summary of comments	Comments received from company Clinicians felt the survival estimations for pembrolizumab seemed reasonable and reflected what is expected to be seen with these treatments in clinical practice. Most clinicians felt greater uncertainty in predicting 10-year overall survival because of a lack of clinical data. 5-year overall survival rate in KN001 trial (NSCLC) with pembrolizumab was 23.2% in previously untreated patients. **Choice of extrapolation** • clinical input suggested that the log-logistic and log-normal curves were good predictors for the overall survival. • company choice based on best AIC/BIC test fit for both treatment arm pairings. • Weibull curve gives the worst goodness-of-fit and use of 5-year trial data shows, underestimates the OS of the cetuximab in combination with platinum chemotherapy and 5-FU arm. • visual inspection shows no discernible difference between parametric curves (except the exponential curve), with all fitting the clinical trial data reasonably.

- clinicians substantiated the survival extrapolation of the company at 3 and 5 years for both pembrolizumab monotherapy and combination therapy arms - agree there is a plateau phase seen with pembrolizumab in other cancers (e.g. NSCLC) between 3 and 5 years and same could be assumed in Head and Neck cancer.
- OS estimates for cetuximab in combination with platinum chemotherapy and 5-FU and platinum chemotherapy and 5-FU are in line with long term follow-up of the EXTREME study (5-year follow up):

5-year Follow-up Data of the EXTREME Study at Random Time Points[1]

Treatment arm	% of patients alive at 28 months (1376 days)	% of patients alive at 36 months (1769 days)	% of patients alive at 42 months (2064 days)	% of patients alive at 59.5 months (2924 days)
	Trial	Trial	Trial	Trial
Cetuximab	11.7	7.1	6.5	2.9
Standard of Care *(platinum +5-FU)*	8.3	4.4	4.4	1.7
Increment	**3.4**	**2.7**	**2.1**	**1.2**

Summary of survival estimates (% of people still alive) using preferred extrapolation curves (company and ERG):

	Pembrolizumab monotherapy				**Pembrolizumab combination therapy**			
Years after starting treatment	Cetuximab plus platinum chemotherapy and 5-FU		Platinum plus 5-FU		Cetuximab plus platinum chemotherapy and 5-FU		Platinum plus 5-FU	
	MSD	**ERG**	**MSD**	**ERG**	**MSD**	**ERG**	**MSD**	**ERG**
1	42.2	42.7	36.5	36.5	42.0	42.0	36.7	36.7
2	14.4	14.7	13.1	13.4	13.5	13.8	10.7	11.1
3	7.2	7.4	6.3	6.2	6.1	5.6	4.7	4.6

5	3.3	2.1	2.3	1.6	2.4	0.9	0.7	0.3
10	1.3	0.1	0.5	0.1	0.6	0	0	0

- choice of Weibull curve underestimates OS of both comparator arms
- choice of company extrapolation more able to predict OS at percentages closer to 2.9%
- company curves fit most of the criteria for extrapolation vs curve chosen by ERG (provide limited evidence to support their choice)

[1]Cetuximab for the treatment of metastatic and/or recurrent squamous cell carcinoma of the head and neck (review of TA172) [ID1016]. CDF Rapid Reconsideration [Internet]. 2016 17-OCT-2019. Available from: https://www.nice.org.uk/guidance/ta473/documents/committee-papers.

Comments received from clinical experts

Company's data possibly valid up to 5 years, no clinical data currently support 10-year survival EXTREME trial and company's data plausible for up to 5 years. No patients alive at 10 years in routine clinical practice

NCRI-ACP-RCP-RCR

Pembrolizumab monotherapy and combination therapy arms - survival difficult to predict. Company modelled survival seem plausible, however ERG modelled data seems more realistic

Company and ERG models for cetuximab in combination with platinum chemotherapy and 5-FU or platinum chemotherapy seem plausible although impression is the actual figure lies somewhere between the two

ERG modelled data seems most plausible for monotherapy and combination therapy survival. Both seem clinically plausible for the chemotherapy outcomes

ERG considerations on company comments received during technical engagement:

	In the absence of evidence this is largely a matter of conjecture. However, the following points should be borne in mind: • As stated in ERG report, the log-logistic and log-normal distributions in company base case lead to patients with Recurrent/Metastatic HNSCC having a lower probability of dying than the general population • AIC/BIC statistics can only be used to assess the extent to which a parametric distribution describes existing data; they are not measures of predictive validity • Visual comparison of a parametric distribution to Kaplan-Meier data is only a descriptive assessment, not a predictive assessment.
Technical team judgement after engagement	There are conflicting viewpoints regarding the choice of extrapolation used for overall survival, but in the absence of long term data from KEYNOTE-048, and clinical opinion that the use of the Weibull distribution resulted in more clinically plausible results, the technical team preferred extrapolation is a piecewise model (K-M data from KEYNOTE-048 up to 80 weeks) followed by a Weibull distribution.

Issue 6 – Duration of treatment effect

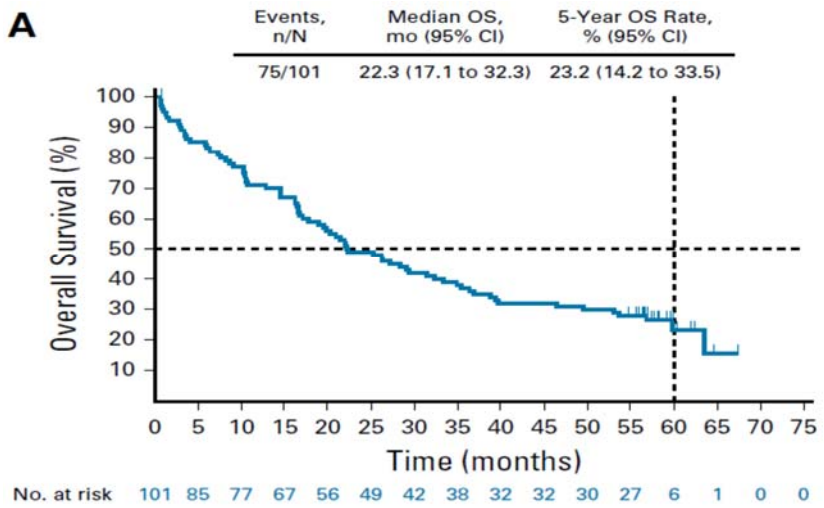
Questions for engagement	9. What is the most plausible assumption of duration of treatment effect?
Background/description of issue	**The company** assumed in its base case a duration of treatment effect of 20 years. This means that from start of treatment for the duration of the time horizon in the model, the mortality rates for people having pembrolizumab monotherapy or pembrolizumab combination therapy are lower than the mortality rates for people having cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) or platinum chemotherapy and 5-FU. **The ERG** stated that such an effect required substantial support from clinical evidence; which had not been presented by the company. In addition, previous appraisals of immunotherapies, such as atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy (TA520), explored scenarios where mortality rates for immunotherapies become the same as those for comparator therapies 3 and 5 years after starting treatment. It noted that although the company highlighted the effect of the treatment duration at 3 and 5 years in its supplementary document, an

algorithmic error in the model was identified that affected the results generated when this was incorporated into the analyses.

Intervention	Comparator	Company base case	Corrected company ICER per QALY gained	
			3-year duration of treatment effect	5-year duration of treatment effect
Pembrolizumab monotherapy	Cetuximab in combination with platinum chemotherapy and 5-FU	Pembrolizumab monotherapy dominant	Pembrolizumab dominant	Pembrolizumab dominant
	Platinum plus 5-FU	£31,212	£92,888	£59,846
Pembrolizumab combination	Cetuximab in combination with platinum chemotherapy and 5-FU	£9,255	£12,358	£10,417
	Platinum plus 5-FU	£31,070	£76,057	£57,011

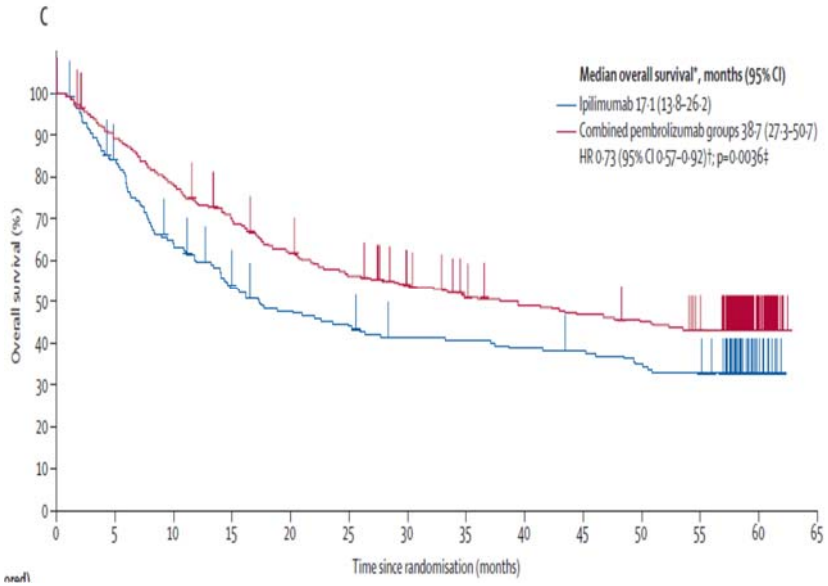
Clinical experts stated that a duration of treatment effect of 10 years was unlikely. Although pembrolizumab has not been used to treat head and neck cancer, experience of using it in other disease areas, such as malignant melanoma, suggests that a 5-year duration of treatment effect is plausible.

Why this issue is important	Usually, decreasing the assumed treatment effect duration increases the ICER.

Technical team preliminary judgement and rationale	The technical team would like to see more evidence to support the longer duration of treatment effect of 20 years. Lacking this and based on previous guidance of immunotherapies (in particular nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [TA490]) and clinical feedback, it is preferable to model a more conservative duration of 5 years.
Summary of comments	Comments received from company Acknowledge treatment waning has been used in previous immunotherapy appraisals. 5-year duration of treatment waning effect inappropriate: • long-term treatment effect of pembrolizumab in other tumours o patients who had pembrolizumab continued to respond with a 5-year survival (recently published study of 5-year follow up data - advanced NSCLC). Plateau phase of curve (below) starts at month 40 and extends through to year 5 **K-M estimates of 5-year Overall Survival for advanced NSCLC treated with pembrolizumab[2]** 

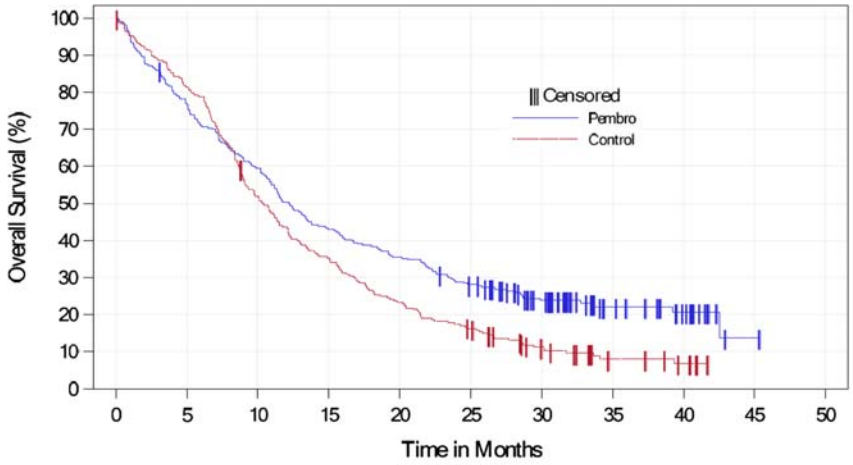
- Pembrolizumab vs ipilimumab in advanced melanoma - beginnings of a plateau phase from 35 months (below)

Overall Survival in Patients Receiving 1st-line Pembrolizumab versus Ipilimumab in Advanced Melanoma[3]

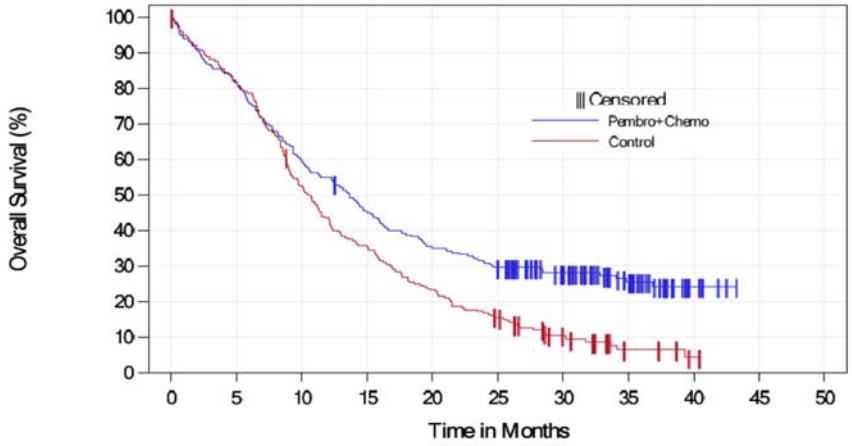


- overall survival in KEYNOTE-048 CPS ≥ 1 subgroup for monotherapy and combination therapy - plateau phase has begun at roughly 35 months in both intervention arms (below).

K-M estimates of OS (monotherapy vs cetuximab + platinum + 5-FU [Control])



K-M estimates of OS (combination therapy vs cetuximab + platinum + 5-FU [Control])



- clinical expert input in TA490 states "I believe that the majority of patients who enter the plateau phase will continue to enjoy the health benefits (including out to 5 – 10 years)".
- NICE clinical expert (for this appraisal) responses:
    - "duration of treatment effect with pembrolizumab or other immuno-oncology (IO) agents are likely to be 5 years or more, but unlikely to be 10 years; at least with current experience and we need actual long-term clinical follow-up data".
    - "all treatment effect beyond 5 years is by definition due to the pembrolizumab as there are almost zero survivors without pembrolizumab beyond 5 years".

Based on the data provided, and clinician responses:

- do not believe clinically plausible that the plateau would drop off after 5 years
- assume plateau phase to extend through to 5 years in KEYNOTE-048 data (durable responses).
- effect of pembrolizumab highly likely to last to 5 years and beyond (although acknowledge more uncertainty at 10 years).

Explored a range of potential treatment waning timepoints (below):

Company and ERG preferred extrapolation curves (non-oral cavity)

Treatment Waning	Pembrolizumab Monotherapy		Pembrolizumab Combination Therapy	
	Company	ERG	Company	ERG
5 years	£43,158	£51,063	£57,011	£60,242

6 years	£40,209	£48,071	£51,742	£54,828
7 years	£38,122	£46,047	£47,836	£51,050
8 years	£36,570	£44,617	£44,775	£48,257
9 years	£35,378	£43,580	£42,320	£46,146
10 years	£34,442	£42,812	£40,317	£44,523

Company and ERG preferred extrapolation curves (oral cavity)

Treatment Waning	**Pembrolizumab Monotherapy**		**Pembrolizumab Combination Therapy**	
	Company	**ERG**	**Company**	**ERG**
5 years	Dominant	Dominant	£10,417	£14,023
6 years	Dominant	Dominant	£10,110	£13,270
7 years	Dominant	Dominant	£9,921	£12,819
8 years	Dominant	Dominant	£9,785	£12,501

	<table><tr><td>9 years</td><td>Dominant</td><td>Dominant</td><td>£9,682</td><td>£12,267</td></tr><tr><td>10 years</td><td>Dominant</td><td>Dominant</td><td>£9,602</td><td>£12,092</td></tr></table> [2]Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ, et al. Five-year overall survival for patients with advanced non-small-cell lung cancer treated with pembrolizumab: Results from the phase I KEYNOTE-001 study. J Clin Oncol. 2019;37(28):2518-27. [3]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. 2019;20(9):1239-51. NCRI-ACP-RCP-RCR The duration of treatment effect for the sub-group that get significant benefit would be expected to be beyond the 2 years of therapy extending to 5 years and 10 years in some patients. In absence of this technology, the 5-year survival would be less than 10%- and 10-year survival negligible. Given both models show a five-year survival of approx. 20% and 10-year survival of 5-10% it is only possible that this is due to the new treatment. ERG considerations on company comments received during technical engagement: In the absence of evidence this is a matter of conjecture.
Technical team judgement after engagement	There is no robust evidence suggesting that pembrolizumab maintains a longer duration of treatment effect beyond 5-years.

Issue 7 – End of life criteria

This issue was resolved at technical engagement and is addressed in Table 3.

4. Other issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Tables 1a, 1b: People whose tumour started inside the oral cavity and 1c, 1d, 1e, 1f: People whose tumour started outside of the oral cavity: Technical team preferred assumptions and impact on the cost-effectiveness estimate. All estimates are pairwise comparisons (with the exception of tables 1e and 1f as these are fully incremental analyses) where the confidential commercial agreement discount is applied for pembrolizumab and list price for all other drugs (first line and subsequent treatment).

Table 1a: People whose tumour started inside the oral cavity: pembrolizumab monotherapy compared with cetuximab in combination with platinum chemotherapy and 5-fluorouracil

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**Dominant**	**-**
1. Using all patients from the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab in combination with platinum chemotherapy and 5-fluorouracil (referenced by the ERG as preferred scenario R1)	Technical team agreed with ERG's amendments. See page 106 of ERG report and issue 4.	**n/a**	**-**
2. Using Weibull distribution for OS projections beyond 80 weeks (referenced by the ERG as preferred scenario R2)	Technical team agreed with ERG's amendments. See page 104 of ERG report and issue 5.	**Dominant**	**-**

Alteration	Technical team rationale	ICER	Change from base case
3. 5-year duration of treatment effect (referenced by the ERG as preferred scenario R4)	Technical team agreed with clinical feedback and was considered acceptable in TA520 (see issue 6)	**Dominant**	**-**
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**Dominant**	**-**

Table 1b: People whose tumour started inside the oral cavity: pembrolizumab combination therapy compared with cetuximab in combination with platinum chemotherapy and 5-fluorouracil

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**£9,255**	
1. Using all patients from the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab in combination with platinum chemotherapy and 5-fluorouracil (referenced by the ERG as preferred scenario R1)	Technical team agreed with ERG's amendments. See page 106 of ERG report and issue 4.	£10,398	+£1,143
2. Using Weibull distribution for OS projections beyond 80 weeks (referenced by the ERG as preferred scenario R2)	Technical team agreed with ERG's amendments. See page 104 of ERG report and issue 5.	£11,437	+£2,182
3. 5-year duration of treatment effect (referenced by the ERG as preferred scenario R4)	Technical team agreed with clinical feedback and was considered acceptable in TA520 (see issue 6)	£10,417	+£1,162

Alteration	Technical team rationale	ICER	Change from base case
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£16,553**	**+£7,298**

Table 1c: People whose tumour started outside of the oral cavity: pembrolizumab monotherapy compared with platinum chemotherapy and 5-fluorouracil

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**£31,212**	
1. Using all patients from the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab in combination with platinum chemotherapy and 5-fluorouracil regimen (referenced by the ERG as preferred scenario R1)	Technical team agreed with ERG's amendments. See page 106 of ERG report and issue 4.	£34,124	+£2,912
2. Using Weibull distribution for OS projections beyond 80 weeks (referenced by the ERG as preferred scenario R2)	Technical team agreed with ERG's amendments. See page 104 of ERG report and issue 5.	£40,546	+£9,334
3. 5-year duration of treatment effect (referenced by the ERG as preferred scenario R4)	Technical team agreed with clinical feedback and was considered acceptable in TA520 (see issue 6)	£59,846	+£28,634

Alteration	Technical team rationale	ICER	Change from base case
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£56,085**	**+£24,873**

Table 1d: People whose tumour started outside of the oral cavity: pembrolizumab combination therapy compared with platinum chemotherapy and 5-fluorouracil

Alteration	Technical team rationale	ICER	Change from base case
Company base case	**–**	**£31,070**	
1. Using all patients from the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm of KEYNOTE-048 trial to model OS, PFS and TTD for oral cavity patients receiving cetuximab in combination with platinum chemotherapy and 5-fluorouracil (referenced by the ERG as preferred scenario R1)	Technical team agreed with ERG's amendments. See page 106 of ERG report and issue 4.	£34,685	+£3,615
2. Using Weibull distribution for OS projections beyond 80 weeks (referenced by the ERG as preferred scenario R2)	Technical team agreed with ERG's amendments. See page 104 of ERG report and issue 5.	£38,639	+£7,569
3. 5-year duration of treatment effect (referenced by the ERG as preferred scenario R4)	Technical team agreed with clinical feedback and was considered acceptable in TA520 (see issue 6)	£57,011	+£25,941
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	**£67,386**	**+£36,316**

Table 1e: Fully incremental analysis for people whose cancer started outside of the oral cavity

Treatment	Total costs	Total QALYS	Incremental costs	Incremental QALYs	ICER per QALY gained
Platinum plus 5-FU chemotherapy	£22,076	0.839	-	-	-
Pembrolizumab monotherapy	£47,644	1.422	£25,568	0.583	**extendedly dominated**
Pembrolizumab in combination with platinum and 5-fluorouracil	£61,956	1.771	£14,312	0.349	**£42,790**

Please note: The results in table 1e were calculated using the ERG's preferred scenario 1 and 2 (that is, using all patients from the cetuximab in combination with platinum chemotherapy and 5-fluorouracil arm of KEYNOTE-048 to model overall survival, progression-free survival and time to treatment discontinuation for those whose tumour started in the oral cavity receiving cetuximab in combination with platinum chemotherapy and 5-fluorouracil. In addition, using Weibull distribution for overall survival projections beyond 80 weeks). The 5-year duration of treatment effect (ERG preferred scenario 4) has not been applied.

Fully incremental analysis for people whose tumour started in the oral cavity using the ERG's preferred scenario 1 and 2 cannot be reported here as they include the commercial arrangements for cetuximab that are confidential.

Table 1f: Fully incremental analysis for people whose cancer started outside of the oral cavity with a 5-year duration of treatment effect applied

Treatment	Total costs	Total QALYS	Incremental costs	Incremental QALYs	ICER per QALY gained
Platinum plus 5-FU chemotherapy	£22,076	0.839	-	-	-
Pembrolizumab monotherapy	£46,907	1.282	£24,831	0.443	**£56,052**
Pembrolizumab in combination with platinum and 5-fluorouracil	£59,129	1.389	£12,222	0.107	**£114,224**

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
The relative effectiveness of pembrolizumab compared with cetuximab in combination with platinum chemotherapy and 5-fluorouracil or platinum plus 5-FU chemotherapy regimens	There is no head-to-head trial comparing pembrolizumab (monotherapy or in combination) with platinum chemotherapy and 5-fluouracil in recurrent or metastatic squamous cell head and neck cancer (see issue 3). Therefore, the relative effectiveness has to be estimated. This adds uncertainty in the assessment of clinical effectiveness.	Unknown impact on the ICER.
Standard care in KEYNOTE-048 only included people with ECOG PS 0 or 1	There is increased uncertainty in the true relative clinical effectiveness of the treatments because in clinical practice this	Unknown impact on the ICER.

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
	population may have a poorer prognosis than those in trial and in the economic model.	

Table 3: Other issues for information

Issue	Comments
2-year stopping rule for pembrolizumab (Issue 1)	The summary of product characteristics for other indications of pembrolizumab (including for the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy) states that people should receive pembrolizumab until disease progression or unacceptable toxicity. The use of a 2-year stopping rule is in line with previous pembrolizumab appraisals; pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer (TA531), pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer (TA557), pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA519) and pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable (TA522). In addition, it appears that only a small proportion of patients in the intervention arms of KEYNOTE-048 remained alive and on pembrolizumab monotherapy treatment (approximately [redacted]%) or pembrolizumab combination treatment (approximately [redacted]%) at 2 years. **Following technical engagement, the technical team was satisfied that a 2-year stopping rule for pembrolizumab is appropriate for decision making.**
End of life criteria (Issue 7)	The technical team agreed with the company and ERG that both pembrolizumab monotherapy and pembrolizumab combination therapy could provide an overall-survival gain of over 3 months, based on the trial evidence presented, and the economic modelled data. The company preferred base case for pembrolizumab monotherapy predicts that compared with cetuximab in combination with platinum chemotherapy and 5-FU or platinum chemotherapy and 5-FU, pembrolizumab monotherapy offers life extensions of 1.06 life years (12.72 months) and 1.44 life years (17.28 months) respectively. For pembrolizumab combination therapy the company preferred base case predicts life extensions of 1.19 life years (14.28 months) and 1.61 life years (19.32 months) respectively. In addition, the technical team considered that both pembrolizumab monotherapy and pembrolizumab combination therapy also met the short life expectancy criteria and so met

Issue	Comments
	the end of life criteria as results from KEYNOTE-048 showed that median overall survival for people receiving cetuximab in combination with platinum chemotherapy and 5-fluorouracil (5-FU) was 10.3 months (95% CI: 9.0 to 11.5 months). **Following technical engagement, the technical team was satisfied that both pembrolizumab monotherapy and pembrolizumab combination therapy met NICE's end of life criteria.**
No evidence for the population whose tumours do not express PD-L1 with a combined positive score (CPS) ≥1	The company did not provide any clinical or cost-effectiveness evidence for this population. Without such evidence, the clinical and cost effectiveness of pembrolizumab monotherapy and pembrolizumab combination therapy in this population is unknown. This means that the appraisal committee would be unable to make a recommendation on this population. **During technical engagement, the company received CHMP opinion that removed this issue as an area of uncertainty.**
Implementation of company model	The ERG highlighted an algorithmic error in the company model (relating to the duration of treatment effect). Correction of this error increased the ICER for the 3-year and 5-year duration of treatment effect (see issue 6).
Innovation	The company considered the drug to be innovative. However, the technical team considers that these aspects have been adequately captured in the economic model. Therefore, the technical team believes further consideration of the innovative nature of pembrolizumab is not needed.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

Authors

Lindsay Smith

Appraisal committee vice-chair

Stephen Robinson

Technical lead

Nicola Hay

Technical adviser

Jasdeep Hayre

Associate director

With input from the lead team:

Rob Hodgson

Lead team member

Paula Ghaneh

Lead team member

Rebecca Harmston

Lead team member